

UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MICHIGAN

COUNTY OF WAYNE and COUNTY) Civ. No.
OF OAKLAND,)
Plaintiffs,) COMPLAINT FOR (1) VIOLATION
vs.) OF MICHIGAN CONSUMER
PURDUE PHARMA L.P.,) PROTECTION ACT; (2) PUBLIC
CEPHALON, INC., TEVA) NUISANCE; (3) NEGLIGENCE; (4)
PHARMACEUTICAL INDUSTRIES) UNJUST ENRICHMENT; AND (5)
LTD., TEVA PHARMACEUTICALS) INFLUENCED AND CORRUPT
USA, INC., ENDO INTERNATIONAL) ORGANIZATION ACT
PLC, JANSSEN)
PHARMACEUTICALS, INC., INSYS)
THERAPEUTICS, INC.,) DEMAND FOR JURY TRIAL
MALLINCKRODT PLC,)
MALLINCKRODT)
PHARMACEUTICALS,)
AMERISOURCEBERGEN)
CORPORATION, CARDINAL)
HEALTH, INC. and McKESSON)
CORPORATION,)
Defendants.)

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I. INTRODUCTION

1. Michigan, like many states across the country, is facing an unprecedented opioid addiction epidemic. Michigan healthcare providers wrote 11 million prescriptions for opioid drugs in 2015 and another 11 million in 2016 – more annual opioid prescriptions than Michigan has people. On June 18, 2015, Governor Rick Snyder appointed a task force to address the prescription opioid, heroin and fentanyl crisis and appointed Lieutenant Governor Brian Calley to lead the effort. On October 26, 2015, the task force issued a comprehensive report of their findings and issued more than two dozen recommendations to address the growing problem. On receiving the report, Governor Snyder stated: ““The impact of prescription drug and opioid abuse is being felt in every community across Michigan. It crosses all demographic, geographic and political lines . . .”¹ On June 23, 2016, Governor Snyder issued an executive order creating an advisory commission to review the Report of Findings and

¹ Ex. 1 (Press Release, Office of Governor Rick Snyder, Prescription Drug and Opioid Abuse Task Force releases findings and recommendations (Oct. 26, 2015), <http://www.michigan.gov/snyder/0,4668,7-277--367961--,00.html>). All exhibits referenced herein are attached hereto unless otherwise stated.

Recommendations for Action from the Michigan Prescription Drug and Abuse Task Force and develop policies to implement the report's recommendations.²

2. In 2014, more than 47,000 people died in the United States from lethal drug overdoses. In 2015, that number exceeded 52,000,³ more deaths than caused by car crashes and gun homicides combined. Sadly, this trend shows no sign of slowing.⁴ More than three out of five of these deaths involve opioids – a dangerous, highly addictive and often lethal class of natural, synthetic and semi-synthetic painkillers. Nearly half of those involve legal opioids prescribed by doctors to treat pain. These prescription opioids have included brand-name medications like OxyContin, Opana, Subsys, Fentora and Duragesic, as well as generics like oxycodone, methadone and fentanyl. In all, more than 183,000 people died in the United States between 1999 and

² Ex. 2 (*Michigan Prescription Drug and Opioid Abuse Commission*, Office of Governor Rick Snyder, http://www.michigan.gov/snyder/0,4668,7-277-57738_57679_57726-394018--,00.html).

³ Ex. 3 (Rose A. Rudd, *et al.*, *Increases in Drug and Opioid-Involved Overdose Deaths – United States, 2010-2015*, 65 Morbidity & Mortality Weekly Report 1445-52 (2016), <https://www.cdc.gov/mmwr/volumes/65/wr/mm655051e1.htm> (hereinafter “Rudd, *Increases in Drug and Opioid-Involved Overdose*”)).

⁴ Ex. 4 (Midwest Intervention Group, <http://www.midwestinterventions.com/TheDizzyingIncreaseofOverdoseDeathsinIndianaandNationwide.en.html> (last visited Oct. 9, 2017)).

2015 from overdoses directly related to prescription opioids.⁵ Public health officials have called the current epidemic the worst drug crisis in American history.⁶ The following chart⁷ illustrates the rise of opioid-related deaths in the U.S.:

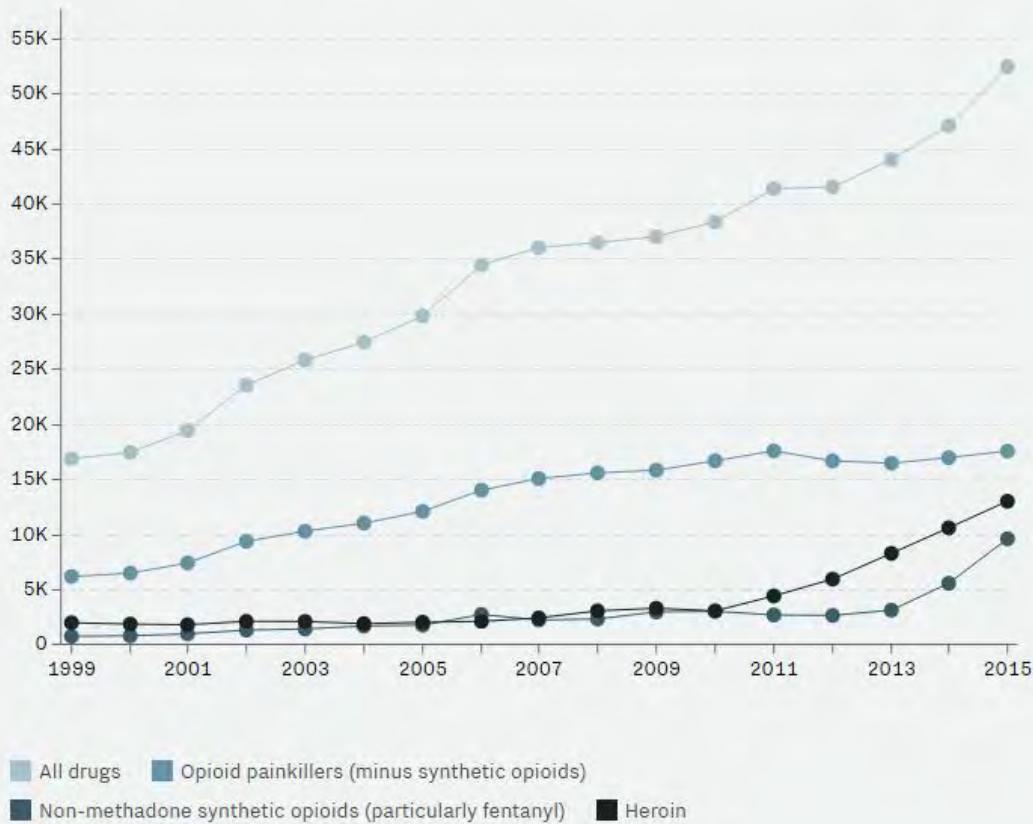
⁵ That number does not take into account the staggering number of additional illicit opioid deaths that can be related back to doctor-prescribed opioids; indeed, four out of five new heroin users began first with prescription opioid misuse. Ex. 5 (Christopher M. Jones, *Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers – United States, 2002-2004 and 2008-2010*, 132 (1-2) Drug & Alcohol Dependence 95-100 (Sept. 1, 2013), [http://www.drugandalcoholdependence.com/article/S0376-8716\(13\)00019-7/pdf](http://www.drugandalcoholdependence.com/article/S0376-8716(13)00019-7/pdf)). Still, most misused prescription drugs are obtained directly or indirectly from a doctor’s prescription; only 4% of persons misusing or addicted to prescription drugs report getting them from a drug dealer or stranger. Anna Lembke, *Drug Dealer, MD: How Doctors Were Duped, Patients Got Hooked, and Why It’s So Hard to Stop* 18 (Johns Hopkins University Press 2016). “[U]nintentional poisoning deaths’ from prescription opioids quadrupled between 1999 and 2010, outnumbering deaths from heroin and cocaine combined.” Ex. 6 (Kathleen Frydl, *Purdue Pharma: Corporate Fraud With a Body Count*, Alternet (May 18, 2016), <https://www.alternet.org/drugs/purdue-pharma-corporate-fraud-body-count> (hereinafter “Frydl, *Purdue Pharma*”)).

⁶ Ex. 7 (Julie Borman, *Inside a Killer Drug Epidemic: A Look at America’s Opioid Crisis*, N.Y. Times (Jan. 6, 2017), <https://www.nytimes.com/2017/01/06/us/opioid-crisis-epidemic.html>).

⁷ Ex. 8 (German Lopez & Sarah Frostenson, *How the opioid epidemic became America’s worst drug crisis ever, in 15 maps and charts*, Vox (Mar. 23, 2017, 10:30 AM), <http://www.vox.com/science-and-health/2017/3/23/14987892/opioid-heroin-epidemic-charts> (hereinafter “Lopez, *How the opioid epidemic*”)).

Drug overdose deaths in America

Note: Some deaths on this chart may overlap if they involve multiple drugs.

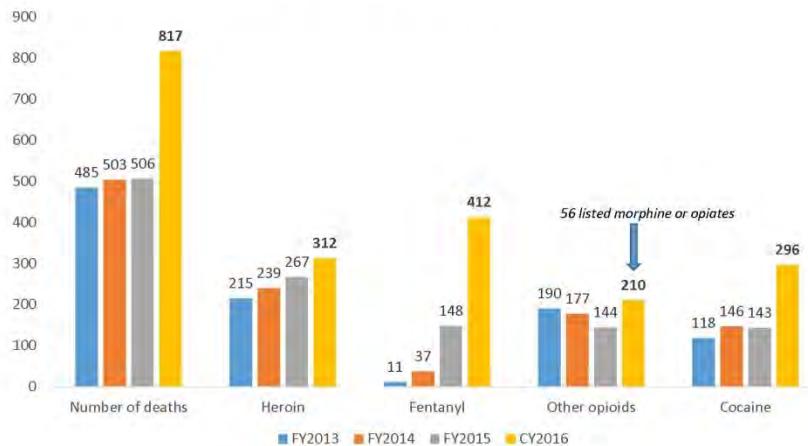


Source: [National Institute on Drug Abuse](#)

3. Wayne County and Oakland County, Michigan, sit squarely in the crosshairs of this opioid-fueled epidemic. According to the Wayne County Medical Examiner, between 2013 and 2015, opioid-related deaths in Wayne County increased

from 478 to 506, then skyrocketed to 817 in 2016 – more than 32 overdose deaths for every 100,000 residents:⁸

The number of drug-related deaths has increased



SOURCE: Wayne County Medical Examiner PROVISIONAL DATA.
FY 2015 was October 1 2014 – September 30, 2015

According to the Michigan Automated Prescription System, there were 743,969 opioid prescriptions filled in 2016 and, according to the Oakland County Health Division, 165 opioid-related overdose deaths in 2016 alone.⁹

⁸ Ex. 9 (Greater Detroit Area Health Council, *2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit: Moving Forward to Affect Change*, at 10-11 (May 11, 2017), <http://gdahc.org/sites/default/files/GDAHC%20Program%20Presentation-v2.pdf>).

⁹ Ex. 10 (*Prevent Prescription Drug Abuse, Access Oakland*, <http://accessoakland.oakgov.com/pages/oakland-county-opioid-initiative> (last visited Oct. 11, 2017)).

4. One of the main drivers of this catastrophic epidemic is drug manufacturers' deceptive marketing and sale of opioids to treat chronic pain. Prescription opioids have historically been used for short-term, post-surgical and trauma-related pain, and for palliative end-of-life care primarily in cancer patients. Because opioids are, by their very nature, highly addictive and dangerous, the U.S. Food and Drug Administration ("FDA") regulates them as Schedule II Controlled Substances, *i.e.*, drugs that have a high potential for abuse and that may lead to severe psychological or physical dependence.

5. This demonstrated need for caution comports with the historical understanding of both the medical community and the American culture at large regarding the serious consequences of opioid use and misuse. Indeed, thousands of years of experience have taught that opium's ability to relieve pain comes at a steep price; it is a dangerously addictive and often lethal substance. For generations, physicians were taught that opioid painkillers were highly addictive and should be used sparingly and primarily for patients near death.¹⁰ The medical community also understood that opioids were poorly suited for long-term use because tolerance would

¹⁰ Ex. 11 (Harriet Ryan, *et al.*, *OxyContin goes global – "We're only just getting started,"* L.A. Times (Dec. 18, 2016), <http://www.latimes.com/projects/la-me-oxycontin-part3/> (hereinafter "Ryan, *OxyContin goes global*")).

require escalating doses and dependence would make it extremely difficult to discontinue their use.

6. However, the prevailing and accurate understanding of the risks and benefits of long-term opioid use limited drug manufacturers' ability to drive sales. In order to decrease reasonable concerns about opioids and to maximize profits, opioid manufacturers, including defendants Purdue, Janssen, Endo, Cephalon, Insys and Mallinckrodt (individually defined in §II *infra*) (collectively, the "Manufacturing Defendants") engaged in a concerted, coordinated strategy to shift the way in which doctors and patients think about pain and, specifically, to encourage the use of opioids to treat not just the relative few who suffer from acute post-surgical pain and end-stage cancer pain, but the masses who suffer from common chronic pain conditions.

7. Borrowing from the tobacco industry's playbook, the Manufacturing Defendants employed ingenious marketing strategies, as detailed further herein, designed to "reeducate" the public and prescribers. They deliberately conceived these strategies to create, and in fact did create, an entirely new "health care" narrative – one in which opioids are considered safe and effective for long-term use, and pain is aggressively treated at all costs. According to this newly fabricated narrative, pain was seriously under-treated throughout the U.S. because opioids were

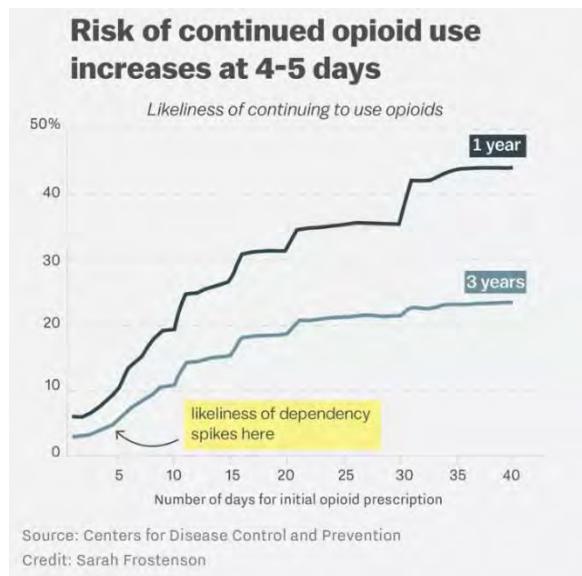
underprescribed, and doctors came under enormous pressure to treat all kinds of pain with opioids.

8. The Manufacturing Defendants' intention was to normalize aggressive prescribing of opioids for chronic pain by downplaying the very real risks of opioids, especially the risk of addiction, and by exaggerating the benefits of use for chronic pain. To accomplish this goal, they intentionally misled doctors and patients about the appropriate uses, risks, safety and efficacy of prescription opioids. They did so directly through sales representatives and marketing materials and indirectly through financial relationships with academic physicians, professional societies, hospitals, the trade association for state medical boards and seemingly neutral third party foundations. False messaging was disseminated by infiltrating professional medical societies and crafting and influencing industry guidelines in order to disseminate false and deceptive pro-opioid communiques under the guise of science and truth.

9. The Manufacturing Defendants assured the public and prescribers that the risk of becoming addicted to prescription opioids among patients being treated for pain was less than 1%. In reality, many people with no addiction history can become addicted after just days or weeks of use.¹¹ Estimates for the risk of addiction range up

¹¹ Lembke (2016), *supra* n.5, at 22.

to 56% of patients receiving long-term prescription opioid painkillers.¹² Indeed, almost one in five people who take an opioid for only ten days will still be taking opioids one year later.¹³ The following chart¹⁴ illustrates the degree to which the risk of dependency exists even after just several days of opioid therapy:

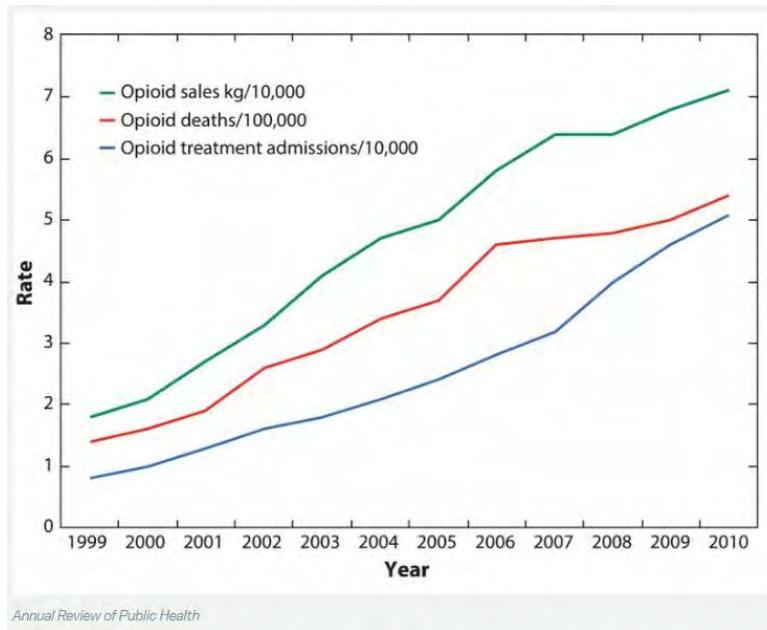


¹² Ex. 12 (Bridget A. Martell, *et al.*, *Systematic Review: Opioid Treatment for Chronic Back Pain: Prevalence, Efficacy, and Association with Addiction*, 146(2) Ann. Intern. Med. 116-27 (2007), <http://annals.org/aim/article/732048/systematic-review-opioid-treatment-chronic-back-pain-prevalence-efficacy-association>).

¹³ Ex. 13 (Sarah Frostenson, *The risk of a single 5-day opioid prescription, in one chart*, Vox (Mar. 18, 2017, 7:30 AM), www.vox.com/2017/3/18/14954626/one-simple-way-to-curb-opioid-overuse-prescribe-them-for-3-days-or-less).

¹⁴ Lopez, *How the opioid epidemic*, *supra* n.7.

10. By 2012, Michigan doctors were writing 107 opioid prescriptions for every hundred Michigan state residents.¹⁵ In essence, the Manufacturing Defendants manipulated and misrepresented medical science to serve their own agenda at great human cost:



11. Defendants McKesson Corporation (“McKesson”), Cardinal Health, Inc. (“Cardinal Health”) and AmerisourceBergen Corporation (“AmerisourceBergen”) (collectively, the “Wholesaler Defendants”) are major distributors of controlled substances that act as middlemen between drug companies and pharmacies. Not just the Manufacturing Defendants, but also the Wholesaler Defendants were aware of a

¹⁵ Ex. 14 (*Opioid Painkiller Prescribing infographic*, Centers for Disease Control and Prevention: Vital Signs (July 2014), <https://www.cdc.gov/vitalsigns/opioid-prescribing/infographic.html#map>).

growing epidemic from the addiction to, and abuse of, prescription opioids they supplied. The Manufacturing Defendants and the Wholesaler Defendants were aware of the quantities and frequency with which those drugs were distributed to entities in Wayne County and Oakland County. However, both the Manufacturing Defendants and the Wholesaler Defendants persisted in failing to report suspicious sales as required by state and federal law. Their failure to follow the law significantly contributed to soaring addiction and overdose rates in Wayne County and Oakland County.

12. Defendants wholly failed to meet their obligation to timely report and put a halt to these and other suspicious sales, fueling the epidemic in Wayne County and Oakland County. Indeed, in August of 2017, a Dearborn pill mill was raided, and the doctor and an employee were arraigned on multiple felony charges for overprescribing opioids and other controlled substances. This single doctor, Mohammed Derani, allegedly prescribed **more than 500,000** opioid pills since January of 2017 alone. In addition, Oakland County residents Mashiyat Rashid (“Rashid”), Yasser Mozeb, Joseph Betro, Tariz Omar and Mohammed Zahoor were recently arrested by the U.S. Department of Justice (“DOJ”) for Medicare fraud related to the prescription of opioids. According to the DOJ’s allegations, Rashid orchestrated a conspiracy through a web of companies he controlled that cheated Medicare of \$132 million by

recruiting homeless people as patients, sending phony bills to Medicare, subjecting drug addicts to unnecessary back injections and prescribing powerful pain medication that ended up being diverted to black market sales. U.S. Attorney General Jeff Sessions stated that the violations arose out of the prescription to patients of “unnecessary opioids, some of which ended up for sale on the street.” If convicted, Rashid could be sentenced to life in federal prison.

13. The Wholesaler Defendants’ violations have already led to fines elsewhere. McKesson, the largest prescription drug wholesaler company in the United States, agreed on January 17, 2017, to pay a \$150 million fine to the federal government for such misconduct. In December 2016, Cardinal Health reached a \$44 million settlement with the federal government. One month later, Cardinal Health reached a \$20 million settlement with the State of West Virginia, which has been among the states hardest hit by opioid abuse. AmerisourceBergen also recently agreed to pay West Virginia \$16 million for similar violations.¹⁶

14. Defendants’ scheme was met with tremendous success, if measured by profit. According to *Fortune* magazine, McKesson, AmerisourceBergen and Cardinal

¹⁶ Ex. 15 (Charles Ornstein, *Drug Distributors Penalized For Turning Blind Eye In Opioid Epidemic*, National Public Radio (Jan. 27, 2017), <http://www.npr.org/sections/health-shots/2017/01/27/511858862/drug-distributors-penalized-for-turning-blind-eye-in-opioid-epidemic>).

Health are each among the top 15 companies in the Fortune 500. The Sackler family, which owns Purdue – a privately held company – is listed on *Fortune*'s list of America's wealthiest families. However, the impact of opioid addiction has devastated the nation, emerging as one of the country's, and Wayne County's and Oakland County's, major health threats. As reported by *National Public Radio*, opioid addiction is thought to be among factors contributing to the United States' increase in overall rate for mortality from 2014 to 2015, the first time in a decade that the mortality rate increased. Former FDA Commissioner David A. Kessler has called the failure to recognize the dangers of painkillers “one of the greatest mistakes of modern medicine.” As alleged herein, that “mistake” resulted in large part from defendants’ false and misleading messaging, which was carefully calculated to reach as many prescribers as possible, and willingness to turn a blind eye to suspicious orders.

15. Even where some defendants have previously been forced to admit the unlawful marketing and sale of opioids and/or the failure to report suspicious orders, the conduct does not abate because profits realized by the aggressive marketing and prescribing of opioids dwarf the penalties imposed as a result of violations found. Thus, the incentive to push opioids remains. The scheme was so financially successful, in fact, that despite the clear and obvious devastation it caused at home,

Purdue's owners, the Sackler family, are now pursuing the same strategy abroad. As reported by the *Los Angeles Times*, Purdue states “[w]e're only just getting started,” and intends to “[p]ut the painkiller that set off the United States opioid crisis into medicine cabinets around the world. A network of international companies owned by the family is moving rapidly into Latin America, Asia, the Middle East, Africa and other regions, and pushing for broad use of painkillers in places ill-prepared to deal with the ravages of opioid abuse and addiction.”¹⁷

II. PARTIES

16. Plaintiff County of Wayne is one of the 83 counties in the State of Michigan that is authorized to bring this action and recover costs under Mich. Comp. Laws §45.3.

17. Plaintiff County of Oakland is one of the 83 counties in the State of Michigan that is authorized to bring this action and recover costs under Mich. Comp. Laws §45.3. Oakland County Voluntary Employees' Benefit Association Plan and Trust (“VEBA”) is located in Oakland County, Michigan, and is responsible for the payment of certain retiree medical health benefits. VEBA is organized and exists pursuant to Michigan law and the Internal Revenue Code and is authorized to bring this action and recover costs under Mich. Comp. Laws Ann. §600.2051. County of

¹⁷ Ryan, *OxyContin goes global*, *supra* n.10.

Oakland and VEBA are collectively referred to herein as “County of Oakland” or “Oakland County.”

18. Defendant Purdue Pharma L.P. is a Delaware limited partnership formed in 1991 with headquarters located in Stamford, Connecticut. The company maintains four operational branches: Purdue Pharma L.P., the Purdue Frederick Company, Purdue Pharmaceutical Products L.P. and Purdue Products L.P. (referred to collectively herein as “Purdue”).

19. Defendant Cephalon, Inc. is a Delaware corporation with its headquarters and principal place of business located in Frazer, Pennsylvania. Cephalon, Inc. was acquired by Teva Pharmaceutical Industries Ltd. (“Teva Ltd.”) in October 2011. Teva Ltd. is incorporated under the laws of Israel with its principal place of business in Petah Tikva, Israel. Since Teva Ltd. acquired Cephalon, Inc., its United States sales and marketing activities have been conducted by Teva Pharmaceuticals USA, Inc. (“Teva USA” and, together with Teva Ltd., “Teva”), a wholly-owned operating subsidiary of Teva Ltd. Teva USA’s headquarters and principal place of business are in North Wales, Pennsylvania. Cephalon, Inc., Teva Ltd. and Tera USA are collectively referred to herein as “Cephalon.”

20. Defendant Endo International plc is an Irish public limited company with its headquarters in Dublin, Ireland. Endo Pharmaceuticals Inc. (together with Endo

International plc, “Endo”) is a Delaware corporation with its headquarters and principal place of business in Malvern, Pennsylvania. Endo Pharmaceuticals Inc. is an indirectly wholly-owned subsidiary of Endo International plc.

21. Defendant Janssen Pharmaceuticals, Inc. (“Janssen”) (formerly known as Ortho-McNeil-Janssen Pharmaceuticals, Inc. and Janssen Pharmaceutica) is headquartered in Titusville, New Jersey and Raritan, New Jersey. Janssen is a wholly-owned subsidiary of Johnson & Johnson, a New Jersey corporation with its principal place of business in New Brunswick, New Jersey.

22. Defendant Insys Therapeutics, Inc. (“Insys”) is a Delaware corporation with its principal place of business in Chandler, Arizona.

23. Defendant Mallinckrodt plc is an Irish public limited company with its headquarters in Staines-Upon-Thames, Surrey, United Kingdom. Mallinckrodt Pharmaceuticals (together with Mallinckrodt plc, “Mallinckrodt”) is a Delaware corporation with its headquarters in Hazelwood, Missouri.

24. Defendant AmerisourceBergen is a Delaware corporation with its headquarters and principal place of business located in Chesterbrook, Pennsylvania.

25. Defendant Cardinal Health is a Delaware corporation with its headquarters and principal place of business located in Dublin, Ohio.

26. Defendant McKesson is a Delaware corporation with its headquarters and principal place of business located in San Francisco, California.

III. JURISDICTION AND VENUE

27. This Court has jurisdiction over this action pursuant to 28 U.S.C. §1332.

28. Venue is proper pursuant to 28 U.S.C. §1391. This Court has personal jurisdiction over each defendant as each purposefully availed itself of the privilege of exploiting forum-based business opportunities, and the exercise of personal jurisdiction is consistent with Mich. Comp. Laws §600.715.

IV. FACTUAL ALLEGATIONS

A. Over the Course of More than Two Decades, the Manufacturing Defendants Misled the Public Regarding the Dangers of Opioid Addiction and the Efficacy of Opioids for Long-Term Use, Causing Sales and Overdose Rates to Soar

29. From the mid-90s to the present, the Manufacturing Defendants aggressively marketed and falsely promoted liberal opioid prescribing as presenting little to no risk of addiction, even when used long term for chronic pain. They infiltrated academic medicine and regulatory agencies to convince doctors that treating chronic pain with long-term opioids was evidence-based medicine when, in fact, it was not. Huge profits resulted from these efforts, as did the present addiction and overdose crisis.

1. Background on Opioid Overprescribing

30. The Manufacturing Defendants' scheme to drive their rapid and dramatic expansion of prescription opioids was rooted in two pieces of so-called evidence. First was the publication of a 100-word letter to the editor published in 1980 in the *New England Journal of Medicine* ("1980 Letter to the Editor").¹⁸ A recent article about the letter, titled "A 5-sentence letter helped trigger America's deadliest drug overdose crisis ever," quoted a 2017 study in the *New England Journal of Medicine*, in which researchers concluded:

[W]e found that a five-sentence letter published in the *Journal* in 1980 was heavily and uncritically cited as evidence that addiction was rare with long-term opioid therapy. We believe that this citation pattern

¹⁸ In 1980, the *New England Journal of Medicine* published a 100-word letter to the editor by Jane Porter ("Porter") and Dr. Herschel Jick ("Jick"), reporting that less than 1% of patients at Boston University Medical Center who received narcotics while hospitalized became addicted. Jane Porter & Hershel Jick, *Addiction rate in patients treated with narcotics*, 302(2) New Eng. J. Med. 123 (Jan. 10, 1980). However, the letter did not support the conclusion for which it was often cited by the industry. Ex. 16 (Harrison Jacobs, *This one-paragraph letter may have launched the opioid epidemic*, Bus. Insider (May 26, 2016), <http://www.businessinsider.com/porter-and-jick-letter-launched-the-opioid-epidemic-2016-5> (hereinafter "Jacobs, *One-paragraph letter*")). As discussed in a 2009 article in the *American Journal of Public Health*, the 1980 Letter to the Editor "shed[] some light on the risk of addiction for acute pain, [but did] not help establish the risk of iatrogenic addiction when opioids are used daily for a prolonged time in treating chronic pain. [Indeed, t]here are a number of studies . . . that demonstrate that in the treatment of chronic non-cancer-related pain with opioids, there is a high incidence of prescription drug abuse." Art Van Zee, *The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy*, 99(2) Am. J. Pub. Health 221-27 (Feb. 2009).

contributed to the North American opioid crisis by helping to shape a narrative that allayed prescribers' concerns about the risk of addiction associated with long-term opioid therapy.¹⁹

31. Second was a single medical study published by Drs. Russell Portenoy ("Portenoy") and Kathleen Foley ("Foley") ("Portenoy Publication").²⁰ Portenoy emerged as one of the industry's most vocal proponents of long-term opioid use, who essentially made it his life's work to campaign for the movement to increase use of prescription opioids. He was one of Big Pharma's²¹ "thought leaders" and was paid to

¹⁹ Ex. 17 (German Lopez, *A 5-sentence letter helped trigger America's deadliest drug overdose crisis ever*, Vox (June 1, 2017), <https://www.vox.com/science-and-health/2017/6/1/15723034/opioid-epidemic-letter-1980-study>).

²⁰ In 1986, the medical journal *Pain*, which would eventually become the official journal of the American Pain Society ("APS"), published an article by Portenoy and Foley summarizing the results of a "study" of 38 chronic non-cancer pain patients who had been treated with opioid painkillers. Portenoy and Foley concluded that, for non-cancer pain, opioids "can be safely and effectively prescribed to selected patients with relatively little risk of producing the maladaptive behaviors which define opioid abuse." However, their study was neither scientific nor did it meet the rigorous standards commonly used to evaluate the validity and strength of such studies in the medical community. For instance, there was no placebo control group, and the results were retroactive (asking patients to describe prior experiences with opioid treatment rather than less biased, in-the-moment reports). The authors themselves advised caution, stating that the drugs should be used as an "alternative therapy" and recognizing that longer-term studies of patients on opioids would have to be performed. None was. See Russell K. Portenoy & Kathleen M. Foley, *Chronic use of opioid analgesics in non-malignant pain: report of 38 cases*, 25(2) *Pain* 171-86 (May 1986).

²¹ "Big Pharma" is used herein to refer to large pharmaceutical companies considered especially as a politically influential group.

travel the country to promote more liberal opioid prescribing for many types of pain. His talks were sponsored by the Manufacturing Defendants and organizations paid by them as continuing medical education (“CME”) programs for doctors. He had financial relationships with at least a dozen pharmaceutical companies, most of which produced prescription opioids.²²

32. Portenoy has now admitted that he minimized the risks of opioids.²³ In a 2011 interview released by Physicians for Responsible Opioid Prescribing, Portenoy stated that his earlier work purposefully relied on evidence that was not “real” and left real evidence behind:

I gave so many lectures to primary care audiences in which the Porter and Jick article was just one piece of data that I would then cite, and I would cite six, seven, maybe ten different avenues of thought or avenues of evidence, ***none of which represented real evidence***, and yet what I was trying to do was to create a narrative so that the primary care audience would look at this information in [total] and feel more comfortable about opioids in a way they hadn’t before. ***In essence this***

²² Lembke (2016), *supra* n.5, at 59 (citing Barry Meier, *Pain Killer: A “Wonder” Drug’s Trail of Addiction and Death* (St. Martin’s Press, 1st ed. 2003)).

²³ Ex. 18 (Celine Gounder, *Who Is Responsible for the Pain-Pill Epidemic?*, New Yorker (Nov. 8, 2013), <http://www.newyorker.com/business/currency/who-is-responsible-for-the-pain-pill-epidemic> (hereinafter “Gounder, *Who Is Responsible*”)).

was education to destigmatize [opioids], and because the primary goal was to destigmatize, we often left evidence behind.²⁴

33. The damage, however, was already done. The Manufacturing Defendants used these two publications, the 1980 Letter to the Editor and the Portenoy Publication, as the foundation for a massive, far-reaching campaign to dramatically shift the thinking of healthcare providers, patients, policymakers and the public on the risk of addiction presented by opioid therapy. By 1997, the APS and the American Academy of Pain Medicine (“AAPM”) (both funded by the Manufacturing Defendants) issued a “landmark consensus,” co-authored by Portenoy, stating there is little risk of addiction or overdose in pain patients.²⁵

34. In the years following publication of the 1980 Letter to the Editor and the Portenoy Publication, the Manufacturing Defendants introduced powerful prescription opioids into the market. Purdue introduced MS Contin in 1987 and OxyContin in 1995, Janssen introduced Duragesic in 1990 and Cephalon’s Actiq was first approved by the FDA in 1998. More recently, Endo’s Opana and Opana ER were approved by

²⁴ Jacobs, *One-paragraph letter*, *supra* n.18; Ex. 19 (Andrew Kolodny, *Opioids for Chronic Pain: Addiction is NOT Rare*, YouTube (Oct. 30, 2011), <https://www.youtube.com/watch?v=DgyuBWN9D4w&feature=youtu.be>).

²⁵ Jacobs, *One-paragraph letter*, *supra* n.18.

the FDA in 2006, as was Janssen's Nucynta in 2008 and Nucynta ER in 2011, Cephalon's Fentora in 2006 and Insys' Subsys in 2012.

35. These branded prescription opioids and their generic counterparts are highly addictive. Between doses, patients can suffer body aches, nausea, sweats, racing heart, hypertension, insomnia, anxiety, agitation, opioid cravings, opioid-induced hyperalgesia (heightened sensitivity to pain) and other symptoms of withdrawal. When the agony is relieved by the next dose, it creates a cycle of dysphoria and euphoria that fosters addiction and dependence.

36. Despite the prescription opioids' highly addictive qualities, the Manufacturing Defendants launched aggressive pro-opioid marketing efforts that effected a dramatic shift in the public's and prescribers' perception of the safety and efficacy of opioids for chronic long-term pain and everyday use. Contrary to what doctors had previously understood about opioid risks and benefits, they were encouraged for the last two decades by the Manufacturing Defendants to prescribe opioids aggressively and were assured, based on false evidence provided directly by the Manufacturing Defendants and numerous medical entities funded by the Manufacturing Defendants and others with financial interests in generating more opioid prescriptions, that: (i) the risk of becoming addicted to prescription opioids among patients being treated for pain was low, even as low as less than 1%; and

(ii) great harm was caused by “under-treated pain.” These two foundational falsehoods led directly to the current opioid crisis.

37. The strategy was a brilliant marketing success. It was designed to redefine back pain, neck pain, headaches, arthritis, fibromyalgia and other common conditions suffered by most of the population at some point in their lives as a distinct malady – chronic pain – that doctors and patients should take seriously and for which opioids were an appropriate, successful and low-risk treatment. Indeed, studies now show more than 85% of patients taking OxyContin at common doses are doing so for chronic non-cancer pain.²⁶

38. This false and misleading marketing strategy continued despite studies revealing that up to 56% of patients receiving long-term prescription opioid painkillers for chronic back pain progress to addictive opioid use, including patients with no prior history of addiction.²⁷

39. Thus, based on false and incomplete evidence, the Manufacturing Defendants expanded their market exponentially from patients with end-stage cancer and acute pain, an obviously limited customer base, to anyone suffering from chronic

²⁶ Ryan, *OxyContin goes global*, *supra* n.10.

²⁷ Lembke (2016), *supra* n.5, at 22 (citing Martell, *et al.*, *Systematic review: opioid treatment for chronic back pain: prevalence, efficacy and association with addiction*, 146(2) Ann. Intern. Med. 116-27 (2007)).

pain, which by some accounts includes approximately 100 million Americans – nearly one-third of the country’s population.²⁸ The treatment of chronic pain includes patients whose general health is good enough to refill prescriptions month after month, year after year, and the promotion, distribution (without reporting suspicious sales) and rampant sale of opioids for such treatment has made defendants billions of dollars. It has also led to the opioid addiction and overdose crisis in Wayne County and Oakland County.

2. The Fraudulent Sales Practices

40. As set forth below, the Manufacturing Defendants employed a variety of strategies to normalize the use of opioids for chronic long-term pain without informing the public and prescribers about the very significant risk of addiction, overdose and death.

- a. The Manufacturing Defendants Funded Front Organizations that Published and Disseminated False and Misleading Marketing Materials**

41. Defendants sponsored purportedly neutral medical boards and foundations that educated doctors and set guidelines for the use of opioids in medical treatment in order to promote the liberal prescribing of opioids for chronic pain. The

²⁸ Ex. 20 (*AAPM Facts and Figures on Pain*, The American Academy of Pain Medicine, http://www.painmed.org/patientcenter/facts_on_pain.aspx#refer (last visited Oct. 9, 2017)).

following organizations, funded by the Manufacturing Defendants, advised doctors that liberal prescribing of opioids was both safe and effective. In truth, it was neither.

42. **Federation of State Medical Boards**: The Federation of State Medical Boards (“FSMB”) is a national organization that functions as a trade group representing the 70 medical and osteopathic boards in the United States. The FSMB often develops guidelines that serve as the basis for model policies with the stated goal of improving medical practice. Defendants Purdue, Cephalon and Endo have provided substantial funding to the FSMB. Among its members are the Michigan Board of Medicine and the Michigan Board of Osteopathic Medicine and Surgery.

43. In 2007, the FSMB printed and distributed a physician’s guide on the use of opioids to treat chronic pain titled “Responsible Opioid Prescribing” by Dr. Scott M. Fishman (“Fishman”). After the guide (in the form of a book, still available for sale on Amazon) was adopted as a model policy, the FSMB reportedly asked Purdue for \$100,000 to help pay for printing and distribution. Ultimately, the guide was disseminated by the FSMB to **700,000** practicing doctors.

44. The guide’s clear purpose is to focus prescribers on the purported under-treatment of pain and falsely assure them that opioid therapy is an appropriate treatment for chronic, non-cancer pain:

- Pain management is integral to good medical practice and for all patients;

- *Opioid therapy to relieve pain and improve function is a legitimate medical practice for acute and chronic pain of both cancer and non-cancer origins;*
- *Patients should not be denied opioid medications except in light of clear evidence that such medications are harmful to the patient.*

* * *

Four key factors contribute to the ongoing problem of under-treated pain:

1. Lack of knowledge of medical standards, current research, and clinical guidelines for appropriate pain treatment;
2. The perception that prescribing adequate amounts of opioids will result in unnecessary scrutiny by regulatory authorities;
3. ***Misunderstanding of addiction and dependence;*** and
4. Lack of understanding of regulatory policies and processes.²⁹
45. While it acknowledges the risk of “abuse and diversion” (with little attention to addiction), the guide purports to offer “professional guidelines” that will “easily and efficiently” allow physicians to manage that risk and “minimize the potential for [such] abuse.”³⁰ Indeed, it states that even for those patients assessed to have risk of substance abuse, “it does not mean that opioid use will become

²⁹ Scott M. Fishman, *Responsible Opioid Prescribing: A Physician’s Guide* 8-9 (Waterford Life Sciences 2007).

³⁰ *Id.* at 9.

problematic or that opioids are contraindicated,” just that physicians should use additional care in prescribing.

46. The guide further warns physicians to “[b]e aware of the distinction between pseudoaddiction and addiction” and teaches that behaviors such as “[r]equesting [drugs] by name,” “[d]emanding or manipulative behavior,” “[o]btaining opioid drugs from more than one physician” and “[h]oarding opioids,” which are, in fact, signs of genuine addiction, are all really just signs of “pseudoaddiction.”³¹ It defines “Physical Dependence” as an acceptable result of opioid therapy not to be equated with addiction and states that while “[i]t may be tempting to assume that patients with chronic pain and a history of recreational drug use who are not adherent to a treatment regimen are abusing medications,” there could be other acceptable reasons for non-adherence.³² The guide, sponsored by the Manufacturing Defendants and their pain foundations, became the seminal authority on opioid prescribing for the medical profession and dramatically overstated the safety and efficacy of opioids and understated the risk of opioid addiction.

³¹ *Id.* at 62.

³² *Id.*

47. In 2012, Fishman updated the guide and continued emphasizing the “catastrophic” “under-treatment” of pain and the “crisis” such under-treatment created:

Given the magnitude of the problems related to opioid analgesics, it can be tempting to resort to draconian solutions: clinicians may simply stop prescribing opioids, or legislation intended to improve pharmacovigilance may inadvertently curtail patient access to care. As we work to reduce diversion and misuse of prescription opioids, ***it's critical to remember that the problem of unrelieved pain remains as urgent as ever.***³³

48. The updated guide still assures that “***[o]pioid therapy to relieve pain and improve function is legitimate medical practice for acute and chronic pain of both cancer and noncancer origins.***³⁴”

49. In another guide by Fishman, he continues to downplay the risk of addiction: “***I believe clinicians must be very careful with the label ‘addict.’ I draw a distinction between a ‘chemical coper’ and an addict.***³⁵” The guide also continues to present symptoms of addiction as symptoms of “pseudoaddiction.”

³³ Scott M. Fishman, *Responsible Opioid Prescribing: A Guide for Michigan Clinicians*, 10-11 (Waterford Life Sciences 2012).

³⁴ *Id.* at 11.

³⁵ Scott M. Fishman, *Listening to Pain: A Physician’s Guide to Improving Pain Management Through Better Communication* 45 (Oxford University Press 2012).

50. The heightened focus on the under-treatment of pain was a concept designed by Big Pharma to sell opioids. ***The FSMB actually issued a report calling on medical boards to punish doctors for inadequately treating pain.***³⁶ Among the drafters of this policy was Dr. J. David Haddox (“Haddox”), who coined the term “pseudoaddiction,” which wholly lacked scientific evidence but quickly became a common way for the Manufacturing Defendants and their allies to promote the use of opioids even to patients displaying addiction symptoms. Haddox later became a Purdue Vice President.³⁷

51. As noted in ¶¶83-94 *infra*, in 2012 and again in 2017, the guides and the sources of their funding became the subject of a Senate investigation.

52. On June 8, 2012, the FSMB submitted a letter to the Senate Finance Committee concerning its investigation into the abuse and misuse of opioids.³⁸ While the letter acknowledged the escalation of drug abuse and related deaths resulting from prescription painkillers, the FSMB continued to focus on the “serious and related problem” that “[m]illions of Americans suffer from debilitating pain – a condition

³⁶ Ex. 21 (Thomas Catan & Evan Perez, *A Pain-Drug Champion Has Second Thoughts*, Wall St. J., Dec. 17, 2012, at A1).

³⁷ Gounder, *Who Is Responsible*, *supra* n.23.

³⁸ Ex. 22 (June 8, 2012 Letter from Federation of State Medical Boards to U.S. Senators Max Baucus and Charles Grassley).

that, for some, can be relieved through the use of opioids.” Among other things, the letter stated, “Studies have concluded that both acute pain and chronic pain are often under-treated in the United States, creating serious repercussions that include the loss of productivity and quality of life.” The letter cited no such studies. The letter also confirmed that the FSMB’s “Responsible Opioid Prescribing: A Physician’s Guide” has been distributed in each of the 50 states and the District of Columbia.

53. In addition, the FSMB letter disclosed payments the FSMB received from organizations that develop, manufacture, produce, market or promote the use of opioid-based drugs from 1997 through the present. Included in the payments received are the following payments from defendants:

<i>Company</i>	<i>Fiscal Year</i>	<i>Amount</i>
Purdue	2001	\$38,324.56
	2002	\$10,000.00
	2003	\$85,180.50
	2004	\$87,895.00
	2005	\$244,000.00
	2006	\$207,000.00
	2007	\$50,000.00
	2008	\$100,000.00
	<i>Total Purdue Payments</i>	<i>\$822,400.06</i>
Endo	2007	\$40,000.00
	2008	\$100,000.00
	2009	\$100,000.00
	2011	\$125,000.00
	2012	\$46,620.00
	<i>Total Endo Payments</i>	<i>\$371,620.00</i>

<i>Company</i>	<i>Fiscal Year</i>	<i>Amount</i>
Cephalon	2007	\$30,000.00
	2008	\$100,000.00
	2011	\$50,000.00
	Total Cephalon Payments	\$180,000.00
Mallinckrodt	2011	\$100,000.00
	Total Mallinckrodt Payments	\$100,000.00

54. The letter also disclosed payments of \$40,000 by Endo and \$50,000 by Purdue to directly fund the production of “Responsible Opioid Prescribing” and disclosed that 42,366 copies of “Responsible Opioid Prescribing” were distributed in Michigan alone.

55. **The Joint Commission:** The Joint Commission is an organization that establishes standards for treatment and accredits healthcare organizations in the United States. The Manufacturing Defendants, including Purdue, contributed misleading and groundless teaching materials and videos to the Joint Commission, which emphasized what Big Pharma coined the “under-treatment of pain,” referenced pain as the “fifth vital sign” (the first and only unmeasurable/subjective vital sign) that must be monitored and treated, and encouraged the use of prescription opioids for chronic pain while minimizing the danger of addiction. It also called doctors’ concerns about addiction “inaccurate and exaggerated.”

56. In 2000, the Joint Commission printed a book for purchase by doctors as part of required continuing education seminars that cited studies claiming “***there is no evidence that addiction is a significant issue when persons are given opioids for pain control.***” The book was sponsored by Purdue.

57. In 2001, the Joint Commission and the National Pharmaceutical Council (founded in 1953 and supported by the nation’s major research-based biopharmaceutical companies³⁹) collaborated to issue a 101-page monograph titled “Pain: Current understanding of assessment, management, and treatments.” The monograph states falsely that beliefs about opioids being addictive are “erroneous”:

Societal issues that contribute to the undertreatment of pain include drug abuse programs and erroneous beliefs about tolerance, physical dependence, and addiction (see I.E.5). For example, some clinicians incorrectly assume that exposure to an addictive drug usually results in addiction.

* * *

b. Etiology, issues, and concerns

Many medications produce tolerance and physical dependence, and some (e.g., opioids, sedatives, stimulants, anxiolytics, some muscle relaxants) may cause addiction in vulnerable individuals. Most experts agree that ***patients who undergo prolonged opioid therapy usually develop physical dependence but do not develop addictive disorders. In general, patients in pain do not become addicted to opioids. Although the actual risk of addiction is unknown, it is thought to be quite low.*** A

³⁹ Currently funded by Johnson & Johnson, Purdue and Teva, among others.

recent study of opioid analgesic use revealed “low and stable” abuse of opioids between 1990 and 1996 despite significant increases in opioids prescribed. . . .

Fear of causing addiction (i.e., iatrogenic addiction), particularly with opioid use, is a major barrier to appropriate pain management. This fear sometimes reflects a lack of understanding of the risk of addiction with therapeutic drug use. Although studies suggest that the risk of iatrogenic addiction is quite low (e.g., Perry and Heidrich, Zenz et al.), surveys indicate that clinicians often overestimate this risk.⁴⁰

58. Additionally, the monograph recommends that “[p]ain . . . is assessed in all patients” and suggests that long-acting (*i.e.*, extended release) pain medications are superior and should be used whenever possible:

Long-acting and sustained-release opioids are useful for patients with continuous pain, as they lessen the severity of end-of-dose pain and often allow the patient to sleep through the night.

* * *

- Administer opioids primarily via oral or transdermal routes, using long-acting medications when possible.⁴¹

In truth, such medications often do not last as long as promised, and there is evidence to suggest that the use of long-acting drugs may actually create more addicts.

⁴⁰ Ex. 23 (*Pain: Current Understanding of Assessment, Management, and Treatments* 16-17 (Dec. 2001), <http://www.npcnow.org/system/files/research/download/Pain-Current-Understanding-of-Assessment-Management-and-Treatments.pdf> (footnotes and citations omitted)).

⁴¹ *Id.* at 38, 68 (Table 38).

59. The Manufacturing Defendants' infiltration and influence over the Joint Commission's standards and literature exerted overwhelming pressure on doctors to treat and eliminate pain. As more and more doctors migrated from private practice to integrated healthcare systems in the 2000s, treatment options were dictated by, among other things, the Joint Commission's guidelines.⁴² Consistent with the guidelines, doctors who left pain untreated were viewed as demonstrating poor clinical skills and/or being morally compromised.⁴³

60. The U.S. General Accounting Office's December 2003 Report to Congressional Requesters confirms that Purdue funded the "pain management educational courses" that taught the new standard of care for treating pain. It further revealed that Purdue disseminated educational materials on pain management, which "facilitated [Purdue's] access to hospitals to promote OxyContin."⁴⁴

61. **American Pain Foundation**: The American Pain Foundation ("APF"), headquartered in Baltimore, Maryland, described itself as the nation's largest

⁴² Lembke (2016), *supra* n.5, at 119.

⁴³ *Id.* at 42.

⁴⁴ Gounder, *Who Is Responsible*, *supra* n.23; Ex. 24 (U.S. General Accounting Office, GAO-04-110, *Prescription Drugs, OxyContin Abuse and Diversion and Efforts to Address the Problem* (Dec. 2003), <http://www.gao.gov/new.items/d04110.pdf>).

organization for pain patients.⁴⁵ While APF held itself out as an independent patient advocacy organization, in reality it received 90% of its funding in 2010 from the drug and medical-device industry, including from defendants Purdue, Endo, Janssen and Cephalon. It received more than \$10 million in funding from opioid manufacturers from 2007 to 2012, when it shut down days after the U.S. Senate Committee on Finance (“Senate Finance Committee”) launched an investigation of APF’s promotion of prescription opioids.

62. The APF’s guides for patients, journalists and policymakers trivialized the risk of addiction and greatly exaggerated the benefits associated with opioid painkillers.⁴⁶

63. For example, in 2001, APF published “Treatment Options: A Guide for People Living with Pain.”⁴⁷ The guide, which was produced due to support from

⁴⁵ The APF was the focus of a December investigation by ProPublica in the *Washington Post* that detailed its close ties to drugmakers.

⁴⁶ Ex. 25 (Charles Ornstein & Tracy Weber, *American Pain Foundation Shuts Down as Senators Launch Investigation of Prescription Narcotics*, ProPublica (May 8, 2012, 8:57 PM), http://www.opb.org/news/article/america_pain.foundation_shuts_down_as_senators_launch_investigation_of_prescription_narcotics/ (hereinafter “Ornstein, *American Pain Foundation*”)).

⁴⁷ Ex. 26 (*Treatment Options: A Guide for People Living with Pain*, American Pain Foundation, <https://assets.documentcloud.org/documents/277605/apf-treatment-options.pdf>).

companies including defendants Cephalon and Purdue, misrepresented the risks associated with opioid use. Among other things, the guide:

- lamented that opioids were sometimes called narcotics because “[c]alling opioid analgesics ‘narcotics’ reinforces myths and misunderstandings as it places emphasis on their potential abuse rather than on the importance of their use as pain medicines”;⁴⁸
- stated that “[o]pioids are an essential option for treating **moderate** to severe pain associated with surgery or trauma”;⁴⁹ and
- opined that “[r]estricting access to the most effective medications for treating pain [opioids] is not the solution to drug abuse or addiction.”⁵⁰

The guide included blurbs from Portenoy, who is quoted as saying “[t]his is a very good resource for the pain patient,” and Fishman, who is quoted as saying, “[w]hat a great job! Finally, a pill consumer resource created for patients with pain. A ‘must have’ for every physician’s waiting room.”⁵¹

64. In 2003, APF published a newsletter titled “Best of . . . The Pain Community News” that purported to clarify any confusion over addiction and opioids and emphasized the “tragic consequence of leaving many people with severe pain under-treated because they – or their doctors – fear that opioids will cause addiction.”

⁴⁸ *Id.* at 11.

⁴⁹ *Id.*

⁵⁰ *Id.* at 15.

⁵¹ *Id.* at 76.

65. In 2009, Endo sponsored APF's publication and distribution of "Exit Wounds: A Survival Guide to Pain Management for Returning Veterans & Their Families" ("Exit Wounds"), a book described as "the inspirational story of how one courageous veteran, with the aid of his family, recovered and thrived despite near death, traumatic brain injury, and the loss of a limb." It also purported to "offer[] veterans and their families comprehensive and authoritative information on . . . treatment options, and strategies for self-advocating for optimal pain care and medical resources inside and outside the VA system."

66. Among other false statements, Exit Wounds reported: "Long experience with opioids shows that ***people who are not predisposed to addiction are very unlikely to become addicted to opioid pain medications.***" Endo, through APF, thus distributed false information with the purpose of providing veterans false information they could use to "self-advocat[e]" for opioids while omitting a discussion of the risks associated with opioid use.

67. In 2009, APF played a central role in a first-of-its-kind web-based series called "Let's Talk Pain," hosted by veteran TV journalist Carol Martin. The series brought together healthcare providers and "people with pain to discuss a host of issues from managing health care for pain to exploring integrative treatment approaches to addressing the psychological aspects associated with pain." The "Let's Talk Pain"

talk show is still available online. In the very first episode of this talk show, the following exchange took place:

[Teresa Shaffer (APF Action Network Leader):] As a person who has been living with pain for over 20 years, opioids are a big part of my pain treatment. And I have been hearing such negative things about opioids and the risk factors of opioids. Could you talk with me a little bit about that?

[Dr. Al Anderson (AAPM Board of Directors):] The general belief system in the public is that the opioids are a bad thing to be giving a patient. Unfortunately, it's also prevalent in the medical profession, so patients have difficulty finding a doctor *when they are suffering from pain for a long period of time*, especially *moderate* to severe pain. And *that's the patients that we really need to use the opioids* methods of treatment, because they are the ones who need to have some help with the function and they're the ones that need to be controlled enough so that they can increase their quality of life.⁵²

68. In reality, there is little scientific evidence to support the contention that opioids taken long-term improve function or quality of life for chronic pain patients.⁵³ To the contrary, there is ample evidence that opioids impose significant risks and

⁵² Ex. 27 (*Episode 1: Safe Use of Opioids (PainSAFE)*), Let's Talk Pain (Sept. 28, 2010), <https://www.youtube.com/watch?v=zeAIvAMRgsk>).

⁵³ Lembke (2016), *supra* n.5, at 59 (citing Ex. 28 (*Agency for Healthcare Research and Quality (US): The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain*, Evid. Rep./Tech. Assess., No. 218 (2014), <https://ahrq-ehc-application.s3.amazonaws.com/media/pdf/chronic-pain-opioid-treatment-research.pdf>)).

adverse outcomes on long-term users and that they may actually reduce function.⁵⁴

As a recent article in the *New England Journal of Medicine* concluded: “Although opioid analgesics rapidly relieve many types of acute pain and improve function, the benefits of opioids when prescribed for chronic pain are much more questionable.”

The article continues, “opioid analgesics are widely diverted and improperly used, and the widespread use of the drugs has resulted in a national epidemic of opioid overdose deaths and addictions.”⁵⁵

69. The APF also developed the National Initiative on Pain Control (“NIPC”), which ran a facially unaffiliated website called www.painknowledge.org.

⁵⁴ Discussing the CDC’s “March 2016 Guideline for Prescribing Opioids for Chronic Pain,” doctors wrote:

Most placebo-controlled, randomized trials of opioids have lasted 6 weeks or less, and we are aware of no study that has compared opioid therapy with other treatments in terms of long-term (more than 1 year) outcomes related to pain, function, or quality of life. The few randomized trials to evaluate opioid efficacy for longer than 6 weeks had consistently poor results. In fact, several studies have showed that use of opioids for chronic pain may actually worsen pain and functioning, possibly by potentiating pain perception.

Ex. 29 (Thomas Frieden & Debra Houry, *Reducing the Risks of Relief – The CDC Opioid-Prescribing Guideline*, 374 New Eng. J. Med. 1501-04 (Apr. 21, 2016), <http://www.nejm.org/doi/full/10.1056/NEJMp1515917?af=R&rss=currentIssue&t=article>).

⁵⁵ Ex. 30 (Nora D. Volkow & A. Thomas McLellan, *Opioid Abuse in Chronic Pain – Misconceptions and Mitigation Strategies*, 374 New Eng. J. Med. 1253-63 (Mar. 31, 2016), <http://www.nejm.org/doi/full/10.1056/NEJMra1507771#t=article>).

NIPC promoted itself as an education initiative and promoted its expert leadership team, including purported experts in the pain management field. The website painknowledge.org promised that, on opioids, “your level of function should improve; you may find you are now able to participate in activities of daily living, such as work and hobbies, that you were not able to enjoy when your pain was worse.” Elsewhere, the website touted improved quality of life (as well as “improved function”) as benefits of opioid therapy. In a brochure available on painknowledge.org titled “Pain: Opioid Facts,” the NIPC misled that “people who have no history of drug abuse, including tobacco, and use their opioid medication as directed will probably not become addicted” and even refused to rule out the use of opioid pain relievers for patients who have a history of addiction to opioids.⁵⁶

70. In or around 2011, the APF published the “Policymaker’s Guide,” sponsored by Purdue, which dispelled the notion that “strong pain medication leads to addiction” by characterizing it as a “***common misconception[]***”:

Many people living with pain, and even some health care practitioners, falsely believe that opioid pain medicines are universally addictive. As with any medication, there are risks, but these risks can be managed when these medicines are properly prescribed and taken as directed. For

⁵⁶ Ex. 31 (*Pain: Opioid Facts*, Pain Knowledge https://web.archive.org/web/20101007102042/http://painlessknowledge.org/patient/pdf/Patient%20Education%20b380_b385%20%20pf %20opioid.pdf (last visited Oct. 10, 2017)).

more information about safety issues related to opioids and other pain therapies, visit <http://www.painsafe.org>.⁵⁷

71. The guide describes “pain in America” as “an evolving public health crisis” and characterizes concerns about opioid addiction as misconceptions: “Unfortunately, too many Americans are not getting the pain care they need and deserve. Some common reasons for difficulty in obtaining adequate care include: . . . ***Misconceptions about opioid addiction.***”⁵⁸ It even characterizes as a “***myth***” that “[c]hildren can easily become addicted to pain medications.”⁵⁹ The guide further asserts that “multiple clinical studies” have shown that opioids are effective in improving daily function, psychological health and health-related quality of life for chronic pain patients, which was not the case.⁶⁰

⁵⁷ Ex. 32 (*A Policymaker’s Guide to Understanding Pain & Its Management*, American Pain Foundation at 5, <http://s3.documentcloud.org/documents/277603/apf-policymakers-guide.pdf> (last visited Oct. 9, 2017)).

⁵⁸ *Id.* at 6.

⁵⁹ *Id.* at 40.

⁶⁰ The “Policymaker’s Guide” cites for support “Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects,” a review published in 2006 in the *Canadian Medical Association Journal*. *Id.* at 34. However, the review concludes: “For functional outcomes, ***the other analgesics were significantly more effective than were opioids.***” Ex. 33 (Andrea D. Furlan, *et al.*, *Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects*, 174(11) Canadian Med. Assoc. J. 1589-94 (May 23, 2006), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1459894/>). The Purdue-sponsored guide failed to disclose both this conclusion and the fact that

72. In December 2011, the *Washington Post* reported on ProPublica's investigation of the APF, which detailed APF's close ties to drugmakers:

[T]he pills continue to have an influential champion in the American Pain Foundation, which describes itself as the nation's largest advocacy group for pain patients. Its message: The risk of addiction is overblown, and the drugs are underused.

What the nonprofit organization doesn't highlight is the money behind that message.

The foundation collected nearly 90 percent of its \$5 million in funding last year from the drug and medical-device industry – and closely mirrors its positions, an examination by ProPublica found.⁶¹

73. **American Academy of Pain Medicine and American Pain Society:**

The Manufacturing Defendants, including at least Endo, Janssen and Purdue, have contributed funding to the AAPM and the APS for decades.

74. In 1997, the AAPM issued a "consensus" statement that endorsed opioids to treat chronic pain and claimed that the risk that patients would become addicted to opioids was low. The chairman of the committee that issued the statement, Haddox, was, at the time, a paid speaker for Purdue. Haddox was later hired as Purdue's vice

the review analyzed studies that lasted, on average, five weeks and therefore could not support the long-term use of opioids.

⁶¹ Ex. 34 (Charles Ornstein & Tracy Weber, *Patient advocacy group funded by success of painkiller drugs, probe finds*, Wash. Post (Dec. 23, 2011), https://www.washingtonpost.com/national/health-science/patient-advocacy-group-funded-by-success-of-painkiller-drugs-probe-finds/2011/12/20/gIQAgvczDP_story.html?utm_term=.22049984c606).

president for health policy. The consensus statement, which also formed the foundation of the 1998 guidelines, was published on the AAPM's website. AAPM's corporate council includes Purdue, Depomed, Teva and other pharmaceutical companies. AAPM's past presidents include Haddox (1998), Fishman (2005), Dr. Perry G. Fine ("Fine") (2011) and Lynn R. Webster ("Webster") (2013), all of whose connections to the opioid manufacturers are well-documented as set forth below.

75. At or about the same time, the APS introduced the "pain as the 5th vital sign" campaign, followed soon thereafter by the U.S. Department of Veterans Affairs adopting that campaign as part of their national pain management strategy.

76. AAPM and APS issued guidelines in 2009 ("2009 Guidelines") that continued to recommend the use of opioids to treat chronic pain. Fourteen of the 21 panel members who drafted the 2009 Guidelines received funding from defendants Janssen, Cephalon, Endo or Purdue.

77. The 2009 Guidelines falsely promoted opioids as safe and effective for treating chronic pain and concluded that the risk of addiction was manageable for patients regardless of past abuse histories.⁶² The 2009 Guidelines have been a

⁶² Ex. 35 (Roger Chou, et al., *Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Non-Cancer Pain*, 10(2) J. Pain 113 (Feb. 2009), [http://www.jpain.org/article/S1526-5900\(08\)00831-6/pdf](http://www.jpain.org/article/S1526-5900(08)00831-6/pdf)(hereinafter "Chou, *Clinical Guidelines*").).

particularly effective channel of deception and have influenced not only treating physicians but also the body of scientific evidence on opioids; they were reprinted in the journal *Pain*, have been cited hundreds of times in academic literature and remain available online. The Manufacturing Defendants widely cited and promoted the 2009 Guidelines without disclosing the lack of evidence to support their conclusions.

b. The Manufacturing Defendants Paid Key Opinion Leaders and Sponsored Speakers, Bureaus to Disseminate False and Misleading Messaging

78. The Manufacturing Defendants have paid millions of dollars to physicians to promote aggressive prescribing of opioids for chronic pain. Recently released federal data shows that the Manufacturing Defendants increased such payments to physicians who treat chronic pain even while the opioid crisis accelerated and overdose deaths from prescription opioids and related illicit drugs, such as heroin, soared to record rates.⁶³ These payments come in the form of consulting and speaking fees, free food and beverages, discount coupons for drugs and other freebies. The total payments from the Manufacturing Defendants to doctors related to opioids doubled from 2014 to 2015. Moreover, according to experts, research shows even

⁶³ Ex. 36 (Joe Lawlor, *Even amid crisis, opioid makers plied doctors with perks*, Portland Press Herald (Dec. 25, 2016), <http://www.pressherald.com/2016/12/25/even-amid-crisis-opioid-makers-plied-doctors-with-perks/>).

small amounts of money can have large effects on doctors' prescribing practices.⁶⁴

Physicians who are high prescribers are more likely to be invited to participate in defendants' speakers' bureaus. According to a study published by the U.S. National Institutes of Health, “[i]n the speakers' bureau system, physicians are recruited and trained by pharmaceutical, biotechnology, and medical device companies to deliver information about products to other physicians, in exchange for a fee.”⁶⁵

79. The use of speakers' bureaus has led to substantial ethical concerns within the medical field. According to a 2013 publication by the Institute on Medicine as a Profession, speakers' bureaus are ethically compromised because they often present information as objective when it is heavily biased toward the interests of the industry sponsor and, in fact, may lead to the dissemination of false or biased information. These findings are substantiated by citations to research in the *Journal of the American Medical Association*, *The Journal of Law, Medicine & Ethics* and *Academic Psychiatry*.

⁶⁴ *Id.*

⁶⁵ Ex. 37 (Lynette Reid & Matthew Herder, *The Speakers' bureau system: a form of peer selling*, 7(2) Open Med. e31-e39 (Apr. 2, 2013), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3863750/>).

The Problem:

Pharmaceutical companies often recruit physicians to perform speeches or presentations for the purpose of marketing a specific drug. In 2010, 8.6% of physicians reported having received payments for participating in speakers' bureaus. These speakers' bureaus leverage the credibility of physicians in order to promote the use of pharmaceutical products. *The physicians are generally trained to present a certain message, or are provided with pre-produced slides. The audience may assume that these presentations are objective, when in fact they are heavily biased towards the interests of the industry sponsor.*

Speakers' bureaus may lead to the dissemination of false or biased information. Exposure to industry-sponsored speaking events is associated with decreased quality of prescribing. Additionally, the compensation provided for these engagements may influence the attitudes or judgment of the presenter.⁶⁶

80. For example, Fishman is a physician whose ties to the opioid drug industry are legion. He has served as an APF board member and as president of the AAPM, and has participated yearly in numerous CME activities for which he received “market rate honoraria.” As discussed above, he has authored publications, including the seminal guides on opioid prescribing, which were funded by the Manufacturing Defendants. He has also worked to oppose legislation requiring doctors and others to consult pain specialists before prescribing high doses of opioids to non-cancer patients. He has himself acknowledged his failure to disclose all potential conflicts of

⁶⁶ Ex. 38 (*Speakers' Bureaus: Best Practices for Academic Medical Centers*, IMAP (Oct. 10, 2013), http://imapny.org/wp-content/themes/imapny/File%20Library/Best%20Practice%20 toolkits/Best-Practices_Speakers--bureaus.pdf).

interest in a letter in the *Journal of the American Medical Association* titled “Incomplete Financial Disclosures in a Letter on Reducing Opioid Abuse and Diversion.”⁶⁷

81. Similarly, Fine’s ties to the Manufacturing Defendants have been well documented.⁶⁸ He has authored articles and testified in court cases and before state and federal committees, and he, too, has served as president of the AAPM and argued against legislation restricting high-dose opioid prescription for non-cancer patients. Multiple videos feature Fine delivering educational talks about prescription opioids. He even testified at trial that the 1,500 pills a month prescribed to celebrity Anna Nicole Smith for pain did not make her an addict before her death.⁶⁹ He has also acknowledged having failed to disclose numerous conflicts of interest.

⁶⁷ Scott M. Fishman, *Incomplete Financial Disclosures in a Letter on Reducing Opioid Abuse and Diversion*, 306(13) JAMA 1445 (2011); Ex. 39 (Tracy Weber & Charles Ornstein, *Two Leaders in Pain Treatment Have Long Ties to Drug Industry*, ProPublica (Dec. 23, 2011, 2:14 PM), <https://www.propublica.org/article/two-leaders-in-pain-treatment-have-long-ties-to-drug-industry> (hereinafter “Weber, *Two Leaders in Pain*”)).

⁶⁸ Weber, *Two Leaders in Pain*, *supra* n.67.

⁶⁹ Ex. 40 (Linda Deutsch, *Doctor: 1,500 pills don’t prove Smith was addicted*, Seattle Times (Sept. 22, 2010, 5:16 PM), <http://www.seattletimes.com/entertainment/doctor-1500-pills-dont-prove-smith-was-addicted/>).

82. Fishman and Fine are only two of the many physicians whom the Manufacturing Defendants paid to present false or biased information on the use of opioids for chronic pain.

c. Senate Investigations of the Manufacturing Defendants

83. In May 2012, the Chair and Ranking Member of the Senate Finance Committee, Max Baucus (D-MT) and Chuck E. Grassley (R-IA), launched an investigation into makers of narcotic painkillers and groups that champion them. The investigation was triggered by “an epidemic of accidental deaths and addiction resulting from the increased sale and use of powerful narcotic painkillers,” including popular brand names like OxyContin, Vicodin and Opana.

84. The Senate Finance Committee sent letters to Purdue, Endo and Johnson & Johnson, as well as five groups that support pain patients, physicians or research, including the APF, AAPM, APS, University of Wisconsin Pain & Policy Studies Group and the Center for Practical Bioethics. Letters also went to the FSMB and the Joint Commission.

85. As shown from the below excerpt from the Senators’ letter to APF, the Senators addressed the magnitude of the epidemic and asserted that mounting evidence supports that the pharmaceutical companies may be responsible:

It is clear that the United States is suffering from an epidemic of accidental deaths and addiction resulting from the increased sale and use of powerful narcotic painkillers such as Oxycontin (oxycodone), Vicodin (hydrocodone), Opana (oxymorphone). According to CDC data, “more than 40% (14,800)” of the “36,500 drug poisoning deaths in 2008” were related to opioid-based prescription painkillers. Deaths from these drugs rose more rapidly, “from about 4,000 to 14,800” between 1999 and 2008, than any other class of drugs, [killing] more people than heroin and cocaine combined. More people in the United States now die from drugs than car accidents as a result of this new epidemic. Additionally, the CDC reports that improper “use of prescription painkillers costs health insurers up to \$72.5 billion annually in direct health care costs.”

* * *

Concurrent with the growing epidemic, the *New York Times* reports that, based on federal data, “*over the last decade, the number of prescriptions for the strongest opioids has increased nearly fourfold, with only limited evidence of their long-term effectiveness or risks*” while “[d]ata suggest that hundreds of thousands of patients nationwide may be on potentially dangerous doses.”

There is growing evidence pharmaceutical companies that manufacture and market opioids may be responsible, at least in part, for this epidemic by promoting misleading information about the drugs’ safety and effectiveness. Recent investigative reporting from the *Milwaukee Journal Sentinel/MedPage Today* and *ProPublica* revealed extensive ties between companies that manufacture and market opioids and non-profit organizations such as the American Pain Foundation, the American Academy of Pain Medicine, the Federation of State Medical Boards, and University of Wisconsin Pain and Policy Study Group, and the Joint Commission.

In a *ProPublica* story published in the *Washington Post*, the watchdog organization examined the *American Pain Foundation, a “health advocacy” organization that received “nearly 90 percent of its \$5 million funding from the drug and medical device industry.”*

ProPublica wrote that its review of the American Pain Foundation's "guides for patients, journalists, and policymakers **play down the risks associated with opioids and exaggerate their benefits**. Some of the foundation's materials on the drugs include statements that are misleading or based on scant or disputed research."

According to the *Milwaukee Journal Sentinel/MedPage Today*, a "**network of national organizations and researchers with financial connections to the makers of narcotic painkillers . . . helped create a body of dubious information**" favoring opioids "**that can be found in prescribing guidelines, patient literature, position statements, books and doctor education courses.**"⁷⁰

Although it is critical that patients continue to have access to opioids to treat serious pain, **pharmaceutical companies and health care organizations must distribute accurate and unbiased information about these drugs in order to prevent improper use and diversion to drug abusers.**⁷¹

86. The Senators demanded substantial discovery, including payment information from the companies to various groups, including the front organizations identified above, and to physicians, including Portenoy, Fishman and Fine, among

⁷⁰ For example, the *Sentinel* reported that the Federation of State Medical Boards, with financial support from opioid manufacturers, distributed "[m]ore than 160,000 copies" of a model policy book that drew criticism from doctors because "it failed to point out the lack of science supporting the use of opioids for chronic, non cancer pain." Ex. 41 (John Fauber, *Follow the Money: Pain, Policy, and Profit*, MedPage Today (Feb. 19, 2012), <http://www.medpagetoday.com/Neurology/PainManagement/31256>).

⁷¹ Ex. 42 (May 8, 2012 Letter from U.S. Senators Charles E. Grassley and Max Baucus to Catherine Underwood, Executive Director, American Pain Society, <https://www.finance.senate.gov/imo/media/doc/05092012%20Baucus%20Grassley%20Opioid%20Investigation%20Letter%20to%20American%20Pain%20Society.pdf>) (footnote added).

others. They asked about any influence the companies had on a 2004 pain guide for physicians that was distributed by the FSMB, on the APS' guidelines and on the APF's Military/Veterans Pain Initiative. Almost immediately upon the launch of the Senate investigation, the APF shut down "due to irreparable economic circumstances." The opioid report resulting from this investigation has not been released publicly.⁷²

87. On March 29, 2017, it was widely reported⁷³ that yet another Senate investigation had been launched:

Missouri Senator Claire McCaskill has launched an investigation into some of the country's leading prescription drug manufacturers, demanding documents and records dating back the past five years which indicate just what the companies knew of the drugs' risk for abuse as well as documents detailing marketing practices and sales presentations. Her office has sent letters to the heads of Purdue, Janssen/Johnson & Johnson, Insys, Mylan, and Depomed.

The above-referenced companies were reportedly targeted based on their role in manufacturing some of the opioid painkillers with the highest sales in 2015.

⁷² Ex. 43 (Paul D. Thacker, *Senators Hatch and Wyden: Do your jobs and release the sealed opioids report*, Stat News (June 27, 2016), <https://www.statnews.com/2016/06/27/opioid-addiction-orrin-hatch-ron-wyden/>); see also Ornstein, *American Pain Foundation*, *supra* n.46.

⁷³ Ex. 44 (Nadia Kounang, *Senator opens investigation into opioid manufacturers*, CNN (Mar. 29, 2017, 11:06 AM), <http://www.cnn.com/2017/03/28/health/senate-opioid-manufacturer-investigation/index.html>).

88. On September 6, 2017, Senator McCaskill's report, "Fueling an Epidemic: Insys Therapeutics and the Systemic Manipulation of Prior Authorization" was published. The report finds that Insys manipulated the prior authorization process by misleading pharmacy benefit managers about the role of Insys in the prior authorization process and the presence of breakthrough cancer pain in potential Subsys patients.⁷⁴

89. On September 12, 2017, Senator McCaskill convened a Roundtable Discussion on Opioid Marketing. During the hearing, Senator McCaskill stated:

The opioid epidemic is the direct result of a calculated marketing and sales strategy developed in the 90's, which delivered three simple messages to physicians. First, that chronic pain was severely undertreated in the United States. Second, that opioids were the best tool to address that pain. And third, that opioids could treat pain without risk of serious addiction. As it turns out, these messages were exaggerations at best and outright lies at worst.

* * *

Our national opioid epidemic is complex, but one explanation for this crisis is simple, pure greed.

90. Professor Adriane Fugh-Berman ("Fugh-Berman"), Associate Professor at Georgetown University Medical Center and director of a program at Georgetown called Pharmed Out, which conducts research on and educates the public about

⁷⁴ HSGAC Minority Staff Report, Insys Therapeutics and the Systemic Manipulation of Prior Authorization (2017).

inappropriate pharmaceutical company marketing, also testified during the hearing. She, too, placed the blame for the opioid crisis squarely at the feet of pharmaceutical companies:

Since the 1990's, pharmaceutical companies have stealthily distorted the perceptions of consumers and healthcare providers about pain and opioids. Opioid manufacturers use drug reps, physicians, consumer groups, medical groups, accreditation and licensing bodies, legislators, medical boards and the federal government to advance marketing goals to sell more opioids. This aggressive marketing pushes resulted in hundreds of thousands of deaths from the overprescribing of opioids. The U.S. is about – comprises about five percent of the world population, but we use about two-thirds of the world supply of opioids.

91. Fugh-Berman also answered why doctors were able to be convinced by pharmaceutical companies' marketing efforts:

Why the physicians fall for this? Well, physicians are overworked, overwhelmed, buried in paperwork and they feel unappreciated. Drug reps are cheerful. They're charming. They provide both appreciation and information. Unfortunately, the information they provide is innately unreliable.

Pharmaceutical companies influence healthcare providers' attitudes and their therapeutic choices through financial incentives that include research grants, educational grants, consulting fees, speaking fees, gifts and meals.

92. Fugh-Berman further described the false information provided by pharmaceutical companies and the industry creation of front organizations, including the APF, to pass industry-influenced regulations and policies:

Pharmaceutical companies convinced healthcare providers that they were opioid-phobic and that they were causing suffering to their patients by denying opioids to patients with back pain or arthritis. They persuaded prescribers that patients with pain were somehow immune to addiction. Even when addiction was suspected, physicians were taught that it might not really be addiction, it might be pseudo-addiction, an invented (ph) condition that's treated by increasing opioid dosages.

Industry created the American Pain Foundation co-opted other groups including medical organizations, and they change state laws to eliminate curbs on opioid prescribing. Between 2006 and 2015, pharmaceutical companies and the advocacy groups they control employ 1,350 lobbyists a year in legislative hubs. Industry-influenced regulations and policies ensure that hospitalized patients were and are berated paraded constantly about their level of pain and overmedicated with opioids for that pain. Even a week of opioids can lead a patient into addiction so many patients are discharged from hospitals already dependent on opioids.

93. In addition, Fugh-Berman pointed out that promotion of opioids remains ongoing despite increasing public concern about their use:

Promotion of opioids is not in the past. Between 2013 and 2015, one in 12 physicians took out money from opioid manufacturers, a total of more than \$46 million. Industry-friendly messages that pharmaceutical companies are currently perpetuating reassure physicians that prescribing opioids is safe as long as patients do not have a history of substance abuse or mental illness.

94. Fugh-Berman concluded by stating: "It is a misperception to think that most opioid deaths are caused by misuse of opioids or overdoses. In fact, many deaths occur when people are using opioids in exactly the way they were prescribed. Misuse isn't the problem; use is the problem."

3. The Devastating Impact

95. The impact of the Manufacturing Defendants' false messaging has been profound. The drug companies profited handsomely as more and more people became addicted to opioids and died of overdoses.⁷⁵

96. For Purdue, sales grew from \$48 million per year in 1996, to over \$1 billion per year in 2000, to \$3.1 billion per year ten years later. In 2011, pharmaceutical companies generated revenues of \$11 billion from opioid sales alone.

97. The United States, including specifically Wayne County and Oakland County, is experiencing an unprecedeted opioid addiction and overdose epidemic, costing millions in health insurance and public safety as well as lost productivity in the workforce.

98. By 2002, “[l]ifetime ***nonmedical*** use of OxyContin increased from 1.9 million to 3.1 million people between 2002 and 2004, and in 2004 there were 615,000 new nonmedical users of OxyContin.”⁷⁶

⁷⁵ Ex. 45 (German Lopez, *How big pharma got people hooked on dangerous opioids – and made tons of money off it*, Vox (Sept. 22, 2016, 3:00 PM), <http://www.vox.com/2016/2/5/10919360/opioid-epidemic-chart>).

⁷⁶ Ex. 46 (Art Van Zee, *The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy*, 99(2) Am. J. Pub. Health 221-27 (Feb. 2009), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2622774/> (hereinafter “Van Zee, *Promotion and Marketing*”)).

99. By 2004, OxyContin had “become the most prevalent prescription opioid abused in the United States.”⁷⁷ The severity of the problem was first felt in states including Maine, West Virginia, eastern Kentucky, southwestern Virginia and Alabama, where, from 1998 through 2000, hydrocodone and oxycodone were being prescribed 2.5-5 times more often than the national average. By 2000, these same areas had a prescription rate up to 5-6 times higher than the national average. These areas were also the first to suffer increased abuse and diversion, which became apparent by 1999 and 2000. Manufacturers then expanded the geographic market by investing hundreds of millions of dollars in marketing, and the once-regional problem began to spread nationally. “[B]y 2004 OxyContin had become a leading drug of abuse in the United States.”⁷⁸

100. As OxyContin sales grew between 1999 and 2002, so did sales of other opioids, including fentanyl (226%), morphine (73%) and oxycodone (402%). And, as prescriptions surged between 1999 and 2010, so did deaths from opioid overdoses (from about 4,000 to almost 17,000).⁷⁹

⁷⁷ *Id.*

⁷⁸ *Id.*

⁷⁹ Gounder, *Who Is Responsible*, *supra* n.23.

101. In 2012 alone, an estimated 259 million opioid prescriptions were filled, enough to medicate every adult in the United States for a month on a round-the-clock basis.⁸⁰ In 2014, there were more than 47,000 drug overdose deaths nationwide, 61% involving a prescription or illicit opioid.⁸¹ The use of prescription painkillers cost health insurers up to \$72.5 billion annually in direct healthcare costs.⁸²

102. According to the Centers for Disease Control and Prevention (“CDC”), opioid overdose deaths in Michigan increased by 13.2% from 2013 to 2014, and by 13.3% from 2014 to 2015, with deaths increasing from 1,553, to 1,762, to 1,980 over the three-year period. During that timeframe, drug overdose deaths for Wayne County residents increased from approximately 20 per 100,000 to 32.8 per 100,000. According to the Oakland County Medical Examiner, drug overdose deaths in Oakland County also increased 14% from 2013 to 2015.

103. Wayne County and Oakland County continue to suffer significant financial consequences as a result of opioid over-prescription and addiction, including,

⁸⁰ Ex. 47 (*Opioid Painkiller Prescribing*, Centers for Disease Control and Prevention: Vital Signs (July 2014), <https://www.cdc.gov/vitalsigns/opioid-prescribing/>).

⁸¹ Rudd, *Increases in Drug and Opioid-Involved Overdose*, *supra* n.3.

⁸² Ex. 48 (Katherine Eban, *OxyContin: Purdue Pharma’s painful medicine*, Fortune Magazine (Nov. 9, 2011), <http://fortune.com/2011/11/09/oxycontin-purdue-pharmas-painful-medicine/> (hereinafter “Eban, *Painful Medicine*”)).

but not limited to, increased law enforcement and judicial expenditures, increased jail and public works expenditures, increased substance abuse treatment and diversion plan expenditures, increased emergency and medical care services, and lost economic opportunity.

B. The Manufacturing Defendants' Specific Unlawful Practices that Targeted Wayne County and Oakland County Prescribers

1. Purdue

104. Purdue, which is privately held by the Sackler family, manufactures, markets, sells and distributes opioids in Wayne County, Oakland County and nationwide, including the following:

OxyContin (oxycodone hydrochloride extended release)	Opioid agonist ⁸³ indicated for pain severe enough to require daily, around-the-clock, long-term opioid treatment; not indicated as an as-needed (p.r.n.) analgesic. It was first approved by the FDA in December 1995.	Schedule II
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⁸³ An “agonist” medication is one that binds to and fully activates targeted receptors in the brain. They activate these neurotransmitter receptors to illicit a certain response. An “antagonist” medication, on the other hand, works to prevent the binding of other chemicals to neurotransmitters in order to block a certain response. Both may be used to offer pain relief. Ex. 49 (*Health Q&A*, Reference*, <https://www.reference.com/health/difference-between-agonist-antagonist-drugs-838e9e0994a788eb> (last visited Oct. 9, 2017)).

MS Contin (morphine sulfate extended release)	Opioid agonist; controlled-release tablet form of morphine sulfate indicated for the management of severe pain; not intended for use as a p.r.n. analgesic; first approved in May 1987 as the first formulation of an opioid pain medicine that allowed dosing every 12 hours.	Schedule II
Dilaudid (hydromorphone hydrochloride)	Opioid analgesic; injectable and oral formulation; eight times more potent than morphine. ⁸⁴	Schedule II
Dilaudid-HP (hydromorphone hydrochloride)	Opioid analgesic; injectable and oral high-potency and highly concentrated formulation indicated for relief of moderate-to-severe pain in opioid-tolerant patients.	Schedule II
Hysingla ER (hydrocodone bitrate)	Brand-name extended-release form of hydrocodone bitrate that is indicated for the management of severe pain.	Schedule II
Targiniq ER (oxycodone hydrochloride and naloxone hydrochloride)	Brand-name extended-release opioid analgesic made of a combination of oxycodone hydrochloride and naloxone hydrochloride. It was approved by the FDA on July 23, 2013.	Schedule II

For example, according to public records, 50,601 prescriptions for 3,471,121 units of OxyContin were written for Wayne County residents and 37,996 prescriptions for 2,761,390 units of OxyContin were written for Oakland County residents from 2014 to 2016, inclusive.

⁸⁴ Ex. 50 (*Dilaudid Addiction*, Suboxone California, <http://www.suboxonecalifornia.com/suboxone-treatment/dilaudid-addiction.html> (last visited Oct. 9, 2017)).

a. Purdue Falsely Marketed Extended-Release Drugs as Safer and More Effective than Regular-Release Drugs

105. Purdue launched OxyContin 20 years ago with a bold marketing claim: “One dose relieves pain for 12 hours, more than twice as long as generic medications.”⁸⁵ Purdue told doctors in its OxyContin press release that one tablet would provide “smooth and sustained pain control all day and all night.” Based in large part on that promise, and repeated assurances that opioids were both effective and non-addictive, OxyContin became America’s bestselling painkiller.⁸⁶

106. Purdue’s nationwide marketing claims were highly deceptive. OxyContin was not superior to immediate-release opioids. And not only does OxyContin wear off early, as Purdue’s own early studies showed, it is highly addictive:

OxyContin’s stunning success masked a fundamental problem: The drug wears off hours early in many people, a Los Angeles Times investigation found. ***OxyContin is a chemical cousin of heroin, and when it doesn’t***

⁸⁵ Ex. 51 (Harriet Ryan, *et al.*, “*You Want A Description of Hell?*” *OxyContin’s 12-Hour Problem*, L.A. Times (May 5, 2016), <http://www.latimes.com/projects/oxycontin-part1/> (hereinafter “Ryan, *Description of Hell*”).)

⁸⁶ Ex. 52 (Press Release, Purdue Pharma L.P., New Hope for Millions of Americans Suffering from Persistent Pain: Long-Acting OxyContin Tablets Now Available to Relieve Pain (May 31, 1996), [https://www.freelibrary.com/NEW+HOPE+FOR+MILLIONS+OF+AMERICANS+SUFFERING+FROM+PERSISTENT+PAIN%3A...-a018343260\)\)](https://www.freelibrary.com/NEW+HOPE+FOR+MILLIONS+OF+AMERICANS+SUFFERING+FROM+PERSISTENT+PAIN%3A...-a018343260)).

*last, patients can experience excruciating symptoms of withdrawal, including an intense craving for the drug.*⁸⁷

107. Furthermore, experts call the 12-hour dosing “an addiction producing machine.”⁸⁸ Purdue had reportedly known for decades that it falsely promised 12-hour relief and nevertheless mobilized hundreds of sales representatives to “refocus” physicians on 12-hour dosing:

- . . . Even before OxyContin went on the market, *clinical trials showed many patients weren’t getting 12 hours of relief*. Since the drug’s debut in 1996, the company has been confronted with additional evidence, including complaints from doctors, reports from its own sales reps and independent research.
- The company has held fast to the claim of 12-hour relief, in part to protect its revenue. OxyContin’s market dominance and its high price – up to hundreds of dollars per bottle – hinge on its 12-hour duration. Without that, it offers little advantage over less expensive painkillers.
- When many doctors began prescribing OxyContin at shorter intervals in the late 1990s, Purdue executives mobilized hundreds of sales reps to “refocus” physicians on 12-hour dosing. Anything shorter “needs to be nipped in the bud. NOW!!” one manager wrote to her staff.

⁸⁷ The *Los Angeles Times* investigation, reported in three parts on May 5, July 10 and December 18, 2016, included the review of thousands of pages of confidential Purdue documents and court and other records. They span three decades, from the conception of OxyContin in the mid-1980s to 2011, and include e-mails, memoranda, meeting minutes and sales reports, as well as sworn testimony by executives, sales representatives and other employees. Ryan, *Description of Hell*, *supra* n.85. The *Los Angeles Times* reporters also examined FDA records, Patent Office files and medical journal articles, and interviewed experts in pain treatment, addiction medicine and pharmacology. *Id.*

⁸⁸ Frydl, *Purdue Pharma*, *supra* n.5.

- Purdue tells doctors to prescribe stronger doses, not more frequent ones, when patients complain that OxyContin doesn't last 12 hours. That approach creates risks of its own. Research shows that the more potent the dose of an opioid such as OxyContin, the greater the possibility of overdose and death.
- More than half of long-term OxyContin users are on doses that public health officials consider dangerously high, according to an analysis of nationwide prescription data conducted for The Times.⁸⁹

108. As reported by *The New York Times*, “internal Purdue Pharma documents show that company officials recognized even before the drug was marketed that they would face stiff resistance from doctors who were concerned about the potential of a high-powered narcotic like OxyContin to be abused by patients or cause addiction.” To combat this resistance, Purdue promised the long-acting, extended-release formulation as safer and “less prone to such problems.”⁹⁰

109. Purdue’s sales culture in Michigan, in particular, was one that required aggressive sales of its opioids and embraced the sell-at-any-cost notion: “sell or be gone.” Aggressive quotas were put into place for opioids including OxyContin, at all dosage levels, as well as Hysingla products. The highest dosage for OxyContin was referred to by Purdue sales representatives as “hillbilly heroin.” When sales

⁸⁹ Ryan, *Description of Hell*, *supra* n.85.

⁹⁰ Ex. 53 (Barry Meier, *In Guilty Plea, OxyContin Maker to Pay \$600 Million*, N.Y. Times (May 10, 2007), <http://www.nytimes.com/2007/05/10/business/11drug-web.html> (hereinafter “Meier, *Guilty Plea*”)).

representatives failed to meet their quotas, they were placed on performance employment plans and/or terminated. When they were successful, they were richly rewarded with extravagant bonuses and prizes. For example, in or about the 2011-2012 timeframe, the Detroit sales group received an award for being one of Purdue's highest-performing sales teams with respect to OxyContin sales, and the entire team was sent to Hawaii. Notably, the astronomical sales of that group at the time were driven in part by one or more pill mills in the area, which eventually had to be shut down. There was so much money to be made, and so much pressure to meet quotas, that sales representatives became desensitized to what they were selling.

b. Purdue Falsely Marketed Low Addiction Risk to Wide Swaths of Physicians

110. In addition to pushing OxyContin as safe and non-addictive by equating extended-release with a lower risk, Purdue also promoted the use of prescription opioids for use in non-cancer patients, who make up 86% of the total opioid market today.⁹¹

111. Rather than targeting merely those physicians treating acute severe short-term (like post-operative) pain or oncologists treating end-stage cancer pain, reports indicate that Purdue heavily promoted OxyContin nationwide to doctors such as

⁹¹ Ornstein, *American Pain Foundation*, *supra* n.46.

general practitioners, who often had little training in the treatment of serious pain or in recognizing signs of drug abuse in patients.⁹²

112. Sales representatives plied these and other physicians with coupons that were redeemable for a 7- to 30-day supply of free OxyContin, a Schedule II narcotic that by definition cannot be prescribed for more than one month at a time, with the promise that OxyContin was a safe opioid. Purdue “trained its sales representatives to carry the message that the risk of addiction was ‘less than one percent,’” and “[a] consistent feature in the promotion and marketing of OxyContin was a systematic effort to minimize the risk of addiction in the use of opioids for the treatment of chronic non-cancer-related pain.”⁹³ Even as late as 2015 if not later, Purdue sales representatives were telling physicians OxyContin was “addiction resistant” and had “abuse-deterrant technology.”

113. Purdue tracked physicians’ prescribing practices by reviewing pharmacy prescription data it obtained from IMS Health, a company that buys bulk prescription data from pharmacies and resells it to drug makers for marketing purposes. Rather than reporting highly suspicious prescribing practices, Purdue used the data to track physicians who prescribed some opioids and might be persuaded to prescribe more.

⁹² Meier, *Guilty Plea*, *supra* n.90.

⁹³ Van Zee, *Promotion and Marketing*, *supra* n.76.

Purdue also could identify physicians writing large numbers of prescriptions, and particularly for high-dose 80 mg pills – potential signs of diversion and drug dealing.⁹⁴

114. Purdue knew about many suspicious doctors and pharmacies from prescribing records, pharmacy orders, field reports from sales representatives and, in some instances, its own surveillance operations.⁹⁵ Since 2002, Purdue maintained a confidential roster of suspected reckless prescribers known as “Region Zero.” By 2013, there were more than 1,800 doctors in Region Zero, but Purdue had reported only 8% of them to authorities. The *Los Angeles Times* reported that “[a] former

⁹⁴ An 80 mg tablet is equivalent in strength to 16 Vicodin tablets, and was generally reserved by doctors for patients with severe, chronic pain who had built up a tolerance over months or years. In the illegal drug trade, however, “80s” were the most in demand. For those attempting to detect how OxyContin was getting onto the black market, a physician writing a high volume of 80s was a red flag. Ex. 54 (Harriet Ryan, *et al.*, *More than 1 million OxyContin pills ended up in the hands of criminals and addicts. What the drugmaker knew*, L.A. Times (July 10, 2016), <http://www.latimes.com/projects/la-me-oxycontin-part2/> (hereinafter “Ryan, *More than 1 million*”)).

⁹⁵ Purdue’s “Abuse and Diversion Detection” program requires its sales representatives to report to the company any facts that suggest a healthcare provider to whom it markets opioids may be involved in the abuse or illegal diversion of opioid products. When a provider is reported under the program, Purdue purportedly conducts an internal inquiry regarding the provider to determine whether he or she should be placed on a “no-call” list. If a provider is placed on this list, Purdue sales representatives may no longer contact the provider to promote the company’s opioid products. Ex. 55 (Bill Fallon, *Purdue Pharma agrees to restrict marketing of opioids*, Stamford Advocate (Aug. 25, 2015, 3:32 PM), <http://www.stamfordadvocate.com/business/article/Purdue-Pharma-agrees-to-restrict-marketing-of-6464800.php> (hereinafter “Fallon, *Purdue Pharma agrees*”)).

Purdue executive, who monitored pharmacies for criminal activity, acknowledged that even when the company had evidence pharmacies were colluding with drug dealers, it did not stop supplying distributors selling to those stores.”⁹⁶

c. Purdue Funded Publications and Presentations with False and Misleading Messaging

115. As explained above, Purdue’s false marketing scheme did not end with its own sales representatives and branded marketing materials. It extended far beyond, engaging third parties including doctors and front groups to spread the false message of prescription opioids’ safety and efficacy.

116. Purdue caused the publication and distribution of false and deceptive guidelines on opioid prescribing. For example, as set forth above, Purdue paid \$100,000 to the FSMB to help print and distribute its guidelines on the use of opioids to treat chronic pain to **700,000** practicing doctors; and among the FSMB’s members are the Michigan Board of Medicine and the Michigan Board of Osteopathic Medicine and Surgery.

117. One of the advisors for Fishman’s 2007 publication “Responsible Opioid Prescribing: A Physician’s Guide” and its 2012 update was Haddox, a longtime member of Purdue’s speakers’ bureau who later became a Purdue vice president.

⁹⁶ Ryan, *More than 1 Million*, *supra* n.94.

118. Similarly,⁹⁷ multiple videos feature Fine delivering educational talks about the drugs. In one video from 2011 titled “Optimizing Opioid Therapy,” he sets forth a “Guideline for Chronic Opioid Therapy” discussing “opioid rotation” (switching from one opioid to another) not only for cancer patients, but for non-cancer patients, and suggests it may take four or five switches over a person’s “lifetime” to manage pain.⁹⁸ He states the “goal is to improve effectiveness which is different from efficacy and safety.” Rather, for chronic pain patients, effectiveness “is a balance of therapeutic good and adverse events *over the course of years.*” The entire program assumes that opioids are appropriate treatment over a “protracted period of time” and even over a patient’s entire “lifetime.” He even suggests that opioids can be used to treat *sleep apnea*. He further states that the associated risks of addiction and abuse can be managed by doctors and evaluated with “tools,” but leaves that for “a whole other lecture.”⁹⁹

119. Purdue provided many “teaching” materials free of charge to the Joint Commission.

⁹⁷ Weber, *Two Leaders in Pain*, *supra* n.67.

⁹⁸ Ex. 56 (Perry A. Fine, *Safe and Effective Opioid Rotation*, YouTube (Nov. 8, 2012), https://www.youtube.com/watch?v=_G3II9yqgXI).

⁹⁹ *Id.*

120. Purdue also deceptively marketed the use of opioids for chronic pain through the APF, which was shut down after the launching of the Senate investigation in 2012. In 2010 alone, the APF received 90% of its funding from drug and medical device companies, including from Purdue. Purdue paid APF unspecified amounts in 2008 and 2009 and between \$100,000 and \$499,999 in 2010.¹⁰⁰

d. The Guilty Pleas

121. In May 2007, Purdue and three of its executives pled guilty to federal charges of misbranding OxyContin in what the company acknowledged was an attempt to mislead doctors about the risk of addiction. Purdue was ordered to pay \$600 million in fines and fees. In its plea, Purdue admitted that its promotion of OxyContin was misleading and inaccurate, misrepresented the risk of addiction and was unsupported by science. Additionally, Michael Friedman (“Friedman”), the company’s president, pled guilty to a misbranding charge and agreed to pay \$19 million in fines; Howard R. Udell (“Udell”), Purdue’s top lawyer, also pled guilty and agreed to pay \$8 million in fines; and Paul D. Goldenheim (“Goldenheim”), its former medical director, pled guilty as well and agreed to pay \$7.5 million in fines.

¹⁰⁰ Ex. 57 (American Pain Foundation Partner Report, GuideStar, <http://www.guidestar.org/PartnerReport.aspx?ein=52-2002328&Partner=Demo> (last visited Oct. 9, 2017)) (links to annual reports at bottom of page).

122. In a statement announcing the guilty plea, John Brownlee (“Brownlee”), the U.S. Attorney for the Western District of Virginia, stated:

Purdue claimed it had created the miracle drug – a low risk drug that could provide long acting pain relief but was less addictive and less subject to abuse. *Purdue’s marketing campaign worked, and sales for OxyContin skyrocketed – making billions for Purdue and millions for its top executives.*

But OxyContin offered no miracles to those suffering in pain. Purdue’s claims that OxyContin was less addictive and less subject to abuse and diversion were false – and Purdue knew its claims were false. The result of their misrepresentations and crimes sparked one of our nation’s greatest prescription drug failures. . . . OxyContin was the child of marketeers and bottom line financial decision making.¹⁰¹

123. Brownlee characterized Purdue’s criminal activity as follows:

First, *Purdue trained its sales representatives to falsely inform health care providers that it was more difficult to extract the oxycodone from an OxyContin tablet for the purpose of intravenous abuse.* Purdue ordered this training even though its own study showed that a drug abuser could extract approximately 68% of the oxycodone from a single 10 mg OxyContin tablet by simply crushing the tablet, stirring it in water, and drawing the solution through cotton into a syringe.

Second, *Purdue falsely instructed its sales representatives to inform health care providers that OxyContin could create fewer chances for addiction* than immediate-release opioids.

Third, *Purdue sponsored training that falsely taught Purdue sales supervisors that OxyContin had fewer “peak and trough” blood*

¹⁰¹ Ex. 58 (Press Release, U.S. Attorney for the Western District of Virginia, Statement of United States Attorney John Brownlee on the Guilty Plea of the Purdue Frederick Company and Its Executives for Illegally Misbranding OxyContin (May 10, 2007), <https://assets.documentcloud.org/documents/279028/purdue-guilty-plea.pdf>).

level effects than immediate-release opioids resulting in less euphoria and less potential for abuse than short-acting opioids.

Fourth, ***Purdue falsely told certain health care providers that patients could stop therapy abruptly without experiencing withdrawal symptoms and that patients who took OxyContin would not develop tolerance*** to the drug.

And fifth, ***Purdue falsely told health care providers that OxyContin did not cause a “buzz” or euphoria, caused less euphoria, had less addiction potential, had less abuse potential, was less likely to be diverted than immediate-release opioids***, and could be used to “weed out” addicts and drug seekers.¹⁰²

124. Specifically, Purdue pled guilty to illegally misbranding OxyContin in an effort to mislead and defraud physicians and consumers, while Friedman, Udell and Goldenheim pled guilty to the misdemeanor charge of misbranding OxyContin, for introducing misbranded drugs into interstate commerce in violation of 21 U.S.C. §§331(a), 333(a)(1)-(2) and 352(a).

125. Nevertheless, even after the settlement, Purdue continued to pay doctors on speakers’ bureaus to promote the liberal prescribing of OxyContin for chronic pain and fund seemingly neutral organizations to disseminate the message that opioids were effective and non-addictive. Purdue continues to aggressively market the liberal prescribing of opioids for chronic pain while diminishing the associated dangers of addiction.

¹⁰² *Id.*

126. Purdue has earned more than \$31 billion from OxyContin, the nation's bestselling painkiller, which constitutes approximately 30% of the United States market for painkillers. Since 2009, Purdue's national annual sales of OxyContin have fluctuated between \$2.47 billion and \$2.99 billion, up threefold from 2006 sales of \$800 million.¹⁰³

127. Purdue also made thousands of payments to physicians nationwide, including to Wayne County and Oakland County physicians, for activities including participating on speakers' bureaus, providing consulting services, assisting in post-marketing safety surveillance and other services.

128. Publicly disclosed payments for the years 2013 through 2016 reveal that Purdue made more than \$42,000 in payments to Wayne County physicians and more than \$22,000 in payments to Oakland County physicians. The vast majority of these payments were made to allopathic and osteopathic physicians who specialize in alternative medicine. Such physicians are often involved in treating chronic pain. OxyContin has been widely prescribed in Wayne County and Oakland County. According to data collected by ProPublica, during 2014 and 2015, Michigan doctors' prescriptions of OxyContin to patients insured by the Medicare Part D program totaled more than \$35 million and \$32.7 million, respectively. Five of the top 18 prescribers

¹⁰³ Eban, *Painful Medicine*, *supra* n.82.

of OxyContin during 2014 practiced in Wayne County, including the physician who filed the second most Medicare claims during 2014 for prescriptions of the drug. Not surprisingly, several of these five doctors also received payments from Purdue between 2013 and 2015. Additionally, six of the top 25 prescribers of OxyContin during 2015 practiced in Oakland County, including the physician who filed the second most Medicare claims during 2015 for prescriptions of the drug.

e. Purdue Failed to Report Suspicious Sales as Required

129. The Comprehensive Drug Abuse Prevention and Control Act of 1970, 21 U.S.C §801 *et seq.* (“CSA” or “Controlled Substances Act”), and the regulations promulgated thereunder, 21 C.F.R. §1300 *et seq.*, which is incorporated into Michigan law by Mich. Admin. Code R. 338.493c(i), imposes on all “registrants” the obligation to design and operate a system to disclose to the registrant suspicious orders of controlled substances and requires the registrant to notify the U.S. Drug Enforcement Administration (“DEA”) field division office in its area of any suspicious orders. “Suspicious orders include orders of unusual size, orders deviating substantially from a normal pattern, and orders of unusual frequency.” 21 C.F.R. §1301.74(b).

130. Purdue is a “registrant” under the federal CSA. 21 C.F.R. §1300.02(b) defines a registrant as any person who is registered with the DEA under 21 U.S.C.

§823. Section 823, in turn, requires manufacturers of Schedule II controlled substances to register with the DEA.

131. Purdue failed to design and operate a system to disclose suspicious orders of controlled substances and/or failed to notify the appropriate DEA field division of suspicious orders. By way of example, just two months ago, the doctor of a Dearborn-based pill mill was arrested and arraigned on multiple felony charges for overprescribing opioids, including prescribing more than 500,000 opioid pills since January 2017. Five Oakland County residents were also recently arrested for Medicare fraud related to the prescription of unnecessary opioids to patients, some of which ended up sold illegally on the streets. Other doctors practicing in Wayne County and Oakland County and/or prescribing opioids to Wayne County or Oakland County residents, have been similarly arrested and arraigned for writing an egregiously high number of opioid prescriptions. Purdue's failure to timely report these and other suspicious sales violated the CSA.

2. Janssen

132. Janssen manufactures, markets, sells and distributes the following opioids in Wayne County, Oakland County and nationwide:

Duragesic (fentanyl)	Opioid analgesic delivered via skin patch; contains gel form of fentanyl, a synthetic opioid that is up to 100 times more potent than morphine; delivers fentanyl at regulated rate for up to 72 hours; first approved by the FDA in August 1990.	Schedule II
Nucynta ER (tapentadol hydrochloride)	Opioid agonist; extended-release formulation indicated for severe pain.	Schedule II
Nucynta (tapentadol hydrochloride)	Immediate-release version of tapentadol hydrochloride for the management of moderate to severe acute pain.	Schedule II

According to public records, more than 300,000 units of Duragesic, Nucynta ER and Nucynta were prescribed to Wayne County residents and more than 270,000 units of Duragesic, Nucynta ER and Nucynta were prescribed to Oakland County residents from 2014 to 2016, inclusive.

133. Janssen introduced Duragesic in 1990. It is indicated for the “management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.” Janssen also markets Nucynta, which was first approved by the FDA in 2008, formulated in tablet form and in an oral solution and indicated for the “relief of moderate to severe acute pain in patients 18 years of age or older.” Additionally, Janssen markets Nucynta ER, which was first approved by the FDA in 2011 in tablet form. Initially, it was indicated for the “management of . . . pain severe

enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.” This pain indication was later altered to “management of moderate to severe chronic pain in adults” and “neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults.” Janssen sold Nucynta and Nucynta ER to Depomed in 2015 for \$1.05 billion.

a. The FDA Warned Janssen Regarding Its False Messaging

134. On February 15, 2000, the FDA sent Janssen a letter concerning the alleged dissemination of “homemade” promotional pieces that promoted Duragesic in violation of the Federal Food, Drug, and Cosmetic Act. In a subsequent letter, dated March 30, 2000, the FDA explained that the “homemade” promotional pieces were “false or misleading because they contain misrepresentations of safety information, broaden Duragesic’s indication, contain unsubstantiated claims, and lack fair balance.”

135. The March 30, 2000 letter identified specific violations, including misrepresentations that Duragesic had a low potential for abuse:

- You present the claim, “Low abuse potential!” This claim suggests that Duragesic has less potential for abuse than other currently available opioids. However, this claim has not been demonstrated by substantial evidence. Furthermore, this claim is contradictory to information in the approved product labeling (PI) that states, “Fentanyl is a Schedule II controlled substance and can

produce drug dependence similar to that produced by morphine.”¹⁰⁴ Therefore, this claim is false or misleading.

136. The March 30, 2000 letter also stated that the promotional materials represented that Duragesic was “more useful in a broader range of conditions or patients than has been demonstrated by substantial evidence.” Specifically, the FDA stated that Janssen was marketing Duragesic for indications beyond the treatment of chronic pain that cannot otherwise be managed, for which it was approved:

- You present the claim, “It’s not just for end stage cancer anymore!” This claim suggests that Duragesic can be used for any type of pain management. However, the PI for Duragesic states, “Duragesic (fentanyl transdermal system) is indicated in the management of chronic pain in patients who require continuous opioid analgesia for pain that cannot be managed by lesser means . . .” Therefore, the suggestion that Duragesic can be used for any type of pain management promotes Duragesic[] for a much broader use than is recommended in the PI, and thus, is misleading. In addition, the suggestion that Duragesic can be used to treat any kind of pain is contradictory to the boxed warning in the PI. Specifically, the PI states,

BECAUSE SERIOUS OR LIFE-THREATENING HYPOVENTILATION COULD OCCUR, DURAGESIC® (FENTANYL TRANSDERMAL SYSTEM) IS CONTRAINDICATED:

- In the management of acute or post-operative pain, including use in out-patient surgeries . . .¹⁰⁵

¹⁰⁴ Ex. 59 (NDA 19-813 Letter from Spencer Salis, U.S. Food & Drug Administration, to Cynthia Chianese, Janssen Pharmaceutica (Mar. 30, 2000)) at 2.

¹⁰⁵ *Id.* at 2-3.

137. The March 30, 2000 letter also stated Janssen failed to adequately present “contraindications, warnings, precautions, and side effects with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of the product”:

Although this piece contains numerous claims for the efficacy and safety of Duragesic, ***you have not presented any risk information*** concerning the boxed warnings, contraindications, warnings, precautions, or side effects associated with Duragesic’s use Therefore, this promotional piece is lacking in fair balance, or otherwise misleading, because it fails to address important risks and restrictions associated with Duragesic therapy.¹⁰⁶

138. On September 2, 2004, the U.S. Department of Health and Human Services (“HHS”) sent Janssen a warning letter concerning Duragesic due to “false or misleading claims about the abuse potential and other risks of the drug, and . . . unsubstantiated effectiveness claims for Duragesic,” including, specifically, “suggesting that Duragesic has a lower potential for abuse compared to other opioid products.”

139. The September 2, 2004 letter warned Janssen regarding its claims that Duragesic had a low reported rate of mentions in the Drug Abuse Warning Network (“DAWN”) as compared to other opioids. The letter stated that the claim was false or misleading because the claim was not based on substantial data and because the lower

¹⁰⁶ *Id.* at 3 (emphasis in original).

rate of mentions was likely attributable to Duragesic's lower frequency of use compared to other opioids listed in DAWN:

The file card presents the prominent claim, "Low reported rate of mentions in DAWN data," along with Drug Abuse Warning Network (DAWN) data comparing the number of mentions for Fentanyl/combinations (710 mentions) to other listed opioid products, including Hydrocodone/combinations (21,567 mentions), Oxycodone/combinations (18,409 mentions), and Methadone (10,725 mentions). The file card thus suggests that Duragesic is less abused than other opioid drugs.

This is false or misleading for two reasons. First, we are not aware of substantial evidence or substantial clinical experience to support this comparative claim. The DAWN data cannot provide the basis for a valid comparison among these products. As you know, DAWN is not a clinical trial database. Instead, it is a national public health surveillance system that monitors drug-related emergency department visits and deaths. If you have other data demonstrating that Duragesic is less abused, please submit them.

Second, Duragesic is not as widely prescribed as other opioid products. As a result, the relatively lower number of mentions could be attributed to the lower frequency of use, and not to a lower incidence of abuse. The file card fails to disclose this information.¹⁰⁷

140. The September 2, 2004 letter also details a series of unsubstantiated, false or misleading claims regarding Duragesic's effectiveness. The letter concluded that various claims made by Janssen were insufficiently supported, including that:

¹⁰⁷ Ex. 60 (Warning Letter from Thomas W. Abrams, U.S. Department of Health and Human Services, to Ajit Shetty, Janssen Pharmaceutica, Inc. (Sept. 2, 2004), https://www.pharmamedtechbi.com/~media/Images/Publications/Archive/The%20Pink%20Sheet/66/038/00660380018/040920_duragesic_letter.pdf) at 2.

- ““Demonstrated effectiveness in chronic back pain with additional patient benefits, . . . 86% of patients experienced overall benefit in a clinical study based on: pain control, disability in ADLs, quality of sleep.””
- ““All patients who experienced overall benefit from DURAGESIC would recommend it to others with chronic low back pain.””
- ““Significantly reduced nighttime awakenings.””
- ““Significant improvement in disability scores as measured by the Oswestry Disability Questionnaire and Pain Disability Index.””
- ““Significant improvement in physical functioning summary score.””
- ““Significant improvement in social functioning.””¹⁰⁸

141. In addition, the September 2, 2004 letter identifies “outcome claims [that] are misleading because they imply that patients will experience improved social or physical functioning or improved work productivity when using Duragesic.” The claims include ““1,360 loaves . . . and counting,’ ‘[w]ork, uninterrupted,’ ‘[l]ife, uninterrupted,’ ‘[g]ame, uninterrupted,’ ‘[c]hronic pain relief that supports functionality,’ ‘[h]elps patients think less about their pain,’ and ‘[i]mprove[s] . . . physical and social functioning.”” The September 2, 2004 letter states: “Janssen has not provided references to support these outcome claims. We are not aware of substantial evidence or substantial clinical experience to support these claims.”¹⁰⁹

¹⁰⁸ *Id.* at 2-3.

¹⁰⁹ *Id.* at 3.

142. On July 15, 2005, the FDA issued a public health advisory warning doctors of deaths resulting from the use of Duragesic and its generic competitor, manufactured by Mylan N.V. The advisory noted that the FDA had been “examining the circumstances of product use to determine if the reported adverse events may be related to inappropriate use of the patch” and noted the possibility “that patients and physicians might be unaware of the risks” of using the fentanyl transdermal patch, which is a potent opioid analgesic meant to treat chronic pain that does not respond to other painkillers.

143. Regardless, even after receiving these letters, Janssen instructed Michigan sales representatives to market Duragesic as having better efficacy, better tolerability and better patient compliance because it was a patch instead of a pill. Michigan sales representatives were instructed to tell doctors that the patch provided better control in the event of patient opioid abuse because patients could not increase the patch dosage. However, sales representatives were aware of patients who increased the dosage by applying more than one patch at a time and were also aware that some patients abused the patch by freezing, then chewing on it. When concerns about patients’ application of multiple patches at once was raised in a Michigan sales meeting, sales representatives were told that information about the manner in which

certain patients abused Duragesic patches was not what the company wanted to focus on in communications with doctors.

b. Janssen Funded False Publications and Presentations

144. Despite these repeated warnings, Janssen continued to falsely market the risks of opioids. In 2009, PriCara, a “Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.,” sponsored a 2009 brochure, “Finding Relief: Pain Management for Older Adults,” aimed at potential patients. The brochure included a free DVD featuring actress Kathy Baker, who played a doctor in the popular television series “Picket Fences.”

145. The brochure represented that it was a source for older adults to gain accurate information about treatment options for effective pain relief:

This program is aimed specifically at older adults and what they need to know to get effective pain relief. You will learn that there are many pathways to this relief.

You will learn about your options for pain management and how to find the treatment that’s right for you. By learning more about pain and the many ways it can be treated, you are taking solid steps toward reducing the pain you or a loved one may be feeling.¹¹⁰

¹¹⁰ Ex. 61 (*Finding Relief, Pain Management for Older Adults* (2009)).

146. Despite representing itself as a source of accurate information, the brochure included false and misleading information about opioids, including a section seeking to dispel purported “myths” about opioid usage:

Opioid Myths

Myth: Opioid medications are always addictive.

Fact: Many studies show that opioids are *rarely* addictive when used properly for the management of chronic pain.

Myth: Opioids make it harder to function normally.

Fact: When used correctly for appropriate conditions, opioids may make it *easier* for people to live normally.

Myth: Opioid doses have to get bigger over time because the body gets used to them.

Fact: Unless the underlying cause of your pain gets worse (such as with cancer or arthritis), you will probably remain on the same dose or need only small increases over time.¹¹¹

147. Among the “Partners” listed in “Finding Relief: Pain Management for Older Adults” are the AAPM, the American Geriatrics Society (“AGS”) and the AGS Foundation for Health in Aging. Janssen (along with Purdue and Endo) funded AAPM. The AGS and the AGS Foundation for Health in Aging published a pain

¹¹¹ *Id.* (emphasis in original).

guide titled “Finding Relief: Pain Management for Older Adults,” which was funded by Janssen.¹¹²

148. In addition, Janssen disseminated false information about opioids on the website Prescribe Responsibly, which remains publicly accessible at www.prescriberesponsibly.com. According to the website’s legal notice, all content on the site “is owned or controlled by Janssen.”¹¹³ The website includes numerous false or misleading representations concerning the relative safety of opioids and omissions of the risks associated with taking them. For example, it states that while practitioners are often concerned about prescribing opioids due to “questions of addiction,” such concerns “are often overestimated. According to clinical opinion polls, true addiction occurs only in a small percentage of patients with chronic pain who receive chronic opioid analgesic[] . . . therapy.”¹¹⁴

149. Prescribe Responsibly also compared the risks of opioid use favorably to those associated with nonsteroidal anti-inflammatory drugs (“NSAIDs”), such as

¹¹² *Id.*

¹¹³ Ex. 62 (*Legal Notice*, Prescribe Responsibly, <http://www.prescriberesponsibly.com/legal-notice> (last visited Oct. 9, 2017)).

¹¹⁴ Ex. 63 (*Use of Opioid Analgesics in Pain Management*, Prescribe Responsibly, <http://www.prescriberesponsibly.com/articles/opioid-pain-management> (last visited Oct. 9, 2017)).

aspirin and ibuprofen, and stated that many patients develop tolerance for opioid side effects:

Opioid analgesics are often the first line of treatment for many painful conditions and may offer advantages over nonsteroidal anti-inflammatory drugs (NSAIDs). Opioid analgesics, for example, have no true ‘ceiling dose’ for analgesia and do not cause direct organ damage; however, they do have several possible side effects, including constipation, nausea, vomiting, a decrease in sexual interest, drowsiness, and respiratory depression. With the exception of constipation, many patients often develop tolerance to most of the opioid analgesic-related side effects.¹¹⁵

150. Further, Prescribe Responsibly repeats the scientifically unsupported discussion of “pseudoaddiction” as “a syndrome that causes patients to seek additional medications due to inadequate pharmacotherapy being prescribed. Typically when the pain is treated appropriately, the inappropriate behavior ceases.”¹¹⁶ Thus, pseudoaddiction is defined as a condition requiring the prescription of more or stronger opioids.

151. Janssen also made thousands of payments to physicians nationwide, including to Wayne County and Oakland County physicians, for activities including

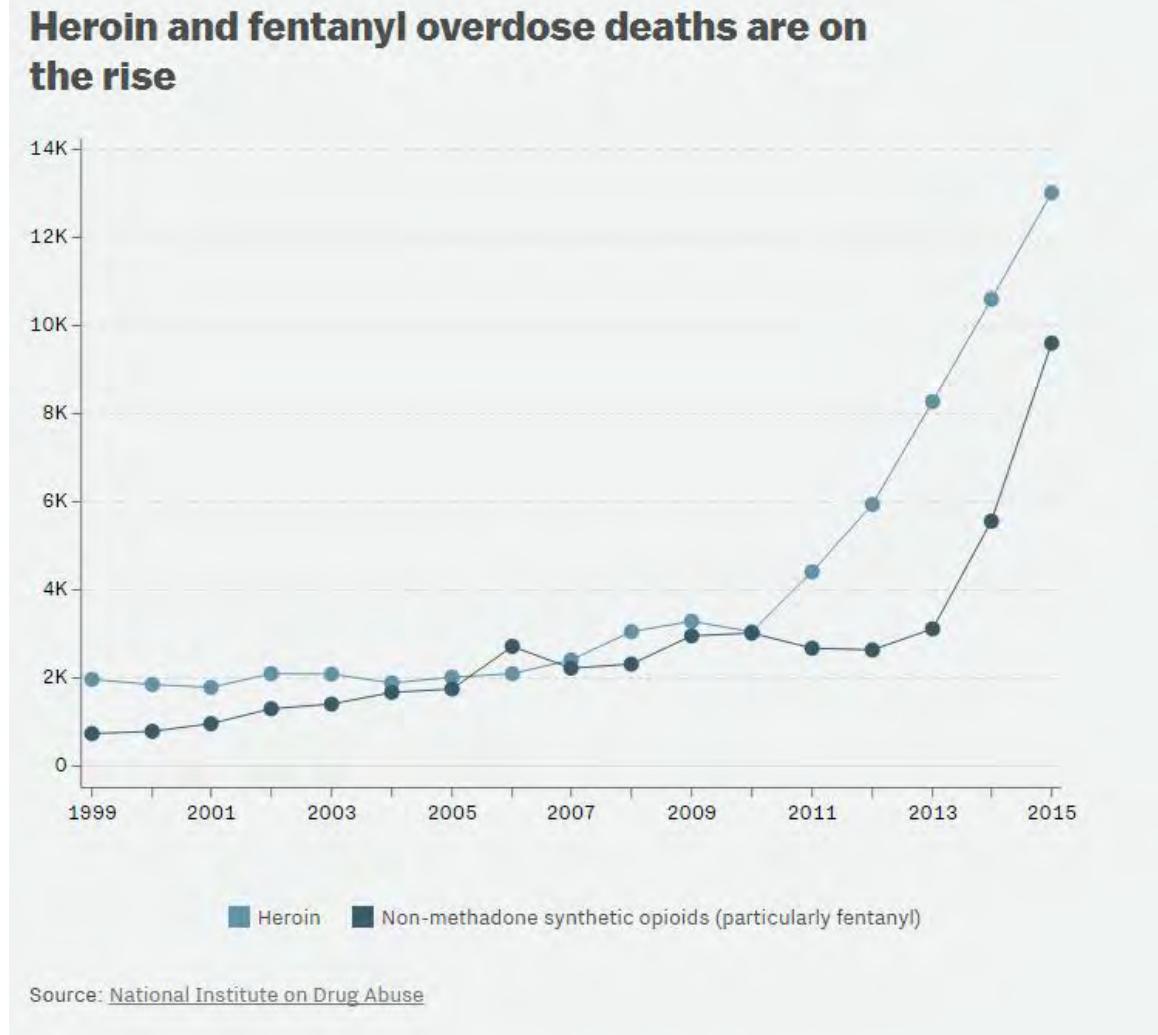
¹¹⁵ *Id.*

¹¹⁶ Ex. 64 (*What a Prescriber Should Know Before Writing the First Prescription*, Prescribe Responsibly, <http://www.prescriberesponsibly.com/articles/before-prescribing-opioids> (last visited Oct. 9, 2017)).

participating on speakers' bureaus, providing consulting services, assisting in post-marketing safety surveillance and other services.

152. Based on an analysis of publicly disclosed reports from the years 2013 through 2016, Janssen paid Wayne County physicians approximately \$2 million and Oakland County physicians approximately \$1.06 million for consulting, speakers' bureau participation, post-marketing safety surveillance and other services provided to Janssen. The vast majority of the recipients were listed as allopathic – *i.e.*, alternative medicine – physicians. According to data collected by ProPublica, in 2014, Michigan doctors prescribed nearly \$1 million worth of Duragesic, more than \$500,000 worth of Nucynta and almost \$400,000 worth of Nucynta ER to patients insured by Medicare Part D. In 2015, those amounts rose to more than \$1 million worth of Duragesic, almost \$780,000 worth of Nucynta and more than \$675,000 of Nucynta ER.

153. As people became more and more hooked on prescription pain killers, they moved to heroin, and increasingly to fentanyl, which is even more potent and cheaper than heroin, and which as set forth above was being deceptively marketed by Janssen, causing a dramatic spike in heroin and fentanyl overdose deaths:



c. Janssen Failed to Report Suspicious Sales as Required

154. The federal CSA imposes on all “registrants” the obligation to design and operate a system to disclose to the registrant suspicious orders of controlled substances and requires the registrant to notify the DEA field division office in its area of any suspicious orders. “Suspicious orders include orders of unusual size, orders

deviating substantially from a normal pattern, and orders of unusual frequency.” 21 C.F.R. §1301.74(b).

155. Janssen is a “registrant” under the federal CSA. 21 C.F.R. §1300.02(b) defines a registrant as any person who is registered with the DEA under 21 U.S.C. §823. Section 823, in turn, requires manufacturers of Schedule II controlled substances to register with the DEA.

156. Janssen failed to design and operate a system to disclose suspicious orders of controlled substances and/or failed to notify the appropriate DEA field division of suspicious orders. By way of example, just two months ago, the doctor of a Dearborn-based pill mill was arrested and arraigned on multiple felony charges for overprescribing opioids, including prescribing more than 500,000 opioid pills since January 2017. Five Oakland County residents were also recently arrested for Medicare fraud related to the prescription of unnecessary opioids to patients, some of which ended up sold illegally on the streets. Other doctors practicing in Wayne County and Oakland County and/or prescribing opioids to Wayne County or Oakland County residents, have been similarly arrested and arraigned for writing an egregiously high number of opioid prescriptions. Janssen’s failure to timely report these and other suspicious sales violated the CSA.

3. Endo

157. Endo manufactures, markets, sells and distributes the following opioids in Wayne County, Oakland County and nationwide:

Opana ER (oxymorphone hydrochloride)	Opioid agonist; extended-release tablet formulation; first drug in which oxymorphone is available in an oral, extended-release formulation; first approved in 2006.	Schedule II
Opana (oxymorphone hydrochloride)	Opioid agonist; first approved in 2006.	Schedule II
Percodan (oxymorphone hydrochloride and aspirin)	Branded tablet combining oxymorphone hydrochloride and aspirin; first approved in 1950; first marketed by Endo in 2004.	Schedule II
Percocet (oxymorphone hydrochloride and acetaminophen)	Branded tablet that combines oxymorphone hydrochloride and acetaminophen; first approved in 1999; first marketed by Endo in 2006.	Schedule II
Oxycodone	Generic product.	Schedule II
Oxymorphone	Generic product.	Schedule II
Hydromorphone	Generic product.	Schedule II
Hydrocodone	Generic product.	Schedule II

For example, based on public records, more than 10,500 prescriptions for more than 674,000 units of Opana ER were prescribed to Wayne County residents and more than 3,000 prescriptions for more than 200,098 units of Opana ER were prescribed to Oakland County residents from 2014 to 2016, inclusive.

158. The FDA first approved an injectable form of Opana in 1959. The injectable form of Opana was indicated “for the relief of moderate to severe pain” and “for preoperative medication, for support of anesthesia, for obstetrical analgesia, and for relief of anxiety in patients with dyspnea associated with pulmonary edema secondary to acute left ventricular dysfunction.” However, oxymorphone drugs were removed from the market in the 1970s due to widespread abuse.¹¹⁷

159. In 2006, the FDA approved a tablet form of Opana in 5 mg and 10 mg strengths. The tablet form was “indicated for the relief of moderate to severe acute pain where the use of an opioid is appropriate.” Also in 2006, the FDA approved Opana ER, an extended-release tablet version of Opana available in 5 mg, 10 mg, 20 mg and 40 mg tablet strengths. Opana ER was indicated “for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.” Endo’s goal was to use Opana ER to take market share away from OxyContin; thus it was marketed as being safer, with less abuse potential than OxyContin because of its crush-resistance.

¹¹⁷ Ex. 65 (John Fauber & Kristina Fiore, *Opana gets FDA approval despite history of abuse, limited effectiveness in trials*, Milwaukee Journal Sentinel (May 9, 2015), <http://archive.jsonline.com/watchdog/watchdogreports/opana-gets-fda-approval-despite-history-of-abuse-limited-effectiveness-in-trials-b99494132z1-303198321.html/>).

160. According to Endo's annual reports, sales of Opana and Opana ER regularly generate several hundred million dollars in annual revenue for the company, growing from \$107 million in 2007 to as high as \$384 million in 2011. Over the last ten years, Percocet has generated an average of well over \$100 million in annual revenue for the company.

a. Endo Falsey Marketed Opana ER as Crush Resistant

161. In December 2011, the FDA approved a reformulated version of Opana ER, which Endo claimed offered "safety advantages" over the original formulation because the latter "is resistant to crushing by common methods and tools employed by abusers of prescription opioids . . . [and] is less likely to be chewed or crushed even in situations where there is no intent for abuse, such as where patients inadvertently chew the tablets, or where caregivers attempt to crush the tablets for easier administration with food or by gastric tubes, or where children accidentally gain access to the tablets.***"

162. Endo publicized the reformulated version of Opana ER as "crush-resistant." To combat the fear of opioids, sales representatives touted it to doctors as a safer option due to its crush-resistance and extended release. In a December 12, 2011, press release announcing FDA approval of the reformulated Opana ER, Endo's

executive vice president for research and development and chief scientific officer highlighted the reformulated version's safety characteristics:

“FDA’s approval of this new formulation of Opana ER is an important milestone for both the Long Acting Opioid category as well as Endo’s branded pharmaceutical portfolio. . . . Patient safety is our top concern and addressing appropriate use of opioids is a responsibility that we take very seriously. We firmly believe this new formulation of Opana ER, coupled with our long-term commitment to awareness and education around appropriate use of opioids will benefit patients, physicians and payers.”

163. However, in October 2012, the CDC issued a health alert noting that 15 people in Tennessee had contracted thrombotic thrombocytopenic purpura, a rare blood-clotting disorder, after injecting reformulated Opana ER. In response, Endo’s chief scientific officer stated that, while Endo was looking into the data, he was not especially concerned: ““Clearly, we are looking into this data, . . . but it’s in a very, very distinct area of the country.””¹¹⁸

164. Shortly thereafter, the FDA determined that Endo’s conclusions about the purported safety advantages of the reformulated Opana ER were unfounded. In a May 10, 2013 letter to Endo, the FDA found that the tablet was still vulnerable to ““cutting, grinding, or chewing,”” ““can be prepared for insufflation (snorting) using commonly

¹¹⁸ Ex. 66 (Jake Harper & Kelly McEvers, *How A Painkiller Designed To Deter Abuse Helped Spark An HIV Outbreak*, National Public Radio (Apr. 1, 2016), <http://www.npr.org/sections/health-shots/2016/04/01/472538272/how-a-painkiller-designed-to-deter-abuse-helped-spark-an-hiv-outbreak>).

available tools and methods,”” and ““can [be readily] prepared for injection.”” It also warned that preliminary data suggested “the troubling possibility that a higher percentage of reformulated Opana ER abuse is via injection than was the case with the original formulation.”

165. A 2014 study co-authored by an Endo medical director corroborated the FDA’s warning. This 2014 study found that while overall abuse of Opana had fallen following Opana ER’s reformulation, it also found that injection had become the preferred way of abusing the drug.¹¹⁹ However, the study reassured that it was not possible to draw a causal link between the reformulation and injection abuse.

166. The study’s failure to adequately warn healthcare providers and the public was catastrophic. On April 24, 2015, the CDC issued a health advisory concerning its investigation of “a large outbreak of recent human immunodeficiency virus (HIV) infections among persons who inject drugs.”¹²⁰ The CDC specifically attributed the outbreak to the injection of Opana ER. As the advisory explained:

From November 2014 to January 2015, ISDH identified 11 new HIV infections in a rural southeastern county where fewer than 5 infections have been identified annually in the past. As of April 21,

¹¹⁹ *Id.*

¹²⁰ Ex. 67 (*Outbreak of Recent HIV and HCV Infections Among Persons Who Inject Drugs*, Centers for Disease Control and Prevention, <https://emergency.cdc.gov/han/han00377.asp> (last visited Oct. 9, 2017)).

2015, an on-going investigation by ISDH with assistance from CDC has identified 135 persons with newly diagnosed HIV infections in a community of 4,200 people; 84% were also HCV infected. Among 112 persons interviewed thus far, 108 (96%) injected drugs; all reported dissolving and injecting tablets of the prescription-type opioid oxymorphone (OPANA® ER) using shared drug preparation and injection equipment.¹²¹

b. New York's Investigation Found Endo Falsely Marketed Opana ER

167. On February 18, 2017, the State of New York announced a settlement with Endo requiring it "to cease all misrepresentations regarding the properties of Opana ER [and] to describe accurately the risk of addiction to Opana ER."¹²² In the Assurance of Discontinuance that effectuated the settlement, the State of New York revealed evidence showing that Endo had known about the risks arising from the reformulated Opana ER even before it received FDA approval.

168. Among other things, the investigation concluded that:

- *Endo improperly marketed Opana ER as designed to be crush resistant, when Endo's own studies dating from 2009 and 2010 showed that the pill could be crushed and ground;*
- *Endo improperly instructed its sales representatives to diminish and distort the risks associated with Opana ER, including the serious danger of addiction; and*

¹²¹ *Id.*

¹²² Ex. 68 (Press Release, Attorney General Eric T. Schneiderman, A.G. Schneiderman Announces Settlement With Endo Health Solutions Inc. & Endo Pharmaceuticals Inc. Over Marketing Of Prescription Opioid Drugs (Mar. 3, 2016), <https://ag.ny.gov/press-release/ag-schneiderman-announces-settlement-endo-health-solutions-inc-endo-pharmaceuticals>).

- *Endo made unsupported claims comparing Opana ER to other opioids and failed to disclose accurate information regarding studies addressing the negative effects of Opana ER.*

169. In October 2011, Endo's director of project management e-mailed the company that had developed the formulation technology for reformulated Opana ER to say there was little or no difference between the new formulation and the earlier formulation, which Endo withdrew due to risks associated with grinding and chewing:

“We already demonstrated that there was little difference between [the original and new formulations of Opana] in Study 108 when both products were ground. FDA deemed that there was no difference and this contributed to their statement that we had not shown an incremental benefit. The chewing study (109) showed the same thing no real difference which the FDA used to claim no incremental benefit.”¹²³

170. Endo conducted two additional studies to test the reformulated Opana ER's crush resistance. Study 901 tested whether it was more difficult to extract reformulated Opana ER than the original version, and whether it would take longer to extract from reformulated Opana ER than from the original version. The test revealed that both formulations behaved similarly with respect to manipulation time and produced equivalent opioid yields.

¹²³ Ex. 69 (*In the Matter of Endo Health Solutions Inc. and Endo Pharmaceuticals Inc.*, Assurance No. 15-228, Assurance of Discontinuance Under Executive Law Section 63, Subdivision 15 at 5 (Mar. 1, 2016), https://ag.ny.gov/pdfs/Endo_AOD_030116-Fully_Executed.pdf).

171. The settlement also identified and discussed a February 2013 communication from a consultant hired by Endo to the company, in which the consultant concluded that “[t]he initial data presented do not necessarily establish that the reformulated Opana ER is tamper resistant.” The same consultant also reported that the distribution of the reformulated Opana ER had already led to higher levels of abuse of the drug via injection.¹²⁴

172. Regardless, pamphlets produced by Endo and distributed to physicians misleadingly marketed the reformulated Opana ER as “‘designed to be’ crush resistant,” and Endo’s sales representative training identified Opana ER as “CR,” short for crush resistant.¹²⁵

173. The Office of the Attorney General of New York also revealed that the “managed care dossier” Endo provided to formulary committees of healthcare plans and pharmacy benefit managers misrepresented the studies that had been conducted on Opana ER. The dossier was distributed in order to assure the inclusion of reformulated Opana ER in their formularies.

174. According to Endo’s vice president for pharmacovigilance and risk management, the dossier was presented as a complete compendium of all research on

¹²⁴ *Id.* at 6.

¹²⁵ *Id.*

the drug. However, it omitted certain studies: Study 108 (completed in 2009) and Study 109 (completed in 2010), which showed that reformulated Opana ER could be ground and chewed.

175. The settlement also detailed Endo's false and misleading representations about the non-addictiveness of opioids and Opana. Until April 2012, Endo's website for the drug, www.opana.com, contained the following representation: ““Most healthcare providers who treat patients with pain agree that patients treated with prolonged opioid medicines usually do not become addicted.””¹²⁶ However, Endo neither conducted nor possessed a survey demonstrating that most healthcare providers who treat patients with pain agree with that representation.

176. The Office of the Attorney General of New York also disclosed that training materials provided by Endo to sales representatives stated: ““Symptoms of withdrawal do not indicate addiction.””¹²⁷ This representation is inconsistent with the diagnosis of opioid-use disorder as provided in the Diagnostic and Statistical Manual of Mental Disorders by the American Psychiatric Association (Fifth Edition).

177. The Office of the Attorney General of New York also found that Endo trained its sales representatives to falsely distinguish addiction from

¹²⁶ *Id.*

¹²⁷ *Id.* at 7.

“pseudoaddiction,” which it defined as a condition in which patients exhibit drug-seeking behavior that resembles but is not the same as addiction. However, Endo’s vice president for pharmacovigilance and risk management testified that he was not aware of any research validating the concept of pseudoaddiction.

178. On June 9, 2017, the FDA asked Endo to voluntarily cease sales of Opana ER after determining that the risks associated with its abuse outweighed the benefits. According to Dr. Janet Woodcock, director of the FDA’s Center for Drug Evaluation and Research, the risks include “several serious problems,” including “outbreaks of HIV and Hepatitis C from sharing the drug after it was extracted by abusers” and “[a]n outbreak of serious blood disorder.” If Endo does not comply with the request, Dr. Woodcock stated that the FDA would issue notice of a hearing and commence proceedings to compel its removal.

c. Endo Funded False Publications and Presentations

179. Like several of the other Manufacturing Defendants, Endo provided substantial funding to purportedly neutral medical organizations, including APF.

180. For example, in April 2007, Endo sponsored an article aimed at prescribers, written by Dr. Charles E. Argoff in *Pain Medicine News*, titled “Case Challenges in Pain Management: Opioid Therapy for Chronic Pain.”¹²⁸

181. The article commenced with the observation that “[a]n estimated 50 to 60 million people . . . suffer from chronic pain.” It continued:

Opioids represent a highly effective but controversial and often misunderstood class of analgesic medications for controlling both chronic and acute pain. The phenomenon of tolerance to opioids – the gradual waning of relief at a given dose – and fears of abuse, diversion, and misuse of these medications by patients have led many clinicians to be wary of prescribing these drugs, and/or to restrict dosages to levels that may be insufficient to provide meaningful relief.¹²⁹

182. The article included a case study that focused on the danger of extended use of NSAIDs, including that the subject was hospitalized with a massive upper gastrointestinal bleed believed to have resulted from his protracted NSAID use. In contrast, the article did not provide the same detail concerning the serious side effects associated with opioids. It concluded by saying that “use of opioids may be effective in the management of chronic pain.”

¹²⁸ Ex. 70 (Charles E. Argoff, *Case Challenges in Pain Management: Opioid Therapy for Chronic Pain*, Pain Med. News, http://www.painmedicinewebs.com/download/BtoB_Opana_WM.pdf).

¹²⁹ *Id.*

183. Later, in 2014, Endo issued a patient brochure titled “Understanding Your Pain: Taking Oral Opioid Analgesics.” It was written by nurses Margo McCaffery and Chris Pasero and edited by APF board member Portenoy.

184. The brochure included numerous false and misleading statements minimizing the dangers associated with prescription opioid use. Among other things, the brochure falsely and misleadingly represented that:

Addiction **IS NOT** when a person develops “withdrawal” (such as abdominal cramping or sweating) after the medicine is stopped quickly or the dose is reduced by a large amount. Your doctor will avoid stopping your medication suddenly by slowly reducing the amount of opioid you take before the medicine is completely stopped. Addiction also **IS NOT** what happens when some people taking opioids need to take a higher dose after a period of time in order for it to continue to relieve their pain. This normal “tolerance” to opioid medications doesn’t affect everyone who takes them and does not, by itself, imply addiction. If tolerance does occur, it does not mean you will “run out” of pain relief. Your dose can be adjusted or another medicine can be prescribed.

* * *

How can I be sure I’m not addicted?

- Addiction to an opioid would mean that your pain has gone away but you still take the medicine regularly when you don’t need it for pain, maybe just to escape from your problems.
- Ask yourself: Would I want to take this medicine if my pain went away? If you answer no, you are taking opioids for the right reasons – to relieve your pain and improve your function. You are not addicted.

* * *

Your doctor or nurse may instruct you to do some of the following:

- Take the next dose before the last dose wears off. If pain is present most of the day and night, the pain medicine may be taken at regularly scheduled times. If you are taking a short-acting opioid, this usually means taking it every 4 hours. You may need to set your alarm, especially at night, to be sure you take your dose before the pain returns and wakes you up.
- If your pain comes and goes, take your pain medicine when pain first begins, before it becomes severe.
- If you are taking a long-acting opioid, you may only need to take it every 8 to 12 hours, but you may also need to take a short-acting opioid in between for any increase in pain.¹³⁰

185. In 2008, Endo also provided an “educational grant” to PainEDU.org, which produced a document titled “Screener and Opioid Assessment for Patients with Pain (SOAPP) Version 1.0-14Q.” Endo and King Pharmaceuticals sponsor PainEDU.org.¹³¹ SOAPP describes itself “as a tool for clinicians to help determine how much monitoring a patient on long-term opioid therapy might require.” It falsely

¹³⁰ Ex. 71 (Margo McCaffery & Chris Pasero, *Understanding Your Pain: Taking Oral Opioid Analgesics*, Endo Pharmaceuticals (2004), http://www.thblack.com/links/RSD/Understand_Pain_Opioid_Analgesics.pdf) (emphasis in original).

¹³¹ Ex. 72 (B. Eliot Cole, *Resources for Education on Pain and Its Management: A Practitioner’s Compendium* 2 (Am. Society of Pain Educators 2009), <https://www.paineducators.org/wp-content/uploads/2012/12/ASPE-ResForEducationOnPainAn.pdf>).

highlights purportedly “recent findings suggesting that most patients are able to successfully remain on long-term opioid therapy without significant problems.”

186. Endo also sponsored the now-defunct website painknowledge.com, which was created by APF and stated it was “a one-stop repository for print materials, educational resources, and physician tools across the broad spectrum of pain assessment, treatment, and management approaches.”¹³² Among other featured content, painknowledge.com included a flyer titled “Pain: Opioid Therapy,” which failed to warn of significant adverse effects that could arise from opioid use, including hyperalgesia, immune and hormone dysfunction, cognitive impairment, decreased tolerance, dependence and addiction.

187. Endo, along with Janssen and Purdue, also provided grants to APF to distribute Exit Wounds, discussed above. *See supra ¶¶65-66.*¹³³

¹³² Ex. 73 (*AboutPainKnowledge.org*, PainKnowledge, <http://web.archive.org/web/20120119124921/http://www.painknowledge.org/aboutpaink.aspx> (last visited Oct. 10, 2017)).

¹³³ Ex. 74 (*Iraq War Veteran Amputee, Pain Advocate and New Author Release Exit Wounds: A Survival Guide to Pain Management for Returning Veterans and Their Families*, Coalition for Iraq + Afghanistan Veterans, <https://web.archive.org/web/20160804131030/http://coalitionforveterans.org/2009/10/iraq-war-veteran-amputee-pain-advocate-and-new-author-releases-exit-wounds-a-survival-guide-to-pain-management-for-returning-veterans-and-their-families/> (last visited Oct. 10, 2017)).

188. Endo also made thousands of payments to physicians nationwide, including to Wayne County and Oakland County physicians, for activities including participating on speakers' bureaus, providing consulting services, assisting in post-marketing safety surveillance and other services. Based on an analysis of publicly disclosed reports from the years 2013 through 2016, Endo paid Wayne County physicians more than \$8,300 and Oakland County physicians more than \$7,000 for consulting, speakers' bureau participation, post-marketing safety surveillance and other services provided to Endo. All of the recipients were listed as allopathic – *i.e.* alternative medicine – physicians.

189. Indeed, in 2015 and 2016, sales representatives in Detroit received from Endo a list of doctors to target – referred to internally as “the universe” – which included not only pain clinics and anesthesiologists, but also general and family practitioners. While some of the doctors on the list were clearly engaged in problematic prescribing of opioids, including a Detroit internal medicine doctor who wrote so many opioid prescriptions that he was eventually shut down, at no time were sales representatives provided a do not call list of problematic prescribers. During 2015 and 2016, sales representatives of Endo opioids in Detroit were trained to put their heads down and ignore problematic remarks from doctors and their staff regarding their prescription practices.

d. FDA Requests Endo Withdraw Opana ER Due to the Public Health Consequences of Abuse

190. On June 8, 2017, the FDA requested that Endo remove reformulated Opana ER from the market “based on its concern that the benefits of the drug may no longer outweigh its risks.”¹³⁴ According to the FDA’s press release, it sought removal “due to the public health consequences of abuse.” The decision to seek Opana ER’s removal from sale followed a March 2017 FDA advisory committee meeting, during which a group of independent experts voted 18-8 that the drug’s benefits no longer outweigh the risks associated with its use. Should Endo choose not to remove Opana ER due to the FDA’s request, the agency stated that it will take steps to formally require its removal by withdrawing approval.

191. Opana ER has been widely prescribed in Wayne County and Oakland County. According to data collected by ProPublica, during 2014 and 2015, Michigan doctors’ prescriptions of Opana ER to patients insured by the Medicare Part D program totaled more than \$3.8 million and \$5.01 million, respectively. Three of the top 13 prescribers of Opana ER during 2014 practiced in Wayne County, including the physician who filed the most Medicare claims during 2014 for prescriptions of the drug. Additionally, three of the top five prescribers of Opana ER during 2015

¹³⁴ Ex. 75 (Press Release, U.S. Food & Drug Administration, FDA requests removal of Opana ER for risks related to abuse (June 8, 2017), <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm562401.htm>).

practiced in Oakland County, including the physician who filed the second most Medicare claims during 2015 for prescriptions of the drug.

e. Endo Failed to Report Suspicious Sales as Required

192. The federal CSA imposes on all “registrants” the obligation to design and operate a system to disclose to the registrant suspicious orders of controlled substances and requires the registrant to notify the DEA field division office in its area of any suspicious orders. “Suspicious orders include orders of unusual size, orders deviating substantially from a normal pattern, and orders of unusual frequency.” 21 C.F.R. §1301.74(b).

193. Endo is a “registrant” under the federal CSA. 21 C.F.R. §1300.02(b) defines a registrant as any person who is registered with the DEA under 21 U.S.C. §823. Section 823, in turn, requires manufacturers of Schedule II controlled substances to register with the DEA.

194. Endo failed to design and operate a system to disclose suspicious orders of controlled substances and/or failed to notify the appropriate DEA field division of suspicious orders. By way of example, just two months ago, the doctor of a Dearborn-based pill mill was arrested and arraigned on multiple felony charges for overprescribing opioids, including prescribing more than 500,000 opioid pills since January 2017. Five Oakland County residents were also recently arrested for

Medicare fraud related to the prescription of unnecessary opioids to patients, some of which ended up sold illegally on the streets. Other doctors practicing in Wayne County and Oakland County, and/or prescribing opioids to Wayne County or Oakland County residents, have been similarly arrested and arraigned for writing an egregiously high number of opioid prescriptions. Endo's failure to timely report these and other suspicious sales violated the CSA.

4. Cephalon

195. Cephalon manufactures, markets, sells and distributes the following opioids in Wayne County, Oakland County and nationwide:

Actiq (fentanyl citrate)	Opioid analgesic; oral transmucosal lozenge; indicated only for the management of breakthrough pain (or "BTP") in cancer patients – pain that for a short time "breaks through" medication that otherwise effectively controls a patient's persistent pain – in patients 16 and older with malignancies; commonly referred to as a lollipop because designed to look and perform like one; approved in 1998 with restricted distribution program.	Schedule II
Fentora (fentanyl buccal)	Rapid-release tablet for BTP in cancer patients who are already receiving and tolerant of around-the-clock opioid therapy; approved 2006.	Schedule II
Generic of OxyContin (oxycodone hydrochloride)	Opiate agonist.	Schedule II

196. Actiq is designed to resemble a lollipop and is meant to be sucked on at the onset of intense BTP in cancer patients. It delivers fentanyl citrate, a powerful opioid agonist that is 80 times stronger than morphine,¹³⁵ rapidly into a patient's bloodstream through the oral membranes.¹³⁶ Because it is absorbed through those membranes, it passes directly into circulation without having to go through the liver or stomach, thereby providing faster relief.¹³⁷

197. In November 1998, the FDA approved Actiq for only a very narrow group of people – cancer patients “with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.”¹³⁸

198. Understanding the risks of introducing such an intense opioid analgesic to the market, the FDA provided approval of Actiq “**ONLY** for the management of breakthrough cancer pain in patients with malignancies who are already receiving and

¹³⁵ See Ex. 76 (John Carreyrou, *Narcotic “Lollipop” Becomes Big Seller Despite FDA Curbs*, Wall St. J. (Nov. 3, 2006), <https://www.opiates.com/media/narcotic-lollipop-becomes-big-seller-despite-fda-curbs/> (hereinafter “Carreyrou, *Narcotic Lollipop*”)).

¹³⁶ Actiq would later become part of a category of opioids now known as transmucosal immediate-release fentanyl (“TIRF”) products. “Transmucosal” refers to the means through which the opioid is delivered into a patient’s bloodstream, across mucous membranes, such as inside the cheek, under the tongue or in the nose.

¹³⁷ Ex. 77 (Cephalon, Inc., Company-Histories.com, <http://www.company-histories.com/Cephalon-Inc-Company-History.html> (last visited Oct. 10, 2017)).

¹³⁸ 1998 FDA Label.

who are tolerant to opioid therapy for their underlying persistent cancer pain.”¹³⁹

Further, the FDA explicitly stated that Actiq “***must not*** be used in opioid non-tolerant patients,” was contraindicated for the management of acute or postoperative pain, could be deadly to children and was “intended to be used only in the care of opioid-tolerant cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.”

199. The FDA also required that Actiq be provided only in compliance with a strict risk-management program that explicitly limited the drug’s direct marketing to the approved target audiences, defined as oncologists, pain specialists, their nurses and office staff.¹⁴⁰

200. In October 2000, Cephalon acquired the worldwide product rights to Actiq and began marketing and selling Actiq in the United States.

201. Cephalon purchased the rights to Fentora, an even faster-acting tablet formulation of fentanyl, from Cima Labs, and submitted a new drug application to the FDA in August 2005. In September 2006, Cephalon received FDA approval to sell this faster-acting version of Actiq; but once again, concerned about the power and

¹³⁹ Ex. 78 (NDA 20-747 Letter from Cynthia McCormick, Center for Drug Evaluation and Research, to Patricia J. Richards, Anesta Corporation, http://www.accessdata.fda.gov/drugsatfda_docs/appletter/1998/20747ltr.pdf).

¹⁴⁰ Carreyrou, *Narcotic Lollipop*, *supra* n.135.

risks inherent to fentanyl, the FDA limited Fentora's approval to the treatment of BTP in cancer patients who were already tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Cephalon began marketing and selling Fentora in October 2006.

202. Based on public records, more than 29,000 units of Fentora were prescribed to Wayne County residents and more than 33,000 units of Fentora were prescribed to Oakland County residents from 2014 to 2016, inclusive.

a. Cephalon Aggressively Marketed Cancer Drug to Non-Cancer Treating Physicians

203. Due to the FDA's restrictions, Actiq's consumer base was limited, as was its potential for growing revenue. In order to increase its revenue and market share, Cephalon needed to find a broader audience and thus began marketing its lollipop to treat headaches, back pain, sports injuries and other chronic non-cancer pain, targeting non-oncology practices, including, but not limited to, pain doctors, general practitioners, migraine clinics, anesthesiologists and sports clinics. It did so in violation of applicable regulations prohibiting the marketing of medications for off-label use and in direct contravention of the FDA's strict instructions that Actiq be prescribed only to terminal cancer patients and by oncologists and pain management doctors experienced in treating cancer pain.

204. According to “[d]ata gathered from a network of doctors by research firm ImpactRx between June 2005 and October 2006” (“ImpactRx Survey”), Cephalon sales representatives’ visits to non-oncologists to pitch Actiq increased sixfold between 2002 and 2005. Cephalon representatives would reportedly visit non-oncologists monthly, providing up to 60 or 70 coupons (each coupon was good for six free Actiq lozenges) and encouraging prescribers to try Actiq on their non-cancer patients.¹⁴¹

205. Cephalon’s efforts paid off. In 2000, Actiq generated \$15 million in sales.¹⁴² By 2002, it attributed a 92% increase in Actiq sales to “a dedicated sales force for ACTIQ” and “ongoing changes to [its] marketing approach including hiring additional sales representatives and targeting our marketing efforts to pain specialists.”¹⁴³ By 2005, Actiq’s sales total had jumped to \$412 million, making it (a drug approved for only a narrow customer base) Cephalon’s second-bestselling drug. By the end of 2006, Actiq’s sales had exceeded \$500 million.¹⁴⁴

¹⁴¹ *Id.*

¹⁴² *Id.*

¹⁴³ Ex. 79 (Cephalon, Inc. Annual Report (Form 10-K) (Mar. 31, 2003), <https://www.sec.gov/Archives/edgar/> data/873364/000104746903011137/a2105971z10-k.htm) at 28.

¹⁴⁴ Carreyrou, *Narcotic Lollipop*, *supra* n.135.

206. Only 1% of the 187,076 prescriptions for Actiq filled at retail pharmacies during the first six months of 2006 were prescribed by oncologists. Results of the ImpactRx Survey suggested that “more than 80 percent of patients who use[d] the drug don’t have cancer.”¹⁴⁵

b. Government Investigations Found Cephalon Falsely Marketed Actiq for Off-Label Uses

207. Beginning in or about 2003, former Cephalon employees filed four whistleblower lawsuits claiming the company had wrongfully marketed Actiq for unapproved, off-label uses. On September 29, 2008, Cephalon finalized and entered into a corporate integrity agreement with the Office of the Inspector General of HHS and agreed to pay \$425 million in civil and criminal penalties for its off-label marketing of Actiq and two other drugs (Gabitril and Provigil). According to a DOJ press release, Cephalon trained sales representatives to disregard restrictions of the FDA-approved label, employed sales representatives and healthcare professionals to speak to physicians about off-label uses of the three drugs and funded CME to promote off-label uses. Specifically, the DOJ stated:

From 2001 through at least 2006, *Cephalon was allegedly promoting [Actiq] for non-cancer patients to use for such maladies as migraines, sickle-cell pain crises, injuries, and in anticipation of changing wound dressings or radiation therapy. Cephalon also promoted Actiq for use*

¹⁴⁵ *Id.*

in patients who were not yet opioid-tolerant, and for whom it could have life-threatening results.¹⁴⁶

208. Then-acting U.S. Attorney Laurie Magid commented on the dangers of Cephalon's unlawful practices:

"This company subverted the very process put in place to protect the public from harm, and put patients' health at risk for nothing more than boosting its bottom line. People have an absolute right to their doctors' best medical judgment. They need to know the recommendations a doctor makes are not influenced by sales tactics designed to convince the doctor that the drug being prescribed is safe for uses beyond what the FDA has approved.”¹⁴⁷

209. Upon information and belief, documents uncovered in the government's investigations confirm that Cephalon directly targeted non-oncology practices and pushed its sales representatives to market Actiq for off-label use. For instance, the government's investigations confirmed:

- Cephalon instructed its sales representatives to ask non-cancer doctors whether they have the potential to treat cancer pain. Even if the doctor answered “no,” a decision tree provided by Cephalon instructed the sales representatives to give these physicians free Actiq coupons;
- Cephalon targeted neurologists in order to encourage them to prescribe Actiq to patients with migraine headaches;
- Cephalon sales representatives utilized the assistance of outside pain management specialists when visiting non-cancer physicians to pitch Actiq. The pain management specialist would falsely inform the

¹⁴⁶ Ex. 80 (Press Release, U.S. Department of Justice, Pharmaceutical Company Cephalon To Pay \$425 Million For Off-Label Drug Marketing (Sept. 29, 2008), <https://www.justice.gov/archive/usao/pae/News/2008/sep/cephalonrelease.pdf>).

¹⁴⁷ *Id.*

physician that Actiq does not cause patients to experience a “high” and carries a low risk of diversion toward recreational use;

- Cephalon set sales quotas for its sales and marketing representatives that could not possibly have been met solely by promoting Actiq for its FDA-approved indication;
- Cephalon promoted the use of higher doses of Actiq than patients required by encouraging prescriptions of the drug to include larger-than-necessary numbers of lozenges with unnecessarily high doses of fentanyl; and
- Cephalon promoted Actiq for off-label use by funding and controlling CME seminars that promoted and misrepresented the efficacy of the drug for off-label uses such as treating migraine headaches and for patients not already opioid-tolerant.¹⁴⁸

210. Still, the letters, the FDA’s safety alert, DOJ and state investigations and the massive settlement seemed to have had little impact on Cephalon as it continued its deceptive marketing strategy for both Actiq and Fentora.

c. Cephalon Focused on Non-Cancer Treating Physicians in Falsely Marketing Fentora

211. From the time it first introduced Fentora to the market in October 2006, Cephalon targeted non-cancer doctors, falsely represented Fentora as a safe, effective off-label treatment for non-cancer pain and continued its disinformation campaign about the safety and non-addictiveness of Fentora specifically and opioids generally. In fact, Cephalon targeted the same pain specialists and non-oncologists that it had targeted with its off-label marketing of Actiq, simply substituting Fentora.

¹⁴⁸ Ex. 81 (John Carreyrou, *Cephalon Used Improper Tactics to Sell Drug, Probe Finds*, Wall St. J., Nov. 21, 2006, at B1 (hereinafter “Carreyrou, *Cephalon Used Improper Tactics*”)).

212. During an investor earnings call shortly after Fentora's launch, Cephalon's chief executive officer ("CEO") described the "opportunity" presented by the use of Fentora for non-cancer pain:

The other opportunity of course is the prospect for FENTORA outside of cancer pain, in indications such as breakthrough lower back pain and breakthrough neuropathic pain.

* * *

Of all the patients taking chronic opioids, 32% of them take that medication to treat back pain, and 30% of them are taking their opioids to treat neuropathic pain. In contrast only 12% are taking them to treat cancer pain, 12%.

We know from our own studies that breakthrough pain episodes experienced by these non-cancer sufferers respond very well to FENTORA. And for all these reasons, we are tremendously excited about the significant impact FENTORA can have on patient health and well being and the exciting growth potential that it has for Cephalon.

In summary, we have had a strong launch of FENTORA and continue to grow the product aggressively. Today, that growth is coming from the physicians and patient types that we have identified through our efforts in the field over the last seven years. In the future, with new and broader indications and a much bigger field force presence, the opportunity that FENTORA represents is enormous.¹⁴⁹

¹⁴⁹ Ex. 82 (Seeking Alpha, Transcript of Q1 2007 Cephalon, Inc. Earnings Conference Call, May 1, 2007, <http://seekingalpha.com/article/34163-cephalon-q1-2007-earnings-call-transcript?all=true&find =Q1%2B2007%2BCephalon%2BMay%2B1%2C%2B2007>) at 6-7.

d. The FDA Warned Cephalon Regarding its False and Off-Label Marketing of Fentora

213. On September 27, 2007, the FDA issued a public health advisory to address numerous reports that patients who did not have cancer or were not opioid tolerant had been prescribed Fentora, and death or life-threatening side effects had resulted. The FDA warned: “Fentora should not be used to treat any type of short-term pain.”¹⁵⁰

214. Nevertheless, in 2008, Cephalon pushed forward to expand the target base for Fentora and filed a supplemental drug application requesting FDA approval of Fentora for the treatment of non-cancer BTP. In the application and supporting presentations to the FDA, Cephalon admitted both that it knew the drug was heavily prescribed for off-label use and that the drug’s safety for such use had never been clinically evaluated.¹⁵¹ An FDA advisory committee lamented that Fentora’s existing risk management program was ineffective and stated that Cephalon would have to institute a risk evaluation and mitigation strategy for the drug before the FDA would

¹⁵⁰ Ex. 83 (Press Release, U.S. Food & Drug Administration, Public Health Advisory: Important Information for the Safe Use of Fentora (fentanyl buccal tablets) (Sept. 26, 2007), <https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051273.htm>).

¹⁵¹ Ex. 84 (*FENTORA (fentanyl buccal tablet) CII, Joint Meeting of Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committee*, U.S. Food & Drug Administration (May 6, 2008), <https://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4356s2-03-Cephalon.pdf>).

consider broader label indications. In response, Cephalon revised Fentora’s label and medication guide to add strengthened warnings.

215. But in 2009, the FDA once again informed Cephalon that the risk management program was not sufficient to ensure the safe use of Fentora for already approved indications.

216. On March 26, 2009, the FDA warned Cephalon against its misleading advertising of Fentora (“Warning Letter”). The Warning Letter described a Fentora Internet advertisement as misleading because it purported to broaden “the indication for Fentora by implying that any patient with cancer who requires treatment for breakthrough pain is a candidate for Fentora . . . when this is not the case.” Rather, Fentora was only indicated for those who were already opioid tolerant. It further criticized Cephalon’s other direct Fentora advertisements because they did not disclose the risks associated with the drug.

217. Flagrantly disregarding the FDA’s refusal to approve Fentora for non-cancer BTP and its warning against marketing the drug for the same, Cephalon continued to use the same sales tactics to push Fentora as it did with Actiq.

218. For example, on January 13, 2012, Cephalon published an insert in *Pharmacy Times* titled “An Integrated Risk Evaluation and Mitigation Strategy (REMS) for FENTORA (Fentanyl Buccal Tablet) and ACTIQ (Oral Transmucosal

Fentanyl Citrate).” Despite the repeated warnings of the dangers associated with the use of the drugs beyond their limited indication, as detailed above, the first sentence of the insert states: “It is well recognized that the judicious use of opioids can facilitate effective and safe management of chronic pain.”¹⁵²

e. Cephalon Funded False Publications and Presentations

219. In addition to its direct marketing, Cephalon indirectly marketed through third parties to change the way doctors viewed and prescribed opioids – disseminating the unproven and deceptive messages that opioids were safe for the treatment of chronic, long-term pain, that they were non-addictive and that they were woefully under-prescribed to the detriment of patients who were needlessly suffering. It did so by sponsoring pro-opioid front groups, misleading prescription guidelines, articles and CMEs, and it paid physicians thousands of dollars every year to publicly opine that opioids were safe, effective and non-addictive for a wide variety of uses.

220. Cephalon sponsored numerous CMEs, which were made widely available through organizations like Medscape, LLC (“Medscape”) and which disseminated

¹⁵² Ex. 85 (*An Integrated Risk Evaluation and Mitigation Strategy (REMS) for FENTORA (Fentanyl Buccal Tablet) and ACTIQ (Oral Transmucosal Fentanyl Citrate)*), Pharmacy Times (Jan. 13, 2012), <http://www.pharmacytimes.com/publications/issue/2012/january2012/r514-jan-12-rems>).

false and misleading information to physicians in Wayne County, Oakland County and across the country.

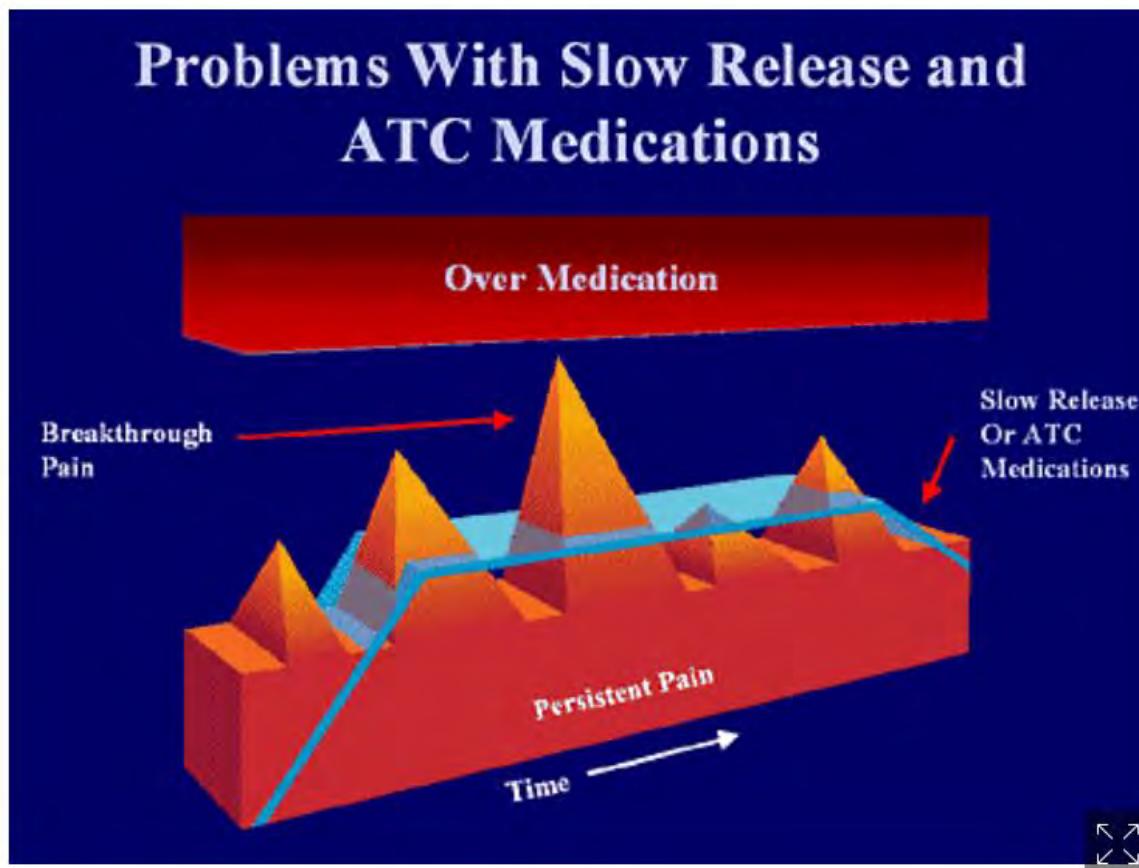
221. For example, a 2003 Cephalon-sponsored CME presentation titled “Pharmacologic Management of Breakthrough or Incident Pain,” posted on Medscape in February 2003, teaches:

[C]hronic pain is often undertreated, particularly in the noncancer patient population. . . . The continued stigmatization of opioids and their prescription, coupled with often unfounded and self-imposed physician fear of dealing with the highly regulated distribution system for opioid analgesics, remains a barrier to effective pain management and must be addressed. Clinicians intimately involved with the treatment of patients with chronic pain recognize that the majority of suffering patients lack interest in substance abuse. In fact, patient fears of developing substance abuse behaviors such as addiction often lead to undertreatment of pain. The concern about patients with chronic pain becoming addicted to opioids during long-term opioid therapy may stem from confusion between physical dependence (tolerance) and psychological dependence (addiction) that manifests as drug abuse.¹⁵³

222. Another Cephalon-sponsored CME presentation titled “Breakthrough Pain: Treatment Rationale with Opioids” was available on Medscape starting September 16, 2003 and was given by a self-professed pain management doctor who “previously operated back, complex pain syndromes, the neuropathies, and interstitial

¹⁵³ Ex. 86 (Michael J. Brennan, *et al.*, *Pharmacologic Management of Breakthrough or Incident Pain*, Medscape, <http://www.medscape.org/viewarticle/449803> (last visited Oct. 10, 2017)).

cystitis.” He describes the pain process as a non-time-dependent continuum that requires a balanced analgesia approach using “targeted pharmacotherapeutics to affect multiple points in the pain-signaling pathway.”¹⁵⁴ The doctor lists fentanyl as one of the most effective opioids available for treating BTP, describing its use as an expected and normal part of the pain management process. Nowhere in the CME is cancer or cancer-related pain even mentioned.



¹⁵⁴ Ex. 87 (Daniel S. Bennett, *Breakthrough Pain: Treatment Rationale With Opioids*, Medscape, <http://www.medscape.org/viewarticle/461612> (last visited Oct. 10, 2017)).

223. Dr. Stephen H. Landy (“Landy”) authored a 2004 CME available on Medscape titled “Oral Transmucosal Fentanyl Citrate for the Treatment of Migraine Headache Pain In Outpatients: A Case Series.” The manuscript preparation was supported by Cephalon. Landy describes the findings of a study of fentanyl citrate for the use of migraine headache pain and concluded that “OTFC rapidly and significantly relieved acute, refractory migraine pain in outpatients . . . and was associated with high patient satisfaction ratings.”¹⁵⁵ Based on an analysis of publicly available data, Cephalon paid Landy approximately \$190,000 in 2009-2010 alone, and in 2015-2016, Cephalon paid Landy another \$75,000.

224. In 2006, Cephalon sponsored a review of scientific literature to create additional fentanyl-specific dosing guidelines titled “Evidence-Based Oral Transmucosal Fentanyl Citrate (OTFC®) Dosing Guidelines.”¹⁵⁶ The article purports to review the evidence for dosing and efficacy of oral transmucosal fentanyl citrate in the management of pain and produce dosing guidelines in both cancer and non-cancer patients. In pertinent part, it states:

¹⁵⁵ Ex. 88 (Stephen H. Landy, *Oral Transmucosal Fentanyl Citrate for the Treatment of Migraine Headache Pain In Outpatients: A Case Series*, 44(8) Headache (2004), http://www.medscape.com/viewarticle/488337_2).

¹⁵⁶ Gerald M. Aronoff, et al., *Evidence-Based Oral Transmucosal Fentanyl Citrate (OTFC) Dosing Guidelines*, 6(4) Pain Med. 305-14 (Aug. 2005).

Oral transmucosal fentanyl citrate has a proven benefit in treating cancer-associated breakthrough pain in opioid-tolerant patients with cancer, which is the Food and Drug Administration (FDA)-approved indication for Actiq. *Pain medicine physicians have also used OTFC successfully to provide rapid pain relief in moderate to severe noncancer pain in both opioid-tolerant and opioid-nontolerant patients.*¹⁵⁷

225. Deeper into the article, the authors attempt to assuage doctors' concerns regarding possible overdose and respiratory distress in non-cancer patients by arguing “*[t]here is no evidence that opioid safety and efficacy differs in opioid-tolerant patients with chronic noncancer pain.*” Regarding the use of fentanyl to treat non-opioid-tolerant patients, the article's authors stated:

Alternatively, *OTFC might also be used cautiously and safely for acute pain experienced by patients who are not opioid tolerant. Parenteral opioids are routinely used for acute pain in patients who are not opioid tolerant.* Examples include episodic pain (*i.e.*, refractory migraine pain, recurrent renal calculi, etc.) and acute pain that follows surgery, trauma, or painful procedures (burn dressing change, bone marrow aspiration, lumbar puncture). Assuming that clinical experience with IV morphine in patients who are not opioid tolerant can be extrapolated, OTFC should be safe and efficacious in such settings as well.¹⁵⁸

226. Through its sponsorship of the FSMB's “Responsible Opioid Prescribing: A Physician's Guide” (*see supra ¶¶43-48*), Cephalon continued to encourage the prescribing of opioid medication to “reverse . . . and improve” patient function,

¹⁵⁷ *Id.*

¹⁵⁸ *Id.*

attributing patients' displays of traditional drug-seeking behaviors as merely "pseudoaddiction."

227. Cephalon also disseminated its false messaging through speakers' bureaus and publications. For example, at an AAPM annual meeting held February 22 through 25, 2006, Cephalon sponsored a presentation by Webster and others titled "Open-label study of fentanyl effervescent buccal tablets in patients with chronic pain and breakthrough pain: Interim safety results." The presentation's agenda description states: "Most patients with chronic pain experience episodes of breakthrough pain (BTP), yet no currently available pharmacologic agent is ideal for its treatment." The presentation purports to cover a study analyzing the safety of a new form of fentanyl buccal tablets in the chronic pain setting and promises to show the "[i]nterim results of this study suggest that FEBT is safe and well-tolerated in patients with chronic pain and BTP."

228. Cephalon sponsored another CME written by Webster and M. Beth Dove titled "Optimizing Opioid Treatment for Breakthrough Pain" and offered on Medscape from September 28, 2007 through December 15, 2008. The CME teaches that non-opioid analgesics and combination opioids containing non-opioids such as aspirin and

acetaminophen are less effective at treating BTP than pure opioid analgesics because of dose limitations on the non-opioid component.¹⁵⁹

229. Fine authored a Cephalon-sponsored CME titled “Opioid-Based Management of Persistent and Breakthrough Pain,” with Drs. Christine A. Miaskowski and Michael J. Brennan. Cephalon paid to have this CME published in a “Special Report” supplement of the journal *Pain Medicine News* in 2009.¹⁶⁰ The CME targeted a wide variety of non-oncologist healthcare providers who treat patients with chronic pain with the objective of educating “health care professionals about a semi-structured approach to the opioid-based management of persistent and breakthrough pain,” including the use of fentanyl. The CME purports to analyze the “combination of evidence- and case-based discussions” and ultimately concludes:

Chronic pain is a debilitating biopsychosocial condition prevalent in both cancer and noncancer pain populations. . . . Opioids have an established role in pain related to cancer and other advanced medical illnesses, as well as an increasing contribution to the long-term treatment of carefully selected and monitored patients with certain [chronic noncancer pain] conditions. ***All individuals with chronic, moderate to severe pain associated with functional impairment should be***

¹⁵⁹ Ex. 89 (Lynn Webster, *Optimizing Opioid Treatment for Breakthrough Pain*, Medscape, http://www.medscape.org/viewarticle/563417_6 (last visited Oct. 10, 2017)).

¹⁶⁰ Ex. 90 (Perry G. Fine, *et al.*, *Opioid-Based Management of Persistent and Breakthrough Pain*, Special Report (2009), <https://www.yumpu.com/en/document/view/11409251/opioid-based-management-of-persistent-and-breakthrough-pain/9>).

considered for a trial or opioid therapy, although not all of them will be selected.¹⁶¹

230. Along with Purdue, Cephalon sponsored APF's guide (*see supra ¶¶70-71*), which warned against the purported ***under*-prescribing** of opioids, taught that addiction is ***rare*** and suggested that opioids have "***no ceiling dose***" and are therefore the most appropriate treatment for severe pain.

231. A summary of the February 12-16, 2008 AAPM annual meeting reinforced the message, promoted both by the AAPM and the APS, that "the undertreatment of pain is unjustified." It continues:

Pain management is a fundamental human right in all patients not only with acute postoperative pain but also ***in patients suffering from chronic pain***. Treating the underlying cause of pain does not usually treat all of the ongoing pain. Minimal pathology with maximum dysfunction remains the enigma of chronic pain. Chronic pain is only recently being explored as a complex condition that requires individual treatment and a multidisciplinary approach. It is considered to be a disease entity.¹⁶²

232. Cephalon was one of several opioid manufacturers who collectively paid 14 of the 21 panel members who drafted the 2009 APS-AAPM opioid treatment guidelines.¹⁶³

¹⁶¹ *Id.*

¹⁶² Mohamed A. Elkersh & Zahid H. Bajwa, *Highlights From the American Academy of Pain Medicine 24th Annual Meeting*, 2(1) Advances in Pain Management 50-52 (2008).

¹⁶³ See Chou, *Clinical Guidelines*, *supra* n.62.

233. In the March 2007 article titled “Impact of Breakthrough Pain on Quality of Life in Patients with Chronic, Noncancer Pain: Patient Perceptions and Effect of Treatment with Oral Transmucosal Fentanyl Citrate,”¹⁶⁴ published in the nationally circulated journal *Pain Medicine*, physicians paid by Cephalon (including Webster) described the results of a Cephalon-sponsored study seeking to expand the definition of BTP to the chronic, non-cancer setting. The authors stated that the “OTFC has been shown to relieve BTP more rapidly than conventional oral, normal-release, or ‘short acting’ opioids” and that “[t]he purpose of [the] study was to provide a qualitative evaluation of the effect of BTP on the [quality of life] of noncancer pain patients.”¹⁶⁵ The number-one-diagnosed cause of chronic pain in the patients studied was back pain (44%), followed by musculoskeletal pain (12%) and head pain (7%). The article cites Portenoy and recommends fentanyl for non-cancer BTP patients:

In summary, BTP appears to be a clinically important condition in patients with ***chronic noncancer pain*** and is associated with an adverse impact on QoL. This qualitative study on the negative impact of BTP ***and the potential benefits of BTP-specific therapy*** suggests several

¹⁶⁴ Donald R. Taylor, *et al.*, *Impact of Breakthrough Pain on Quality of Life in Patients With Chronic, Noncancer Pain: Patient Perceptions and Effect of Treatment With Oral Transmucosal Fentanyl Citrate (OTFC, ACTIQ)*, 8(3) *Pain Med.* 281-88 (Mar. 2007).

¹⁶⁵ *Id.*

domains that may be helpful in developing BTP-specific, QoL assessment tools.¹⁶⁶

234. Cephalon also sponsored, through an educational grant, the regularly published journal *Advances in Pain Management*. In a single 2008 issue of the journal, there are numerous articles from Portenoy, Dr. Steven Passik (“Passik”), Dr. Kenneth L. Kirsh (“Kirsh”) and Webster, all advancing the safety and efficacy of opioids. In an article titled “Screening and Stratification Methods to Minimize Opioid Abuse in Cancer Patients,” Webster expresses disdain for the prior 20 years of opioid phobia.

235. In another article from the same issue, “Appropriate Prescribing of Opioids and Associated Risk Minimization,” Passik and Kirsh state: “[c]hronic pain, currently experienced by approximately 75 million Americans, is becoming one of the biggest public health problems in the US.” They assert that addiction is rare, that “[m]ost pain specialists have prescribed opioids for long periods of time with success demonstrated by an improvement in function” and that then-recent work had shown “that opioids do have efficacy for subsets of patients who can remain on them long term and have very little risk of addiction.”¹⁶⁷

¹⁶⁶ *Id.*

¹⁶⁷ Steven D. Passik & Kenneth L. Kirsh, *Appropriate Prescribing of Opioids and Associated Risk Minimization*, 2(1) *Advances in Pain Management* 9-16 (2008).

236. In November 2010, Fine and others published an article presenting the results of another Cephalon-sponsored study titled “Long-Term Safety and Tolerability of Fentanyl Buccal Tablet for the Treatment of Breakthrough Pain in Opioid-Tolerant Patients with Chronic Pain: An 18-Month Study.”¹⁶⁸ In that article, Fine explained that the 18-month “open-label” study “assessed the safety and tolerability of FBT [Fentora] for the [long-term] treatment of BTP in a large cohort . . . of opioid-tolerant patients receiving around-the-clock . . . opioids for noncancer pain.” The article acknowledges that: (a) “[t]here has been a steady increase in the use of opioids for the management of chronic noncancer pain over the past two decades”; (b) the “widespread acceptance” had led to the publishing of practice guidelines “to provide evidence- and consensus-based recommendations for the optimal use of opioids in the management of chronic pain”; and (c) those guidelines lacked “data assessing the long-term benefits and harms of opioid therapy for chronic pain.”¹⁶⁹

237. They conclude: “[T]he safety and tolerability profile of FBT in this study was generally typical of a potent opioid. The [adverse events] observed were, in most

¹⁶⁸ Perry G. Fine, *et al.*, *Long-Term Safety and Tolerability of Fentanyl Buccal Tablet for the Treatment of Breakthrough Pain in Opioid-Tolerant Patients with Chronic Pain: An 18-Month Study*, 40(5) J. Pain & Symptom Management 747-60 (Nov. 2010).

¹⁶⁹ *Id.*

cases, predictable, manageable, and tolerable.” They also conclude that the number of abuse-related events was “small.”¹⁷⁰

238. From 2000 forward, Cephalon has paid doctors nationwide millions of dollars for programs relating to its opioids, many of whom were not oncologists and did not treat cancer pain. These doctors included Portenoy, Webster, Fine, Passik, Kirsh, Landy and others.

239. Publicly disclosed payments for the years 2013 through 2016 show that Teva made more than \$888,000 in payments to Wayne County physicians and almost \$750,000 to Oakland County physicians. Further, Fentora has been widely prescribed in Wayne County and Oakland County. According to data collected by ProPublica, during 2015, Michigan doctors’ prescriptions to patients insured by the Medicare Part D program totaled more than \$245,012 for Fentora.

240. Cephalon’s payments to doctors have resulted in studies that support its sales but, on closer examination, are biased or irreparably flawed. For instance, and upon information and belief, the governmental whistleblower investigation into Actiq revealed that two studies touted by Cephalon had tested fewer than 28 patients and had no control group whatsoever.¹⁷¹ A 2012 article evaluating the then-current status

¹⁷⁰ *Id.*

¹⁷¹ Carreyrou, *Cephalon Used Improper Tactics*, *supra* n.148.

of transmucosal fentanyl tablet formulations for the treatment of BTP in cancer patients noted that clinical trials to date used varying criteria, that “the approaches taken . . . [did] not uniformly reflect clinical practice” and that “the studies ha[d] been sponsored by the manufacturer and so ha[d] potential for bias.”¹⁷²

f. Cephalon Failed to Report Suspicious Sales as Required

241. The federal CSA imposes on all “registrants” the obligation to design and operate a system to disclose to the registrant suspicious orders of controlled substances and requires the registrant to notify the DEA field division office in its area of any suspicious orders. “Suspicious orders include orders of unusual size, orders deviating substantially from a normal pattern, and orders of unusual frequency.” 21 C.F.R. §1301.74(b).

242. Cephalon is a “registrant” under the federal CSA. 21 C.F.R. §1300.02(b) defines a registrant as any person who is registered with the DEA under 21 U.S.C. §823. Section 823, in turn, requires manufacturers of Schedule II controlled substances to register with the DEA.

¹⁷² Eric Prommer & Brandy Fleck, *Fentanyl transmucosal tablets: current status in the management of cancer-related breakthrough pain*, 2012(6) Patient Preference and Adherence 465-75 (June 25, 2012).

243. Cephalon failed to design and operate a system to disclose suspicious orders of controlled substances and/or failed to notify the appropriate DEA field division of suspicious orders. By way of example, just two months ago, the doctor of a Dearborn-based pill mill was arrested and arraigned on multiple felony charges for overprescribing opioids, including prescribing more than 500,000 opioid pills since January 2017. Five Oakland County residents were also recently arrested for Medicare fraud related to the prescription of unnecessary opioids to patients, some of which ended up sold illegally on the streets. Other doctors practicing in Wayne County or Oakland County and/or prescribing opioids to Wayne County or Oakland County residents, have been similarly arrested and arraigned for writing an egregiously high number of opioid prescriptions. Cephalon's failure to timely report these and other suspicious sales violated the CSA.

5. Insys

244. Insys manufactures, markets, sells and distributes the following pharmaceutical drug in Wayne County, Oakland County and nationwide:

Subsys (fentanyl)	Fentanyl sublingual spray; semi-synthetic opioid agonist, approved in 2012.	Schedule II
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245. Subsys is indicated "for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and are tolerant to opioid

therapy for their underlying persistent cancer pain.”¹⁷³ The indication also specifies that “SUBSYS is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.” In addition, the indication provides that “[p]atients must remain on around-the-clock opioids when taking SUBSYS.” Subsys is contraindicated for, among other ailments, the “[m]anagement of acute or postoperative pain including headache/migraine and dental pain.” It is available in 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg dosage strengths.

246. Insys’ revenue is derived almost entirely from Subsys. According to its Form 10-K for 2015, Insys reported revenues of \$331 million. Of that total, \$329.5 million was derived from sales of Subsys. According to public records, almost 20,000 units of Subsys were prescribed to Wayne County residents and more than 6,400 units of Subsys were prescribed to Oakland County residents from 2014 to 2016, inclusive. According to data collected by ProPublica, during the single year of 2014, Michigan doctors’ prescriptions of Subsys to patients insured by the Medicare Part D program totaled more than \$5.1 million, and in 2015, Subsys Medicare Part D prescriptions

¹⁷³ The indication provides that “[p]atients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid daily for a week or longer.”

totaled more than \$1.5 million. The majority of Insys' sales of Subsys are through wholesalers including: defendants AmerisourceBergen, McKesson and Cardinal Health. In 2015, those wholesalers respectively comprised 20%, 17% and 14% of Insys' total gross sales of Subsys.

247. According to Dr. Andrew Kolodny, executive director of Physicians for Responsible Opioid Prescribing and chief medical officer of the Phoenix House Foundation, fentanyl products are ““the most potent and dangerous opioids on the market.””¹⁷⁴

248. The dangers associated with Subsys are reflected by its extremely limited and specific indication, as it is approved solely for BTP in cancer patients already receiving opioids for persistent cancer-related pain.

249. Despite Subsys' limited indication and the potent danger associated with fentanyl, Insys falsely and misleadingly marketed Subsys to doctors as an effective treatment for back pain, neck pain and other off-label pain conditions.¹⁷⁵ Moreover, as of June 2012, Insys defined BTP in cancer patients to include mild pain: a “flare of

¹⁷⁴ Ex. 91 (Dina Gusovsky, *The pain killer: A drug company putting profits above patients*, CNBC (Nov. 5, 2015, 10:13 AM), <http://www.cnbc.com/2015/11/04/the-deadly-drug-appeal-of-insys-pharmaceuticals.html>).

¹⁷⁵ Ex. 92 (*In the Matter of Insys Therapeutics, Inc.*, Notice of Unlawful Trade Practices and Proposed Resolution (July 10, 2015), <https://www.documentcloud.org/documents/2195731-insysdoj.html>).

mild-to-severe pain in patients with otherwise stable persistent pain,” based on a misleading citation to a paper written by Portenoy.¹⁷⁶ Insys trained and instructed its sales representatives to use the false definition of breakthrough pain and specifically to use a core visual aid, including the improper definition, whenever they detailed Subsys to a healthcare provider or provider’s office.

250. According to a 2014 article in *The New York Times*, only 1% of prescriptions for Subsys were written by oncologists. Approximately half the prescriptions were written by pain specialists, with others written by other specialists including dentists and podiatrists.¹⁷⁷

a. The Indictment of Insys Executives

251. On December 8, 2016, several former Insys executives were arrested and indicted for conspiring to bribe practitioners in numerous states, many of whom operated pain clinics, in order to get them to prescribe Subsys. In exchange for bribes

¹⁷⁶ Portenoy’s paper, “Breakthrough pain: definition, prevalence and characteristics,” which was featured in the 1990 issue of *Pain*, actually defined breakthrough pain as “a transitory increase in pain to greater than moderate intensity (that is, to an intensity of ‘severe’ or ‘excruciating’) . . . on a baseline pain of moderate intensity or less.” Russell K. Portenoy & Neil A. Hagen, *Breakthrough pain: Definition, prevalence and characteristics*, 41(3) *Pain* 273-81 (July 1990).

¹⁷⁷ Ex. 93 (Katie Thomas, *Doubts Raised About Off-Label Use of Subsys, a Strong Painkiller*, N.Y. Times (May 13, 2014), [https://www.nytimes.com/2014/05/14/business/doubts-raised-about-off-label-use-of-subsy...a-strong-painkiller.html?action=click&contentCollection=Business%20Day®ion=Footer&module=MoreInSection&pgtype=Blogs&_r=2](https://www.nytimes.com/2014/05/14/business/doubts-raised-about-off-label-use-of-subsy...)).

and kickbacks, the practitioners wrote large numbers of prescriptions for patients, most of whom were not diagnosed with cancer.¹⁷⁸

252. The indictment alleged that the former executives conspired to mislead and defraud health insurance providers, who were reluctant to approve payment for Subsys when it was prescribed for patients without cancer. In response, the former executives established a “reimbursement unit” at Insys, which was dedicated to assisting physicians by obtaining prior authorization for prescribing Subsys directly from insurers and pharmacy benefit managers. Insys’ reimbursement unit employees were told to inform agents of insurers and pharmacy benefit managers that they were calling “from” or that they were “with” the doctor’s office, or that they were calling “on behalf of” the doctor.

253. The executive defendants in the indictment are Insys’ former CEO and president, former vice president of sales, former national director of sales, former vice president of managed markets and several former regional sales directors. The charges include alleged violations of the federal Anti-Kickback Law, the federal

¹⁷⁸ Ex. 94 (Press Release, U.S. Attorney’s Office for the District of Massachusetts, Pharmaceutical Executives Charged in Racketeering Scheme (Dec. 8, 2016), <https://www.justice.gov/usao-ma/pr/pharmaceutical-executives-charged-racketeering-scheme> (hereinafter “Insys Indictment Press Release”)); Ex. 95 (*United States v. Babich, et al.*, No. 1:16-cr-10343-ADB, Dkt. No. 1 (D. Mass. Dec. 6, 2016), <https://www.justice.gov/usao-ma/press-release/file/916681/download> (hereinafter “Insys Indictment”).)

Racketeer Influenced and Corrupt Organizations (“RICO”) statute and conspiracy to commit wire and mail fraud, as well as allegations of bribery and defrauding insurers.

254. If found guilty, the defendants face possible sentences of up to 20 years for conspiracy to commit RICO and conspiracy to commit mail and wire fraud, as well as a fine of \$250,000 or twice the amount of the pecuniary gain or loss. For the charge of conspiracy to violate the Anti-Kickback Law, the defendants face a sentence of up to five years in prison and a \$25,000 fine.

255. The indictment details a coordinated, centralized scheme by Insys to illegally drive profits. The company defrauded insurers from a call center at corporate headquarters where Insys employees, acting at the direction of Insys’ former CEO and vice president of managed markets, disguised their identity and the location of their employer and lied about patient diagnoses, the type of pain being treated and the patient’s course of treatment with other medication.

b. Insys Targeted Non-Cancer Treating Physicians and Funded False Publications and Presentations

256. Insys targeted and bribed practitioners in a number of ways. Insys bribed Subsys prescribers through strategic hires, employing sales representatives and other employees at practitioners’ behest and with the expectation that such hires would provide inroads with key practitioners. Further, the indictment alleges that Insys

bribed practitioners through a sham speakers' bureau that was purportedly intended to increase brand awareness using peer-to-peer educational lunches and dinners.

257. The indictment alleges that in June 2012, former executives began using in-person meetings, telephone calls and texts to inform Insys sales representatives that the key to sales was using the speakers' bureau to pay practitioners to prescribe Subsys. As one of the company's vice presidents for sales texted one of his sales representatives about potential physicians for the speakers' bureau: "[t]hey do not need to be good speakers, they need to write a lot of [Subsys prescriptions]." The former Insys executives actively recruited physicians known to have questionable prescribing habits for these speakers' bureaus.¹⁷⁹

258. The indictment alleges that speakers' bureaus were often just social gatherings at high-priced restaurants involving neither education nor presentations. Frequently, they involved repeat attendees, including physicians not licensed to prescribe Subsys. Many of the speakers' bureaus had no attendees; sales representatives were instructed to falsely list names of attendees and their signatures on Insys' sign-in sheets.

259. Insys made thousands of payments to physicians nationwide, including to Wayne County and Oakland County physicians, for participating on these speakers'

¹⁷⁹ Insys Indictment Press Release, *supra* n.178.

bureaus and for other services. Based on an analysis of publicly disclosed reports from the years 2013 through 2016, Insys paid Wayne County physicians almost \$32,000 and Oakland County approximately \$17,000 for such services.

260. Moreover, the executives are charged with targeting practitioners who prescribed Subsys not only for cancer pain, but for all pain. One such prescriber, Dr. Gavin Ira Awerbuch (“Awerbuch”), a neurologist based in Saginaw, Michigan, was arraigned in 2014 in the Eastern District of Michigan on charges that he prescribed Subsys outside of legitimate medical indications. According to the complaint against him, Awerbuch was responsible for approximately 20.3% of the Subsys prescribed to Medicare beneficiaries nationwide January 2009 through January 2014. During that time, Insys’ top sales representative, Brett Szymanski, earned up to \$250,000 per quarter covering only Awerbuch. Awerbuch entered into a plea agreement on November 8, 2016.

261. As set forth in the indictment, at one national speakers’ bureau in or about 2014, Insys’ then-vice president of sales stated:

“These [doctors] will tell you all the time, well, I’ve only got like eight patients with cancer. Or, I only have, like, twelve patients that are on a rapid-onset opioids [sic]. Doc, I’m not talking about any of those patients. I don’t want any of those patients. That’s, that’s small potatoes. That’s nothing. That’s not what I’m here doing. I’m here selling [unintelligible] for the breakthrough pain. If I can successfully sell you the [unintelligible] for the breakthrough pain, do you have a thousand people in your practice, a thousand patients, twelve of them are

currently on a rapid-onset opioids [sic]. That leaves me with at least five hundred patients that can go on this drug.”¹⁸⁰

262. The indictment also alleges that, when agents of insurers or pharmacy benefit managers asked if a patient was being treated for BTP in cancer patients, Insys’ reimbursement unit employees were instructed to answer using a written script, sometimes called “the spiel”: “The physician is aware that the medication is intended for the management of breakthrough pain in cancer patients. The physician is treating the patient for their pain (or breakthrough pain, whichever is applicable).”¹⁸¹

263. The indictment alleges that Insys’ former executives also tracked and internally circulated the number of planned and completed speakers’ bureau events for each speaker, as well as the number of Subsys prescriptions each speaker wrote, the percentage of such prescriptions compared to those written for Subsys’ competitor drugs, the total amount of honoraria paid to each speaker and, for a period of time, an explicit calculation of the ratio of return on investment for each speaker. When a speaker did not write an appropriate number of Subsys prescriptions, as determined by Insys, the number of future events for which that speaker would be paid would be reduced unless and until he or she wrote more Subsys prescriptions.

¹⁸⁰ *Insys Indictment, supra* n.178, at 15.

¹⁸¹ *Id.* at 44.

264. In a press release issued when the indictment was announced, the Massachusetts U.S. Attorney, Carmen M. Ortiz, stated: ““I hope that today’s charges send a clear message that we will continue to attack the opioid epidemic from all angles, whether it is corporate greed or street level dealing.””¹⁸²

265. In the same press release, the FBI Special Agent in Charge of the Boston Field Division, Harold H. Shaw, linked the allegations to the national opioid epidemic:

*“As alleged, top executives of Insys Therapeutics, Inc. paid kickbacks and committed fraud to sell a highly potent and addictive opioid that can lead to abuse and life threatening respiratory depression In doing so, they contributed to the growing opioid epidemic and placed profit before patient safety. These indictments reflect the steadfast commitment of the FBI and our law enforcement partners to confront the opioid epidemic impacting our communities, while bringing to justice those who seek to profit from fraud or other criminal acts.”*¹⁸³

266. In the press release, the Special Agent in Charge at the Defense Criminal Investigative Service in the Northeast Field Office, Craig Rupert, focused specifically on the effect the criminal activities had on members of the military: ““Causing the unnecessary use of opioids by current and retired U.S. military service members

¹⁸² Insys Indictment Press Release, *supra* n.178.

¹⁸³ *Id.*

shows disregard for their health and disrespect for their service to our country

.... ,,,¹⁸⁴

c. Insys Failed to Report Suspicious Sales as Required

267. The federal CSA imposes on all “registrants” the obligation to design and operate a system to disclose to the registrant suspicious orders of controlled substances and requires the registrant to notify the DEA field division office in its area of any suspicious orders. “Suspicious orders include orders of unusual size, orders deviating substantially from a normal pattern, and orders of unusual frequency.” 21 C.F.R. §1301.74(b).

268. Insys is a “registrant” under the federal CSA. 21 C.F.R. §1300.02(b) defines a registrant as any person who is registered with the DEA under 21 U.S.C. §823. Section 823, in turn, requires manufacturers of Schedule II controlled substances to register with the DEA.

269. Insys failed to design and operate a system to disclose suspicious orders of controlled substances and/or failed to notify the appropriate DEA field division of suspicious orders. By way of example, just two months ago, the doctor of a Dearborn-based pill mill was arrested and arraigned on multiple felony charges for

¹⁸⁴ *Id.*

overprescribing opioids, including prescribing more than 500,000 opioid pills since January 2017. Five Oakland County residents were also recently arrested for Medicare fraud related to the prescription of unnecessary opioids to patients, some of which ended up sold illegally on the streets. Other doctors practicing in Wayne County or Oakland County and/or prescribing opioids to Wayne County or Oakland County residents, have been similarly arrested and arraigned for writing an egregiously high number of opioid prescriptions. Insys' failure to timely report these and other suspicious sales violated the CSA.

6. Mallinckrodt

270. Mallinckrodt manufactures, markets, sells and distributes pharmaceutical drugs in Wayne County, Oakland County and nationwide. Mallinckrodt is the largest U.S. supplier of opioid pain medications and among the top ten generic pharmaceutical manufacturers in the United States, based on prescriptions.

271. Among the drugs it distributes are the following:

Exalgo (hydromorphone hydrochloride extended release)	Opioid agonist indicated for opioid-tolerant patients for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options (<i>e.g.</i> , non-opioid analgesics) are inadequate. The FDA approved the 8, 12, and 16 mg tablets of Exalgo in March 2010 and 32 mg tablet in August 2012.	Schedule II
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Roxicodone (oxycodone hydrochloride)	Brand-name instant-release form of oxycodone hydrochloride. Indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Acquired from Xanodyne Pharmaceuticals in 2012. Strengths range up to 30 mg per pill. Nicknames include Roxies, blues, and stars.	Schedule II
Xartemis XR (oxycodone hydrochloride and acetaminophen)	The FDA approved Xartemis XR in March 2014 for the management of acute pain severe enough to require opioid treatment and in patients for whom alternative treatment options are ineffective, not tolerated or would otherwise be inadequate. It was the first extended-release oral combination of oxycodone and acetaminophen.	Schedule II
Methadose (methadone hydrochloride)	Branded generic product. Opioid agonist indicated for treatment of opioid addiction.	Schedule II
Morphine sulfate extended release	Generic product.	Schedule II
Fentanyl extended release	Generic product.	Schedule II
Fentanyl citrate	Generic product.	Schedule II
Oxycodone and acetaminophen	Generic product.	Schedule II
Hydrocodone bitartrate and acetaminophen	Generic product.	Schedule II
Hydromorphone hydrochloride	Generic product.	Schedule II
Hydromorphone hydrochloride extended release	Generic product.	Schedule II
Naltrexone hydrochloride	Generic product.	Schedule II

Oxymorphone hydrochloride	Generic product.	Schedule II
Methadone hydrochloride	Generic product.	Schedule II
Oxycodone hydrochloride	Generic product.	Schedule II

272. Mallinckrodt purchased Roxicodone from Xanodyne Pharmaceuticals in 2012.¹⁸⁵

273. Mallinckrodt debuted Xartemis (MNK-795) at the September 4-7, 2013 PAINWeek in Las Vegas.

274. Mallinckrodt's opioids were widely prescribed in Wayne County and Oakland County. For example, according to public records, almost 35,000 units of Roxicodone and Exalgo were prescribed to Wayne County residents and more than 24,500 units of Roxicodone and Exalgo were prescribed to Oakland County residents from 2014 to 2016, inclusive.

a. Mallinckrodt Funded False Publications and Presentations

275. Like several of the other Manufacturing Defendants, Mallinckrodt provided substantial funding to purportedly neutral organizations which disseminated false messaging about opioids.

¹⁸⁵ Ex. 96 (*Mallinckrodt Announces Agreement with Xanodyne to Purchase Roxicodone*, Bus. Wire (Aug. 23, 2012), <http://www.businesswire.com/news/home/20120823005209/en/Mallinckrodt-Announces-Agreement-Xanodyne-Purchase-Roxicodone%C2%AE>).

276. For example, until at least February 2009, Mallinckrodt provided an educational grant to Pain-Topics.org, a now-defunct website that touted itself as “a noncommercial resource for healthcare professionals, providing open access to clinical news, information, research, and education for a better understanding of evidence-based pain-management practices.”¹⁸⁶

277. Among other content, the website included a handout titled “Oxycodone Safety Handout for Patients,” which advised practitioners that: “Patients’ fears of opioid addiction should be dispelled.”¹⁸⁷ The handout included several false and misleading statements concerning the risk of addiction associated with prescription opioids:

Will you become dependent on or addicted to oxycodone?

- After awhile, oxycodone causes physical dependence. That is, if you suddenly stop the medication you may experience uncomfortable withdrawal symptoms, such as diarrhea, body aches, weakness, restlessness, anxiety, loss of appetite, and other ill feelings. These may take several days to develop.
- This is not the same as addiction, a disease involving craving for the drug, loss of control over taking it or compulsive use, and

¹⁸⁶ Ex. 97 (*Pain Treatment Topics*, Pain-Topics.org, <https://web.archive.org/web/20070104235709/http://www.pain-topics.org:80/> (last visited Oct. 10, 2017)).

¹⁸⁷ Ex. 98 (Lee A. Kral & Stewart B. Leavitt, *Oxycodone Safety Handout for Patients*, Pain-Topics.Org (June 2007), <http://paincommunity.org/blog/wp-content/uploads/Oxycodone/Handout.pdf>).

using it despite harm. Addiction to oxycodone in persons without a recent history of alcohol or drug problems is rare.¹⁸⁸

278. Additionally, the FAQ section of Pain-Topics.org contained the following false and misleading information downplaying the dangers of prescription opioid use:

Pseudoaddiction – has been used to describe aberrant patient behaviors that may occur when pain is undertreated (AAPM 2001). Although this diagnosis is not supported by rigorous investigation, it has been widely observed that patients with unrelieved pain may become very focused on obtaining opioid medications, and may be erroneously perceived as “drug seeking.” Pseudoaddiction can be distinguished from true addiction in that the behaviors resolve when the pain is effectively treated. Along with this, two related phenomena have been described in the literature (Alford et al. 2006):

Therapeutic dependence – sometimes patients exhibit what is considered drug-seeking because they fear the reemergence of pain and/or withdrawal symptoms from lack of adequate medication; their ongoing quest for more analgesics is in the hopes of insuring a tolerable level of comfort.

Pseudo-opioid-resistance – other patients, with adequate pain control, may continue to report pain or exaggerate its presence, as if their opioid analgesics are not working, to prevent reductions in their currently effective doses of medication.

Patient anxieties about receiving inadequate pain control can be profound, resulting in demanding or aggressive behaviors that are

¹⁸⁸ *Id.*

misunderstood by healthcare practitioners and ultimately detract from the provision of adequate pain relief.¹⁸⁹

279. Another document available on the website, “Commonsense Oxycodone Prescribing & Safety,” falsely suggests that generic oxycodone is less prone to abuse and diversion than branded oxycodone: “Anecdotally, it has been observed that generic versions of popularly abused opioids usually are less appealing; persons buying drugs for illicit purposes prefer brand names because they are more recognizable and the generics have a lower value ‘on the street,’ which also makes them less alluring for drug dealers.”¹⁹⁰

280. In November 2016, Mallinckrodt paid Dr. Scott Gottlieb (“Gottlieb”), the new commissioner of the FDA, \$22,500 for a speech in London, shortly after the U.S. presidential election.¹⁹¹ Gottlieb has also received money from the Healthcare Distribution Alliance, an industry-funded organization that pushes the agenda of large

¹⁸⁹ Ex. 99 (*FAQs*, Pain-Topics.org,

¹⁹⁰ Ex. 100 (Lee A. Kral, *Commonsense Oxycodone Prescribing & Safety*, Pain-Topics.org (June 2007), <http://paincommunity.org/blog/wp-content/uploads/OxycodoneRxSafety.pdf>).

¹⁹¹ Ex. 101 (Lee Fang, *Donald Trump’s Pick to Oversee Big Pharma Is Addicted to Opioid-Industry Cash*, Intercept (Apr. 4, 2017, 2:15 PM), <https://theintercept.com/2017/04/04/scott-gottlieb-opioid/>).

pharmaceutical wholesalers, and he has often criticized efforts aimed at regulating the pharmaceutical opioid market.¹⁹²

281. Mallinckrodt also made thousands of payments to physicians nationwide, including to Wayne County and Oakland County physicians. Based on an analysis of publicly disclosed reports from the years 2013 through 2016, Mallinckrodt paid more than \$101,000 to Wayne County physicians and almost \$122,000 to Oakland County physicians for consulting, speakers' bureau participation, post-marketing safety surveillance and other services provided to Mallinckrodt.

282. Exalgo, Roxicodone and Xartemis XR have been widely prescribed in Wayne County and Oakland County. According to data collected by ProPublica, during 2015, Michigan doctors' prescriptions of Exalgo to patients insured by the Medicare Part D program totaled almost \$148,000, prescriptions of Roxicodone totaled over \$71,000 and prescriptions of Xartemis XR totaled a little over \$7,000.

b. The DEA Investigates Suspicious Orders

283. In 2008, the DEA and federal prosecutors launched an investigation into Mallinckrodt, charging that the company ignored red flags and supplied – and failed to

¹⁹² *Id.*

report – suspicious orders for its generic oxycodone between 2008 and 2012.¹⁹³ The U.S. Attorney’s office in Detroit, handled the case. The investigation uncovered that from 2008 to 2012, Mallinckrodt sent, for example, 500 million tablets of oxycodone into a single state, Florida – “66 percent of all oxycodone sold in the state.”¹⁹⁴ According to the internal government documents obtained by the Washington Post, Mallinckrodt’s failure to report could have resulted in “nearly 44,000 federal violations and exposed it to \$2.3 billion in fines.”¹⁹⁵

284. Despite learning from the DEA that generic opioids seized in a Tennessee drug operation were traceable to one of its Florida distributors, Sunrise Wholesale (“Sunrise”) of Broward County, Mallinckrodt in the following six weeks sent 2.1 million tablets of oxycodone to Sunrise. In turn, Sunrise sent at least 92,400 oxycodone tablets to a single doctor over an 11-month period, who, in one day, prescribed 1,000 to a single patient.¹⁹⁶

¹⁹³ Ex. 102 (Lenny Bernstein & Scott Higham, *The government’s struggle to hold opioid manufacturers accountable*, Wash. Post (Apr. 2, 2017), https://www.washingtonpost.com/graphics/investigations/dea-mallinckrodt/?utm_term=.7ce8c975dd86).

¹⁹⁴ *Id.*

¹⁹⁵ *Id.*

¹⁹⁶ *Id.*

285. According to documents obtained by the Washington Post, investigators also found “scores of alleged violations” at Mallinckrodt’s plant in Hobart, New York. Those violations included the failure to keep accurate records, to document transfers of drugs and to secure narcotics.¹⁹⁷

286. During the DEA’s investigation, Mallinckrodt sponsored the Healthcare Distribution Alliance (known as the Healthcare Distribution Management Association until 2016), an industry-funded organization that represents pharmaceutical distributors.¹⁹⁸ The HDA initiated the Ensuring Patient Access and Effective Drug Enforcement Act of 2016 (enacted April 19, 2016), which requires the DEA to give notice of violations and an opportunity to comply, to pharmacies and distributors, before withdrawing licenses. This Act substantially lessened the DEA’s ability to regulate manufacturers and wholesalers.¹⁹⁹

¹⁹⁷ *Id.*

¹⁹⁸ Ex. 103 (*Sponsors: HDA’s Annual Circle Sponsors*, Healthcare Distribution Alliance, <https://www.healthcaredistribution.org/hda-sponsors> (last visited Oct. 5, 2017)).

¹⁹⁹ Ex. 104 (Chris McGreal, *Opioid epidemic: ex-DEA official says Congress is protecting drug makers*, *Guardian* (Oct. 31, 2016, 9:26 EDT), <https://www.theguardian.com/us-news/2016/oct/31/opioid-epidemic-dea-official-congress-big-pharma>).

287. In May 2014, Mallinckrodt posted a video titled “Red Flags: Pharmacists Anti-Abuse Video.” The video is a thinly veiled attempt to divert responsibility for the opioid epidemic away from manufacturers and wholesalers, and toward individual pharmacists. The video was sponsored by the Anti-Diversion Industry Working Group, which is composed of Cardinal Health, Actavis, McKesson, Mallinckrodt, AmerisourceBergen, and Qualitest—all of whom are conveniently missing from the list of those responsible.²⁰⁰

288. In April 2017, Mallinckrodt plc reached an agreement with the DEA and the U.S. Attorneys for the Eastern District of Michigan and Northern District of New York to pay \$35 million to resolve a probe of its distribution of its opioid medications.²⁰¹ Mallinckrodt finalized the settlement on July 11, 2017, agreeing to pay \$35 million while admitting no wrongdoing.²⁰²

²⁰⁰ Ex. 105 (Mallinckrodt Pharmaceuticals, *Red Flags: Pharmacists Anti-Abuse Video*, YouTube (May 27, 2014), <https://www.youtube.com/watch?v=fdv0B210bEk&t=1s>).

²⁰¹ Ex. 106 (Linda A. Johnson, *Mallinckrodt to Pay \$35M in Deal to End Feds' Opioid Probe*, U.S. News & World Report (Apr. 3, 2017, 6:47 PM), <https://www.usnews.com/news/business/articles/2017-04-03/mallinckrodt-to-pay-35m-in-deal-to-end-feds-opioid-probe>).

²⁰² Ex. 107 (Press Release, U.S. Department of Justice, Mallinckrodt Agrees to Pay Record \$35 Million Settlement for Failure to Report Suspicious Orders of Pharmaceutical Drugs and for Recordkeeping Violations (July 11, 2017), <https://www.justice.gov/opa/pr/mallinckrodt-agrees-pay-record-35-million-settlement-failure-report-suspicious-orders>).

c. Mallinckrodt Failed to Report Suspicious Sales as Required

289. The federal CSA imposes on all “registrants” the obligation to design and operate a system to disclose to the registrant suspicious orders of controlled substances and requires the registrant to notify the DEA field division office in its area of any suspicious orders. “Suspicious orders include orders of unusual size, orders deviating substantially from a normal pattern, and orders of unusual frequency.” 21 C.F.R. §1301.74(b).

290. Mallinckrodt is a “registrant” under the federal CSA. 21 C.F.R. §1300.02(b) defines a registrant as any person who is registered with the DEA under 21 U.S.C. §823. Section 823, in turn, requires manufacturers of Schedule II controlled substances to register with the DEA.

291. Mallinckrodt failed to design and operate a system to disclose suspicious orders of controlled substances and/or failed to notify the appropriate DEA field division of suspicious orders. By way of example, just two months ago, the doctor of a Dearborn-based pill mill was arrested and arraigned on multiple felony charges for overprescribing opioids, including prescribing more than 500,000 opioid pills since January 2017. Five Oakland County residents were also recently arrested for Medicare fraud related to the prescription of unnecessary opioids to patients, some of which ended up sold illegally on the streets. Other doctors practicing in Wayne

County and Oakland County and/or prescribing opioids to Wayne County and Oakland County residents, have been similarly arrested and arraigned for writing an egregiously high number of opioid prescriptions. Mallinckrodt's failure to timely report these and other suspicious sales violated the CSA.

C. The Wholesaler Defendants Failed to Track and Report Suspicious Sales as Required by Michigan and Federal Law

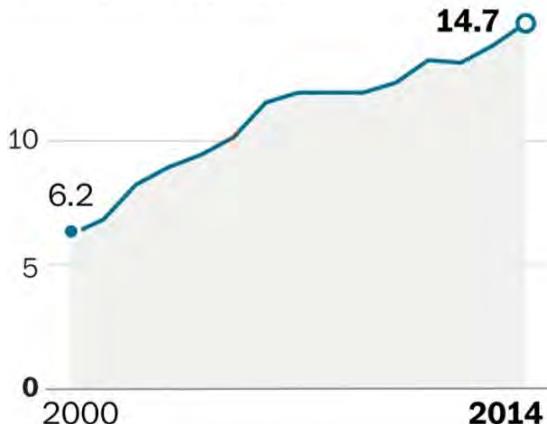
292. Manufacturers rely upon distributors to distribute their drugs. The distributors serve as middlemen, sending billions of doses of opioid pain pills to pharmacists, hospitals, nursing homes and pain clinics. According to the CDC, the increased distribution of opioids directly correlates to increased overdose death rates:

Opioid distribution and overdose death rates rise

Both rates have more than doubled since 2000.

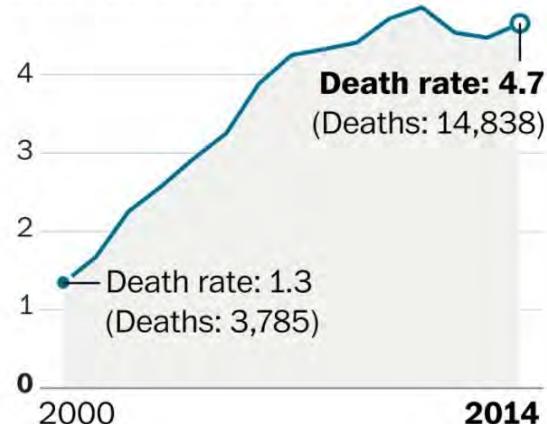
PRESCRIPTION OPIOID DISTRIBUTION RATE

Grams per 100 people



PRESCRIPTION OPIOID OVERDOSE DEATH RATE

Deaths per 100,000 people



Fentanyl overdose deaths are excluded. The CDC removed the drug from the totals because of its growing prevalence as a street drug.

Sources: DEA, Centers for Disease Control and Prevention

THE WASHINGTON POST

1. McKesson

293. McKesson is a wholesale pharmaceutical distributor of controlled and uncontrolled prescription medications, including opioids. It is the largest drug distributor, and the fifth largest company, in the United States. It distributes pharmaceuticals through a network of distribution centers across the country. McKesson ranked fifth on the 2017 Fortune 500 list, with over \$192 billion in revenues.

294. McKesson supplies various United States pharmacies an increasing amount of oxycodone and hydrocodone pills, products frequently misused that are part of the current opioid epidemic. McKesson maintains its corporate pharmacy systems and automation headquarters in Livonia, a city in Wayne County.

295. McKesson is a significant distributor of opioids in the United States and is currently under investigation by Michigan Attorney General Bill Schuette (“Schuette”). The investigation is being handled by Schuette’s Corporate Oversight Division.

296. McKesson distribution centers are required to operate in accordance with the statutory provisions of the CSA. The regulations promulgated under the CSA include a requirement to design and operate a system to detect and report “suspicious orders” for controlled substances, as that term is defined in the regulation. *See* 21 C.F.R. §1301.74(b). The CSA authorizes the imposition of a civil penalty of up to \$10,000 for each violation of 21 C.F.R. §1301.74(b). *See* 21 U.S.C. §842(a)(5) & (c)(1)(B). The provision requiring the reporting of suspicious orders in the federal CSA has been incorporated, via regulation, into Michigan law. Mich. Admin. Code R. 338.493c(i).

297. In or about 2007, the DEA accused McKesson of failing to report suspicious orders and launched an investigation. In 2008, McKesson entered into a

settlement agreement with the DOJ and a memorandum of agreement, agreeing to pay a \$13.25 million fine for failure to report suspicious orders of pharmaceutical drugs and promising to set up a monitoring system.

298. As a result, McKesson developed a Controlled Substance Monitoring Program (“CSMP”) but nevertheless failed to design and implement an effective system to detect and report “suspicious orders” for controlled substances distributed to its independent and small chain pharmacy customers – *i.e.*, orders that are unusual in their frequency, size or other patterns. McKesson continued to fail to detect and disclose suspicious orders of controlled substances. It failed to conduct adequate due diligence of its customers, failed to keep complete and accurate records in the CSMP files maintained for many of its customers and bypassed suspicious order reporting procedures set forth in the CSMP.

299. In 2013, the DEA again began investigating reports that McKesson was failing to maintain proper controls to prevent the diversion of opioids and accused McKesson of failing to design and use an effective system to detect “suspicious orders” from pharmacies for powerful painkillers such as oxycodone, as required by the Controlled Substances Act.

300. On January 17, 2017, in one of the most severe sanctions ever agreed to by a distributor, McKesson agreed to pay a record \$150 million in fines and suspend

sales of controlled substances from distribution centers in four states (Colorado, Ohio, Michigan and Florida) to settle allegations that the company violated federal law. According to the DOJ, McKesson continued to fail to report suspicious orders between 2008 and 2012 and did not fully implement or follow the monitoring program. As part of the agreement, McKesson acknowledged that:

at various times during the Covered Time Period, it did not identify or report to DEA certain orders placed by certain pharmacies, which should have been detected by McKesson as suspicious, in a manner fully consistent with the requirements set forth in the 2008 MOA.

2. Cardinal Health

301. Cardinal Health describes itself as a global integrated healthcare services and products company. It generated \$121.5 billion in total revenue during fiscal year 2016 (ended June 30, 2016). It is ranked 15th on the 2017 Fortune 500 list of top United States companies with revenues of over \$121 billion.

302. Cardinal Health has two operating segments: pharmaceutical and medical. Its pharmaceutical segment, at issue in this action, distributes branded and generic pharmaceutical, special pharmaceutical, over-the-counter and consumer products in the United States. Of Cardinal Health's \$121.5 billion in revenue during fiscal year 2016, \$109.1 billion was derived from the pharmaceutical operating segment.

303. Cardinal Health is a significant distributor of opioids in the United States and is currently under investigation by Michigan Attorney General Schuette. The investigation is being handled by Schuette’s Corporate Oversight Division.

304. Cardinal Health’s largest customer is CVS Health (“CVS”), which accounted for 25% of Cardinal Health’s fiscal year 2016 revenue. According to its website, CVS operates 83 pharmacies in Wayne County and 71 pharmacies in Oakland County.

305. Cardinal Health distribution centers are required to operate in accordance with the statutory provisions of the CSA and the regulations promulgated thereunder, 21 C.F.R. §1300 *et seq.* The regulations promulgated under the CSA include a requirement to design and operate a system to detect and report “suspicious orders” for controlled substances as that term is defined in the regulation. *See* 21 C.F.R. §1301.74(b). The CSA authorizes the imposition of a civil penalty of up to \$10,000 for each violation of 21 C.F.R. §1301.74(b). *See* 21 U.S.C. §842(a)(5) & (c)(1)(B). The provision requiring the reporting of suspicious orders in the federal CSA has been incorporated, via regulation, into Michigan law. Mich. Admin. Code R. 338.493c(i).

306. On December 23, 2016, Cardinal Health agreed to pay the United States \$44 million to resolve allegations that it violated the Controlled Substances Act in

Maryland, Florida and New York by failing to report suspicious orders of controlled substances, including oxycodone, to the DEA.²⁰³

307. In the settlement agreement, Cardinal Health admitted, accepted and acknowledged that it had violated the CSA between January 1, 2009 and May 14, 2012 by failing to:

- “timely identify suspicious orders of controlled substances and inform the DEA of those orders, as required by 21 C.F.R. §1301.74(b);”
- “maintain effective controls against diversion of particular controlled substances into other than legitimate medical, scientific, and industrial channels, as required by 21 C.F.R. §1301.74, including the failure to make records and reports required by the CSA or DEA’s regulations for which a penalty may be imposed under 21 U.S.C. §842(a)(5);” and
- “execute, fill, cancel, correct, file with the DEA, and otherwise handle DEA ‘Form 222’ order forms and their electronic equivalent for Schedule II controlled substances, as required by 21 U.S.C. §828 and 21 C.F.R. Part 1305.”

308. The settlement agreement was announced by the U.S. Attorney for the District of Maryland, Rod J. Rosenstein (“Rosenstein”), and the DEA Special Agent in Charge – Washington Field Division, Karl C. Colder (“Colder”).²⁰⁴

²⁰³ Earlier in 2016, CVS also agreed to pay the United States \$8 million to resolve violations of the CSA by its Maryland pharmacies. According to the settlement agreement, CVS admitted that between 2008 and 2012 certain of its Maryland pharmacies dispensed oxycodone, fentanyl, hydrocodone and other pharmaceuticals in violation of the CSA because the drugs were dispensed without ensuring that the prescriptions were issued for legitimate medical purposes.

²⁰⁴ Ex. 108 (Press Release, U.S. Attorney’s Office for the District of Maryland, Cardinal Health Agrees to \$44 Million Settlement for Alleged Violations of Controlled Substances Act (Dec. 23, 2016), <https://www.justice.gov/usao->

309. In the press release announcing the settlement agreement, Rosenstein stated:

“Pharmaceutical suppliers violate the law when they fill unusually large or frequent orders for controlled substances without notifying the DEA Abuse of pharmaceutical drugs is one of the top federal law enforcement priorities. Cases such as this one, as well as our \$8 million settlement with CVS in February 2016, reflect the federal commitment to prevent the diversion of pharmaceutical drugs for illegal purposes.”²⁰⁵

310. In the press release, Colder clarified that the settlement specifically concerned oxycodone:

“DEA is responsible for ensuring that all controlled substance transactions take place within DEA’s regulatory closed system. All legitimate handlers of controlled substances must maintain strict accounting for all distributions and Cardinal failed to adhere to this policy Oxycodone is a very addictive drug and failure to report suspicious orders of oxycodone is a serious matter. The civil penalty levied against Cardinal should send a strong message that all handlers of controlled substances must perform due diligence to ensure the public safety”²⁰⁶

3. AmerisourceBergen

311. AmerisourceBergen is a wholesale distributor of pharmaceuticals, including controlled substances and non-controlled prescription medications. It handles the distribution of approximately 20% of all pharmaceuticals sold and

md/pr/cardinal-health-agrees-44-million-settlement-alleged-violations-controlled-substances-act).

²⁰⁵ *Id.*

²⁰⁶ *Id.*

distributed in the U.S. through a network of 26 pharmaceutical distribution centers, including one in Williamston, Michigan.²⁰⁷ It ranked 11th on the Fortune 500 list in 2017, with over \$146 billion in annual revenue.

312. AmerisourceBergen is a significant distributor of opioids in the United States and is currently under investigation by Michigan Attorney General Schuette. The investigation is being handled by Schuette's Corporate Oversight Division.

313. AmerisourceBergen distribution centers are required to operate in accordance with the statutory provisions of the CSA and the regulations promulgated thereunder, 21 C.F.R. §1300 *et seq.* The regulations promulgated under the CSA include a requirement to design and operate a system to detect and report “suspicious orders” for controlled substances as that term is defined in the regulation. *See* 21 C.F.R. §1301.74(b). The CSA authorizes the imposition of a civil penalty of up to \$10,000 for each violation of 21 C.F.R. §1301.74(b). *See* 21 U.S.C. §842(a)(5) & (c)(1)(B). The provision requiring the reporting of suspicious orders in the federal CSA has been incorporated, via regulation, into Michigan law. Mich. Admin. Code R. 338.493c(i).

²⁰⁷ Ex. 109 (*AmerisourceBergen*, Wikipedia, <https://en.wikipedia.org/wiki/AmerisourceBergen> (hereinafter “*AmerisourceBergen*”) (last visited Mar. 28, 2017); Ex. 110 (Drug Distribution Locations – Mainland US, <https://batchgeo.com/map/788de3747b01802c0171abfa8a4b5eca>? (last visited Oct. 11, 2017)).

314. In 2012, West Virginia sued AmerisourceBergen and Cardinal Health, as well as several smaller wholesalers, for numerous causes of action, including violations of the CSA, consumer credit and protection, and antitrust laws and the creation of a public nuisance. Unsealed court records from that case demonstrate that AmerisourceBergen, along with McKesson and Cardinal Health, together shipped 423 million pain pills to West Virginia between 2007 and 2012.²⁰⁸ AmerisourceBergen itself shipped 80.3 million hydrocodone pills and 38.4 oxycodone pills during that time period.²⁰⁹ Moreover, public documents also demonstrate that the average dose of each tablet distributed grew substantially during that time period. The Wholesaler Defendants, including AmerisourceBergen, shipped large quantities of oxycodone and hydrocodone tablets to the state. In 2016, AmerisourceBergen agreed to settle the West Virginia lawsuit by paying \$16 million to the state, with the funds set aside to fund drug treatment programs in order to respond to the opioid addiction crisis.

²⁰⁸ Ex. 111 (Eric Eyre, *Drug firms poured 780M painkillers into WV amid rise of overdoses*, Charleston Gazette-Mail (Dec. 17, 2016), <http://www.wvgazettemail.com/news-health/20161217/drug-firms-poured-780m-painkillers-into-wv-amid-rise-of-overdoses>).

²⁰⁹ *AmerisourceBergen, supra* n.207.

FIRST CAUSE OF ACTION

Violation of Michigan Consumer Protection Act Against All Defendants

315. Plaintiffs incorporate herein by reference all of the allegations in the preceding paragraphs.

316. The Michigan Consumer Protection Act (“MCPA”) declares unlawful “[u]nfair, unconscionable, or deceptive methods, acts or practices in the conduct of trade or commerce.” Mich. Comp. Laws §445.903(1). The MCPA defines, among others, the following methods, acts, or practices to be unfair, unconscionable, or deceptive: causing confusion or misunderstanding as to approval or certification of goods; representing that goods have approval, characteristics, uses, and benefits that they do not have; failing to reveal a material fact whose omission tends to mislead or deceive the consumer; making a representation of material fact that misleads a reasonable person; and failing to reveal facts made material in light of positive representations of facts. *Id.*

317. The Manufacturing Defendants and Wholesaler Defendants are each persons within the meaning of Mich. Comp. Laws §445.902(d), and their actions, as set forth herein, occurred in the conduct of trade or commerce, Mich. Comp. Laws §445.902(g).

318. During the relevant period and as detailed further herein, the Manufacturing Defendants have each engaged in unfair and deceptive acts or practices in commerce in violation of the MCPA by actively promoting and marketing the use of opioids for indications not federally approved, circulating false and misleading information concerning opioids' safety and efficacy and downplaying or omitting the risk of addiction arising from their use.

319. Each of the Manufacturing Defendants and Wholesaler Defendants has engaged in unfair and/or deceptive trade practices by omitting the material fact of its failure to design and operate a system to disclose suspicious orders of controlled substances, as well as by failing to actually disclose such suspicious orders, as required of "registrants" by the federal CSA, 21 C.F.R. §1301.74(b), which is incorporated into Michigan law by Mich. Admin. Code R. 338.493c(i). The CSA defines "Registrant" as any person who is registered pursuant to 21 U.S.C. §823. 21 C.F.R. §1300.02(b). Section 823(a)-(b) requires manufacturers and distributors of controlled substances on Schedule II to register.

320. The Manufacturing Defendants' and Wholesaler Defendants' unfair or deceptive acts or practices in violation of the MCPA offend Michigan's public policy, are immoral, unethical, oppressive or unscrupulous, as well as malicious, wanton and manifesting ill will, and caused substantial injury to plaintiffs and their inhabitants.

SECOND CAUSE OF ACTION

Public Nuisance Against All Defendants

321. Plaintiffs incorporate herein by reference all of the allegations in the preceding paragraphs.

322. Defendants, individually and acting through their employees and agents, have unreasonably interfered with a right common to the general public of Wayne County and Oakland County, including by: (a) interfering significantly with the public health, safety, peace, comfort and convenience; (b) engaging in conduct proscribed by statute, ordinance or administrative regulation; and (c) engaging in conduct of a continuing nature that has produced a permanent and long-lasting effect.

323. Each of the Manufacturing Defendants unreasonably interfered with the public health, safety, peace and comfort of Wayne County, Oakland County and their residents by, among other things, promoting and marketing the use of opioids for indications not federally approved, circulating false and misleading information concerning their safety and efficacy and/or downplaying or omitting the risk of addiction arising from their use in violation of the MCPA. In so doing, the Manufacturing Defendants acted unreasonably and with actual malice.

324. Each of the Manufacturing Defendants and Wholesaler Defendants unreasonably interfered with the public health, safety, peace and comfort of Wayne

County, Oakland County and their residents by failing to design and operate a system that would disclose the existence of suspicious orders of controlled substances or by failing to report suspicious orders of opioids as required by the federal CSA, 21 C.F.R. §1301.74(b), and by the State of Michigan, Mich. Admin. Code R. 338.493c(i). In so doing, the Manufacturing Defendants and Wholesaler Defendants acted unreasonably and with actual malice.

325. As detailed herein, defendants' conduct has interfered with and continues to interfere with rights common to the general public of Wayne County and Oakland County and has caused Wayne County and Oakland County to sustain damages special and particular in kind, including, without limitation, increased law enforcement and judicial expenditures, increased prison and public works expenditures, increased substance abuse treatment and diversion plan expenditures, increased emergency and medical care services, the costs of processing and paying for fraudulent prescriptions and lost economic opportunity.

326. Plaintiffs, acting on their own behalf and on behalf of their inhabitants, seeks monetary and injunctive relief to halt the threat of future harm.

THIRD CAUSE OF ACTION

Negligence Against All Defendants

327. Plaintiffs incorporate herein by reference all of the allegations in the preceding paragraphs.

328. Negligence *per se* is established where the defendant violates a statutory duty and where the statute is intended to protect against the result of the violation, the plaintiffs are within the class intended to be protected by the statute and the statutory violation is a proximate cause of the plaintiffs' injury. Negligence is established where the defendant owes the plaintiffs a duty of care, breaches that duty and the plaintiffs sustain an injury or loss proximately caused by the defendant's breach.

329. Each of the Manufacturing Defendants owed plaintiffs, acting on their own behalf and on behalf of their inhabitants, statutory and common-law duties including the duty to comply with the MCPA's prohibition of "[u]nfair, unconscionable, or deceptive methods, acts, or practices in the conduct of trade or commerce"; and the duty to promote and market opioids truthfully and pursuant to their federally approved indications and the duty to disclose the true risk of addiction associated with the use of opioids. Each of the Manufacturing Defendants breached those duties by, among other things, promoting and marketing the use of opioids for indications not federally approved, circulating false and misleading information

concerning their safety and efficacy and downplaying or omitting the risk of addiction arising from their use. In so doing, the Manufacturing Defendants acted with actual malice.

330. Each of the Manufacturing Defendants and Wholesaler Defendants owed plaintiffs, acting on their own behalf and on behalf of their inhabitants, the statutory duty to report suspicious sales, and the duty not to fill suspicious orders, the duty to abide by any government agreements entered regarding the same and the duty to comply with the federal CSA, 21 C.F.R. §1301.74(b), as incorporated by Mich. Admin. Code R. 338.493c(i), which required the design and operation of a system to detect and disclose suspicious orders of controlled substances. Each of the Manufacturing Defendants and Wholesaler Defendants breached these duties by failing to design and operate a system that would disclose the existence of suspicious orders of controlled substances or by failing to report such suspicious orders to the appropriate regulators as required by state and federal law. In so doing, the Manufacturing Defendants and Wholesaler Defendants acted with actual malice.

331. Plaintiffs, acting on their own behalf and on behalf of their inhabitants, suffered both injuries and pecuniary losses proximately caused by the Manufacturing Defendants' and Wholesaler Defendants' breaches. Among other things, Wayne County and Oakland County have experienced an unprecedeted opioid addiction and

overdose epidemic costing millions in health insurance, treatment services, emergency visits, medical care, treatment for related illnesses and accidents, payments for fraudulent prescriptions and lost productivity to Wayne County's and Oakland County's workforces. Defendants' breaches of the statutory and common-law duties they each owed to plaintiffs and their citizens are the proximate cause of this crisis and its resultant harm to plaintiffs and their residents.

FOURTH CAUSE OF ACTION

Unjust Enrichment Against All Defendants

332. Plaintiffs incorporate herein by reference all of the allegations in the preceding paragraphs.

333. Under the doctrine of unjust enrichment, a party who receives a benefit must return the benefit if retention would be inequitable. Unjust enrichment applies if in light of the totality of the circumstances, equity and good conscience demand that the benefitted party return that which was given.

334. Plaintiffs, acting on their own behalf and on behalf of their inhabitants, conferred on each Manufacturing Defendant a benefit, including payments for opioids manufactured by the Manufacturing Defendants for sale in Wayne County and Oakland County, which benefit was known to and accepted by each Manufacturing Defendant, which inured to the profits of each Manufacturing Defendant and for

which retention of such benefit is inequitable based on the Manufacturing Defendants' false and misleading marketing and omissions of and failure to state material facts in connection with marketing opioids, as set forth herein. The Manufacturing Defendants have thus been unjustly enriched by deceptive marketing, contributing to Wayne County's and Oakland County's current opioid epidemic.

335. Plaintiffs, acting on their own behalf and on behalf of their inhabitants, conferred on each Wholesaler Defendant a benefit, including payments for opioids distributed by each Wholesaler Defendant for sale in Wayne County and Oakland County, which benefit was known to and accepted by each Wholesaler Defendant, which inured to the profits of each Wholesaler Defendant and for which retention of such benefit is inequitable based on the Wholesaler Defendants' failure to report suspicious sales as required by law. The Wholesaler Defendants have thus been unjustly enriched by neglecting their duty to distribute drugs only for proper medical purposes, contributing to Wayne County's and Oakland County's current opioid epidemic.

336. Wayne County's and Oakland County's unprecedented opioid addiction and overdose epidemic has cost them millions of dollars in health insurance, treatment services, emergency visits, medical care, treatment for related illnesses and accidents,

payments for fraudulent prescriptions, law enforcement and lost productivity to Wayne County's and Oakland County's workforces.

337. The unjust enrichment of the Manufacturing Defendants and Wholesaler Defendants is directly related to the damage, loss and detriment to Wayne County and Oakland County caused by defendants' false marketing and failure to report suspicious sales. It would be inequitable under these circumstances for the Manufacturing Defendants and Wholesaler Defendants to retain this benefit without compensating plaintiffs for their value. Plaintiffs seek recovery of the amounts the Manufacturing Defendants and Wholesaler Defendants were enriched as a result of their inequitable conduct.

FIFTH CAUSE OF ACTION

Violation of The Racketeer Influenced and Corrupt Organizations Act (18 U.S.C. §1962(c)-(d)) Against Manufacturing Defendants

338. Plaintiffs incorporate by reference each preceding paragraph as though fully set forth herein.

339. Plaintiffs bring this Count on behalf of Wayne County and Oakland County, Michigan against the Manufacturing Defendants.

340. At all relevant times, the Manufacturing Defendants have been "persons" under 18 U.S.C. §1961(3) because they are capable of holding, and do hold, a "legal or beneficial interest in property."

341. RICO makes it “unlawful for any person employed by or associated with any enterprise engaged in, or the activities of which affect, interstate or foreign commerce, to conduct or participate, directly or indirectly, in the conduct of such enterprise’s affairs through a pattern of racketeering activity.” 18 U.S.C. §1962(c).

342. RICO, among other provisions, makes it unlawful for “any person to conspire to violate” the provisions of 18 U.S.C. §1962(c). 18 U.S.C. §1962(d).

343. As alleged herein, at all relevant times, the Manufacturing Defendants moved aggressively to capture a large portion of the opioid sales market. In so doing, the Manufacturing Defendants launched an aggressive nationwide campaign over-emphasizing the under-treatment of pain and deceptively marketing opioids as being: (i) rarely, if ever, addictive; (ii) safe and effective for the treatment of chronic long-term pain; (iii) abuse resistant or deterrent; or (iv) safe and effective for other types of pain for which the drugs were not approved. In particular, the Manufacturing Defendants, along with other entities and individuals, were employed by or associated with, and conducted or participated in the affairs of, one or several RICO enterprises (the “Opioid Fraud Enterprise”), whose purpose was to deceive opioid prescribers and the public into believing that Opioids were safe and effective for the treatment of long-term chronic pain, and presented minimal risk of addiction. In doing so, they sought to maximize revenues from the design, manufacture, distribution and sale of

opioids which, in fact, were highly addictive and often ineffective and dangerous when used for long term, chronic and other types of pain. As a direct and proximate result of their fraudulent scheme and common course of conduct, defendants were able to extract revenues of billions of dollars. As explained in detail below, the Manufacturing Defendants' years-long misconduct violated 18 U.S.C. §1962(c) and (d).

(a) The Opioid Marketing Fraud Enterprise

344. At all relevant times, the Manufacturing Defendants, along with other individuals and entities, including unknown third parties involved in the marketing and sale of opioids, operated an “enterprise” within the meaning of 18 U.S.C. §1961(4) because they are a group of individuals associated in fact, even though they are not a collective legal entity. The opioid marketing fraud enterprise: (a) had an existence separate and distinct from each of its component entities; (b) was separate and distinct from the pattern of racketeering in which the Manufacturing Defendants engaged; and (c) was an ongoing organization consisting of legal entities, including, but not limited to, the Manufacturing Defendants, employees and agents of the FSMB, APF, AAPM, APS, as well as other entities and individuals, including physicians.

345. Within the opioid marketing fraud enterprise, there was a common communication network by which members exchanged information on a regular basis

through the use of wires and mail. The opioid marketing fraud enterprise used this common communication network for the purpose of deceptively marketing and selling opioids to the general public. When their products were contested by other parties, the enterprise members took action to hide the scheme to continue its existence.

346. The participants in the opioid marketing fraud enterprise were systematically linked to each other through corporate ties, contractual relationships, financial ties and continuing coordination of activities. Through the enterprise, the Manufacturing Defendants functioned as a continuing unit with the purpose of furthering the illegal scheme and their common purposes of increasing their revenues and market share, and minimizing losses. Each member of the opioid marketing fraud enterprise shared in the bounty generated by the enterprise by sharing the benefit derived from increased sales of opioids and other revenue generated by the scheme to defraud prescribers and consumers in Wayne County and Oakland County.

347. The opioid marketing fraud enterprise engaged in and continues to engage in the deceptive marketing of opioids as non-addictive, as safe and effective for chronic long-term pain and for uses which have not been FDA-approved. The enterprise has engaged in such activity for the purpose of maximizing the sale and profits of opioids. To fulfill this purpose, the enterprise has advocated for and caused the over-prescription of opioids by marketing, promoting, advertising and selling

opioids throughout the country and across state boundaries. Their receipt of monies from such activities consequentially affected interstate and foreign commerce. The enterprise's past and ongoing practices thus constitute a pattern of racketeering activity under 18 U.S.C. §1961(5).

348. The opioid marketing fraud enterprise functioned by marketing and selling opioids to states, counties, other municipalities, doctors, healthcare organizations and the consuming public. Many of these opioid products are legitimate, including opioids used short-term for acute surgical and end-stage cancer pain. However, the Manufacturing Defendants as co-conspirators, through their illegal enterprise, engaged in a pattern of racketeering activity, which involves a fraudulent scheme to increase revenue for the Manufacturing Defendants and the other entities and individuals associated-in-fact with the enterprise's activities through the deceptive marketing and sale of opioids.

349. The Manufacturing Defendants participated in the operation and management of the opioid marketing fraud enterprise by directing its affairs, as described herein. While the Manufacturing Defendants participated in, and are members of the enterprise, they have a separate existence from the enterprise, including distinct legal statuses, different offices and roles, bank accounts, officers,

directors, employees, individual personhood, reporting requirements and financial statements.

350. As detailed above, each of the Manufacturing Defendants relentlessly promoted opioids as having little to no risk of addiction, as being safe and effective for the treatment of long-term chronic pain and/or other uses for which the drugs were not approved. The Manufacturing Defendants' success in maximizing sales was due to the tight collaboration among the Manufacturing Defendants through and in collaboration with the pain foundations – a formidable partnership that marketed to hundreds of thousands of prescribers across the country, including prescribers in Wayne County and Oakland County. The relationship was strengthened, in part, by individuals including physicians that held different leadership roles at different times across the various entities participating in the enterprise over the years.

351. On numerous occasions, the Manufacturing Defendants funded the pain foundations' marketing efforts. The Manufacturing Defendants specifically chose to partner with the pain foundations and individual physicians to publish and otherwise disseminate misleading pro-opioid material, knowing the public and prescribers would be more receptive to statements made by what they perceived to be scholarly, neutral, third party sources.

352. The members of the opioid marketing fraud enterprise worked together to further the enterprise, by and among the following manner and means:

- (a) jointly planning to deceptively market and manufacture opioids that were purportedly non-addictive, safe and effective for the treatment of chronic, long-term pain;
- (b) concealing the addictive qualities of the opioids from prescribers and the public;
- (c) misleading the public about the addictive quality and safety and efficacy of opioids;
- (d) otherwise misrepresenting or concealing the highly dangerous nature of opioids from prescribers and the public;
- (e) illegally marketing, selling and/or distributing opioids;
- (f) collecting revenues and profits from the sale of such products for uses for which they are unapproved, unsafe or ineffective; and
- (g) failing to report suspicious sales as required by the Controlled Substances Act.

353. To achieve their common goals, the Manufacturing Defendants hid from the general public the full extent of the unsafe and ineffective nature of opioids for chronic pain as described herein. The Manufacturing Defendants suppressed and/or

ignored warnings from third parties, whistleblowers and governmental entities about the addictive, unsafe and often ineffective nature of opioids.

354. The foregoing allegations support that the Manufacturing Defendants were part of an association of entities that shared a common purpose, had relationships across the various members of the enterprise and collaborated to further the goals of the enterprise for a continuous period of time. The Manufacturing Defendants knowingly and intentionally engaged in deceptive marketing practices, and incentivized pain foundations, marketing firms and physicians to do so as well.

(b) Mail and Wire Fraud

355. To carry out and attempt to carry out the scheme to defraud, the Manufacturing Defendants, each of whom is a person associated in fact with the enterprise, did knowingly conduct and participate, directly and indirectly, in the conduct of the affairs of the enterprise through a pattern of racketeering activity within the meaning of 18 U.S.C. §§1961(1), 1961(5) and 1962(c), and which employed the use of the mail and wire facilities, in violation of 18 U.S.C. §§1341 (mail fraud) and 1343 (wire fraud).

356. Specifically, the Manufacturing Defendants have committed, conspired to commit and/or aided and abetted in the commission of, at least two predicate acts of racketeering activity (*i.e.*, violations of 18 U.S.C. §§1341 and 1343), within the past

four years. The multiple acts of racketeering activity which the Manufacturing Defendants committed or aided and abetted in the commission of, were related to each other, and also posed a threat of continued racketeering activity. They therefore constitute a “pattern of racketeering activity.” The racketeering activity was made possible by the Manufacturing Defendants’ regular use of the facilities, services, distribution channels and employees of the enterprise. The Manufacturing Defendants participated in the scheme to defraud by using mail, telephone and the Internet to transmit mailings and wires in interstate or foreign commerce.

357. In devising and executing the illegal scheme, the Manufacturing Defendants devised and knowingly carried out a material scheme and/or artifice to defraud regulators, prescribers and the public to obtain money from plaintiffs by means of materially false or fraudulent pretenses, representations, promises or omissions of material facts. For the purpose of executing the illegal scheme, the Manufacturing Defendants committed these racketeering acts intentionally and knowingly with the specific intent to advance the illegal scheme.

358. The Manufacturing Defendants’ predicate acts of racketeering, 18 U.S.C. §1961(1) include, but are not limited to:

(a) Mail Fraud: The Manufacturing Defendants violated 18 U.S.C. §1341 by sending and receiving, and by causing to be sent and/or received, materials

via U.S. Mail or commercial interstate carriers for the purpose of executing the unlawful scheme to deceptively market, and sell the opioids by means of false pretenses, misrepresentations, promises and omissions; and

(b) Wire Fraud: The Manufacturing Defendants violated 18 U.S.C. §1343 by transmitting and/or receiving, and by causing to be transmitted and/or received, materials by wire for the purpose of executing the unlawful scheme to defraud and obtain money on false pretenses, misrepresentations, promises and omissions.

359. The Manufacturing Defendants' use of the mails and wires include, but are not limited to, the transmission, delivery and shipment of deceptive marketing materials by the Manufacturing Defendants and other members of the opioid marketing fraud enterprise. These materials would not have been delivered but for the Manufacturing Defendants' illegal scheme, including, but not limited to:

- (a) the FSMB's publication of opioid prescribing guidelines entitled "Responsible Opioid Prescribing," by Fishman;
- (b) the FSMB's publication of "Revised and Expanded 2nd Edition [of] Responsible Opioid Prescribing[:] A Guide for Michigan Clinicians";
- (c) the APF's publication of "Exit Wounds: A Survival Guide to Pain Management for Returning Veterans & Their Families";

- (d) the AAPM's "consensus statement" and educational programs featuring Fine;
- (e) false or misleading communications to the public and to regulators;
- (f) sales and marketing materials, including slide decks, presentation materials, purported guidelines, advertising, web sites, product packaging, brochures, labeling and other writings which misrepresented, falsely promoted and concealed the true nature of opioids;
- (g) documents intended to facilitate the manufacture and sale of opioids, including bills of lading, invoices, shipping records, reports and correspondence;
- (h) documents to process and receive payment for opioids, including invoices and receipts;
- (i) payments to the foundations and physicians that deceptively marketed the Manufacturing Defendants' opioids;
- (j) deposits of proceeds; and
- (k) other documents and things, including electronic communications.

360. The Manufacturing Defendants also used the Internet and other electronic facilities to carry out the scheme and conceal the ongoing fraudulent activities. Specifically, the Manufacturing Defendants made misrepresentations about opioids on

their websites, YouTube and through online ads, all of which intended to mislead prescribers and the public about the safety, efficacy and non-addictiveness of opioids.

361. The Manufacturing Defendants also communicated by U.S. Mail, by interstate facsimile and by interstate electronic mail with various other affiliates, regional offices, divisions, distributors and other third party entities in furtherance of the scheme. The mail and wire transmissions described herein were made in furtherance of the Manufacturing Defendants' scheme and common course of conduct to deceive prescribers and consumers and lure consumers into purchasing opioids, which the Manufacturing Defendants knew or recklessly disregarded as being unsafe and ineffective for chronic long-term pain and addictive. The Manufacturing Defendants utilized mail and wire transmissions to create an extensive campaign that advertised the exact opposite message: that opioids were safe and effective and rarely if ever addictive.

362. Many of the precise dates of the fraudulent uses of the U.S. Mail and interstate wire facilities are concealed from plaintiffs, and cannot be alleged without access to the Manufacturing Defendants' books and records. However, plaintiffs have described the types of predicate acts of mail and/or wire fraud that occurred. The secretive nature of the enterprise's activities made its marketing tactics even more deceptive and harmful.

363. The foregoing allegations support that the Manufacturing Defendants engaged in a pattern of racketeering activity by repeatedly engaging in wire and mail fraud to deceptively market their products through the use of both print and electronic outlets.

(c) Conspiracy Allegations

364. The Manufacturing Defendants have not undertaken the practices described herein in isolation, but as part of a common scheme and conspiracy. In violation of 18 U.S.C. §1962(d), the Manufacturing Defendants conspired to violate 18 U.S.C. §1962(c), as described herein.

365. The Manufacturing Defendants conspired to incentivize and encourage various other persons, firms and corporations, including third party entities and individuals not named as defendants in this Complaint, to carry out offenses and other acts in furtherance of the conspiracy. The Manufacturing Defendants conspired to increase or maintain revenues, increase market share and/or minimize losses for the Manufacturing Defendants and their other collaborators throughout the illegal scheme and common course of conduct. In order to achieve this goal, the Manufacturing Defendants engaged in the aforementioned predicate acts on numerous occasions. The Manufacturing Defendants, with knowledge and intent, agreed to the overall objectives of the conspiracy and participated in the common course of conduct to

commit acts of fraud and indecency in defectively marketing and/or selling opioids through the use of mail and wire fraud.

366. Indeed, for the conspiracy to succeed, each of the Manufacturing Defendants had to agree to deceptively market and/or sell opioids. The unanimity of the Manufacturing Defendants' marketing tactics gave their misleading statements credence to prescribers and consumers.

367. The Manufacturing Defendants knew and intended that government regulators, prescribers and consumers including Wayne County and Oakland County, would rely on the collective material misrepresentations and omissions made by them and the other enterprise members about opioids. The Manufacturing Defendants knew and intended that consumers, including Wayne County, would incur costs as a result.

368. The Manufacturing Defendants knew that by partnering with the pain foundations and individual physicians who carried a more neutral public image, they would be able to attribute more scientific credibility to their products, thereby increasing their sales and profits.

369. The foregoing illustrates the Manufacturing Defendants' liability under 18 U.S.C. §1962(d) to engage in their pattern of racketeering conspired to achieve their common goal of maximizing opioid sales.

(d) Effect on Plaintiffs

370. As described herein, the Manufacturing Defendants engaged in a pattern of related and continuous predicate acts for years. The predicate acts constituted a variety of unlawful activities, each conducted with the common purpose of obtaining significant monies and revenues from consumers, including Wayne County and Oakland County, based on their misrepresentations and omissions. The predicate acts also had the same or similar results, participants, victims and methods of commission. The predicate acts were related and not isolated events. The predicate acts all had the purpose of generating significant revenue and profits for the Manufacturing Defendants at the expense of Wayne County, Oakland County and their residents. The predicate acts were committed or caused to be committed by the Manufacturing Defendants through their participation in the enterprise and in furtherance of their fraudulent scheme, and were interrelated in that they involved obtaining Wayne County's, Oakland County's and their residents' funds.

371. As fully alleged herein, plaintiffs, along with scores of other counties and municipalities, relied upon representations and omissions that were made or caused by the Manufacturing Defendants. Plaintiffs' reliance is evidenced by the fact that they purchased opioids which never should have been introduced into the U.S. stream

of commerce and whose use has now caused a nationwide epidemic of addiction and overdose.

372. Plaintiffs' injuries, and those of other consumers, were proximately caused by the Manufacturing Defendants' racketeering activity. But for the Manufacturing Defendants' misstatements and omissions and their scheme employed by the opioids marketing fraud enterprise, consumers would not have paid for opioid prescriptions for chronic pain. Though the Manufacturing Defendants' misstatements were largely directed toward opioid prescribers, plaintiffs were directly injured by the Manufacturing Defendants' conduct because they caused the over-prescription of opioids and thus the over-purchase and over-consumption of opioids as well.

373. By reason of, and as a result of the conduct of the Manufacturing Defendants, and in particular, their pattern of racketeering activity, Wayne County, Oakland County and their residents have been injured financially in multiple ways, including, but not limited to, suffering increased expenditures for emergency and medical care services, substance abuse treatment and diversion plans, the processing and payment of fraudulent prescriptions, law enforcement, judicial proceedings and prisons.

374. The Manufacturing Defendants' violations of 18 U.S.C. §1962(c) and (d) have directly and proximately caused injuries and damages to plaintiffs and their

residents, and plaintiffs are entitled to bring this action for three times its actual damages, as well as injunctive/equitable relief, costs and reasonable attorneys' fees pursuant to 18 U.S.C. §1964(c).

PRAYER FOR RELIEF

WHEREFORE, plaintiffs, acting on behalf of themselves and on behalf of their inhabitants, prays that the Court grant the following relief:

- A. Enjoin the Manufacturing Defendants from violating the MCPA by making any further false or misleading statements or omissions related to opioids;
- B. Enjoin the Wholesaler Defendants from failing to report suspicious orders as required by the federal CSA, as incorporated by Mich. Admin. Code R. 338.493c(i);
- C. Order defendants to pay costs, losses and damages for injuries sustained by plaintiffs, acting on their own behalf and on behalf of their inhabitants, as a proximate result of the Manufacturing Defendants' and Wholesaler Defendants' unlawful conduct as set forth herein, including restitution, civil penalties, disgorgement of unjust enrichment, exemplary damages, punitive damages and attorneys' fees; and
- D. Grant any such further relief as this Court deems appropriate.

JURY DEMAND

Plaintiffs demand trial by jury.

DATED: October 12, 2017

THE MILLER LAW FIRM, P.C.

/s/ E. Powell Miller

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UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF MICHIGAN

COUNTY OF WAYNE and COUNTY) Civ. No.
OF OAKLAND,) COMPLAINT FOR (1) VIOLATION
Plaintiffs,) OF MICHIGAN CONSUMER
vs.) PROTECTION ACT; (2) PUBLIC
PURDUE PHARMA L.P.,) NUISANCE; (3) NEGLIGENCE; (4)
CEPHALON, INC., TEVA) UNJUST ENRICHMENT; AND (5)
PHARMACEUTICAL INDUSTRIES) VIOLATION OF THE RACKETEER
LTD., TEVA PHARMACEUTICALS) INFLUENCED AND CORRUPT
USA, INC., ENDO INTERNATIONAL) ORGANIZATION ACT
PLC, JANSSEN) DEMAND FOR JURY TRIAL
PHARMACEUTICALS, INC., INSYS)
THERAPEUTICS, INC.,)
MALLINCKRODT PLC,)
MALLINCKRODT
PHARMACEUTICALS,
AMERISOURCEBERGEN
CORPORATION, CARDINAL
HEALTH, INC. and McKESSON
CORPORATION,
Defendants.

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Prescription Drug and Opioid Abuse Task Force releases findings and recommendations

Group chaired by Lt. Gov. Brian Calley makes more than two dozen recommendations for change

Monday, October 26, 2015

DETROIT – Gov. Rick Snyder today announced that the Michigan Prescription Drug and Opioid Abuse Task Force has presented him with a comprehensive report of their findings and more than two dozen recommendations for changes in regulations and practices that could address a growing problem in Michigan.

The governor formed the task force in mid-June and appointed Lt. Gov. Brian Calley as the chair with the direction to examine the recent trends, evaluate strategic options, and develop a statewide action plan by fall 2015.

“The impact of prescription drug and opioid abuse is being felt in every community across Michigan. It crosses all demographic, geographic and political lines,” Snyder said. “This problem is something we must work together to address as soon as possible and I appreciate the dedication of Lt. Gov. Calley and the task force in working on this issue and presenting their findings in such a short time frame.”

Pain killers are powerful opioids that are highly addictive and opioid dependence affects millions of people in the United States. Prescribed opioids can lead to the use of highly addictive and dangerous illegal substances, especially heroin. Michigan ranks 10th nationally in per capita prescription rates of opioid pain relievers and 18th in the nation for all overdose deaths.

Task force members varied greatly in their professional backgrounds to provide a solid cross-section of input. They represented the Executive Office, the state Legislature, state departments, law enforcement, prosecutors, mental health commissions, pharmacists, doctors, hospitals and insurance companies.

The task force also held a public hearing and subcommittees gathered input from experts involved with the growing problem of prescription drug and opioid abuse in Michigan and across the country. Attorney General Bill Schuette and Michigan Department of Health and Human Services Director Nick Lyon served as subcommittee chairs.

The full report makes 25 primary recommendations and seven contingent recommendations in the areas of prevention, treatment, regulation, policy and outcomes, and enforcement. Highlights of the recommendations include:

- Updating or replacing the Michigan Automated Prescription System.

- Requiring registration and use of MAPS by those who are prescribing and dispensing prescription drugs.
- Updating regulations on the licensing of pain clinics, which hasn't been done since 1978.
- Increasing licensing sanctions for health professionals who violate proper prescribing and dispensing practices.
- Providing easier access to Naloxone, a drug that reduces the effects of an opioid overdose.
- Limiting criminal penalties for low-level offenses for those who seek medical assistance with an overdose.
- Increasing access to care through wraparound services and Medication Assisted Treatment programs.
- Requiring additional training for professionals who prescribe controlled substances.
- Reviewing successful drug takeback programs for possible replication and expansion.
- Increasing the number of addiction specialists practicing in Michigan.
- Reviewing programs to eliminate doctor and pharmacy shopping and requiring a bona-fide doctor-patient relationship for prescribing controlled substances.
- Creating a public awareness campaign about the dangers of prescription drug use and abuse and how people can get help for themselves or family members.
- Increasing training for law enforcement in recognizing and dealing with addiction for those officers who do not deal directly with narcotics regularly.
- Considering pilot programs for the development of testing to reduce the increasing incidence of Neonatal Abstinence Syndrome, which leads to severe withdrawal symptoms for babies born to mothers who have been using opioids.

"We clearly have a lot to address but one of the goals of the task force was to present recommendations that we knew were achievable," Calley said. "By working with our partners in the state Legislature and the medical community, I am certain we can achieve the recommendations presented. I want to thank Gov. Snyder for his leadership in calling for this review of current laws and practices and his commitment to protecting the people of Michigan."

###

Related Documents

[Prescription Drug and Opioid Abuse Task Force's recommendations](#) 

[\[Hand out\] Recommendations of the Michigan Prescription Drug and Opioid Abuse Task Force](#) 

[\[Infographic\] Michigan's growing drug and opioid abuse problem by the numbers](#) 

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Michigan Prescription Drug and Opioid Abuse Commission

Pursuant to Executive Order 2016-15, the Michigan Prescription Drug and Opioid Abuse Commission. The Commission will review the Report of Findings and Recommendations for Action from the Michigan Prescription Drug and Opioid Abuse Task Force and develop and propose policies and an action plan to implement the recommendation from the report.

The Commission will consist of the following 17 members: one allopathic doctor (MD), one osteopathic doctor (DO), one dentist, one veterinarian, one physician's assistant, one registered professional nurse, one pharmacist, two law enforcement officers, one psychologist, one representative from a Michigan hospice organization, one chronic pain sufferer, one representative from a Michigan medical school, one representative from a statewide pharmacy association, one representative of a pharmaceutical manufacturers, one substance abuse treatment provider, and one member representing the general public.

Statute**Executive Order 2016-15****Contact Information****LARA – Bureau of Professional Licensing**

Phone: (517) 373-8068

FAX: (517) 241-2389

Web: www.michigan.gov/bplEmail: BPL-BoardSupport@michigan.gov**Members****Dr. Stephen Bell, Carleton**

Osteopathic Doctors

Term ends: 9/1/18

Dr. Vincent Benivegna, Okemos

Dentists

Term ends: 9/1/18

Dr. Rebecca Cunningham, Ann Arbor

Allopathic Doctors

Term ends: 9/1/18

Richard Detloff, Rockford

Pharmaceutical Manufacturers

Term ends: 9/1/18

Lisa Gigliotti, East Lansing

Chronic Pain Sufferers

Term ends: 9/1/18

Timothy Hurtt, Portage

Law Enforcement Officers

Term ends: 9/1/18

Dr. Stephen Lazar, Marshall

Psychologists

Term ends: 9/1/18

Paula Nelson, Riley

Substance Abuse Treatment Providers

Term ends: 9/1/18

Dr. Melissa Owings, Clarklake

Veterinarians

Term ends: 9/1/18

Dr. Michael Paletta, Northville

Michigan Hospice Organizations

Term ends: 9/1/18

Dr. Gretchen Schumacher, Belmont

Registered Professional Nurses

Term ends: 9/1/18

Mary Sclabassi, Novi

Law Enforcement Officers

Term ends: 9/1/18

Patrick Shannon, Mackinac Island

General Public

Term ends: 9/1/18

Dr. Roy Soto, Bloomfield Hills

Michigan Medical Schools

Term ends: 9/1/18

Larry Wagenknecht, Haslett

Statewide Pharmacy Associations

Term ends: 9/1/18

Dr. Laurie Wesolowicz, Northville

Pharmacists

Term ends: 9/1/18

Adam Wilson, Petoskey

Physician's Assistants

Term ends: 9/1/18

Ex-Officio Members:

Judge Linda Davis - Chair

Designee of the Director of Licensing and Regulatory Affairs

Dr. Debra Pinals

Designee of the Director of Health and Human Services

Col. W. Thomas Sands

Designee of the Director of Michigan State Police

Matthew Schneider, Chief Deputy Attorney General
Michelle Brya, AAG & Division Chief, Licensing & Regulation
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EXHIBIT 3



Increases in Drug and Opioid-Involved Overdose Deaths – United States, 2010–2015

Weekly / December 30, 2016 / 65(50-51);1445–1452

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- Reddit (2) (https://www.altmetric.com/details.php?domain=www.cdc.gov&citation_id=14800964&tab=reddit)
- Mendeley (280)

Metric Details

On December 16, 2016, this report was posted online as an MMWR Early Release.

Please note: An erratum has been published for this report. To view the erratum, please click [here](#).

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affiliations)

View suggested citation

Summary

What is already known about this topic?

The U.S. opioid epidemic is continuing. Drug overdose deaths nearly tripled during 1999–2014. In 2014, among 47,055 drug overdose deaths, 61% involved an opioid. During 2013–2014, deaths associated with the most commonly prescribed opioids (natural/semisynthetic opioids) continued to increase slightly; however, the rapid increase in deaths appears to be driven by heroin and synthetic opioids other than methadone.

What is added by this report?

From 2014 to 2015, the death rate from synthetic opioids other than methadone, which includes fentanyl, increased by 72.2%, and heroin death rates increased by 20.6%. Rates of death involving heroin and synthetic opioids other than methadone increased across all demographic groups, regions, and in numerous states. Natural/semisynthetic opioid death rates increased by 2.6%, whereas, methadone death rates decreased by 9.1%.

What are the implications for public health practice?

There is an urgent need for a multifaceted, collaborative public health and law enforcement approach to the opioid epidemic, including implementing the CDC *Guideline for Prescribing Opioids for Chronic Pain*; improving access to and use of prescription drug monitoring programs; expanding naloxone distribution; enhancing opioid use disorder treatment capacity and linkage into treatment, including medication-assisted treatment; implementing harm reduction approaches, such as syringe services program; and supporting law enforcement strategies to reduce the illicit opioid supply.

The U.S. opioid epidemic is continuing, and drug overdose deaths nearly tripled during 1999–2014. Among 47,055 drug overdose deaths that occurred in 2014 in the United States, 28,647 (60.9%) involved an opioid (1). Illicit opioids are contributing to the increase in opioid overdose deaths (2,3). In an effort to target prevention strategies to address the rapidly changing epidemic, CDC examined overall drug overdose death rates during 2010–2015 and opioid overdose death rates during 2014–2015 by subcategories (natural/semisynthetic opioids, methadone, heroin, and synthetic opioids other than methadone).* Rates were stratified by demographics, region, and by 28 states with high quality reporting on death certificates of specific drugs involved in overdose deaths. During 2015, drug overdoses accounted for 52,404 U.S. deaths, including 33,091 (63.1%) that involved an opioid.

There has been progress in preventing methadone deaths, and death rates declined by 9.1%. However, rates of deaths involving other opioids, specifically heroin and synthetic opioids other than methadone (likely driven primarily by illicitly manufactured fentanyl) (2,3), increased sharply overall and across many states. A multifaceted, collaborative public health and law enforcement approach is urgently needed. Response efforts include implementing the CDC *Guideline for Prescribing Opioids for Chronic Pain* (4), improving access to and use of prescription drug monitoring programs, enhancing naloxone distribution and other harm reduction approaches, increasing opioid use disorder treatment capacity, improving linkage into treatment, and supporting law enforcement strategies to reduce the illicit opioid supply.

The National Vital Statistics System multiple cause-of-death mortality files were used to record drug overdose deaths.[†] Drug overdose deaths were identified using the *International Classification of Disease, Tenth Revision* (ICD-10), based on the ICD-10 underlying cause-of-death codes X40–44 (unintentional), X60–64 (suicide), X85 (homicide), or Y10–Y14 (undetermined intent). Among deaths with drug overdose as the underlying cause, the type of opioid is indicated by the following ICD-10 multiple cause-of-death codes: opioids (T40.0, T40.1, T40.2, T40.3, T40.4, or T40.6); natural/semisynthetic opioids (T40.2); methadone (T40.3); synthetic opioids other than methadone (T40.4); and heroin (T40.1). Some deaths involved more than one type of opioid; these deaths were included in the rates for each subcategory. Therefore, categories of deaths presented are not mutually exclusive.[§]

Changes in drug overdose death rates were analyzed for all 50 states and the District of Columbia (DC) from 2010 to 2015 using joinpoint regression.[¶] Opioid overdose death rates were examined for the period 2014–2015 by subcategories (natural/semisynthetic opioids, methadone, heroin, and synthetic opioids other than methadone) and by demographics, region, and across states. State-level analyses were conducted for 28 states meeting the following criteria: 1) >80% of drug overdose death certificates named at least one specific drug in 2014; 2) change from 2014 to 2015 in the percentage of death certificates reporting at least one specific drug was <10 percentage points**; and 3) ≥20 deaths occurred during 2014 and 2015 in at least two opioid subcategories examined. Analyses comparing changes in age-adjusted death rates from 2014 to 2015 used z-tests when deaths were ≥100 and nonoverlapping confidence intervals based on a gamma distribution when deaths were <100.^{††}

The drug overdose death rate increased significantly from 12.3 per 100,000 population in 2010 to 16.3 in 2015. Death rates increased in 30 states and DC and remained stable in 19 states ([Figure](#)). Two states had changing trends during this period of decreasing rates followed by increases.^{§§} During 2015, a total of 52,404 persons in the United States died from a drug overdose, an increase from 47,055 in 2014; among these deaths, 33,091 (63.1%) involved an opioid, an increase from 28,647 in 2014. The age-adjusted opioid-involved death rate increased by 15.6%, from 9.0 per

100,000 in 2014 to 10.4 in 2015, driven largely by increases in deaths involving heroin and synthetic opioids other than methadone. Death rates for natural/semisynthetic opioids, heroin, and synthetic opioids other than methadone increased by 2.6%, 20.6%, and 72.2%, respectively ([Table 1](#)) ([Table 2](#)). Methadone death rates decreased by 9.1% (Table 1).

During 2014–2015, rates of natural/semisynthetic opioid deaths increased among males overall, both sexes aged 25–44 years, and non-Hispanic whites. Methadone death rates decreased among males and females overall, but increased among persons aged ≥65 years (Table 1). Death rates involving heroin and synthetic opioids other than methadone increased in both males and females, persons aged ≥15 years, and all racial/ethnic populations; however, heroin death rates among males aged 15–24 years remained stable. In 2015, death rates involving synthetic opioids other than methadone were highest among males aged 25–44 years (8.9 per 100,000), increasing 102.3% from 2014 to 2015 (Table 2). Heroin death rates also were highest in this demographic group (13.2), increasing 22.2% from 2014 to 2015. Natural/semisynthetic opioid death rates increased in the Northeast and South U.S. Census regions, and methadone death rates decreased in the South (Table 1). Death rates involving synthetic opioids other than methadone and heroin increased in all regions from 2014 to 2015 (Table 2).

Among the 28 states meeting inclusion criteria for state-level analyses, 16 (57.1%) experienced increases in death rates involving synthetic opioids other than methadone, and 11 (39.3%) experienced increases in heroin death rates from 2014 to 2015. The largest absolute rate change in deaths from synthetic opioids other than methadone occurred in Massachusetts, New Hampshire, Ohio, Rhode Island and West Virginia. The largest percentage increases in rates occurred in New York (135.7%), Connecticut (125.9%) and Illinois (120%) (Table 2). Connecticut, Massachusetts, Ohio, and West Virginia experienced the largest absolute rate changes in heroin deaths, while the largest percentage increases in rates occurred in South Carolina (57.1%), North Carolina (46.4%), and Tennessee (43.5) (Table 2). Three states (New Mexico, Oklahoma, and Virginia) experienced decreases in natural/semi-synthetic opioid death rates, while increases occurred in five states (Massachusetts, New York, North Carolina, Ohio, and Tennessee) (Table 1).

Discussion

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During 2010–2015, the rate of drug overdose deaths in the United States increased in 30 states and DC, remained stable in 19 states, and showed decreasing trends followed by increases in two states.^{§§,¶¶} From 2014 to 2015, drug overdose deaths increased by 5,349 (11.4%), signifying a continuing trend observed since 1999 (1). Opioid death rates increased by 15.6% from 2014 to 2015. These significant increases in death rates were driven by synthetic opioids other than methadone (72.2%), most likely illicitly-manufactured fentanyl (2,3), and heroin (20.6%). Increases

in these opioid subcategories occurred overall and across all demographics and regions. Natural/semisynthetic opioid death rates increased by 2.6%, whereas methadone death rates decreased by 9.1%.

These findings are consistent with recent reports highlighting the increasing trend in deaths involving heroin and synthetic opioids other than methadone (1–3,5). The number of deaths involving synthetic opioids other than methadone have been associated with the number of drug products obtained by law enforcement testing positive for fentanyl, but not with fentanyl prescribing rates (2,3). A recent report found that these increases, likely attributable to illicitly manufactured fentanyl, were concentrated in eight of 27 states examined (2).

The decline in methadone death rates, a trend observed since 2008, followed efforts to reduce methadone use for pain, including Food and Drug Administration warnings, limits on high dose formulations, and clinical guidelines (6). The small increase in natural/semisynthetic opioid death rates illustrates an ongoing problem with prescription opioids; however, the increase has slowed from 2013–2014, potentially because of policy and health system changes, required prescription drug monitoring program review, legislative changes in naloxone distribution, and prescribing guidelines (7,8).***

The findings in this report are subject to at least five limitations. First, factors related to death investigation might affect rate estimates involving specific drugs. At autopsy, the substances tested for, and circumstances under which tests are performed to determine which drugs are present, might vary by jurisdiction and over time. Second, the percentage of deaths with specific drugs identified on the death certificate varies by jurisdiction and over time. Nationally, 19% (in 2014) and 17% (in 2015) of drug overdose death certificates did not include the specific types of drugs involved. Additionally, the percentage of drug overdose deaths with specific drugs identified on the death certificate varies widely by state, ranging from 47.4% to 99%. Variations in reporting across states prevent comparison of rates between states. Third, improvements in testing and reporting of specific drugs might have contributed to some observed increases in opioid-involved death rates. Fourth, because heroin and morphine are metabolized similarly (9), some heroin deaths might have been misclassified as morphine deaths, resulting in underreporting of heroin deaths. Finally, the state-specific analyses of opioid deaths are restricted to 28 states, limiting generalizability.

The ongoing epidemic of opioid deaths requires intense attention and action. In a November 2016 report, the Drug Enforcement Administration referred to prescription drugs, heroin, and fentanyl as the most significant drug-related threats to the United States.††† The misuse of prescription opioids is intertwined with that of illicit opioids; data have demonstrated that nonmedical use of prescription opioids is a significant risk factor for heroin use (10), underscoring the need for continued prevention efforts around prescription opioids. Intensifying efforts to distribute naloxone (an antidote to reverse an opioid overdose), enhancing access to treatment, including

medication-assisted treatment, and implementing harm reduction services are urgently needed. It is important to focus efforts on expanding opioid disorder treatment capacity, including medication-assisted treatment and improving linkage into treatment.^{sss} Implementing harm reduction approaches, such as the scaling up comprehensive syringe services programs can reach persons with opioid use disorders and provide them with access to naloxone and medication-assisted treatment, reduce transmission risk for human immunodeficiency virus or hepatitis C, and reduce other harms from drug use. Law enforcement strategies to reduce the illicit opioid supply must also be supported. A recent report did not find evidence that efforts to reduce opioid prescribing were leading to heroin overdoses; rather, such policies could help reduce the number of persons who are exposed to opioids (⁷). Continued improvements in guideline-recommended opioid prescribing practices for chronic pain (⁴), increased improving access to and use of prescription drug monitoring programs, and increased utilization of nonopioid pain treatments are needed. A multifaceted, coordinated approach between public health and public safety is also necessary to address the U.S. opioid epidemic.

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* Natural opioids include morphine and codeine, and semisynthetic opioids include drugs such as oxycodone, hydrocodone, hydromorphone, and oxymorphone. Methadone is a synthetic opioid. Synthetic opioids, other than methadone, include drugs such as tramadol and fentanyl. Heroin is an illicit opioid synthesized from morphine that can be a white or brown powder, or a black sticky substance.

[†]https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm

(https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm).

[§] For example, a death involving both a synthetic opioid other than methadone and heroin would be included in both the “synthetic other than methadone” and heroin death rates.

[¶] For all analyses, a p-value of <0.05 was considered to be statistically significant.

<https://surveillance.cancer.gov/joinpoint/> (<https://surveillance.cancer.gov/joinpoint/>) .

^{**} States whose reporting of any specific drug or drugs involved in an overdose changed by ≥10 percentage points from 2014 to 2015 were excluded, because drug-specific overdose numbers and rates might change substantially from 2014 to 2015 because of changes in reporting.

†† Age-adjusted death rates were calculated by applying age-specific death rates to the 2000 U.S. Census standard population age distribution

https://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_04.pdf

(https://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_04.pdf). For z-tests, a p-value of <0.05 was considered to be statistically significant.

§§ Florida and South Carolina, had both decreasing and increasing trends during this period. In Florida, rates decreased from 2010 to 2013, then increased to 2015; in South Carolina, rates decreased from 2010 to 2012, then increased to 2015.

¶¶¶ <https://www.cdc.gov/drugoverdose/data/statedeaths.html>

(<https://www.cdc.gov/drugoverdose/data/statedeaths.html>).

*** Some state examples are available. New Mexico:

<https://nmhealth.org/news/information/2016/6/?view=429>

(<https://nmhealth.org/news/information/2016/6/?view=429>) ;

<https://nmhealth.org/news/information/2016/9/?view=484>

(<https://nmhealth.org/news/information/2016/9/?view=484>) ; and

<http://hscnews.unm.edu/news/education-program-successful-in-reducing-opioid-abuse010715>

(<http://hscnews.unm.edu/news/education-program-successful-in-reducing-opioid-abuse010715>) ; Oklahoma:

https://www.ok.gov/health2/documents/UP_Oklahoma_Office_Based_Guidelines.pdf

(https://www.ok.gov/health2/documents/UP_Oklahoma_Office_Based_Guidelines.pdf) ; Oregon:

<http://www.orpdmp.com> (<http://www.orpdmp.com>) . Washington:

<https://ajph.aphapublications.org/doi/abs/10.2105/AJPH.2014.302367?journalCode=ajph>

(<https://ajph.aphapublications.org/doi/abs/10.2105/AJPH.2014.302367?journalCode=ajph>) .

††† <https://www.dea.gov/resource-center/2016%20NDTA%20Summary.pdf>

(<https://www.dea.gov/resource-center/2016%20NDTA%20Summary.pdf>) .

§§§ http://aspe.hhs.gov/sites/default/files/pdf/107956/ib_OpioidInitiative.pdf

(http://aspe.hhs.gov/sites/default/files/pdf/107956/ib_OpioidInitiative.pdf) .

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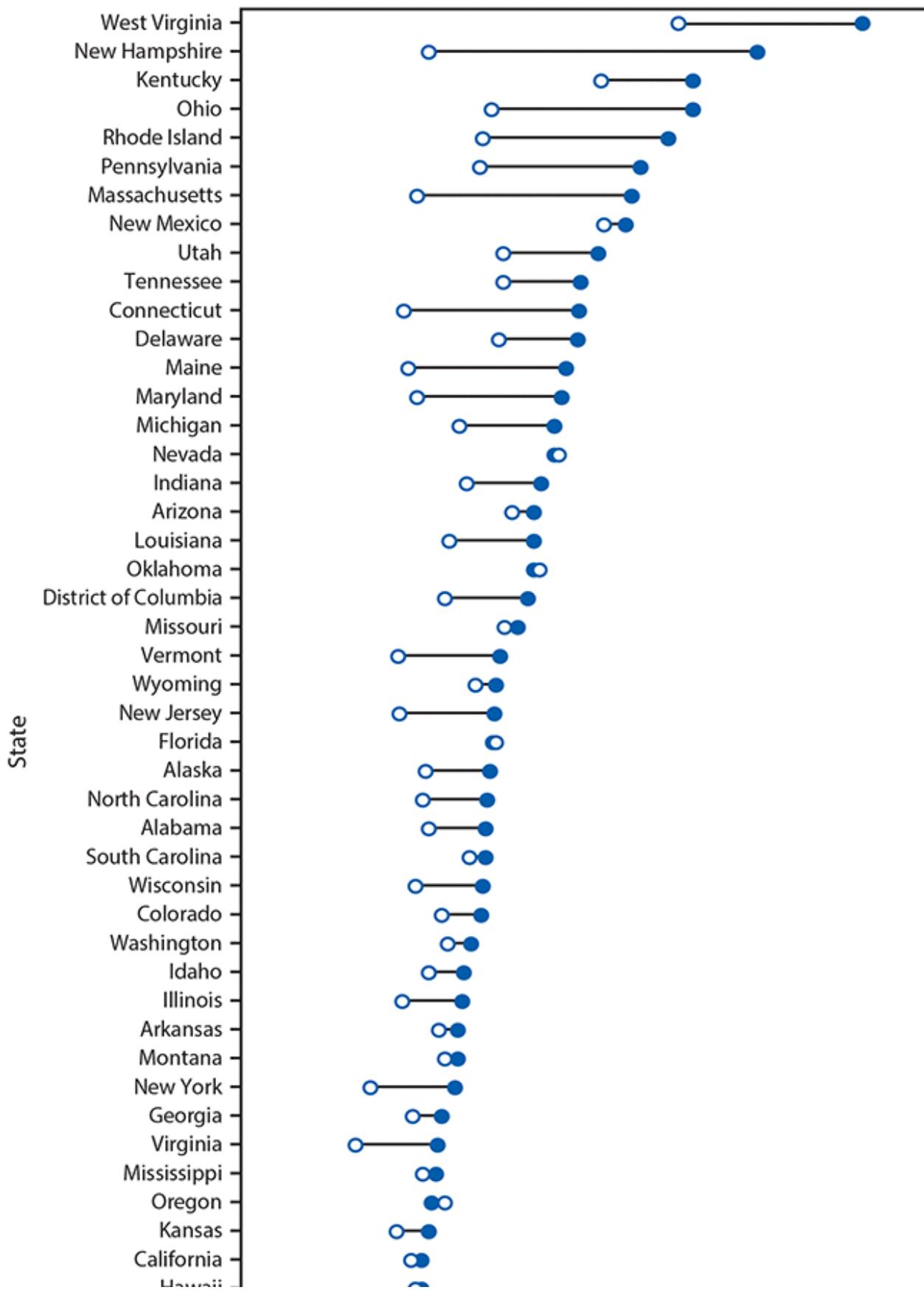
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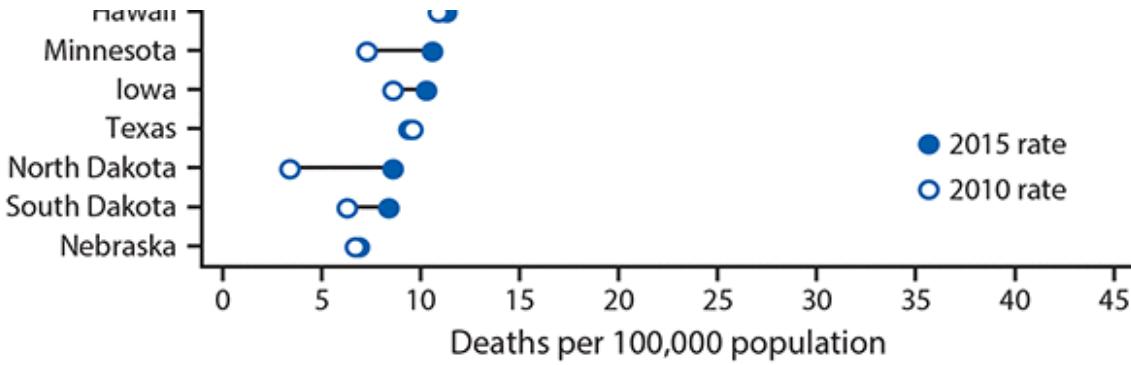
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FIGURE. Age-adjusted rate* of drug overdose deaths,[†] by state – 2010 and 2015[§]

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Source: CDC. National Vital Statistics System, Mortality. CDC WONDER. Atlanta, GA: US Department of Health and Human Services, CDC; 2016. <https://wonder.cdc.gov/> (<https://wonder.cdc.gov/>).

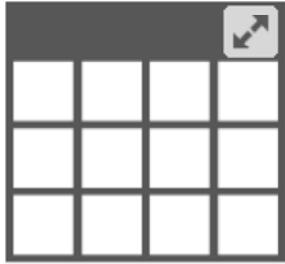
* Rates shown are the number of deaths per 100,000 population. Age-adjusted death rates were calculated by applying age-specific death rates to the 2000 U.S standard population age distribution.

† Deaths were classified using the *International Classification of Diseases, Tenth Revision* (ICD-10). Drug overdose deaths were identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14.

§ Joinpoint regression examining changes in trends from 2010 to 2015 indicated that 30 states had significant increases from 2010 to 2015 (Alabama, Arizona, Connecticut, Delaware, District of Columbia, Georgia, Idaho, Illinois, Indiana, Iowa, Kansas, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Pennsylvania, Rhode Island, Tennessee, Utah, Vermont, Virginia, Wisconsin). In two states, Florida and South Carolina, decreases were followed by increases during this period. In Florida, there was a decrease from 2010 to 2013, followed by an increase to 2015. In South Carolina, there was a decrease from 2010 to 2012, followed by an increase to 2015. All remaining states had nonsignificant trends during this period.

TABLE 1. Number and age-adjusted rate of drug overdose deaths* involving natural and semisynthetic opioids† and methadone,§,¶ by sex, age group, race/ethnicity, U.S. Census region, and selected states†† — United States, 2014 and 2015**

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Characteristic	Natural and semisynthetic opioids			Methadone		
	2014	2015	% change in rate, 2014 to 2015	2014	2015	% change in rate, 2014 to 2015
	No. (Rate)	No. (Rate)		No. (Rate)	No. (Rate)	
Overall	12,159 (3.8)	12,727 (3.9)	2.6 ^{§§}	3,400 (1.1)	3,301 (1.0)	-9.1 ^{§§}
Sex						
Male	6,732 (4.2)	7,117 (4.4)	4.8 ^{§§}	2,009 (1.3)	1,939 (1.2)	-7.7 ^{§§}
Female	5,427 (3.3)	5,610 (3.4)	3.0	1,391 (0.9)	1,362 (0.8)	-11.1 ^{§§}
Age group (yrs)						
0–14	42 (0.1)	48 (0.1)	0.0	14 -11	13 -11	-11
15–24	726 (1.7)	715 (1.6)	-5.9	241 (0.5)	201 (0.5)	0.0
25–34	2,115 (4.9)	2,327 (5.3)	8.2 ^{§§}	796 (1.8)	735 (1.7)	-5.6
35–44	2,644 (6.5)	2,819 (6.9)	6.2 ^{§§}	768 (1.9)	739 (1.8)	-5.3
45–54	3,488 (8.0)	3,479 (8.1)	1.3	854 (2.0)	843 (2.0)	0.0
55–64	2,437 (6.1)	2,602 (6.4)	4.9	629 (1.6)	642 (1.6)	0.0

Characteristic	Natural and semisynthetic opioids			Methadone		
	2014	2015	% change in rate, 2014 to 2015	2014	2015	% change in rate, 2014 to 2015
	No. (Rate)	No. (Rate)		No. (Rate)	No. (Rate)	
≥65	706 (1.5)	736 (1.5)	0.0	98 (0.2)	127 (0.3)	50.0 ^{§§}
Sex/Age group (yrs)						
Male						
15–24	529 (2.3)	493 (2.2)	-4.3	173 (0.8)	149 (0.7)	-12.5
25–44	2,869 (6.8)	3,139 (7.4)	8.8 ^{§§}	969 (2.3)	926 (2.2)	-4.3
45–64	3,015 (7.4)	3,095 (7.5)	1.4	808 (2.0)	777 (1.9)	-5.0
Female						
15–24	197 (0.9)	222 (1.0)	11.1	68 (0.3)	52 (0.2)	-33.3
25–44	1,890 (4.5)	2,007 (4.8)	6.7 ^{§§}	595 (1.4)	548 (1.3)	-7.1
45–64	2,910 (6.8)	2,986 (6.9)	1.5	675 (1.6)	708 (1.6)	0.0
Race/Ethnicity**						
White, non-Hispanic	10,308 (5.0)	10,774 (5.3)	6.0 ^{§§}	2,845 (1.4)	2,725 (1.4)	0.0
Black, non-Hispanic	814 (2.0)	878 (2.1)	5.0	256 (0.6)	247 (0.6)	0.0
Hispanic	727 (1.4)	780 (1.5)	7.1	228 (0.5)	235 (0.5)	0.0
U.S. Census region of residence						

Characteristic	Natural and semisynthetic opioids			Methadone		
	2014	2015	% change in rate, 2014 to 2015	2014	2015	% change in rate, 2014 to 2015
	No. (Rate)	No. (Rate)		No. (Rate)	No. (Rate)	
Northeast	1,851 (3.3)	2,095 (3.6)	9.1 ^{§§}	587 (1.0)	643 (1.1)	10.0
Midwest	2,205 (3.3)	2,302 (3.4)	3.0	675 (1.0)	673 (1.0)	0.0
South	5,101 (4.2)	5,374 (4.4)	4.8 ^{§§}	1,298 (1.1)	1,228 (1.0)	-9.1 ^{§§}
West	3,002 (3.9)	2,956 (3.8)	-2.6	840 (1.1)	757 (1.0)	-9.1
Selected states^{††}						
States with very good or excellent reporting (n = 21)						
Alaska	40 (5.6)	51 (6.5)	16.1	12 -11	10 -11	-11
Connecticut	157 (4.3)	183 (4.8)	11.6	50 (1.4)	72 (1.9)	35.7
Iowa	81 (2.7)	75 (2.5)	-7.4	16 -11	24 (0.8)	-11
Maine	80 (6.1)	102 (7.7)	26.2	29 (2.2)	36 (2.8)	27.3
Maryland	388 (6.2)	398 (6.5)	4.8	153 (2.4)	182 (2.9)	20.8
Massachusetts	178 (2.6)	225 (3.3)	26.9 ^{§§}	88 (1.3)	82 (1.2)	-7.7
Nevada	224 (7.4)	259 (8.6)	16.2	64 (2.2)	57 (1.9)	-13.6
New Hampshire	81 (5.8)	63 (4.4)	-24.1	29 (2.3)	25 (1.9)	-17.4
New Mexico	223 (10.9)	160 (8.1)	-25.7 ^{§§}	45 (2.3)	33 (1.6)	-30.4

Characteristic	Natural and semisynthetic opioids			Methadone		
	2014	2015	% change in rate, 2014 to 2015	2014	2015	% change in rate, 2014 to 2015
	No. (Rate)	No. (Rate)		No. (Rate)	No. (Rate)	
New York	608 (3.0)	705 (3.4)	13.3 ^{§§}	231 (1.1)	246 (1.2)	9.1
North Carolina	462 (4.7)	554 (5.5)	17.0 ^{§§}	131 (1.4)	108 (1.1)	-21.4
Oklahoma	370 (9.6)	277 (7.2)	-25.0 ^{§§}	67 (1.7)	62 (1.7)	0.0
Oregon	137 (3.2)	150 (3.6)	12.5	59 (1.4)	70 (1.7)	21.4
Rhode Island	70 (6.7)	95 (8.3)	23.9	24 (2.2)	30 (2.4)	9.1
South Carolina	319 (6.5)	322 (6.5)	0.0	77 (1.6)	57 (1.2)	-25.0
Utah	367 (13.6)	357 (12.7)	-6.6	47 (1.7)	45 (1.6)	-5.9
Vermont	21 (3.4)	25 (3.9)	14.7	- ^{¶¶}	- ^{¶¶}	- ^{¶¶}
Virginia	323 (3.9)	276 (3.3)	-15.4 ^{§§}	105 (1.2)	67 (0.8)	-33.3 ^{§§}
Washington	288 (3.8)	261 (3.5)	-7.9	115 (1.5)	111 (1.4)	-6.7
West Virginia	363 (20.2)	356 (19.8)	-2.0	35 (2.0)	29 (1.7)	-15.0
Wisconsin	279 (4.8)	249 (4.3)	-10.4	78 (1.4)	73 (1.3)	-7.1
States with good reporting (n = 7)						
Colorado	259 (4.6)	259 (4.5)	-2.2	51 (0.9)	34 (0.6)	-33.3

Characteristic	Natural and semisynthetic opioids			Methadone		
	2014	2015	% change in rate, 2014 to 2015	2014	2015	% change in rate, 2014 to 2015
	No. (Rate)	No. (Rate)		No. (Rate)	No. (Rate)	
Georgia	388 (3.8)	435 (4.2)	10.5	124 (1.2)	115 (1.1)	-8.3
Illinois	253 (1.9)	271 (2.0)	5.3	106 (0.9)	99 (0.8)	-11.1
Minnesota	102 (1.9)	125 (2.2)	15.8	81 (1.6)	55 (1.0)	-37.5
Missouri	237 (4.0)	237 (3.9)	-2.5	53 (0.9)	62 (1.0)	11.1
Ohio	618 (5.4)	690 (6.1)	13.0 ^{§§}	107 (0.9)	109 (1.0)	11.1
Tennessee	554 (8.6)	643 (9.7)	12.8 ^{§§}	71 (1.1)	67 (1.0)	-9.1

Source: CDC. National Vital Statistics System, Mortality. CDC WONDER. Atlanta, GA: US Department of Health and Human Services, CDC; 2016. <https://wonder.cdc.gov/> (<https://wonder.cdc.gov/>).

* Rates are for the number of deaths per 100,000 population. Age-adjusted death rates were calculated using the direct method and the 2000 standard population. Deaths were classified using the *International Classification of Diseases, Tenth Revision*(ICD-10). Drug overdose deaths were identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14.

† Drug overdose deaths, as defined, that have natural and semisynthetic opioids (T40.2) as contributing causes.

‡ Drug overdose deaths, as defined, that have methadone (T40.3) as a contributing cause.

¶ Categories of deaths are not exclusive because deaths might involve more than one drug. Summing categories will result in a number greater than the total number of deaths in a year.

** Data for Hispanic ethnicity should be interpreted with caution; studies comparing Hispanic ethnicity on death certificates and on census surveys have shown inconsistent reporting.

†† Analyses were limited to states meeting the following criteria. For states with very good to excellent reporting, ≥90% of drug overdose death certificates mention at least one specific drug in 2014, with the change in percentage of drug overdose deaths mentioning at least one specific drug

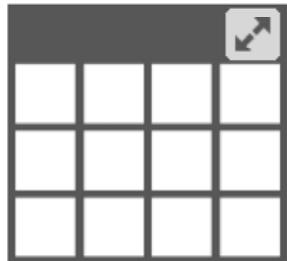
differing by <10 percentage points from 2014 to 2015. States with good reporting had 80% to <90% of drug overdose death certificates mention at least one specific drug in 2014, with the change in the percentage of drug overdose deaths mentioning at least one specific drug differing by <10 percentage points from 2014 to 2015. Rate comparisons between states should not be made because of variations in reporting across states.

^{§§} Statistically significant at p<0.05 level. Gamma tests were used if the number of deaths was <100 in 2014 or 2015, and z-tests were used if the number of deaths was ≥100 in both 2014 and 2015.

^{¶¶} Cells with nine or fewer deaths are not reported, and rates based on <20 deaths are not considered reliable and not reported.

TABLE 2. Number and age-adjusted rate of drug overdose deaths* involving synthetic opioids other than methadone[†] and heroin,^{§,¶} by sex, age group, race/ethnicity, U.S. Census region, and selected states^{††} — United States, 2014 and 2015**

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Characteristic	Synthetic opioids other than methadone			Heroin		
	2014	2015	% change in rate, 2014 to 2015	2014	2015	% change in rate, 2014 to 2015
	No. (Rate)	No. (Rate)		No. (Rate)	No. (Rate)	
Overall	5,544 (1.8)	9,580 (3.1)	72.2 ^{§§}	10,574 (3.4)	12,989 (4.1)	20.6 ^{§§}
Sex						
Male	3,465 (2.2)	6,560 (4.2)	90.9 ^{§§}	8,160 (5.2)	9,881 (6.3)	21.2 ^{§§}
Female	2,079 (1.3)	3,020 (1.9)	46.2 ^{§§}	2,414 (1.6)	3,108 (2.0)	25.0 ^{§§}
Age group (yrs)						
0–14	10 – ^{¶¶}	14 – ^{¶¶}	– ^{¶¶}	– ^{¶¶} – ^{¶¶}	– ^{¶¶} – ^{¶¶}	– ^{¶¶}

Characteristic	Synthetic opioids other than methadone			Heroin		
	2014	2015	% change in rate, 2014 to 2015	2014	2015	% change in rate, 2014 to 2015
	No. (Rate)	No. (Rate)		No. (Rate)	No. (Rate)	
15–24	514 (1.2)	999 (2.3)	91.7 ^{§§}	1452 (3.3)	1,649 (3.8)	15.2 ^{§§}
25–34	1474 (3.4)	2,896 (6.6)	94.1 ^{§§}	3493 (8.0)	4,292 (9.7)	21.3 ^{§§}
35–44	1264 (3.1)	2,289 (5.6)	80.6 ^{§§}	2398 (5.9)	3,012 (7.4)	25.4 ^{§§}
45–54	1359 (3.1)	1,982 (4.6)	48.4 ^{§§}	2030 (4.7)	2,439 (5.6)	19.1 ^{§§}
55–64	742 (1.9)	1,167 (2.9)	52.6 ^{§§}	1064 (2.7)	1,407 (3.4)	25.9 ^{§§}
≥65	181 (0.4)	232 (0.5)	25.0 ^{§§}	136 (0.3)	184 (0.4)	33.3 ^{§§}
Sex/Age group (yrs)						
Male						
15–24	376 (1.7)	718 (3.2)	88.2 ^{§§}	1,079 (4.8)	1,172 (5.2)	8.3
25–44	1,845 (4.4)	3,764 (8.9)	102.3 ^{§§}	4,566 (10.8)	5,602 (13.2)	22.2 ^{§§}
45–64	1,176 (2.9)	1,948 (4.7)	65.5 ^{§§}	2,397 (5.9)	2,953 (7.2)	22.0 ^{§§}
Female						
15–24	138 (0.6)	281 (1.3)	116.7 ^{§§}	373 (1.7)	477 (2.2)	29.4 ^{§§}
25–44	893 (2.1)	1,421 (3.4)	61.9 ^{§§}	1,325 (3.2)	1,702 (4.0)	25.0 ^{§§}

Characteristic	Synthetic opioids other than methadone			Heroin		
	2014	2015	% change in rate, 2014 to 2015	2014	2015	% change in rate, 2014 to 2015
	No. (Rate)	No. (Rate)		No. (Rate)	No. (Rate)	
45–64	925 (2.2)	1,201 (2.8)	27.3 ^{§§}	697 (1.6)	893 (2.1)	31.3 ^{§§}
Race/Ethnicity**						
White, non-Hispanic	4,685 (2.4)	7,995 (4.2)	75.0 ^{§§}	8,253 (4.4)	10,050 (5.4)	22.7 ^{§§}
Black, non-Hispanic	449 (1.1)	883 (2.1)	90.9 ^{§§}	1,044 (2.5)	1,310 (3.1)	24.0 ^{§§}
Hispanic	302 (0.6)	524 (0.9)	50.0 ^{§§}	1,049 (1.9)	1,299 (2.3)	21.1 ^{§§}
U.S. Census region of residence						
Northeast	1,485 (2.7)	3,071 (5.6)	107.4 ^{§§}	2,755 (5.1)	3,461 (6.3)	23.5 ^{§§}
Midwest	1,319 (2.0)	2,548 (3.9)	95.0 ^{§§}	3,385 (5.2)	3,959 (6.1)	17.3 ^{§§}
South	2,087 (1.8)	3,303 (2.8)	55.6 ^{§§}	2,733 (2.4)	3,722 (3.2)	33.3 ^{§§}
West	653 (0.8)	658 (0.9)	12.5 ^{§§}	1,701 (2.2)	1,847 (2.4)	9.1 ^{§§}
Selected states††						
States with very good or excellent reporting (n = 21)						
Alaska	14 – ^{¶¶}	14 – ^{¶¶}	– ^{¶¶}	25 (3.3)	37 (4.7)	42.4
Connecticut	94 (2.7)	211 (6.1)	125.9 ^{§§}	299 (8.9)	390 (11.3)	27.0 ^{§§}
Iowa	29 (1.0)	44 (1.5)	50.0	37 (1.3)	45 (1.6)	23.1

Characteristic	Synthetic opioids other than methadone			Heroin		
	2014	2015	% change in rate, 2014 to 2015	2014	2015	% change in rate, 2014 to 2015
	No. (Rate)	No. (Rate)		No. (Rate)	No. (Rate)	
Maine	62 (5.2)	116 (9.9)	90.4 ^{§§}	38 (3.1)	52 (4.5)	45.2
Maryland	230 (3.8)	357 (5.8)	52.6 ^{§§}	313 (5.2)	405 (6.6)	26.9 ^{§§}
Massachusetts	453 (6.9)	949 (14.4)	108.7 ^{§§}	469 (7.2)	634 (9.6)	33.3 ^{§§}
Nevada	32 (1.0)	32 (1.1)	10.0	64 (2.2)	82 (2.7)	22.7
New Hampshire	151 (12.4)	285 (24.1)	94.4 ^{§§}	98 (8.1)	78 (6.5)	-19.8
New Mexico	66 (3.3)	42 (2.1)	-36.4	139 (7.2)	156 (8.1)	12.5
New York	294 (1.4)	668 (3.3)	135.7 ^{§§}	825 (4.2)	1,058 (5.4)	28.6 ^{§§}
North Carolina	217 (2.2)	300 (3.1)	40.9 ^{§§}	266 (2.8)	393 (4.1)	46.4 ^{§§}
Oklahoma	73 (1.9)	93 (2.4)	26.3	26 (0.7)	36 (1.0)	42.9
Oregon	33 (0.8)	34 (0.9)	12.5	124 (3.2)	102 (2.5)	-21.9
Rhode Island	82 (7.9)	137 (13.2)	67.1 ^{§§}	66 (6.8)	45 (4.3)	-36.8
South Carolina	110 (2.3)	161 (3.3)	43.5 ^{§§}	64 (1.4)	100 (2.2)	57.1 ^{§§}
Utah	68 (2.5)	62 (2.3)	-8.0	110 (3.8)	127 (4.3)	13.2
Vermont	21 (3.6)	33 (5.6)	55.6	33 (5.8)	33 (5.8)	0.0

Characteristic	Synthetic opioids other than methadone			Heroin		
	2014	2015	% change in rate, 2014 to 2015	2014	2015	% change in rate, 2014 to 2015
	No. (Rate)	No. (Rate)		No. (Rate)	No. (Rate)	
Virginia	176 (2.1)	270 (3.3)	57.1 ^{§§}	253 (3.1)	353 (4.3)	38.7 ^{§§}
Washington	62 (0.8)	65 (0.9)	12.5	289 (4.1)	303 (4.2)	2.4
West Virginia	122 (7.2)	217 (12.7)	76.4 ^{§§}	163 (9.8)	194 (11.8)	20.4
Wisconsin	90 (1.6)	112 (2.1)	31.3	270 (4.9)	287 (5.3)	8.2
States with good reporting (n = 7)						
Colorado	80 (1.5)	64 (1.2)	-20.0	156 (2.9)	159 (2.8)	-3.4
Georgia	174 (1.7)	284 (2.8)	64.7 ^{§§}	153 (1.6)	222 (2.2)	37.5 ^{§§}
Illinois	127 (1.0)	278 (2.2)	120.0 ^{§§}	711 (5.6)	844 (6.7)	19.6 ^{§§}
Minnesota	44 (0.8)	55 (1.0)	25.0	100 (1.9)	115 (2.2)	15.8
Missouri	109 (1.9)	183 (3.1)	63.2 ^{§§}	334 (5.8)	303 (5.3)	-8.6
Ohio	590 (5.5)	1,234 (11.4)	107.3 ^{§§}	1,208 (11.1)	1,444 (13.3)	19.8 ^{§§}
Tennessee	132 (2.1)	251 (4.0)	90.5 ^{§§}	148 (2.3)	205 (3.3)	43.5 ^{§§}

Source: CDC. National Vital Statistics System, Mortality. CDC WONDER. Atlanta, GA: US Department of Health and Human Services, CDC; 2016. <https://wonder.cdc.gov/> (<https://wonder.cdc.gov/>).

* Rates are for the number of deaths per 100,000 population. Age-adjusted death rates were

calculated using the direct method and the 2000 standard population. Deaths were classified using the *International Classification of Diseases, Tenth Revision* (ICD-10). Drug overdose deaths were identified using underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14.

† Drug overdose deaths, as defined, that have synthetic opioids other than methadone (T40.4) as contributing causes.

§ Drug overdose deaths, as defined, that have heroin (T40.1) as a contributing cause.

¶ Categories of deaths are not exclusive because deaths might involve more than one drug. Summing categories will result in a number greater than the total number of deaths in a year.

** Data for Hispanic ethnicity should be interpreted with caution; studies comparing Hispanic ethnicity on death certificates and on census surveys have shown inconsistent reporting.

†† Analyses were limited to states meeting the following criteria. For states with very good to excellent reporting, ≥90% of drug overdose death certificates mention at least one specific drug in 2014, with the change in percentage of drug overdose deaths mentioning at least one specific drug differing by <10 percentage points from 2014 to 2015. States with good reporting had 80% to <90% of drug overdose death certificates mention at least one specific drug in 2014, with the change in the percentage of drug overdose deaths mentioning at least one specific drug differing by <10 percentage points from 2014 to 2015. Rate comparisons between states should not be made because of variations in reporting across states.

§§ Statistically significant at p<0.05 level. Gamma tests were used if the number of deaths was <100 in 2014 or 2015, and z-tests were used if the number of deaths was ≥100 in both 2014 and 2015.

¶¶ Cells with nine or fewer deaths are not reported, and rates based on <20 deaths are not considered reliable and not reported.

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EXHIBIT 4

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The Dizzying Increase of Overdose Deaths in Indiana and Nationwide

When Cold Numbers Become Heartbreak – The Dizzying Increase of Overdose Deaths in Indiana and Nationwide

As evidence gathers that mega pop star Prince died from an overdose of opiate prescription drugs, we as a state and a country have an opportunity to examine the epidemic of identical tragedies happening right here in our own communities. Even as we grieve from afar for a beloved pop icon, we can bow our heads and mourn more locally, for the victims and families struck every day by drug overdoses. These are families that we know, families across town or right next door, and their numbers are staggering.

As a state, Indiana reflects a nationwide trend in deaths by drug overdose. According to The Center for Disease Control Website (CDC), 28,000 people died from opiate drug overdoses in 2014. This does not include death from other drugs, but these numbers are substantial as well. 28,000 Americans died from overdoses on prescription opiates and heroin two years ago. This is the highest number ever reported, and it shows no signs of slowing down. And unfortunately, 2014 was not an anomaly; it was simply part of a longer trend.

Expanding our scope to include the last fifteen years, the numbers become more jaw dropping. Since 2000, the death rate by overdose has quadrupled. Yes, you read that right. In fifteen years, overdose deaths have quadrupled. And the total number of deaths since 2000? According to the CDC, it's almost 500,000.

Consider that a moment – nearly half a million Americans have died from drug overdoses in the last fifteen years. That's more than have died from car accidents during the period. And that number doesn't even touch the bereaved family members, which certainly climbs into the millions and millions.

A few other remarks will accent what is clearly a national epidemic. The majority of overdose victims in the United States are middle aged. They are usually people who begin to take opiates because of legitimate medical problems. Eventually however, their use of prescription painkillers becomes drug abuse. Many of them end up obtaining heroin from off the street, because it's actually cheaper and easier to get than prescription drugs. Historically, opiate deaths happen more to men than women. But the mortality gap has been shrinking alarmingly for several years. Women are becoming more and more likely to die from drug overdose. The overdose epidemic does not discriminate.

Bringing the overdose epidemic closer to home, we see a similar explosion of death rates in Indiana. These numbers are from the Indiana State Department of Health Website (ISDH). Along with 36 other states nationwide, drug overdose is the leading cause of injury death in Indiana. In the period from 2011-2013, Indiana ranked 15th highest in overdose deaths. This is a jump of five places since the period 2007-2009, when we ranked 20th. We will address prescription drug abuse more closely in a future post, but according to the CDC, Indiana is ranked 9th in total prescriptions written for opiate painkillers. This is more than enough prescriptions for every Hoosier in the state to have a bottle of opiate painkillers laying around the house.

And the number don't stop there. Since 1999, the number of overdose deaths in Indiana has increased from 111 to 1,152. This is nothing less than horrifying. These numbers represent a 500% jump in our rate of overdose deaths. It is even to conceive of that, much less consider the devastating amount of grief for the families affected. And if you scope to the period between 2010-2014, the increase is perhaps even more glaring. Here, in a five year period, the number increased from 923 in 2010 to 1,152 in 2014. This is 229 more deaths in 2014 than in 2010, a mind boggling increase of 25%. All we can add to these numbers to express the depth of the problem, except to say that the numbers here seem to outpace the national average. And the national average is devastating, as we've already seen. What does this tell us about conditions here in Indiana?

It is impossible to exaggerate the depth of our state's overdose problem. The actual numbers themselves seem to be exaggerations, but sadly they are not. They are quite real, even if they don't even skim the surface of the real problem involved. This is not a Chicken Little scenario, not by a long shot. In a very meaningful way, the sky is indeed falling for many Indiana families. How much more of it must come down around our ears for us to act, for us to begin the examination necessary to curb the explosion of death? Time will tell if our hearts catch up with the numbers.

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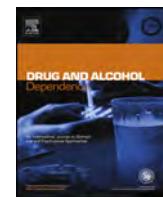
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EXHIBIT 5



Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers – United States, 2002–2004 and 2008–2010

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ABSTRACT

Background: Heroin use and overdose deaths have increased in recent years. Emerging information suggests this is the result of increases in nonmedical use of opioid pain relievers and nonmedical users transitioning to heroin use. Understanding this relationship is critically important for the development of public health interventions.

Methods: Combined data from the 2002–2004 National Surveys on Drug Use and Health were compared to the 2008–2010 surveys to examine patterns of heroin use and risk behaviors among past year nonmedical users of opioid pain relievers.

Results: Between 2002–2004 and 2008–2010, past year heroin use increased among people reporting past year nonmedical use (PYNMU) of opioid pain relievers ($p < 0.01$), but not among those reporting no PYNMU. Frequent nonmedical users – people reporting 100–365 days of PYNMU – had the highest rate of past year heroin use and were at increased risk for ever injecting heroin (aOR 4.3, 95% CI 2.5–7.3) and past year heroin abuse or dependence (aOR 7.8, 95% CI 4.7–12.8) compared to infrequent nonmedical users (1–29 days of PYNMU). In 2008–2010, 82.6% of frequent nonmedical users who used heroin in the past year reported nonmedical use of opioid pain relievers prior to heroin initiation compared to 64.1% in 2002–2004.

Conclusions: Heroin use among nonmedical users of opioid pain relievers increased between 2002–2004 and 2008–2010, with most reporting nonmedical use of opioid pain relievers before initiating heroin. Interventions to prevent nonmedical use of these drugs are needed and should focus on high-risk groups such as frequent nonmedical users of opioids.

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1. Introduction

Drug overdose deaths involving prescription opioid pain relievers such as oxycodone, hydrocodone, fentanyl, and methadone have increased dramatically since 1999 (Paulozzi et al., 2011). The rate of opioid pain reliever overdose deaths in the United States in 2009, 5.0 per 100,000 population, was nearly four times the rate in 1999, 1.4 per 100,000 (Centers for Disease Control and Prevention, 2012). Morbidity associated with the nonmedical use of these drugs has also increased over the last decade (Substance Abuse and Mental Health Services Administration (SAMHSA), 2010; Substance Abuse and Mental Health Services Administration, 2012a). Recent research examining the frequency of nonmedical use of pain relievers found that chronic or frequent nonmedical use has increased in the US, while less frequent use remained stable. This rise in frequent nonmedical use was paralleled by an increase in overdose deaths during the same time period. Over 2 million people in the

US now report nonmedical use of opioid pain relievers for 100 days or more in the past year (Jones, 2012).

Use of the illicit opioid heroin has been increasing as well, with an estimated 400,000 people reporting past year use in 2002 compared with over 600,000 in 2010 (SAMHSA, 2011). Further, heroin-related overdose deaths have been increasing since 2007 after remaining stable between 1999 and 2006 (CDC, 2012). Emerging evidence suggests a connection between increases in nonmedical use of opioid pain relievers and increases in heroin use in the US (Lankenau et al., 2012; Peavy et al., 2012). The scientific literature examining the relationship between nonmedical use of opioids and heroin use has generally focused on people entering opioid treatment programs or urban injection drug users, and typically only provides estimates of lifetime, past year, or past month use of heroin among nonmedical users of opioid pain relievers (Daniulaityte et al., 2006; Cleland et al., 2011; Lankenau et al., 2007, 2012; Rees Davis and Johnson, 2008; Canfield et al., 2010; Brands et al., 2004; Havens et al., 2007; Moore et al., 2007; Rosenblum et al., 2007; Potter et al., 2004; Carise et al., 2007; Young and Havens, 2011; Grau et al., 2007; Cicero et al., 2012).

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A 2007 study of patients in methadone maintenance programs found that 33.0% of primary abusers of opioid pain relievers had ever used heroin and 13.0% had used heroin in the past 30 days; among people whose primary drug of abuse was heroin, 69.0% had ever used opioids and 39.0% had used one in the past 30 days (Rosenblum et al., 2007). In another study, nearly 30.0% of opioid treatment program patients surveyed between 2005 and 2009 had used opioid pain relievers and heroin within the past 30 days, and those interviewed in later years of the survey were more likely to use both (Cleland et al., 2011). A small study of urban nonmedical users of opioids found that poly-opioid use was a significant predictor for transitioning to heroin and/or injection drug use (Grau et al., 2007). A 2012 study of young urban injection drug users found that 86% had used opioid pain relievers nonmedically prior to using heroin, and their initiation into nonmedical use was characterized by three main sources of opioids – family, friends, or personal prescriptions (Lankenau et al., 2012). Studies have also found heroin use to be a predictor for past year nonmedical use of opioids (Tetrault et al., 2008; Becker et al., 2008; Back et al., 2010) and past year opioid pain reliever abuse or dependence (Becker et al., 2008).

Understanding the relationship between nonmedical use of opioid pain relievers and heroin use is critical for the development of effective public health interventions. Considering the large number of nonmedical users of opioid pain relievers, even a small shift to heroin use could have significant public health implications such as increased transmission of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) (Strang et al., 1998; Schoenbaum et al., 1989; Klevens et al., 2012) due to the higher percentage of people reporting injection as the usual route of administration for heroin compared to opioid pain relievers. A recent report found 69.7% of substance abuse treatment admissions for heroin reported injection as the usual route of administration compared to 14.3% for opioid pain relievers (SAMHSA, 2012d).

This study attempts to build on the prior literature by (1) describing patterns of heroin use among nonmedical users of opioid pain relievers in the US in 2002–2004 compared to those in 2008–2010; (2) examining the relationship between initiation of opioid pain relievers and heroin among the two cohorts; (3) determining the association between frequency of nonmedical use of opioids and heroin use and risk behaviors; and (4) identifying populations at greatest risk for public health consequences related to use of heroin and opioid pain relievers.

2. Methods

2.1. Data source

The National Survey on Drug Use and Health (NSDUH), conducted by SAMHSA, is an annual survey that provides estimates on the use of drugs, alcohol, and tobacco among the non-institutionalized U.S. civilian population age 12 or older. The NSDUH employs a 50-State design with an independent, multistage area probability sample for each of the States and the District of Columbia. Each State's sample is approximately equally distributed among the age groups: 12–17 years, 18–25 years, and 26 years and older. The survey uses a combination of computer-assisted personal interviewing and audio computer-assisted self-interviewing to improve reporting about drug use and other sensitive behaviors. Detailed methods of the NSDUH have been reported elsewhere (SAMHSA, 2011). For this study, data from the NSDUH public use files were combined for years 2002–2004 (unweighted $n = 164,911$) and 2008–2010 (unweighted $n = 169,384$) to improve the precision of estimates and detection of differences among subpopulations. Examining trends prior to 2002 were not possible due to methodological differences that affect the comparability of the 2002–2010 estimates with estimates from prior surveys (SAMHSA, 2011). Weighted interview response rates were 77–79% for 2002–2004 and 74–76% for 2008–2010.

2.2. Study variables

2.2.1. Substance use. In the NSDUH, respondents are asked a series of questions to determine their use of specific substances. Past year heroin use is defined as use of heroin within the 12 months prior to the survey. Past year nonmedical use (PYNMU) of prescription pain relievers is defined as use in the past 12 months

without a prescription or use for the feeling or experience the drug causes. In the NSDUH, drugs in this category include opioid pain relievers and select barbiturate combination products. To limit the analysis to past year nonmedical users of opioid pain relievers, respondents reporting PYNMU of only barbiturate combination pain relievers were excluded (2002–2004 unweighted $n = 26$; 2008–2010 unweighted $n = 10$). In the survey, respondents are also asked to report the number of days in the past year they used each substance (frequency of past year use) and their age of first use for each substance.

2.2.2. Heroin use risk behaviors and heroin availability. Individuals who report substance use are asked a set of structured questions modeled after The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association, 1994) criteria for abuse (interference with responsibilities, hazardous use, use associated with legal problems, relationship problems) and dependence (time spent using the substance, inability to set limits on use, taking larger amounts or using more often, inability to cut down or stop using, continued use despite problems, reduced or eliminated involvement in important activities, withdrawal). These questions are designed to identify respondents with past year abuse or dependence on specific substances. In addition, individuals who used heroin are asked about their route(s) of administration. Respondents are asked if they ever: used a needle to inject heroin, smoked heroin, sniffed heroin, or used heroin in some other way. Individuals are also asked to list other drugs they ever injected (including opioid pain relievers). Questions to determine heroin availability are also included in the survey. Respondents are asked how difficult or easy it would be for them to get heroin, with response options of: probably impossible, very difficult, fairly difficult, fairly easy, or very easy.

2.2.3. Sociodemographics. Sociodemographic characteristics from NSDUH included in this analysis are sex; age (12–17 years, 18–25 years, and 26 years and older); race/ethnicity; total family income (less than \$20,000, \$20,000–49,999, \$50,000–74,999, and \$75,000 or more); and county type (large metro, small metro, and non-metro). Each of these characteristics has been shown to have an impact on nonmedical use of opioid pain relievers in the scientific literature (Tetrault et al., 2008; Becker et al., 2008; Back et al., 2010).

2.3. Statistical analysis

All analyses were conducted with SPSS version 20 Complex Samples to account for the design, nonresponse, and weighting of the NSDUH. PYNMU of opioid pain relievers was recoded into a new variable to classify frequency of past year nonmedical use into four categories: no PYNMU, 1–29 days, 30–99 days, and 100–365 days of nonmedical use. Frequency of past year nonmedical use categories were chosen to enable comparisons between people reporting no past year nonmedical use, infrequent nonmedical use, and frequent nonmedical use. Prior research indicates that frequent nonmedical use of opioid pain relievers has increased in recent years while less frequent use remained stable (Jones, 2012). Average annual estimates of past year heroin use stratified by frequency of PYNMU for 2002–2004 and 2008–2010 were produced and converted to rates per 1000 population age 12 years and older in each frequency of PYNMU category. Two-tailed *t*-tests were used to test for significant differences in the average annual rates between the two time periods among all past year heroin users, by frequency category, sex and age. Significance was determined at the $p < 0.05$ level.

To compare age of first use of heroin and opioid pain relievers by frequency of PYNMU between the two time periods, a new age of first use variable was computed to classify age of first use into three categories: age of first use of heroin before first use of opioid pain relievers, age of first use of heroin same as first use of opioid pain relievers, and age of first use of opioid pain relievers before first use of heroin.

Logistic regression analyses were conducted to examine the relationship between frequency of PYNMU of opioids and past year heroin use, ever injecting heroin, ever injecting opioid pain relievers, past year heroin abuse or dependence, past year opioid pain reliever abuse or dependence, and heroin availability. For this analysis, heroin availability was recoded into two categories: heroin fairly or very easy to obtain and otherwise. Adjusted odds ratios, with 1–29 days of PYNMU as the reference group, were produced. Adjustment was made for age, sex, race/ethnicity, total family income, and county type.

3. Results

3.1. Past year heroin use

Table 1 contains the average annual estimates for past year nonmedical use of opioid pain relievers and heroin use by sex and age among people 12 years and older in the 2002–2004 and 2008–2010 surveys. **Table 2** shows the average annual estimates of past year heroin use among people 12 years and older for 2002–2004 and 2008–2010 by frequency of PYNMU of opioid pain relievers. On average, an estimated 379,000 people reported past year heroin use

Table 1

Average annual estimates of study population by past year nonmedical use of opioid pain relievers and past year heroin use by sex and age, 2002–2004 and 2008–2010 (numbers in thousands).

Characteristics	No PYNMU OPR and no PY heroin use		PYNMU OPR and no PY heroin use		PYNMU OPR and PY heroin use		No PYNMU OPR and PY heroin use	
	2002–2004	2008–2010	2002–2004	2008–2010	2002–2004	2008–2010	2002–2004	2008–2010
All respondents	226,197	239,297	11,204	11,865	203	416	176	171
Sex								
Male	108,901	115,311	5847	6621	155	280	120	116
Female	117,296	123,986	5357	5245	48	136	55	55
Age								
12–17 years	23,082	23,028	1860	1553	30	24	15	12
18–25 years	27,857	29,596	3679	3758	78	146	34	31
26 years and older	175,257	186,674	5665	6555	95	246	127	129

Abbreviation: PYNMU OPR, past year nonmedical use of opioid pain relievers.

each year in 2002–2004 compared with 588,000 in 2008–2010. In 2002–2004, 53.6% of past year heroin users reported PYNMU of opioid pain relievers compared to 70.9% in 2008–2010. By 2008–2010, the largest percent of past year heroin users, 34.3%, were found among people who reported 100–365 days of PYNMU of opioid pain relievers.

Average annual rates of past year heroin use by frequency of PYNMU and by sex and age are shown in Table 3. Between 2002–2004 and 2008–2010 there was a statistically significant increase in the overall rate of past year heroin use ($p < 0.01$). Significant increases in heroin use between the two time periods were seen among people who reported any ($p < 0.01$), 1–29 days ($p < 0.05$), 30–99 days ($p < 0.01$), and 100–365 days ($p < 0.05$) of PYNMU of opioid pain relievers. The highest rate of past year heroin use in 2008–2010 was seen in the 100–365 days of PYNMU category (94.7 per 1000). Past year heroin use among people reporting no PYNMU did not change during the two time periods.

The average annual rate of past year heroin use for males (3.2 per 1000) in 2008–2010 was more than two times the rate for females (1.5 per 1000). Statistically significant increases in past year heroin use among males were seen among those reporting any PYNMU of opioid pain relievers ($p < 0.05$). Among females, rates of past year heroin use increased among those reporting any ($p < 0.01$), 30–99 days ($p < 0.01$), and 100–365 days ($p < 0.01$) of PYNMU opioids. Past year heroin use did not increase during the two time periods among males or females who reported no PYNMU of opioid pain relievers.

In 2008–2010, 18–25 year olds had the highest rate of past year heroin use (5.3 per 1000). Statistically significant increases

in average annual rates of past year heroin use were seen among 18–25 year olds who reported any ($p < 0.01$), 30–99 days ($p < 0.05$), and 100–365 days ($p < 0.01$) of PYNMU; and people 26 years and older who reported any ($p < 0.01$), 1–29 days ($p < 0.05$), and 30–99 days ($p < 0.01$) of PYNMU. No significant changes in past year heroin use were found among 12–17 year olds. Past year heroin use among people reporting no PYNMU of opioid pain relievers remained stable across all age groups during the two time periods.

3.2. Age of first use

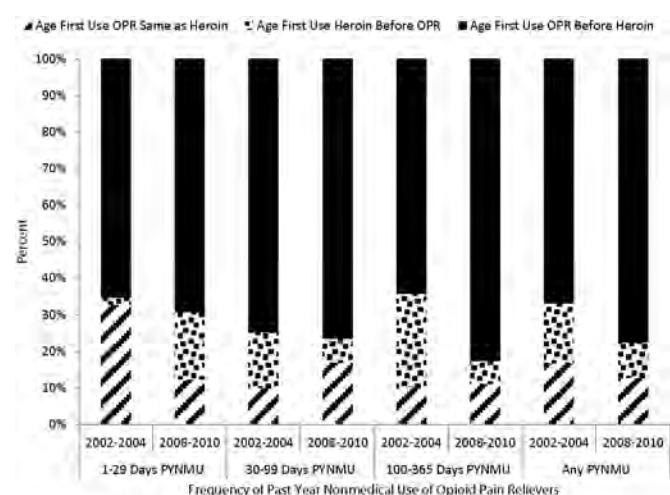
Fig. 1 compares the percent of respondents in the 2002–2004 and 2008–2010 cohorts reporting age of first use of heroin before, the same as, or after their first use of opioid pain relievers among people who used both heroin and opioid pain relievers in the past year. Overall, 66.8% of individuals in the 2002–2004 cohort reported use of opioid pain relievers before initiating heroin compared to 77.4% in the 2008–2010 cohort. In 2002–2004, 16.4% used heroin before opioid pain relievers versus 9.7% in 2008–2010. During the two time periods, the greatest change in individuals initiating opioid pain relievers before heroin was seen among those in the 100–365 days of PYNMU category where 64.1% used opioids before heroin in 2002–2004 compared to 82.6% in 2008–2010. In this same group, 25.4% initiated heroin before opioids in 2002–2004 versus 6.2% in 2008–2010. The percent reporting initiation of heroin and

Table 2

Average annual estimates of past year heroin use among people 12 years and older by frequency of past year nonmedical use of opioid pain relievers, 2002–2004 and 2008–2010 (numbers in thousands).

Characteristic	No past year heroin use N	Past year heroin use N
All respondents		
2002–2004	237,401	379
2008–2010	251,162	588
No PYNMU OPR		
2002–2004	226,197	176
2008–2010	239,297	171
1–29 days PYNMU OPR		
2002–2004	7621	58
2008–2010	7650	115
30–99 days PYNMU OPR		
2002–2004	2083	46
2008–2010	2287	100
100–365 days PYNMU OPR		
2002–2004	1500	99
2008–2010	1928	202

Abbreviations: PYNMU, past year nonmedical use; OPR, opioid pain relievers.



Abbreviations: PYNMU, past year nonmedical use; OPR, opioid pain relievers.

Fig. 1. Comparison of age of first use of heroin before, the same as, or after age of first use of opioid pain relievers among people 12 years and older reporting both past year heroin and nonmedical use of opioid pain relievers by frequency of past year nonmedical use, 2002–2004 and 2008–2010.

Table 3

Average annual rate of past year heroin use among people 12 years and older by frequency of past year nonmedical use of opioid pain relievers, by sex, and by age, 2002–2004 and 2008–2010.^a

Characteristics	No PYNMU OPR	1–29 days PYNMU OPR	30–99 days PYNMU OPR	100–365 days PYNMU OPR	Any PYNMU OPR	Overall past year heroin use
Total						
2002–2004	0.8	7.6	21.5	62.0	17.8	1.6
2008–2010	0.7	14.8	41.9 [±]	94.7 [*]	33.9 [±]	2.3 [±]
Sex						
Male						
2002–2004	1.1	9.0	28.3	98.2	25.8	2.4
2008–2010	1.0	17.8	44.8	115.1	40.6 [*]	3.2
Female						
2002–2004	0.5	6.1	13.1	18.1	8.9	0.8
2008–2010	0.5	11.0	37.9 [±]	66.7 [±]	25.3 [±]	1.5 [±]
Age						
12–17						
2002–2004	0.7	9.9	26.5	29.4	15.9	1.8
2008–2010	0.5	7.7	28.6	29.8	15.0	1.5
18–25						
2002–2004	1.2	10.2	32.2	62.9	20.8	3.6
2008–2010	1.0	12.8	51.7 [*]	122.5 [±]	37.5 [±]	5.3 [±]
26 and older						
2002–2004	0.7	5.0	13.0	71.2	16.5	1.2
2008–2010	0.7	17.7 [*]	39.7 [*]	92.0	36.2 [±]	1.9 [±]

Abbreviation: PYNMU OPR, past year nonmedical use of opioid pain relievers.

^a Data are given as rates per 1000 population of each frequency of use category.

* Difference between the 2008–2010 and 2002–2004 average annual rate are statistically significant at the $p < 0.05$ level.

± Difference between the 2008–2010 and 2002–2004 average annual rate are statistically significant at the $p < 0.01$ level.

Table 4

Adjusted odds ratios^a for past year heroin and opioid pain reliever risk behaviors and past year abuse or dependence on heroin or opioid pain relievers by frequency of past year opioid pain reliever nonmedical use among people 12 years and older, 2008–2010.

Characteristic	1–29 days of PYNMU of opioid pain relievers aOR (95% CI)	30–99 days of PYNMU of opioid pain relievers aOR (95% CI)	100–365 days of PYNMU of opioid pain relievers aOR (95% CI)
Past year heroin use	Referent	2.8 (1.7–4.5)	6.4 (3.7–11.1)
Ever inject heroin	Referent	1.6 (0.9–2.9)	4.3 (2.5–7.3)
Ever inject opioid pain relievers	Referent	3.8 (1.9–7.8)	13.3 (7.7–23.0)
Past year heroin abuse or dependence	Referent	3.2 (1.7–6.1)	7.8 (4.7–12.8)
Past year opioid pain reliever abuse or dependence	Referent	2.9 (2.3–3.8)	8.9 (7.1–11.3)
Heroin fairly or very easy to obtain	Referent	1.4 (1.1–1.7)	2.1 (1.8–2.6)

Abbreviations: PYNMU, past year nonmedical use; aOR, adjusted odds ratio; 95% CI, 95% confidence interval.

^a Odds ratio adjusted for sex, age, race/ethnicity, total family income, and county type.

opioids at the same age was similar during the two time periods in this group, 10.5% in 2002–2004 and 11.2% in 2008–2010.

3.3. Heroin use risk behaviors and availability

Associations between frequency of PYNMU of opioid pain relievers and heroin use risk behaviors and heroin availability are described in Table 4. In the adjusted analysis, compared to people reporting 1–29 days of PYNMU, the odds of past year heroin use, ever injecting heroin, ever injecting opioid pain relievers, past year heroin abuse or dependence, past year opioid pain reliever abuse or dependence and reporting heroin fairly or very easy to obtain increased in a graded fashion with increased frequency of PYNMU of opioids.

4. Discussion

The findings in this study support a relationship between increases in nonmedical use of opioid pain relievers and increases in heroin use. Average annual rates of past year heroin use among non-medical users of opioid pain relievers in 2008–2010 significantly increased compared to nonmedical users in 2002–2004. However, no increase in past year heroin use was seen among people who reported no PYNMU. In fact, past year heroin use among people who reported no PYNMU did not increase during the two time periods

among any sex or age group examined. In addition, the age of first use analysis found that the majority of respondents who used both opioid pain relievers and heroin had used opioids before initiating heroin.

This study expands prior research with the novel examination of the relationship between frequency of nonmedical use of opioids and heroin use and risk behaviors. Among past year nonmedical users, the highest rate of past year heroin use was found among frequent nonmedical users – people reporting 100–365 days of PYNMU. This group was also at increased risk for ever injecting heroin or opioids and past year abuse or dependence on heroin or opioid pain relievers. They also were more likely to report heroin fairly or very easy to obtain. Further, in the 2008–2010 cohort, roughly 83% of this group reported using opioids prior to heroin initiation compared to only 64% in the 2002–2004 cohort. Moreover, only 6% reported initiating heroin before opioid pain relievers in 2008–2010 versus 25% in 2002–2004. This finding is consistent with a study of urban injection drug users where 86% reported initiating opioids prior to transitioning to heroin use (Lankenau et al., 2012). Interestingly, among the 100–365 days of PYNMU cohort in 2008–2010, the frequency of heroin use in the past year, 99 days (95% CI 78.1–119.9), was similar to that for past year heroin users who reported no PYNMU, 75.8 days (95% CI 49.9–101.7).

Certain demographic findings also warrant discussion. Among the three age groups examined, 18–25 year olds had the highest

rate of past year heroin use – 3.5 times the rate of 12–17 year olds and 2.8 times that of people 26 years and over in 2008–2010. A particularly concerning finding was that 12.3% of the 18–25 year olds who reported 100–365 days of PYNNMU also used heroin in the past year, a 95% increase compared to 18–25 year olds in 2002–2004. This increase coincides with increases in chronic non-medical use of opioid pain relievers, and increases in heroin-related emergency department visits, substance abuse treatment admissions, and overdose deaths seen in this age group during a similar time period (Jones, 2012; SAMHSA, 2012b,c; CDC, 2012).

The public health impact of increased heroin use among 18–25 year olds who also abuse opioid pain relievers is evidenced by the recent recognition of a new cohort of young injection drug users with HCV infection in certain areas of the U.S. who began using opioid pain relievers before transitioning to heroin injection (Klevens et al., 2012). This increase in HCV infections has primarily occurred among white, non-urban young adults – a group with high rates of nonmedical use of opioid pain relievers. A study of new HCV infections in Massachusetts found that 95.0% of interview respondents used opioids before initiating heroin (Church et al., 2011), and a study examining new HCV cases in young adults in rural Wisconsin found that 37.5% of the people who reported injecting opioid pain relievers started injecting them and then switched to injecting heroin or methamphetamine (Stanley et al., 2012).

Although the number of people using both opioid pain relievers and heroin in the past year has increased, the percentage of past year heroin users among past year nonmedical users is small, ranging from 1.5% of people reporting 1–29 days of PYNNMU to 9.5% of people reporting 100–365 days of PYNNMU in 2008–2010. Lower costs, increased availability, tolerance and seeking a more potent high have been cited as primary reasons for transitioning to heroin (National Drug Intelligence Center, 2011; Canfield et al., 2010; Lankenau et al., 2012; Cicero et al., 2012). In the present study, frequent past year nonmedical users – the group at greatest risk for past year heroin use – were more likely to report heroin fairly or very easy to obtain compared to people who reported less frequent PYNNMU. A recent study found significant shifts to use of other opioids and heroin among people entering substance abuse treatment after introduction of the abuse deterrent formulation of OxyContin in 2010 (Cicero et al., 2012). Future research should focus on identifying factors associated with the transition from nonmedical use of opioid pain relievers to heroin use, including potential unintended consequences of policies aimed at reducing opioid pain reliever abuse.

Since the majority of opioid pain relievers used nonmedically originally come from a medical source (SAMHSA, 2011), interventions aimed at improving how opioid pain relievers are prescribed are critical to preventing abuse and related health consequences. This includes prescribing opioids only after other therapies have failed to adequately treat pain; having providers follow clinical guidelines for appropriate prescribing, including screening patients for substance abuse or mental health issues prior to prescribing (Chou et al., 2009; Sundwall et al., 2009; Agency Medical Directors Group, 2010); and implementing and enhancing prescription drug monitoring programs and health insurer claims review programs to identify individuals at risk for abuse as well as individuals or providers contributing to the illicit supply of opioid pain relievers.

Access to substance abuse treatment, including medication assisted therapy, is increasingly important as efforts to prevent opioid pain reliever abuse focus on identifying patients in need of treatment and supply control measures which may drive people to seek illicit opioids like heroin. Because people who use both opioid pain relievers and heroin, especially those using them frequently and/or in large quantities or injecting them, are at high-risk for overdose, expanding access to the opioid antagonist naloxone

via overdose prevention programs may reduce the immediate risk of overdose in this high-risk population. At least 188 community-based naloxone distribution programs exist in the United States (Wheeler et al., 2010).

This study has several limitations. First, NSDUH data are self-reported, and their value depends on the truthfulness and accuracy of individual respondents; under or over reporting may occur. Second, the survey is cross-sectional; therefore assessing causality is not possible. Further, this is a serial cross-sectional analysis and external factors such as changes in clinical practice or Federal, state or local policy enacted during the study period may have impacted past year nonmedical use of opioid pain relievers and past year heroin use among the two cohorts. Third, because NSDUH only captures non-institutionalized civilians, a small portion of the population such as active duty military personnel, homeless and incarcerated populations, and people in residential substance abuse treatment programs are excluded. Therefore, the drug use estimates in this study may not generalize to the total U.S. population. This may be particularly true for estimates of rarely used drugs like heroin. Fourth, respondents' recall of their age of first use of a substance may be subject to bias, with respondents moving their age of first use to an older age as length of recall increases (Gfroerer et al., 2004). Fifth, it is not possible to determine whether opioid pain relievers or heroin were initiated first among respondents whose age of first use for both substances were the same. This may lead to an underestimation of the percent of respondents with an age of first use of opioid pain relievers before heroin and vice versa. Despite these limitations, this study is the first to examine changes in heroin use among nonmedical users of opioid pain relievers during two time periods and explore initiation into use of these substances among a nationally representative probability sample of the US population aged 12 years and older.

The present study findings raise some concerns. The fact that over 77% of people using both opioid pain relievers and heroin in the past year report initiating opioid pain relievers prior to heroin initiation underscores the need for effective interventions to prevent the nonmedical use of these powerful drugs. This is especially true among the subset of frequent nonmedical users who are at increased risk for heroin use, injecting heroin or opioid pain relievers, heroin and opioid pain reliever abuse or dependence, and overdose.

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Contributor

Dr. Jones was responsible for study conception, data analysis, and drafting of the manuscript.

Conflict of interest

Dr. Jones has no conflicts of interest to declare.

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EXHIBIT 6



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Purdue Pharma: Corporate Fraud With a Body Count

By [Kathleen Frydl](#) [1] / [Huffington Post](#) [2]

May 18, 2016, 9:10 AM GMT

◀ 2

The *LA Times* [investigation](#) [3] of Purdue Pharma's manufacture and marketing of the narcotic painkiller OxyContin published last week should be regarded as a standard case study in corporate fraud.

Except this particular tale also features a body count.

This fact does nothing to call into question the validity of corporate fraud framework for understanding the story of OxyContin; it only makes its principal victims more visible, and the misbehavior in question more abhorrent, than is typical for the genre.

All the major features of Purdue's handling of OxyContin conform to similar acts of corporate fraud perpetrated in recent years: it encompasses not only what the company did (lie to generate profit), but what government regulatory agencies failed to do (detect and expose those lies), as well as the absence of any serious legal or other penalties imposed on Purdue Pharma as a result (a

\$634.5 million fine on a drug that has earned it \$31 billion in revenue, or 2 percent of earnings).

Still the story is peculiar in some key respects. Many times corporate fraud originates in some fairly innocent business model. Not so with OxyContin, a dubious affair from the start. As the LA Times investigation shows, Purdue formulated the drug because a patent on another its painkillers was set to expire. Anticipating competition from generic brands—and a subsequent loss of revenue—the company pursued an innovation that would render a narcotic painkiller eligible for a new patent, and consequently insulate it from competition. Purdue scientists pioneered a slow-release methodology designed to release a drug into a person's system incrementally instead of all at once.

The problem was, although the innovation was real, the claims made on its behalf did not materialize for many of the drug's users. In early drug trials, OxyContin failed to ensure twelve hours of pain relief in a substantial number of patients. But without twelve hour scheduling, the drug represented no genuine innovation, and no comparative advantage, when compared to other less expensive, long-lasting drugs.

So Purdue Pharma chose to simply ignore inconvenient data, and the Food and Drug Administration (FDA) chose to let them. They could not alter the facts, but they could try to avoid them. Nevertheless, as the saying goes, facts are stubborn things. One study conducted in 2002, seven years after Purdue secured application approval for OxyContin from the FDA, found that almost 87% of people taking the drug were taking it more frequently than every 12 hours. In drug trials and in subsequent clinical use, patients told their physicians that OxyContin wore off after five to eight hours, subjecting them not just to bouts of pain

but narcotic withdrawal. Unwilling to forfeit the feature deemed necessary to persuading insurance companies to continue to reimburse for the high cost of the drug, Purdue formulated a disturbing response. According documents revealed by the *LA Times*, the company instructed doctors “to prescribe stronger doses, not more frequent ones, when patients complain that OxyContin doesn’t last 12 hours.” As the reporters note in a measured tone, this approach “creates risks of its own.”

More accurate would be the assessment of Professor Egilman, a family health doctor who has served as expert witness in lawsuits filed against Purdue: the 12 hour dosing schedule, he told the *Times*, is “an addiction producing machine.” Higher doses only compounded the withdrawal problems patients encountered. Periodically plunged into a ravine of agony, patients were subsequently guided to jump off a higher cliff. To this day, the FDA has not asked Purdue to change its recommendations regarding higher dosing, despite the fact that a recent examination of medical records in Ontario, Canada concluded that one in 32 patients on high doses of the drug fatally overdosed.

Added to this disgrace is the way in which Purdue presented OxyContin as less addictive than its peer narcotics, and therefore a candidate for use in settings previously not treated with opioids. Just like a mortgage securitization machine that eventually resulted in mortgages for homeowners who did not qualify for them, Purdue Pharma recommended OxyContin be prescribed to patients and for durations unprecedented in modern medical practice. The *LA Times* makes the key point: other drug companies quickly followed suit. Since the approval of OxyContin in 1995, the United States has been overdosed with prescription narcotic painkillers—with only 5% of the world’s population, the US

consumes 80% of its painkillers—and spiraling rates of addiction, suicide and deaths from overdose are the inevitable result. Only recently, in the face of complete and ongoing regulatory failure by the FDA, the Center for Disease Control [stepped in](#) [4] to provide new recommendations for the protocols on prescribing narcotic painkillers. The dire circumstances of the opioid epidemic would seem to dictate more rigorous action, but a political establishment under the sway of large corporate donors has yet to summon the will.

Another recurring feature of corporate fraud makes an appearance in the OxyContin saga as well: the revolving door between government and industry. In an age of at least ostensible government regulation, no truly massive corporate fraud scheme can be perpetrated without government complicity, discernable as either a bewildering set of decisions or inexplicable complacency. At critical moments, sometimes nothing more than venal self-interest is in play. In the case of OxyContin, Dr. Curtis Wright, charged with medical review of the drug for the FDA, left the agency shortly after he approved the drug. According to the *Times*, Wright was working at Purdue on new product development within two years of his departure. In the absence of confession or other material evidence of motive, these sorts of career moves are more than merely suggestive; they are, in and of themselves, suspicious.

For all its similarities to other kinds of corporate malfeasance, the shadow of death cast by OxyContin, which, according to federal government surveys, has been abused by more than 7 million Americans over the past 20 years, places Purdue Pharma in exceptional standing among other serial offenders of corporate America.

That's not just because of the incalculable harm that resulted from its actions. After all, other comparable incidents of fraud inflicted grievous personal damage as well—though the news media makes no serious or consistent attempt to measure or take account of this trauma. In the case of opioid overdoses, they sometimes have to. While newspapers decide what to print in their articles, they cannot tell people what to write in their death announcements.

Not surprisingly, thousands of obituaries submitted to commemorate the victims of opioid overdose omit any mention of a cause of death or addiction. Still, it's undeniable that a growing number of families and loved ones opt to reveal both, often in unvarnished terms. As families refuse speak euphemistically or elliptically about the opioid use in their death announcements, an organic movement of "obit activism" is underway across America. Deprived of a voice on the front page, victims' advocates find one in the few remaining media platforms available to them and under their control.

And it is agonizing to read what they have to say. The mother of [Kelsey Endicott](#) [5] reminds us that it is "not true that everything happens for a reason;" her daughter's death from overdose only weeks ago had "no possible reason to justify for the loss." Another family chronicles a life of homelessness and injuries as the result of the untreated mental illness and substance dependence of [Jaime Noelle Velarde](#) [6], who died, in their words, "in a dry tent curled up in a warm sleeping bag." The obituary for [Alex Michael Hesse](#) [7] strikes a familiar note in the world of obit activism: "Growing up [Alex] was just like any other young man," his family says, but "he made some mistakes that ended up costing him his life." In his obituary, [Sean Stem](#) [8]'s family urged communities to "tear down whatever obstacles" exist in the way of treatment. "We have

learned the hard way that no amount of love can cure this illness” of opiate addiction, his family acknowledged, in a confession that implicates us all.

In explaining their decision to claim heroin overdose as cause of death in their daughter’s obituary, [Alison Shuemake](#)’ [9]s parents told USA Today that “Shame doesn’t matter now.”

A [Massachusetts father](#) [10] agreed, asking his local news station, “If parents are too afraid to put it in an obituary, how is the rest of the world going to see it?” Only days ago [Molly Parks](#)’ [11] parents reached the same conclusion. “I see a lot of obituaries from families losing 20-somethings, 30-somethings, and 40-somethings and they are all saying they died suddenly,” her father said. “But that’s not the truth.”

In the United States, fatal overdose from opioids exceeded deaths from car accidents in 2014; it is the leading cause of acute preventable death in America. A non-trivial number of these deaths come at the hands of illicit heroin, not OxyContin or other prescription opioid. However, many of these victims found their way to an underground painkiller because of their initial use of a prescribed one. As [government officials](#) [12] point out, almost half of all young people using heroin today “reported abusing prescription opioids” before they turned to the cheaper illegal street version of the drug.

And in fact, most overdoses do come at the hands of legal substances: “unintentional poisoning deaths” from prescription opioids quadrupled between 1999 and 2010, outnumbering deaths from heroin and cocaine combined.

Too often the call to deliver meaningful justice for corporate fraud is cast as a jeremiad, a retroactive bid to underscore our

resentment. The case of Purdue Pharma, which admitted no wrongdoing in its financial settlement with the Department of Justice and was not forced to change the way it instructed physicians and dentists to prescribe OxyContin, shows us that justice has prospective, even preventive, components. Unless forced to change cost to benefit analysis, corporations will continue to defraud and endanger the American people. A metaphorical back page, community-driven “obituary section” exists for every meek corporate fraud settlement; in the case of Purdue Pharma, it happens to be real.

Kathleen Frydl is an historian studying US state power, policies, and the institutions that shape American life.

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EXHIBIT 7

The New York Times<https://nyti.ms/2jaX3e7>

Inside a Killer Drug Epidemic: A Look at America's Opioid Crisis

The opioid epidemic killed more than 33,000 people in 2015. What follows are stories of a national affliction that has swept the country, from cities on the West Coast to bedroom communities in the Northeast.

JAN. 6, 2017

Opioid addiction is America's 50-state epidemic. It courses along Interstate highways in the form of cheap smuggled heroin, and flows out of "pill mill" clinics where pain medicine is handed out like candy. It has ripped through New England towns, where people overdose in the aisles of dollar stores, and it has ravaged coal country, where addicts speed-dial the sole doctor in town licensed to prescribe a medication.

Public health officials have called the current opioid epidemic the worst drug crisis in American history, killing more than 33,000 people in 2015. Overdose deaths were nearly equal to the number of deaths from car crashes. In 2015, for the first time, deaths from heroin alone surpassed gun homicides.

And there's no sign it's letting up, a team of New York Times reporters found as they examined the epidemic on the ground in states across the country. From New England to "safe injection" areas in the Pacific Northwest, communities are searching for a way out of a problem that can feel inescapable.

MARBLEHEAD, MASS.

In Suburbia, 'Tired of Everything'

Katie Harvey walked out of the house where she lived with friends, shoved her duffel bag into her mother's car and burst into tears.

"I need to go to detox," she told her mother, Maureen Cavanagh. "I'm just tired of everything."

Ms. Harvey, 24, had been shooting heroin for three years. She had been in and out of detox — eight times altogether. But it had always been someone else's idea.

This time, Ms. Harvey made the arrangements herself. She had come to loathe her life. "I haven't even been doing enough to get really high," she said. "I'm just maintaining myself so I don't get sick."

Before she left for detox, Ms. Harvey curled up on the couch in her mother's living room in this well-to-do suburb north of Boston and reflected on her life: her low self-esteem despite model-worthy good looks; her many lies to her family; how she had pawned her mother's jewelry and had sex with strange men for money to pay for drugs.

As she spoke, tears spilled from her eyes. She wiped them with the cuff of her sweater, which covered track marks and a tattoo that said "freedom" — her goal, to be unshackled from the prison of addiction.

Ms. Harvey had been a popular honors student. But she developed anorexia. Alcohol was next. By 21, she was hooked on heroin.

In 2015, she was arrested on charges of prostitution. In an extraordinary act of contrition, she wrote a public apology online to her friends and family.

Still, she plunged in deeper. She estimated that at her worst, she was shooting up a staggering number of times a day, perhaps as many as 15 — heroin, cocaine, fentanyl. She overdosed five times. In Massachusetts, almost five residents die every day from overdoses.

"I don't know how I'm alive, honestly," Ms. Harvey said.

That night in October, she went into detox. Four days later, she checked out. She went back to her friends and drugs, developing an abscess on her arm, probably from dirty needles.

Two weeks later, she was back in detox. This time, she stayed, then entered a 30-day treatment program.

The return trips to detox have been an emotional roller coaster for her mother. To cope, Ms. Cavanagh founded a group, Magnolia New Beginnings, to help drug users and their families.

Among her words of advice: Tell your children you love them, because “it might be the last thing you say to them.” *KATHARINE Q. SEELYE*

MARSHALLTOWN, IOWA

Help May Be Thin on the Ground

Andrea Steen is one of the fortunate ones. For people in this rural community of 28,000, getting medication to help overcome opioid addiction used to require long drives to treatment centers.

That changed about a year ago when two doctors here were licensed to prescribe Suboxone, a drug that eases withdrawal symptoms and helps keep opioid cravings at bay. Now Ms. Steen is one of their patients, coming once a month to check in and renew her prescription.

This epidemic is different from those of the past in significant ways. One is that it has spawned a growing demand for medications that can help modify addiction’s impact.

One of them is naloxone, known as Narcan, a powerful antidote that has jolted hundreds of overdosed users back to life. Another is buprenorphine, typically sold as Suboxone.

By keeping users from experiencing cravings and withdrawal, Suboxone can make it easier for addicts to stay off heroin and other opioids. The number of doctors certified to prescribe buprenorphine has more than doubled since 2011, to about

36,000 from about 16,000, according to the Substance Abuse and Mental Health Services Administration. Yet the drug remains out of reach for many rural Americans.

Ms. Steen, 46, is among 20 patients who get Suboxone from the two doctors authorized to prescribe it here. Until last summer, she said, she abused Vicodin and morphine relentlessly. She would steal them from her disabled husband, who would try in vain to hide them. But sometimes she couldn't root out the pills fast enough, and she would experience what every addict dreads most: withdrawal.

She heard about Suboxone from a friend in Tennessee whom she met through Facebook.

"She could tell when I was high," Ms. Steen said. "Her husband was on Suboxone. She was trying to help me."

Ms. Steen started on Suboxone in July, initially making weekly visits to Dr. Nicole Gastala and Dr. Timothy Swinton, the family practitioners here who prescribe the drug. Then it was every other week.

Unlike methadone, which also helps treat opioid addiction but must be taken under supervision at special clinics, Suboxone can be taken at home. Some doctors fail to follow Suboxone patients closely, or to test their urine to make sure they are not abusing or selling the medication or using other drugs. But the protocol here is strict.

Besides her doctor visits, Ms. Steen must attend group therapy and have regular urine tests.

She has mostly stopped craving opioids, for now. *ABBY GOODNOUGH*

LOS ANGELES

Tough-Love Rehab

They enter through an unmarked turquoise storefront, nestled between fashion boutiques on Melrose Avenue. They gather in a circle, ready for the tough-love approach they have come to expect from Howard C. Samuels, a clinical psychologist

who runs the Hills, a drug rehabilitation center whose location is central to its marketing.

A spot in the room is hard to come by, as are most drug rehabilitation services, especially for the poor and anyone without the proper insurance. The Hills, which can cost around \$50,000, serves a more privileged population, yet its mission is no less daunting.

In 2014, heroin became the most common reported drug of choice among those seeking treatment in Los Angeles County, surpassing marijuana and methamphetamine.

Dr. Samuels began with what he called a reality check. “How many of you have been to at least five treatment centers?” he asked. Nearly every one of the 19 clients in the room raised a hand.

“How about 10?” Still half of the clients raised their hands.

One of them, Jordan, who agreed to tell his story only if his last name was not disclosed, knows he is one of the lucky ones. This is only his third time in rehab, a relative rookie at 33 years old. This was his 118th day sober.

He had smoked pot, taken ecstasy and occasionally snorted cocaine. But heroin seemed off-limits to him, a college-educated son of two therapists, until a friend offered him some to smoke. Four years later, he blew through a \$20,000 inheritance in a month to get what he called the best heroin in the city.

After his first days of detox were over at the Hills, Jordan began what would be months of therapy. He confronted what Dr. Samuels calls “character defects,” and rattles his off easily: lust, anger, lack of discipline.

On this day, he knows he will draw the wrath of Dr. Samuels: Subverting the rules, he recently went out for his seventh tattoo. “My addiction has been replaced with addiction to other things: going to the gym, smoking, girls, getting tattoos.”

“Don’t you owe me an apology?” Dr. Samuels said to him, almost shouting.

Jordan answered quietly: "Yeah, I guess I owe you and some people an apology."

"I'm glad you're apologizing to me. That's good, but what's bad is, it came so naturally," Dr. Samuels said.

"All of us have some real impulse control problems," he continued. "That's why we're drug addicts."

JENNIFER MEDINA

SEATTLE

'For the Grace of God, There Go I'

The girl looked to be barely out of her teens, and was teetering on the brink of consciousness.

"She couldn't even form a sentence," said Dan Manus, a soft-spoken 61-year-old in a Seattle Seahawks cap. His jaw tightened as he recalled the night in October when he and his partner on the King County Emergency Service Patrol found the girl and, he thinks, saved her life.

A former addict, he knows the terrain too well. He's been clean for 22 years now, and working for the county for the last nine.

"I can relate to everybody I work with down there, because for the grace of God, there go I," Mr. Manus said, standing in the patrol parking lot between runs. "So, yeah, I feel like this kind of was my calling."

The Emergency Service Patrol was established in the 1980s by a private charity (later taken over by King County) to rescue street alcoholics by bringing them to a safe "sobering center" to sleep it off.

In October, though, in an acknowledgment of heroin's new ravages — treatment admissions for heroin in King County surpassed alcohol for the first time in 2015 — Mr. Manus and other patrol crew members were trained and equipped with naloxone.

“Harm reduction” is an approach that was to some degree pioneered here. One of the nation’s first clean-needle exchanges started in nearby Tacoma in 1988.

King County is now considering opening what could be the country’s first safe-injection site. There, addicts could use drugs under supervision by a health worker who may, crucially, also open the door to recovery programs, all under one roof.

For Mr. Manus, the crisis is personal. In 1992, he was saved from death by someone who found him in mid-overdose and called paramedics.

Seattle was a different, harder-edged city back then. Grunge music, and the heroin that swirled like a slipstream through the lives and song lyrics of some of its stars, was spilling out of the clubs.

The mix of drugs was changing, too. Heroin’s impact in King County surged in the late 1990s in the number of times it was identified in connection with a drug death, before beginning a near decade-long slide — a period that coincided with an increase in the number of times prescription opioids were found in victims’ bodies, which peaked in 2009. In that same year, heroin’s role began rising again to hit its highest-ever, worst numbers in 2014 with a drop since then, according to county figures.

More people lately seem to be on complex combinations of drugs, Mr. Manus said — like the girl who, at his direction, was treated by paramedics.

“It just seems today that there’s so much more out there, so many more people,” Mr. Manus said quietly. “It feels nonstop.” *KIRK JOHNSON*

NOGALES, ARIZ.

Outwitting the Mules

A tipster warned: Look out for a silver Nissan Sentra approaching the busy Dennis DeConcini Port of Entry in Nogales, Ariz., a crucial gateway for cheap heroin made in Mexico.

Early one morning, the Nissan rolled into passport control. A Customs and Border Protection officer caught the telltale signs of a driver who had something to hide: the darting eyes, the tight grip on the steering wheel.

The driver carried a border-crossing card, an entry permission given only to Mexican citizens. He also carried his wife and two small children and a load of heavy drugs: four pounds of methamphetamine in the passenger's backrest, and seven and a half pounds of heroin between the engine and the dashboard.

Last year, Customs and Border Protection agents seized more than 930 pounds of heroin in Arizona, which is almost one-third of all heroin seized along the entire southern border. Agents acknowledge that they catch only a small fraction of what goes through.

Much of the heroin that enters this country comes hidden in cars, concealed in suitcases, squeezed inside hollowed fire extinguishers, or strapped to the thighs, crotches and chests of Mexicans and Americans who cross between the two countries.

To the special agents assigned to Homeland Security Investigations, a division of Immigration and Customs Enforcement, mules are the first link of a knotted chain that may or may not lead to the agents' ultimate prize: a top drug trafficker.

"It's about preventing the narcotics from entering the community," said Jesus Lozania, the agent in charge in Nogales. "It's taking down the organization from the bottom all the way to the top: the mules, the people who coordinate the logistics, the persons who handle the money after the narcotics are sold in the United States. That cash has to make its way back to Mexico."

It is about building conspiracy cases bit by bit.

That morning at the border, three special agents noticed the black letters stamped on the bricks of heroin: LEY. "That's probably from the Chino Leys, probably Sinaloa," said one of the agents, who declined to provide his name because he works undercover.

The Chino Leys, he said, are one of the drug distribution organizations in the Sinaloa cartel, which controls the routes that slice through Arizona, aimed for the Northeast. Cleveland, New York and New Jersey are main destinations for Sinaloa's heroin these days.

The driver said he had borrowed his cousin's car to come to Nogales to buy sweaters. The disbelieving agent pressed on. The driver crossed his arms.

"The guy's not talking," the agent said. *FERNANDA SANTOS*

HUNTINGTON, UTAH

Staying Clean in the High Desert

As she drives to work each morning, past horse ranches and nodding oil pumps, Marsha World stops to give her son, Kolton, a pale yellow pill to help keep him off heroin for another day.

There are few options for drug treatment in the high desert of central Utah, a remote expanse of struggling coal mines, white-steepled Mormon towns and some of the country's highest opiate death rates.

The lone doctor licensed to prescribe one addiction-treating drug has a waiting list. The main detox center is the county jail. So mothers like Ms. World occupy the lonely front lines of a heroin crisis that has reached deep into the remotest corners of rural America.

The sun was just skimming over the sagebrush hills when Ms. World climbed out of her car and palmed that day's naltrexone pill for her 30-year-old son. Unlike other medications Mr. World has taken over 11 years of addiction and rehab, jail and relapse, this one seemed to help.

Mr. World was in a treatment program ordered by the local drug court, and Ms. World had promised the judge she would keep the pills at her house and bring one to him. Every day.

The rate of prescription overdose deaths among the 32,000 people sprinkled across two neighboring counties in this corner of Utah is nearly four times the state

average. Addiction has rippled through ranks of miners who relied on pain pills after years of digging coal and working in the power plants.

Karen Dolan, who runs the Four Corners Behavioral Health center in the nearby town of Price, the only substance-abuse facility for miles, said three of her staff members had lost family members to addiction. At the power plant where her husband works, some of his co-workers' family members have died of overdoses. Heroin accounts for 31 percent of the clinic's admissions, up from 3 percent in 2010.

"People call every day and say, 'Do you have an opening?'" Ms. Dolan said. "We don't have any money to pay for medication-assisted treatment, and we don't have prescribers to provide treatment."

After years struggling with heroin addiction in Salt Lake City, Mr. World moved back in 2013, to the community where he had grown up in a loving family that went to Mormon services on weekends. (He is no longer a part of the church.)

But it was no sanctuary. When Mr. World found a stray Chihuahua on the road a few months ago, it turned out the dog's young owner was in jail because of an opiate addiction. And getting drugs here proved just as easy as in the city: One Facebook message to an acquaintance did it.

But it has been more than 300 days since he last used. His days now are work, therapy, random drug tests at the sheriff's office and morning visits from Mom.

"Love you," she said after he took his pill. She hugged her son and his boyfriend goodbye, and drove to her job at the dry cleaner. *JACK HEALY*

MILWAUKEE

In the End, Uncomprehending

Sometimes they call themselves "the last responders."

They work in the county medical examiner's office, in a low-slung brick building downtown in the shadow of an old Pabst factory. Here is where they take over after a drug addiction has been more powerful than pleas from family, 12-step programs or even Narcan.

"We're the end of the line," said Sara Schreiber, the forensic technical director, walking through the autopsy rooms to talk about the office's part in the opioid addiction epidemic — a crisis that has hit especially hard here.

Last year, 299 people in Milwaukee County died of drug-related overdoses. One of them was the medical examiner's own son.

Adam Peterson died in September at the age of 29, found unresponsive in a friend's apartment. "At this time I am not speaking publicly about Adam's death, and I appreciate your forbearance as my wife and I work through this issue," his father, Brian L. Peterson, the medical examiner, wrote in an email.

Dr. Peterson has continued his work despite his grief. He oversees a staff of nearly 30 people — administrators, toxicologists and laboratory employees — who have perhaps never been more overwhelmed. They are confronting a surge of drug-related deaths in Milwaukee County, the most populous county in Wisconsin, with nearly one million people in the city and suburbs.

They have witnessed an alarming rise in drug-related deaths for years now: 251 deaths in 2014, 255 in 2015, and they surpassed those figures in 2016. Dr. Peterson's son was among those who died last summer in a surge of overdoses that in seven weeks took more than 70 lives.

Ms. Schreiber has witnessed much of the epidemic. The victims have been mostly middle-aged; more male than female; more white than black.

As she walked through the laboratory, she pointed out the epidemic's effects. Now, the machines that analyze blood to help determine the ever-more-toxic blends of drugs are running far more often. They're juggling more cases and analyzing more specimens than before.

Ms. Schreiber and her colleagues struggle with questions that they cannot answer. What can they do to stem the epidemic? How can they influence people while they are still alive?

It's hard to know where to begin, she said. "You can't outrun it."

JULIE BOSMAN

A version of this article appears in print on January 8, 2017, on Page A11 of the New York edition with the headline: Opioid Tide From Coast to Coast.

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How the opioid epidemic became America's worst drug crisis ever, in 15 maps and charts

Drug overdoses now kill more Americans than HIV/AIDS did at its peak. These maps and charts tell the story.

Updated by German Lopez and Sarah Frostenson | Mar 29, 2017, 12:51pm EDT



America is in the middle of its deadliest drug crisis ever.

With all the other news going on, it can be easy to lose track of this fact. But it's true: In 2015, more than 52,000 people died of drug overdoses, nearly two-thirds of which were linked to opioids like Percocet, OxyContin, heroin, and fentanyl. That's more drug overdose deaths than any other period in US history — even more than past heroin epidemics, the crack epidemic, or the recent meth epidemic. And the preliminary data we have from 2016 suggests that the epidemic may have gotten worse since 2015.

This situation did not develop overnight, but it has quickly become one of the biggest public health crises facing America. To understand how and why, I've put together a series of maps and charts that show the key elements of the epidemic — from its start through *legal* painkillers prescribed in droves by doctors to the recent rise of the highly potent opioid fentanyl.

1) Drug overdoses now kill more people than gun homicides and car crashes combined



To understand just how bad the opioid epidemic has gotten, consider these statistics: Drug overdoses in 2015 were linked to more deaths than car crashes or guns, and in fact killed more people than car crashes and gun homicides combined. Drug overdoses in 2015 also killed more people in the US than HIV/AIDS did during its peak in 1995. So just as HIV/AIDS lives in the American mind as a horrible epidemic, the current opioid epidemic should too.

2) Drug, painkiller, heroin, and other opioid overdose deaths are still on the rise



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Drug overdose deaths in America

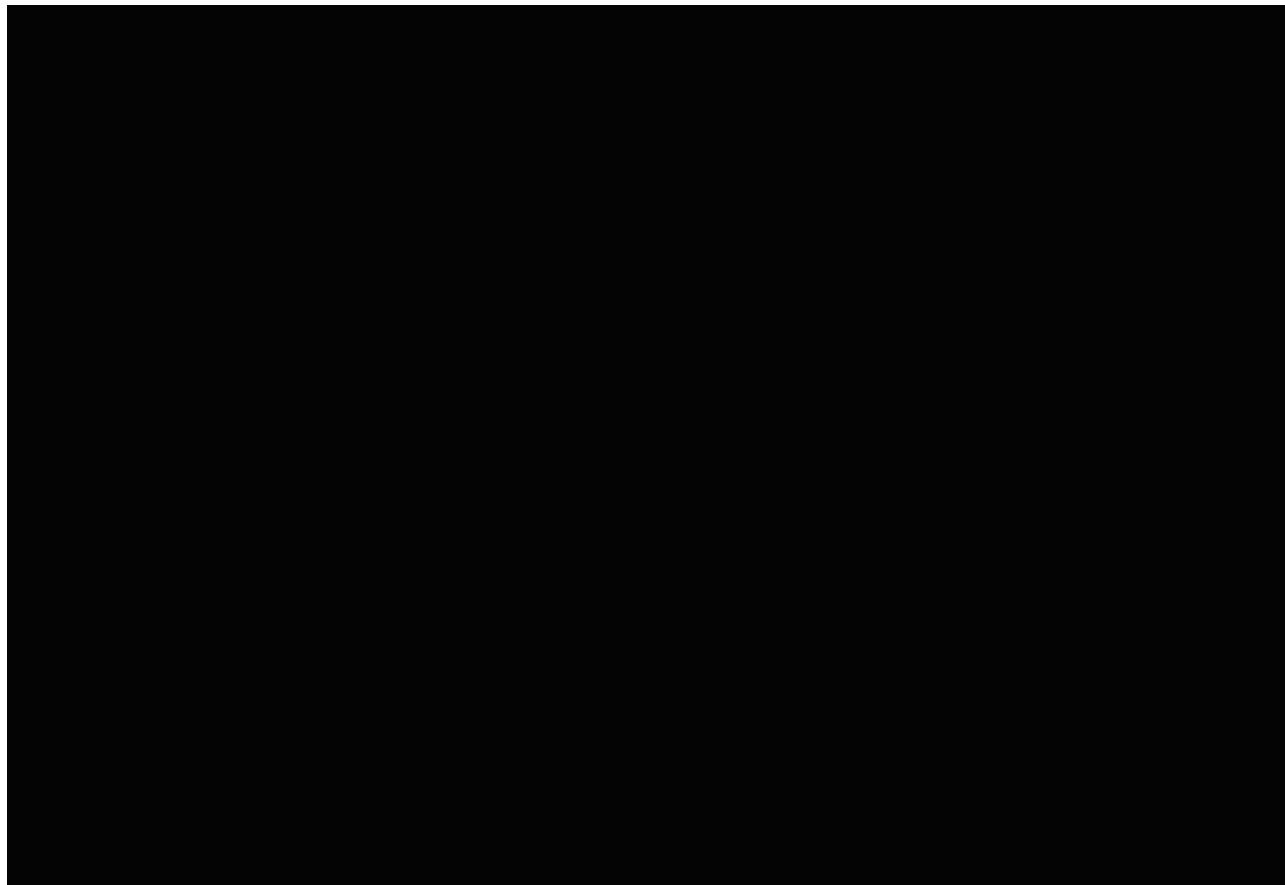
*The numbers for 2016 are preliminary estimates

**Some deaths on this chart may overlap if they involve multiple drugs

It took years of increasing deaths to get to this point, but the opioid epidemic has only gotten worse over time. The result is horrifying: Between 1999 and 2015, more than 560,000 people in the US died to drug overdoses — a death toll larger than the entire population of Atlanta.

The epidemic has by and large been caused by the rise in opioid overdose deaths. First, opioid painkiller overdoses began to rise, as doctors began to fill out a record number of prescriptions for the drugs in an attempt to treat patients' pain conditions. Then, people hooked on painkillers began to move over to heroin as they or their sources of drugs lost their prescriptions. And recently, more people have begun moving to fentanyl, an opioid that's even more potent and cheaper than heroin. The result is a deadly epidemic that so far shows no signs of slowing down.

3) Opioid overdoses are one reason US life expectancy declined for the first time in decades

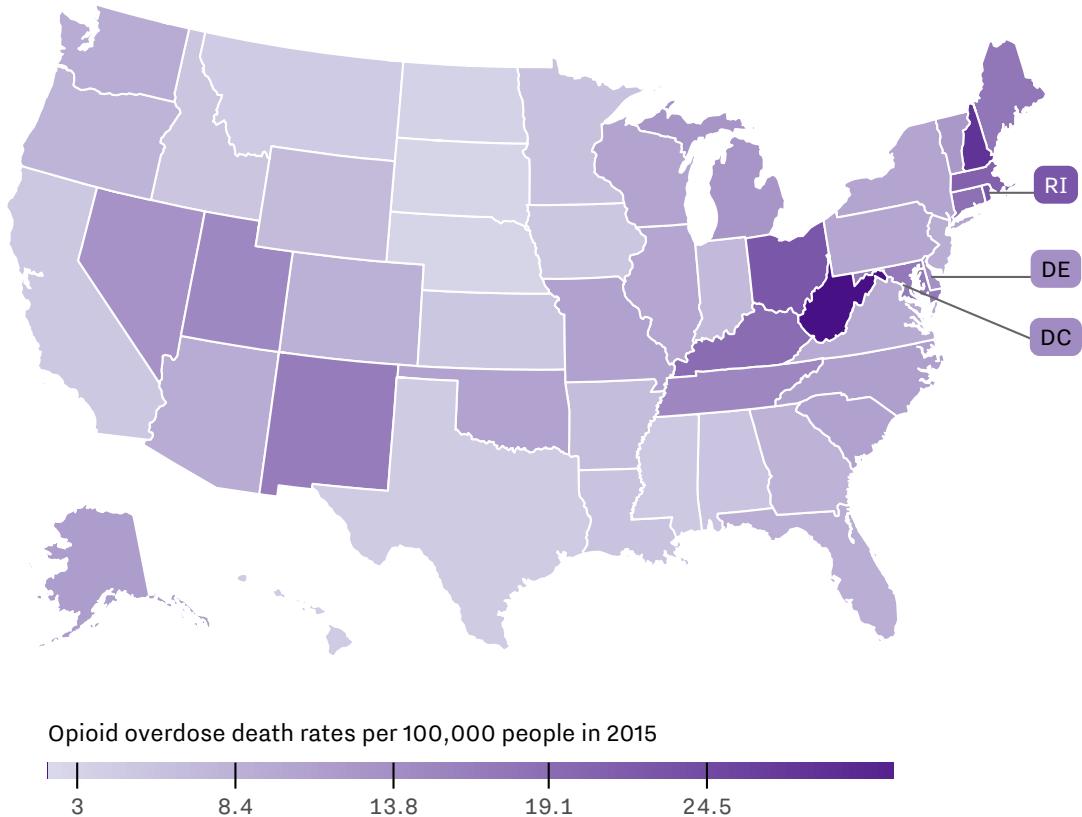




In 2015, US life expectancy dropped for the first time in decades. There are many causes behind the drop, including rising rates of diabetes, obesity, and suicide. But a big reason for the decrease was the rise in alcohol poisonings and drug overdoses.

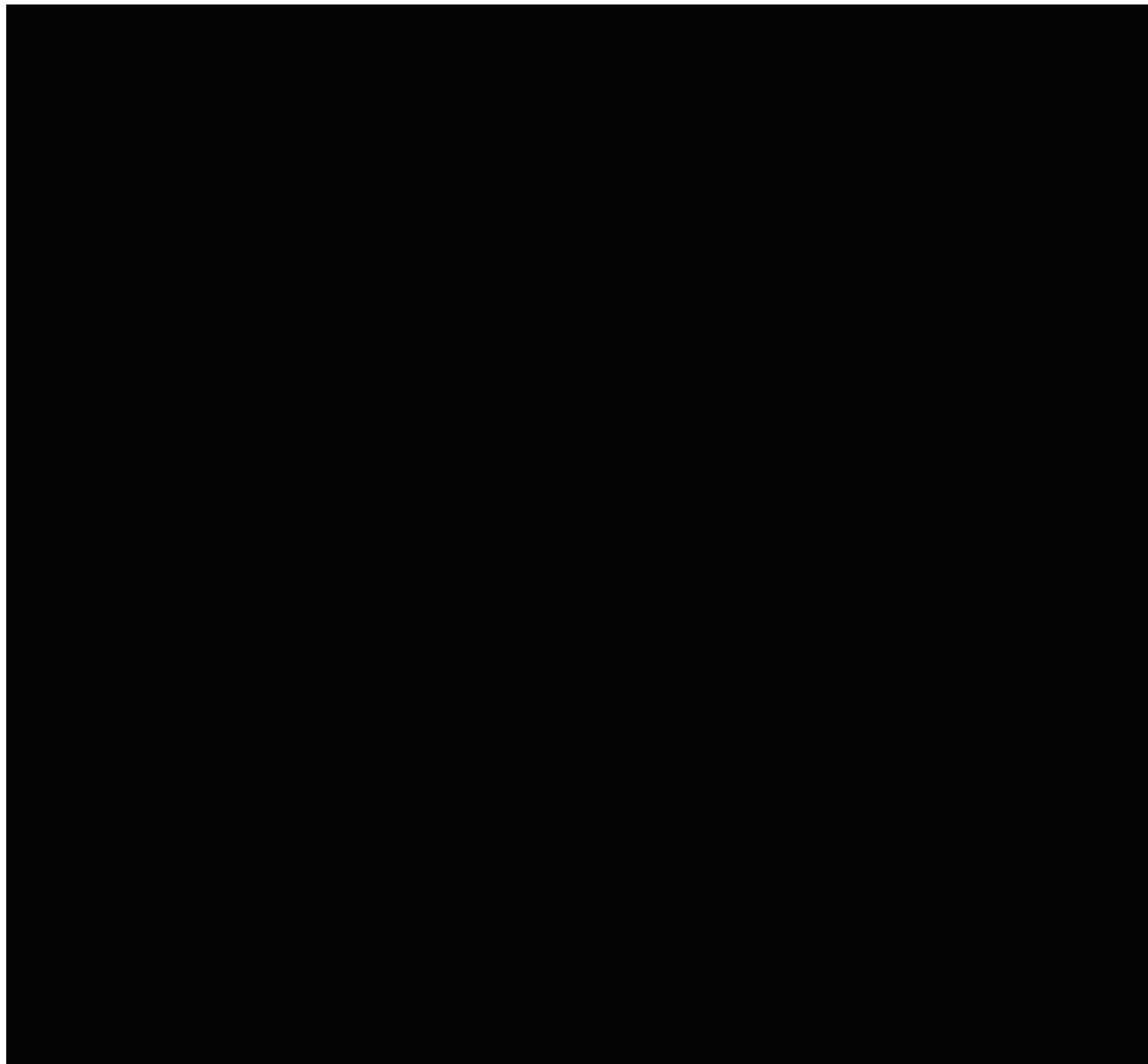
4) The epidemic is much worse in some states than others

The opioid epidemic, by state



Not every state in America has been equally impacted by the opioid epidemic. States like West Virginia, New Hampshire, Rhode Island, and Ohio have been hit particularly hard, suffering far more deaths than even their neighbors on an annual basis. And the epidemic has generally been concentrated along the Rust Belt and New England — due in large part, it seems, to the enormous number of painkiller prescriptions that doctors doled out in those areas.

5) By and large, the drug overdose epidemic has hit white Americans the hardest

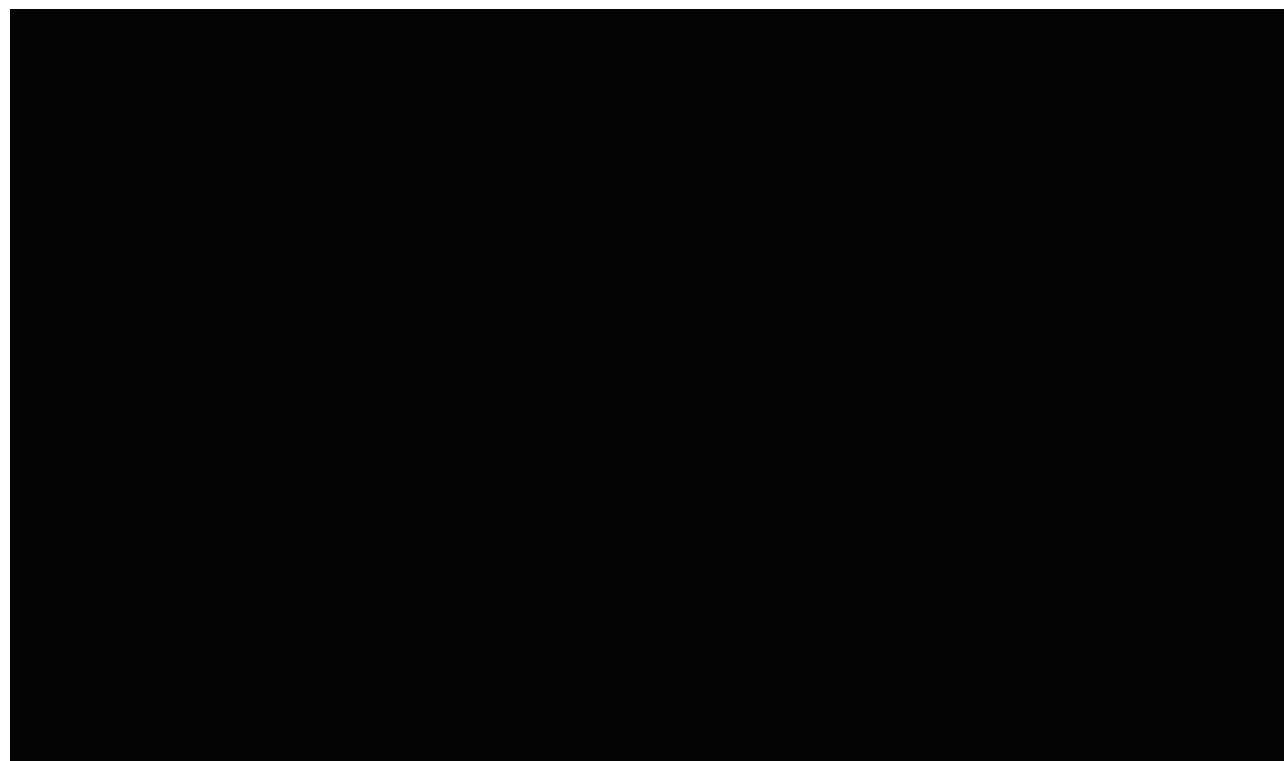


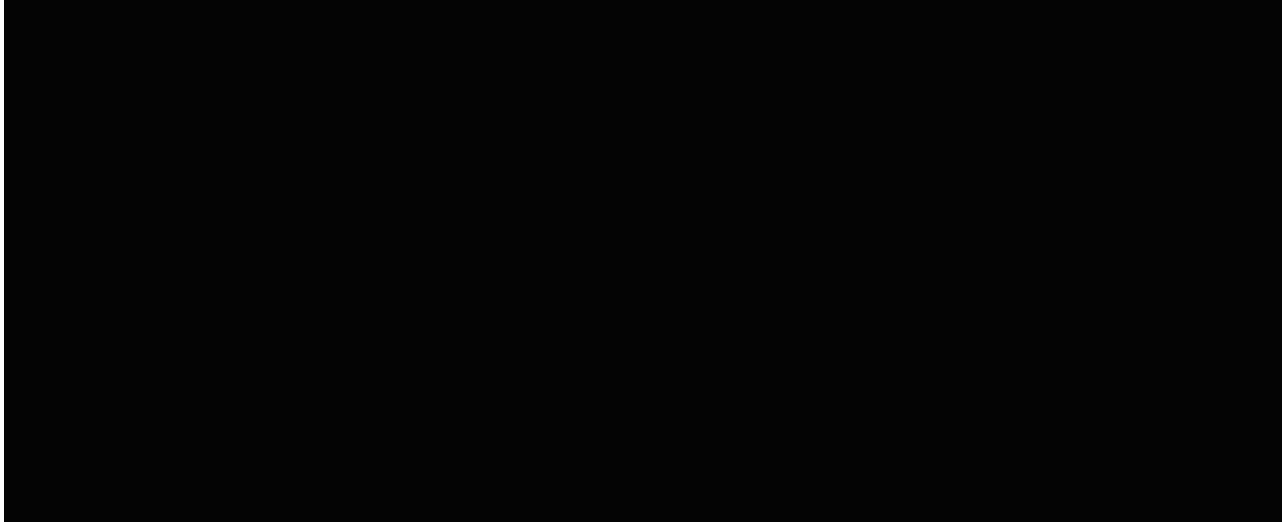


The drug overdose epidemic hasn't hit people of all racial groups equally either, with white Americans suffering far more overdose deaths than their black and Latino peers. As the chart above shows, this is a shift from before the 2000s, when past drug crises tended to hit black, urban communities much harder.

One reason for the disparity may, ironically, be racism against nonwhite Americans. Studies show that doctors are more reluctant to prescribe painkillers to minorities, because doctors mistakenly believe that minority patients feel less pain or are more likely to misuse and sell the drugs. In a perverse way, this shielded minority patients from the tsunami of opioid painkiller prescriptions that got white Americans hooked on opioids and led to a wave of deadly overdoses.

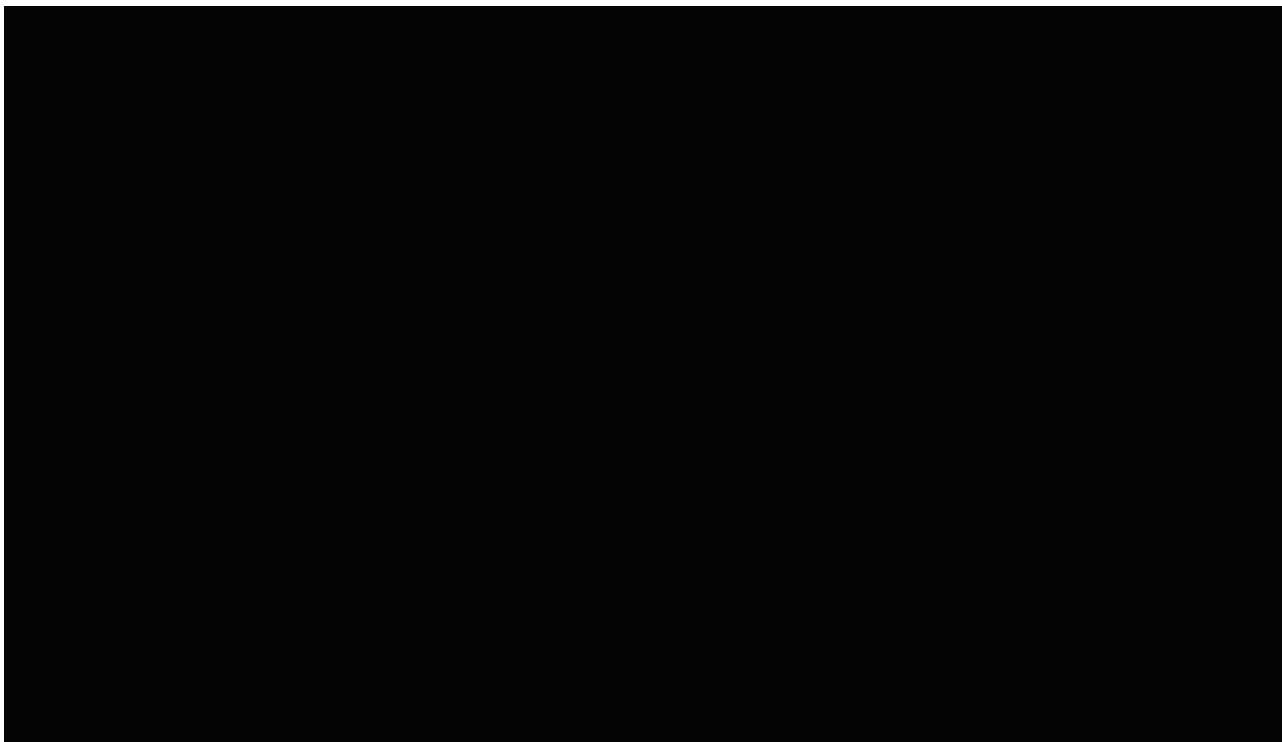
6) Americans consume more opioids than any other country

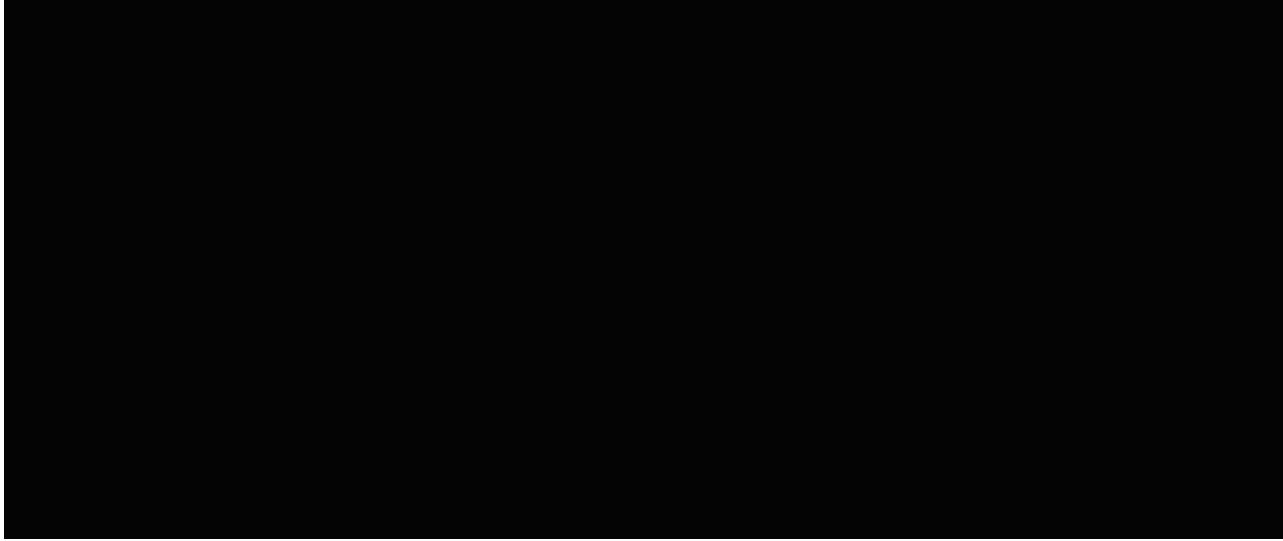




This is perhaps the most important chart to understand why America in particular is suffering from the epidemic: Simply put, the US consumes far more opioid painkillers than any other country in the world. When a country collectively consumes more of a deadly, addictive drug, it's obviously going to have more deaths as a result of those drugs.

7) In some states, doctors have filled out more painkiller prescriptions than there are people



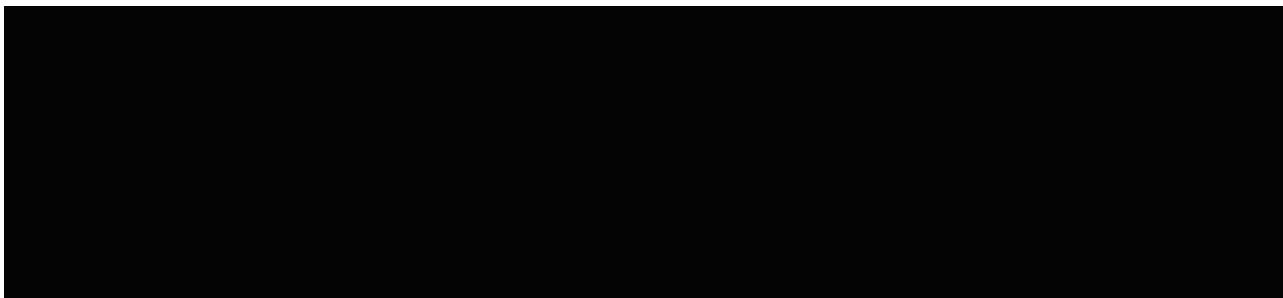


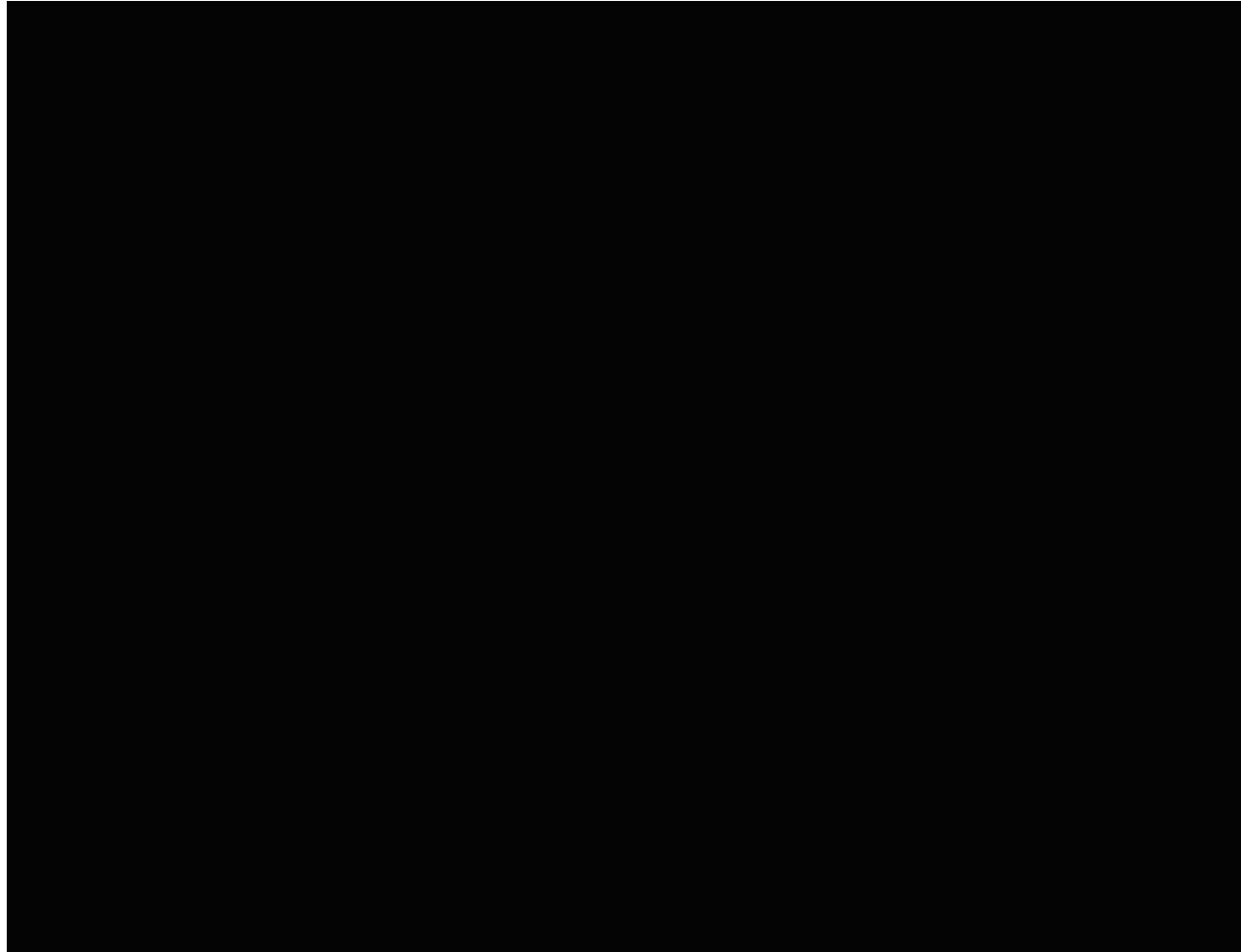
Centers for Disease Control and Prevention

So why do Americans consume so many opioids? In short, it's because doctors have prescribed a lot of them. Starting in the 1980s and '90s, doctors were under pressure to take pain more seriously. There was some good reason for that: About 100 million US adults suffer from chronic pain, according to a 2011 report from the Institute of Medicine. So doctors — under pressure from drug companies, medical organizations, government agencies, and pain patient advocates — resorted to opioids.

The result: In 2012, US physicians wrote 259 million prescriptions for opioid painkillers — enough to give a bottle of pills to every adult in the country. And these pills didn't just end up in patients' hands; they also proliferated to black markets, were shared among friends and family, landed in the hands of teens who rummaged through parents' medicine cabinets, and so on.

8) Drug companies have made a lot of money from opioids



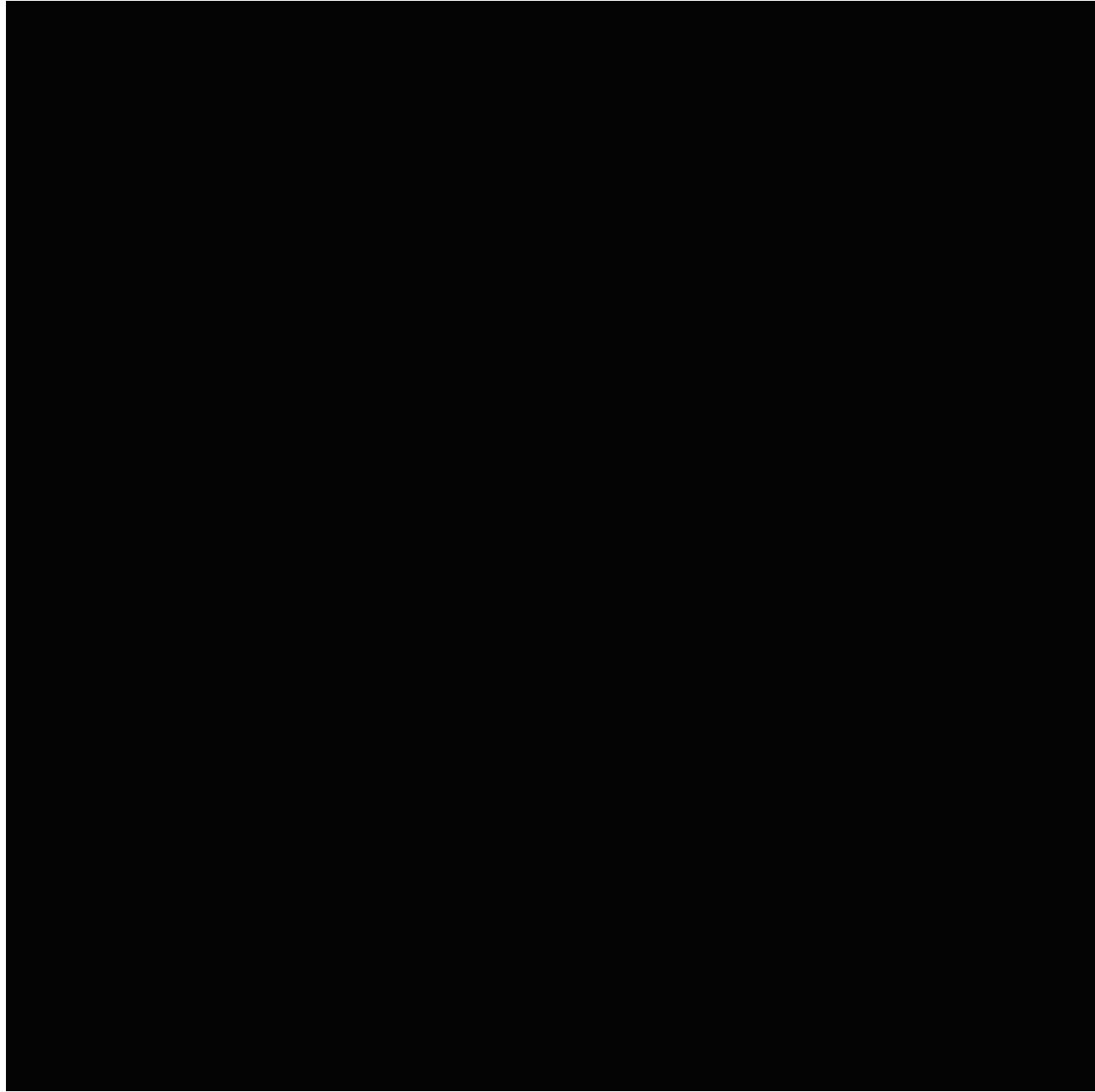


Annual Review of Public Health

One of the undeniable contributors to the opioid epidemic is drug companies. Seeing the demand for doctors to take pain more seriously, drug companies pitched newer products like OxyContin as the big medical solution. The marketing was extremely misleading, often presenting these drugs as safer and more effective than other painkillers and opioids on the market — when these drugs were in fact extremely addictive and dangerous.

Ultimately, some drug companies would pay for their misleading marketing. Purdue Pharma, producer of OxyContin, in 2007 paid hundreds of millions of dollars in fines for its false claims. And Purdue and other opioid producers remain in legal battles over the drugs to this day.

9) At the same time, Americans report greater levels of pain



Despite the increase in painkiller prescriptions, studies show that Americans generally report higher levels of chronic pain than they did before the epidemic started.

This gets to a crucial point in the opioid epidemic: Despite drug companies' marketing, opioid painkillers may not be an effective treatment for chronic pain. There's simply no good scientific evidence that opioid painkillers can actually treat long-term chronic pain as patients grow tolerant of opioids' effects, but there's plenty of evidence that prolonged use can result in very bad complications, including a higher risk of addiction, overdose, and death.

Yet painkillers, due to how they work, can actually trick patients into believing that the drugs are effective for chronic pain. As Stanford psychiatrist Anna Lembke, author of *Drug Dealer, MD*, recently explained:

It's absolutely true that if you were to get opioids for your pain, it would be like a magical cure for about a month or maybe two. But after a while, there's a very high likelihood that they would stop working. And then you would have two problems: You would have your pain, and you would be dependent on this drug and experience painful withdrawal if you try to get off [opioids].

So after prolonged use, some patients who try to stop taking opioids will feel a sudden surge of pain. They'll likely think the pain they're feeling is their chronic pain coming back in full force now that the painkillers are gone. In reality, the opioids have likely stopped working on the original chronic pain due to tolerance, and the surge of pain is an entirely new pain from drug dependence withdrawal. Only by slowly weaning themselves off opioids can they permanently stop this new withdrawal-induced pain.

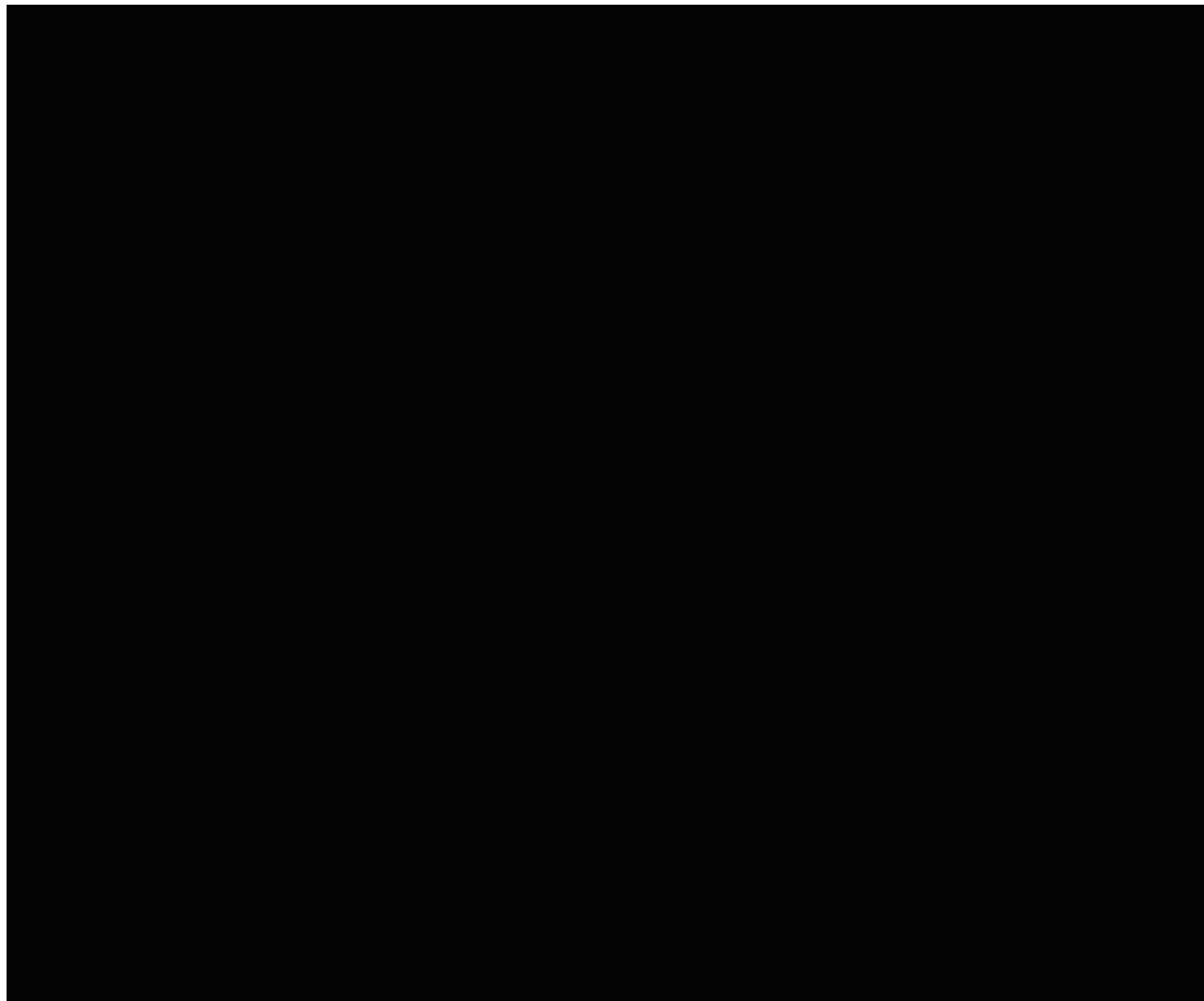
There's also evidence that opioids can make pain worse. Opioids might make people more sensitive to pain. They might weaken the bones, leading to painful fractures.

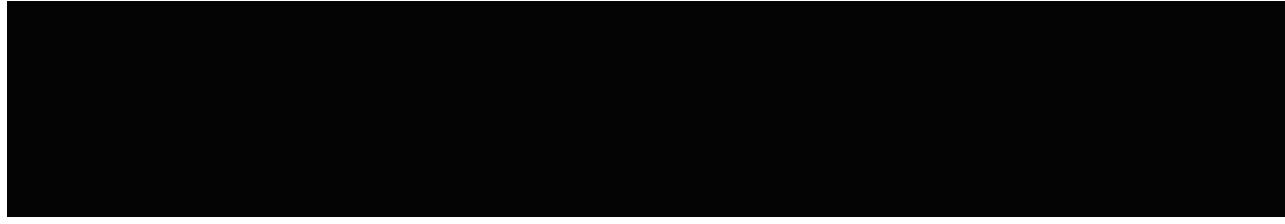
And they might get people to behave in ways that expose them to greater injury, which of course would lead to

far more pain. Lembke gave an example of someone popping extra pills to let them do more yard work: “If you take additional opioids, you can’t hear the signals from your body about what you shouldn’t be doing, and then maybe you’re going to do some long-term damage above what’s already been done.”

AD

10) Painkillers are often prescribed for long periods of time, even though there's no evidence they effectively treat chronic pain





Despite the lack of evidence for opioids' effectiveness in treating chronic pain, doctors have resorted to prescribing the opioids to patients for exorbitant periods of time. (I can't even count the number of people, from friends to family to colleagues, who have told me that a doctor prescribed extra weeks of pills "just to be safe.")

This, it turns out, is extremely dangerous: A recent study from the Centers for Disease Control and Prevention revealed that the risk of dependency increases dramatically for each day someone is prescribed opioids. Overly long prescriptions, then, contribute to the cycle of addiction, overdose, and death that's spread across the US in the past few years.

Ideally, doctors should still be able to get painkillers to patients who truly need them (and they can work for some individual chronic pain patients) — after, for example, evaluating the patient's history of drug addiction. But doctors, who weren't conducting even such basic checks, are now being told to give more thought to their prescriptions.

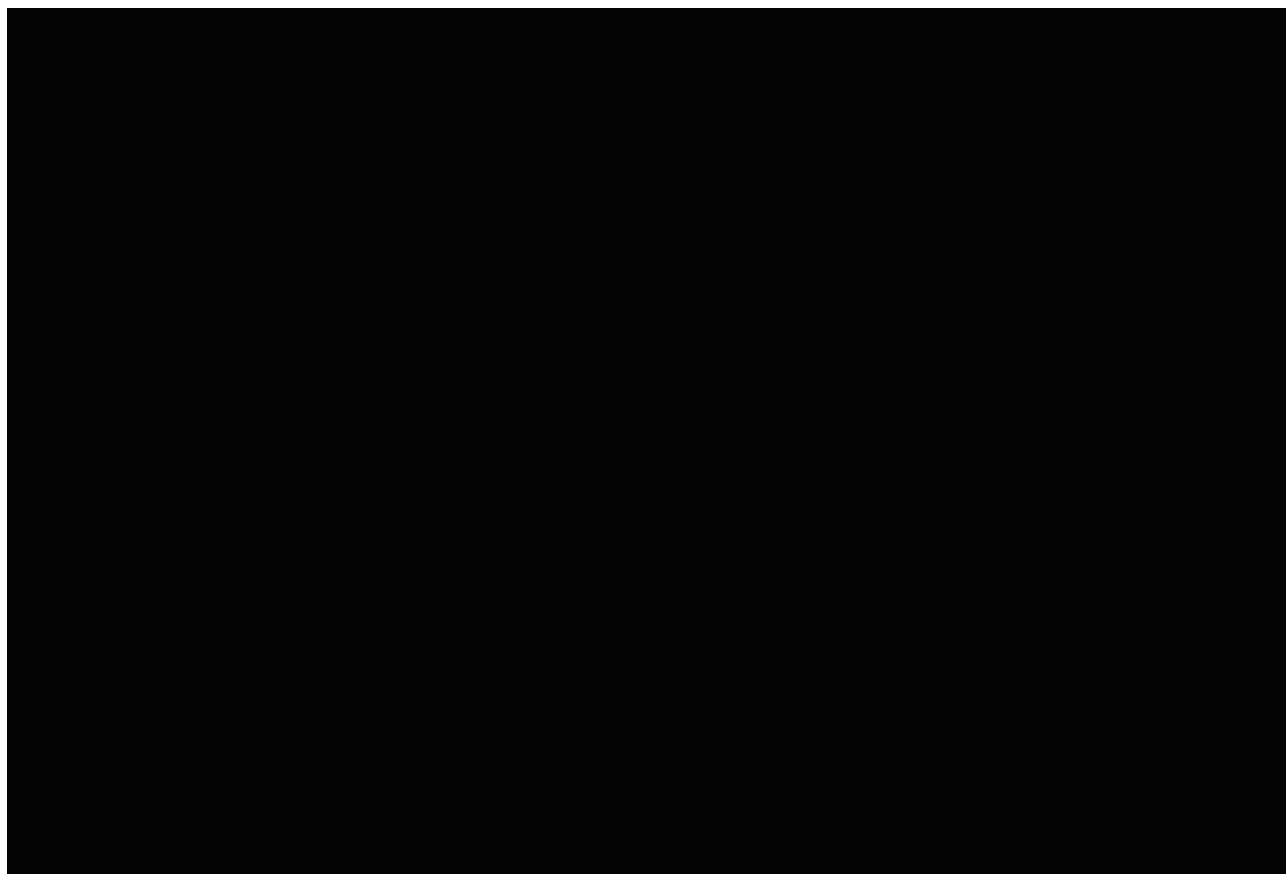
AD

Yet if opioids aren't the answer to chronic pain, what is? There are alternative treatments, although these can involve more work (and money) than just taking a pill — such as physical therapy, massage, and acupuncture. More exotic but less tested ideas include medical marijuana and kratom.

But the reality is that, at some level, some patients struggling with chronic pain may just have to learn to live with the pain. This may sound cruel, but it's something that's asked of patients dealing with other chronic conditions when medicine just has no good answers. For example, a patient with heart disease might be told that she needs to eat less or adjust her activity level — potentially ruining her interests or hobbies — to avoid a heart attack as she becomes older.

"You can't use the pills to extend your limits. You have to accept that there's some things you just won't be able to do anymore," Lembke told me. "People are very resistant to that idea. I think that speaks to some of the core hope for at least Americans that they should really be able to keep doing what they were doing in their 20s, and that somehow a doctor should be able to fix them and make that happen, instead of accepting that maybe that's something that they just can't do anymore."

11) States are now cracking down on opioid prescriptions





As the problem with opioid painkillers continues, different levels of government and regulatory bodies have taken steps to restrict their use. Some states, for example, have limited how long opioid painkillers can be prescribed. The idea is simple: After years of letting these painkillers run amok and kill tens of thousands of people, doctors need to be told to take a much more conservative approach to dangerous drugs.

12) Opioid users moved from painkillers to heroin, because heroin is so cheap



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As governments and regulators cracked down on painkillers, however, many people addicted to the drugs didn't just stop using. Many instead resorted to another opioid to fill their habit: heroin. A 2014 study in JAMA Psychiatry found many painkiller users were moving on to heroin, and a 2015 CDC analysis found people who are addicted to prescription painkillers are 40 times more likely to be addicted to heroin. Not all painkiller users went this way, and not all heroin users started with painkillers, but painkiller use played a big role in leading more people to heroin.

The main reason for this: Heroin is extremely cheap in the black market, despite law enforcement efforts for decades to push up the price of drugs by cracking down on the illicit supply. In fact, over the past few decades, the price of heroin in the US has dramatically dropped — to the point that it's not only cheaper than opioid painkillers sold in the black market, but frequently even candy bars.

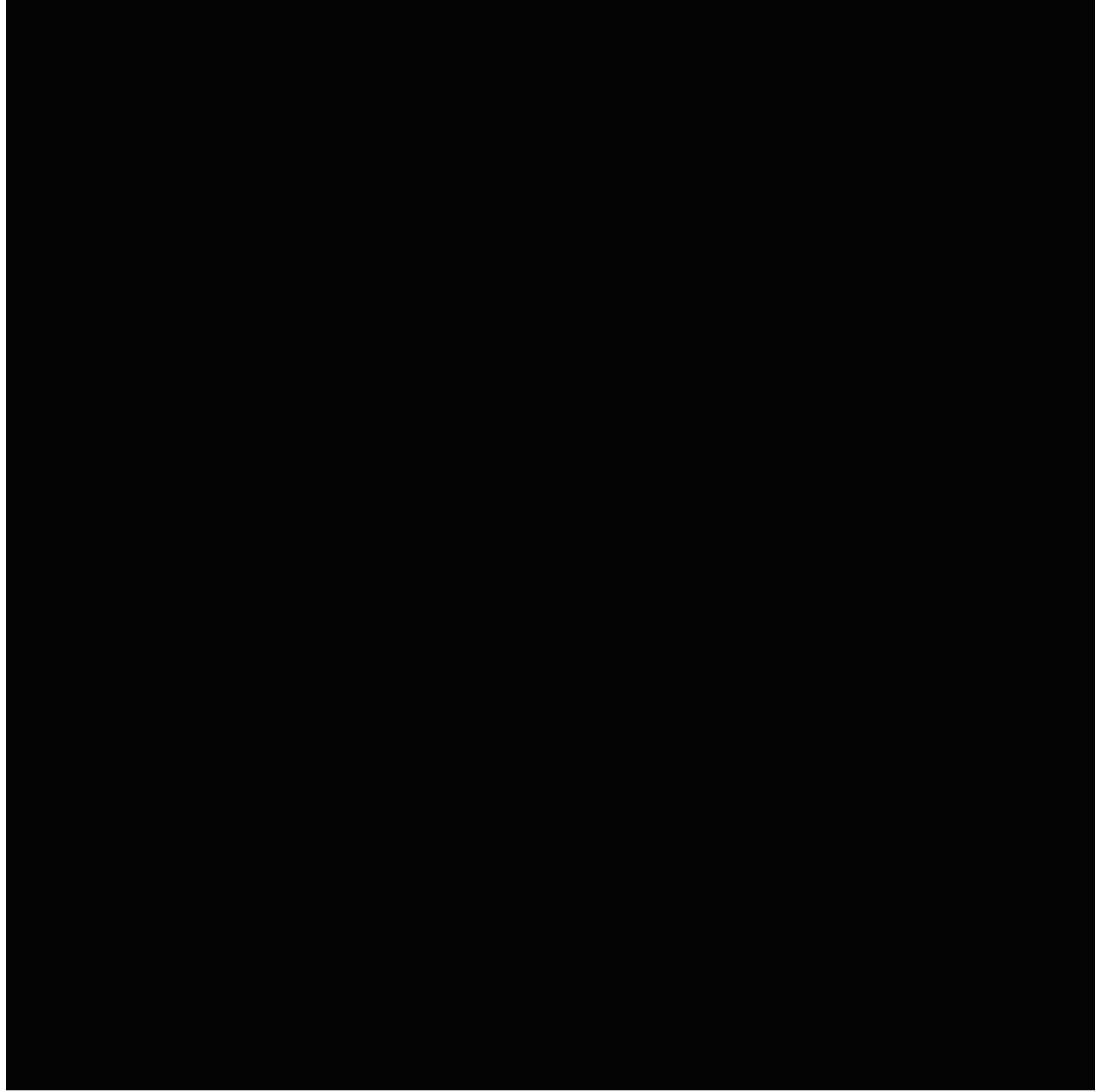
AD

But heroin is also more potent and, therefore, deadlier than opioid painkillers. So even though not every painkiller user went to heroin, just enough did to cause the big spike in heroin overdose deaths that America has seen over the past few years. So now more people die of overdoses linked to heroin than die of overdoses linked to commonly prescribed painkillers.

That doesn't mean cracking down on painkillers was a mistake. It appeared to slow the rising number of painkiller deaths, and may have prevented doctors from prescribing the drugs — or letting them proliferate — to new generations of people who'd develop drug use disorders. So the crackdown did lead to more heroin deaths, but it will hopefully prevent future

populations of drug users, who could have suffered even more overdose deaths.

13) Fentanyl has become a growing problem as well



As if the rise in heroin deaths wasn't bad enough, over the past few years there has been evidence of *another* opioid that's even more potent than heroin leading to more drug overdose deaths: fentanyl. Sometimes drug

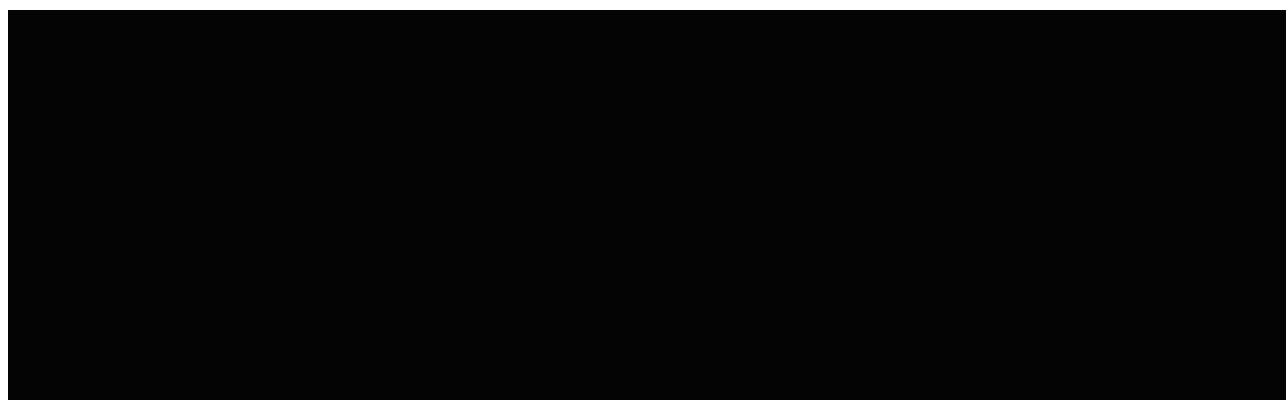
users purposely seek out this drug. But often it's laced in other substances, like heroin and cocaine, without the users knowing it, leading to an overdose.

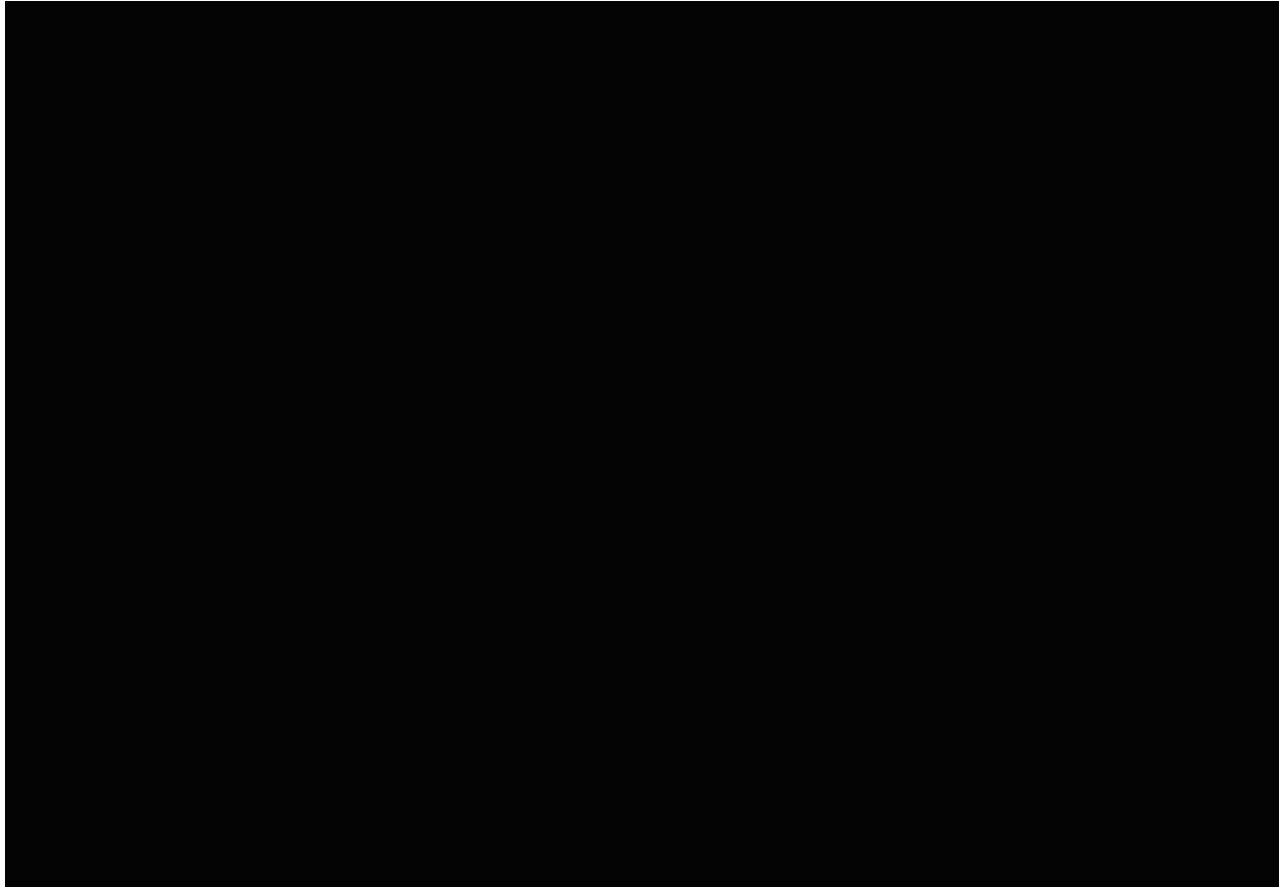
The fact that the efforts to crack down on the supply of opioid painkillers has only led people to even more dangerous drugs hints at another lesson from the epidemic: Just cutting access to opioids isn't enough. As long as people are addicted, they're going to try to find ways to satisfy that addiction, even if it means using more dangerous drugs.

So while cutting access to opioids might in the long term stop the creation of new generations of people with drug use disorders, in the shorter term the country needs to devise solutions for how to get people to stop using drugs and how to make their drug use less deadly and dangerous. That's where drug treatment, including medication-assisted treatment that replaces dangerous opioid use with safer opioids like buprenorphine, and harm reduction efforts, such as clean needle exchanges, can help.

AD

14) Anti-anxiety drugs are involved in more overdoses as well





National Institute on Drug Abuse

Opioid painkillers aren't the only legal drug that's killing more people. Federal data shows that benzodiazepines, such as Xanax and Valium, are also increasingly involved in overdose deaths.

This speaks to another aspect of the drug overdose epidemic: It's not always just one drug killing people. Very often, people use multiple drugs, from painkillers to cocaine to alcohol. This is especially bad because different drugs can heighten other drugs' risk of overdose. Alcohol and benzodiazepines, for instance, are known to compound the overdose risk of opioids.

The data speaks to this: Most benzodiazepine overdoses have involved opioids in the past few years, as the chart above shows. And the Centers for Disease Control and Prevention previously found that 31 percent of opioid painkiller overdose deaths in 2011 were also linked to benzodiazepines.

15) Most people who meet the definition for a drug use disorder don't get treatment



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How many people who meet the definition of a drug use disorder got treatment?



While drug treatment may be the true solution to the opioid epidemic, the reality is it remains inaccessible to a lot of people. According to 2014 federal data, at least 89 percent of people who met the definition for having a drug use disorder didn't get treatment. And that's likely an underestimate: Federal household surveys leave out incarcerated and homeless individuals, who are more likely to have serious, untreated drug problems.

The reasons why vary. People might not have insurance to pay for drug treatment. If they do have insurance, their plans may not fully cover drug treatment. And even if their plans do cover drug treatment, there might not be enough space in treatment facilities to take them, leading to weeks- or months-long waiting periods for care.

In general, all of this suggests that the country as a whole needs to put more resources toward making drug treatment options more widespread, accessible, and affordable. So far, Congress has taken some steps to that end, including a recent \$1 billion boost in drug treatment funding over two years. But as so many people with drug use disorders struggle to get into treatment and the opioid epidemic continues, the call will likely grow for more action.

Was this article helpful?  

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The opioid epidemic: America's deadliest drug overdose crisis

The deadliness of the opioid epidemic has roots in America's failed response to crack

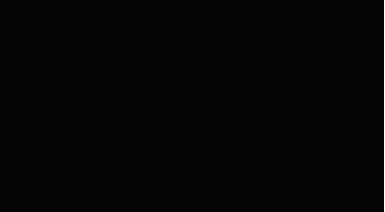
How the opioid epidemic became America's worst drug crisis ever, in 15 maps and charts

The Senate may finally try to hold big pharma accountable for the opioid epidemic

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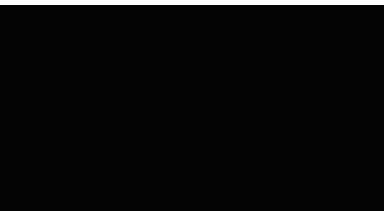
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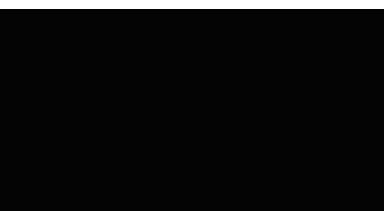
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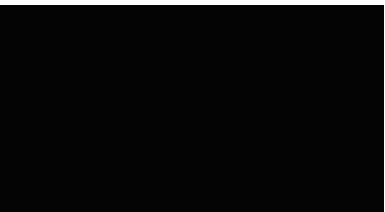
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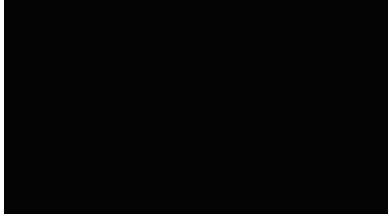
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AD

EXHIBIT 9



GREATER DETROIT AREA HEALTH COUNCIL

2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit



Welcome and
Thank You for Coming!

Moving Forward to Affect Change



GREATER DETROIT AREA HEALTH COUNCIL

2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit



Welcome!

Please Take Your Seats,
The Program is About
to Begin.

Thank You!



GREATER DETROIT AREA HEALTH COUNCIL

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Marie Osborne
WJR Radio Detroit

Emcee



GREATER DETROIT AREA HEALTH COUNCIL

2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit



Kate Kohn-Parrott
President and CEO
Greater Detroit Area Health Council



Tom Watkins
President and CEO
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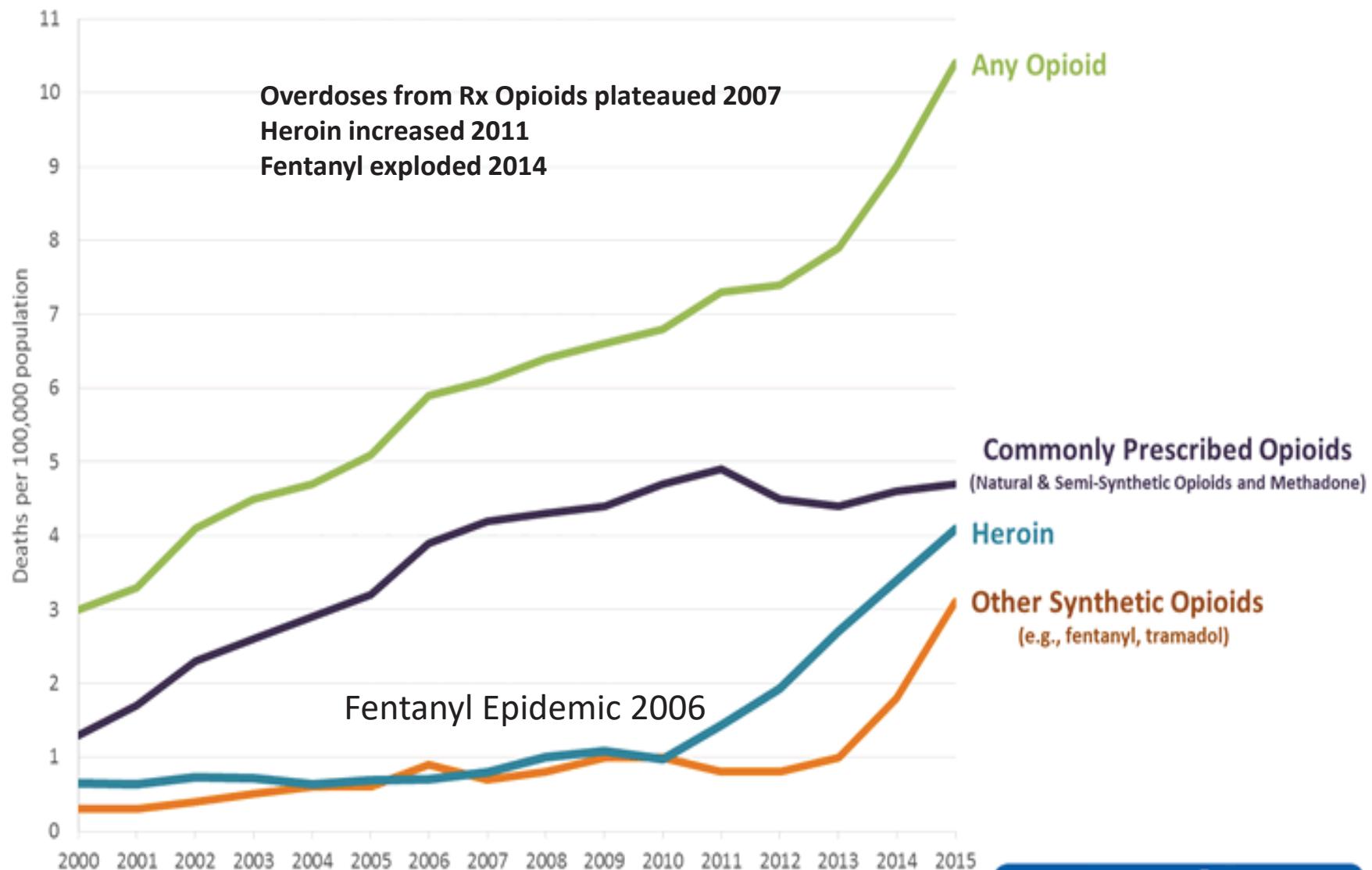


2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit



Cynthia Arfken
Professor
Department of Psychiatry &
Behavioral Neurosciences,
Wayne State University

Overdose Deaths Involving Opioids, United States, 2000-2015

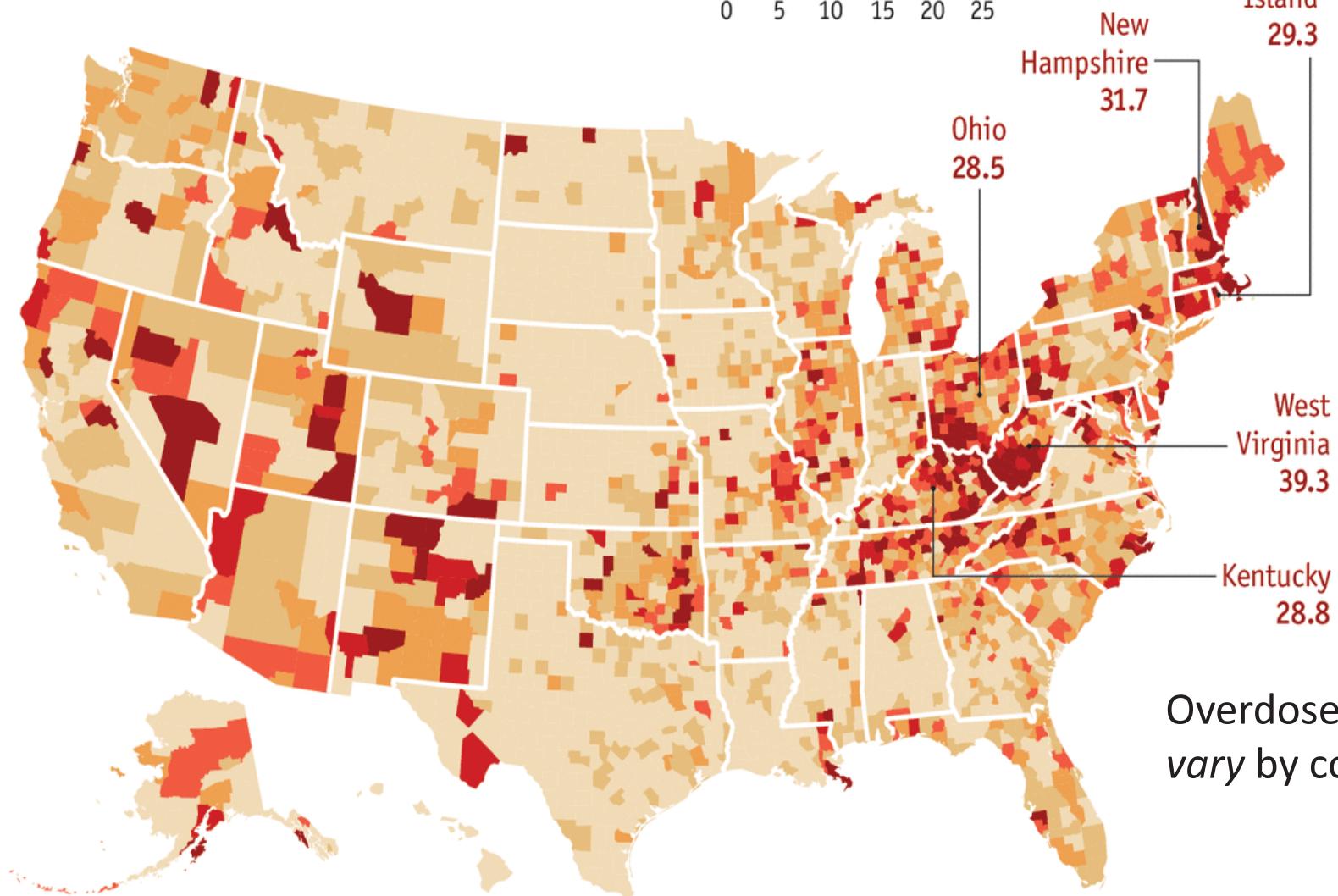


SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2016. <https://wonder.cdc.gov/>.

A deadly dose

United States, overdose deaths involving opioids
By county, 2015

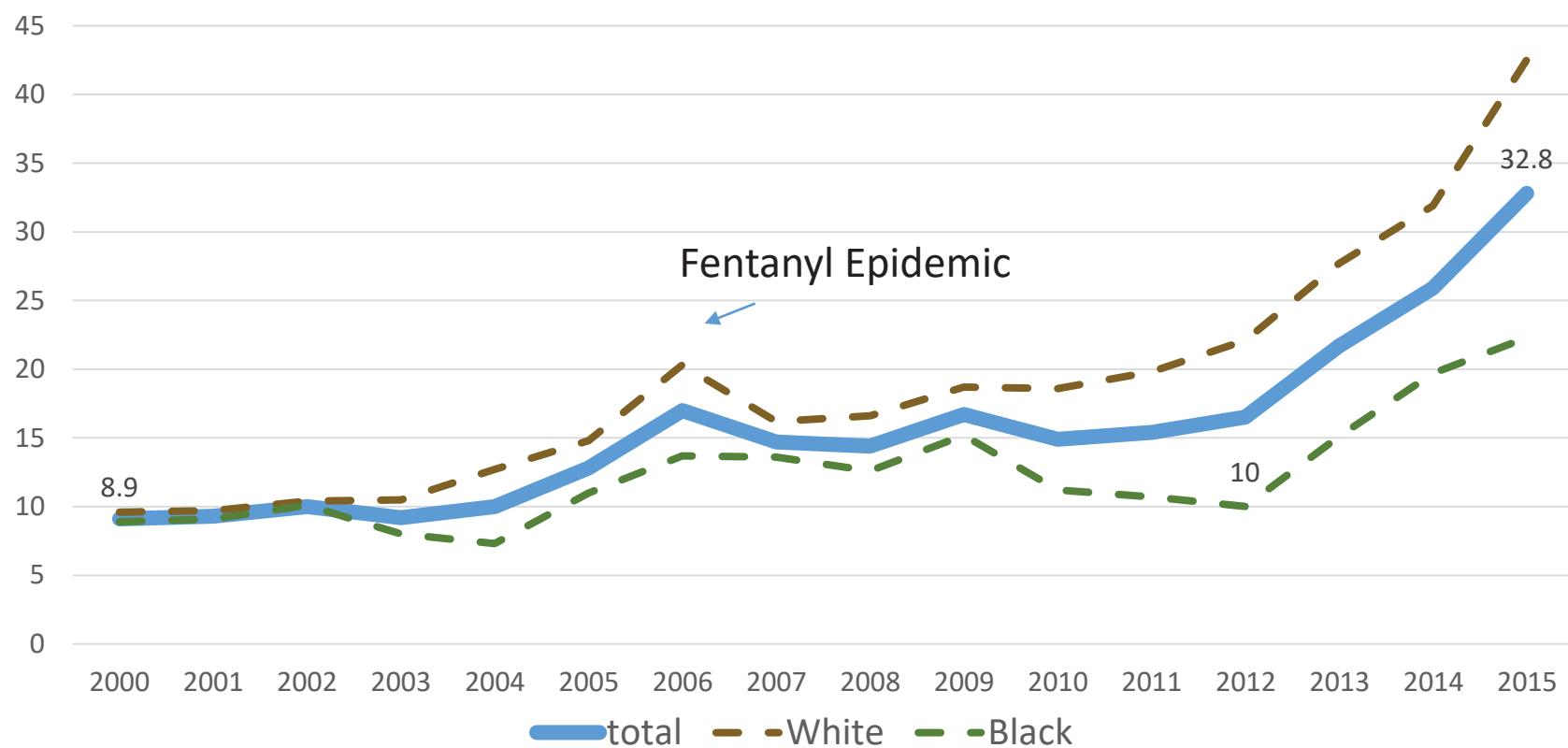
Per 100,000 population



Source: Centres for Disease Control and Prevention

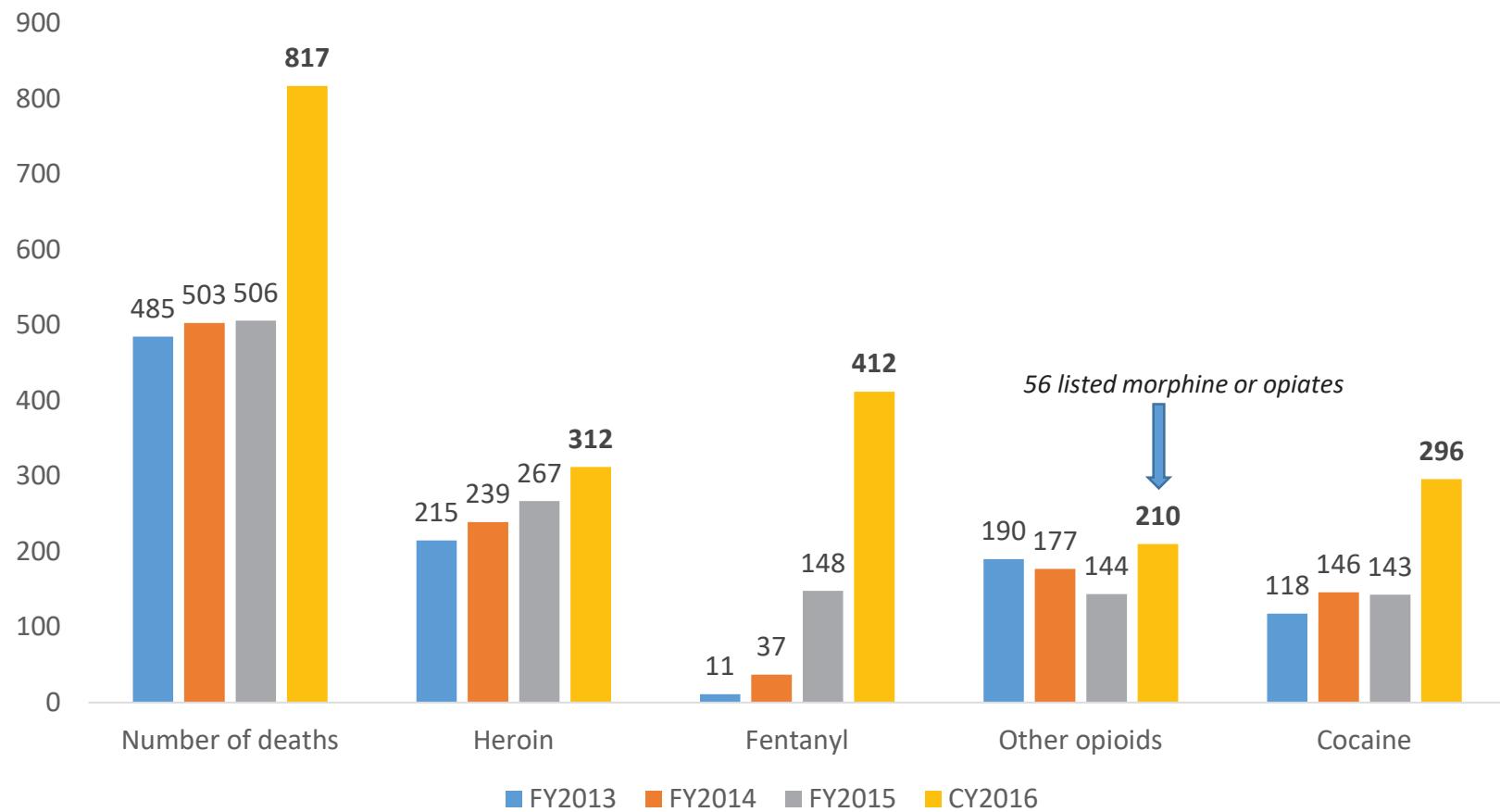
Drug Overdose Deaths per 100,000 residents for Wayne County, total population and by race

Crude Overdose Death Rate



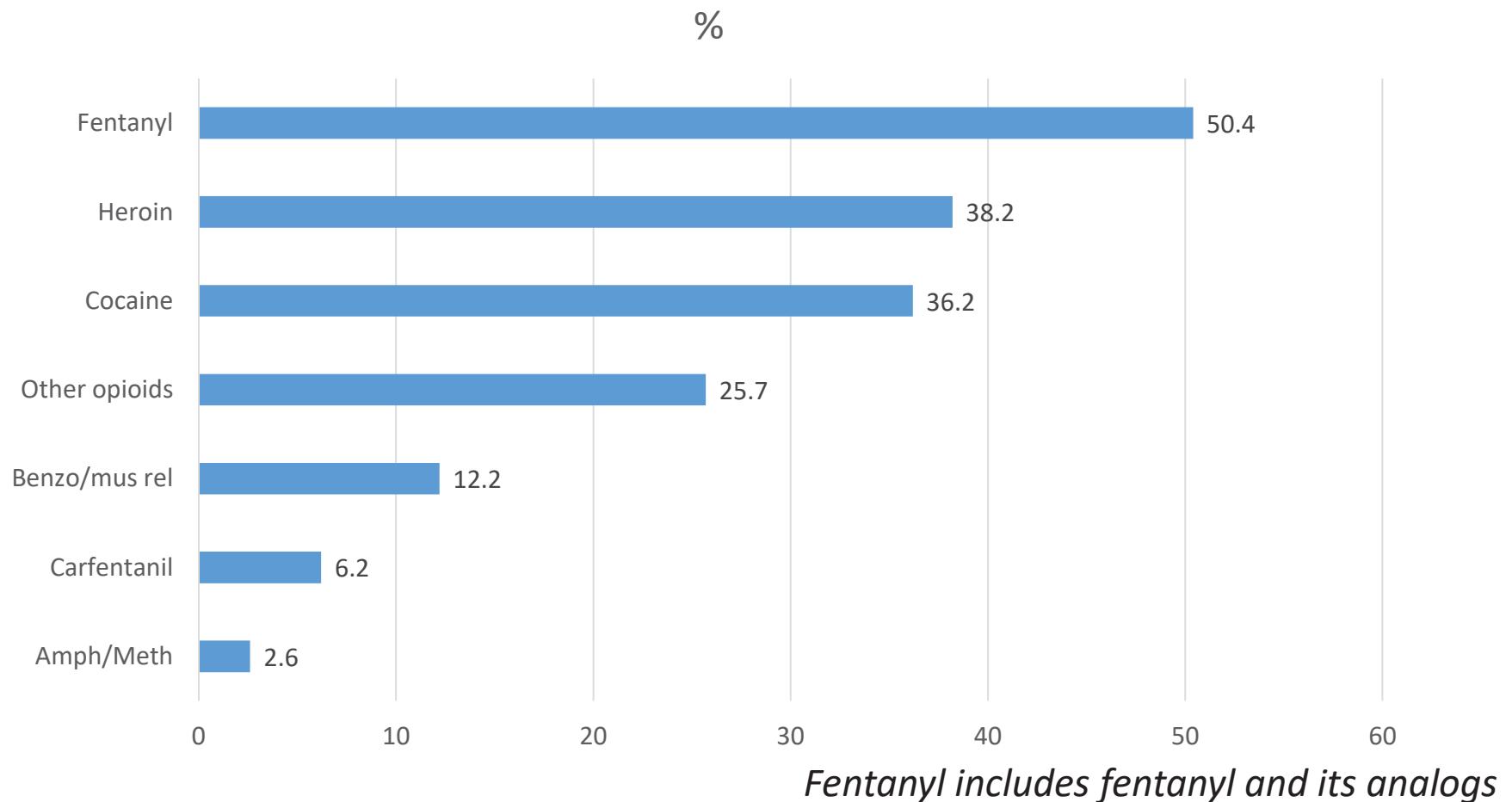
SOURCE: CDC WONDER

The number of drug-related deaths has increased



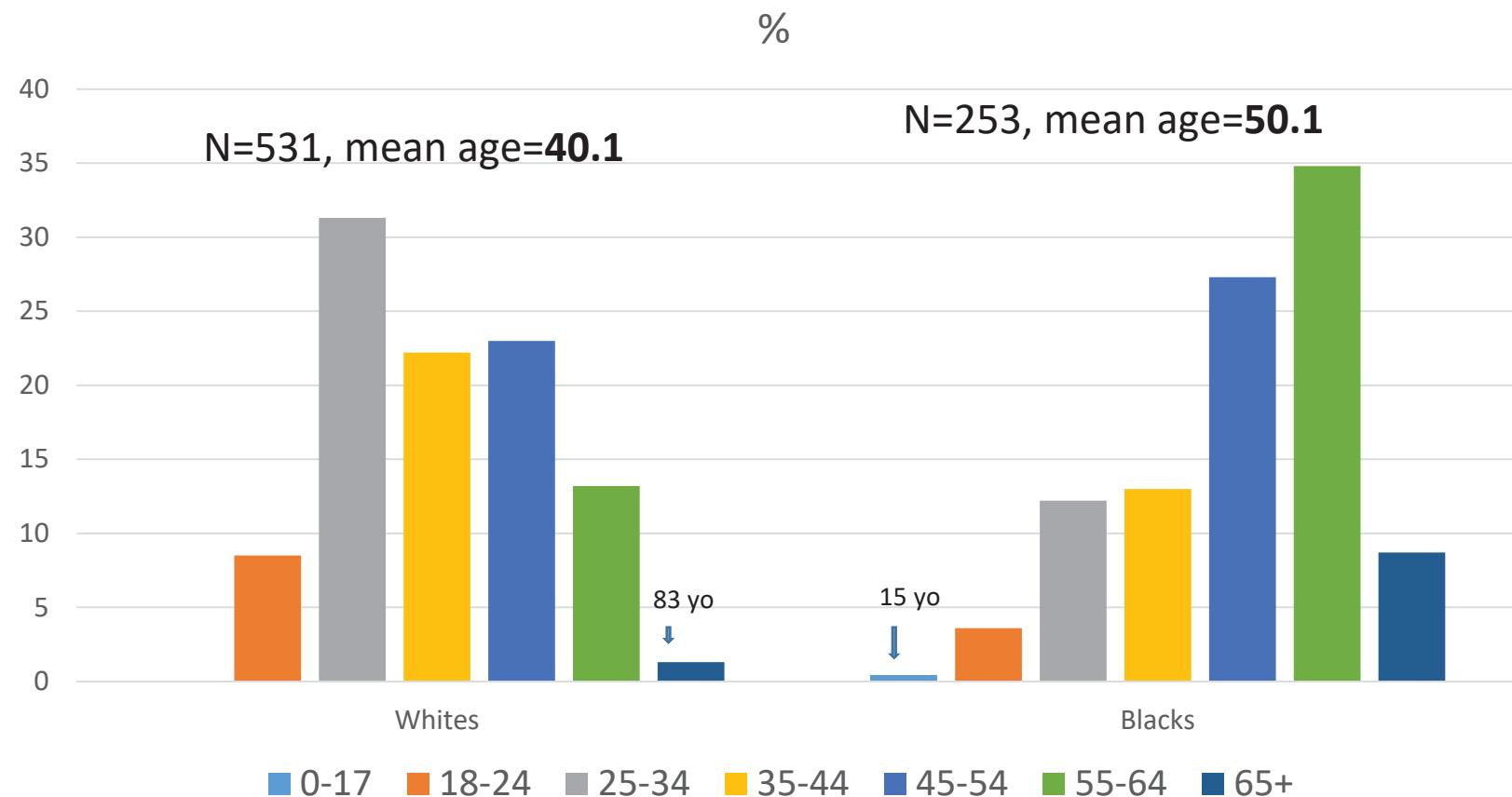
SOURCE: Wayne County Medical Examiner PROVISIONAL DATA.
FY 2015 was October 1 2014 – September 30, 2015

Percentage of 817 deaths caused by select classes of drugs (95.2% ruled accidental) in 2016



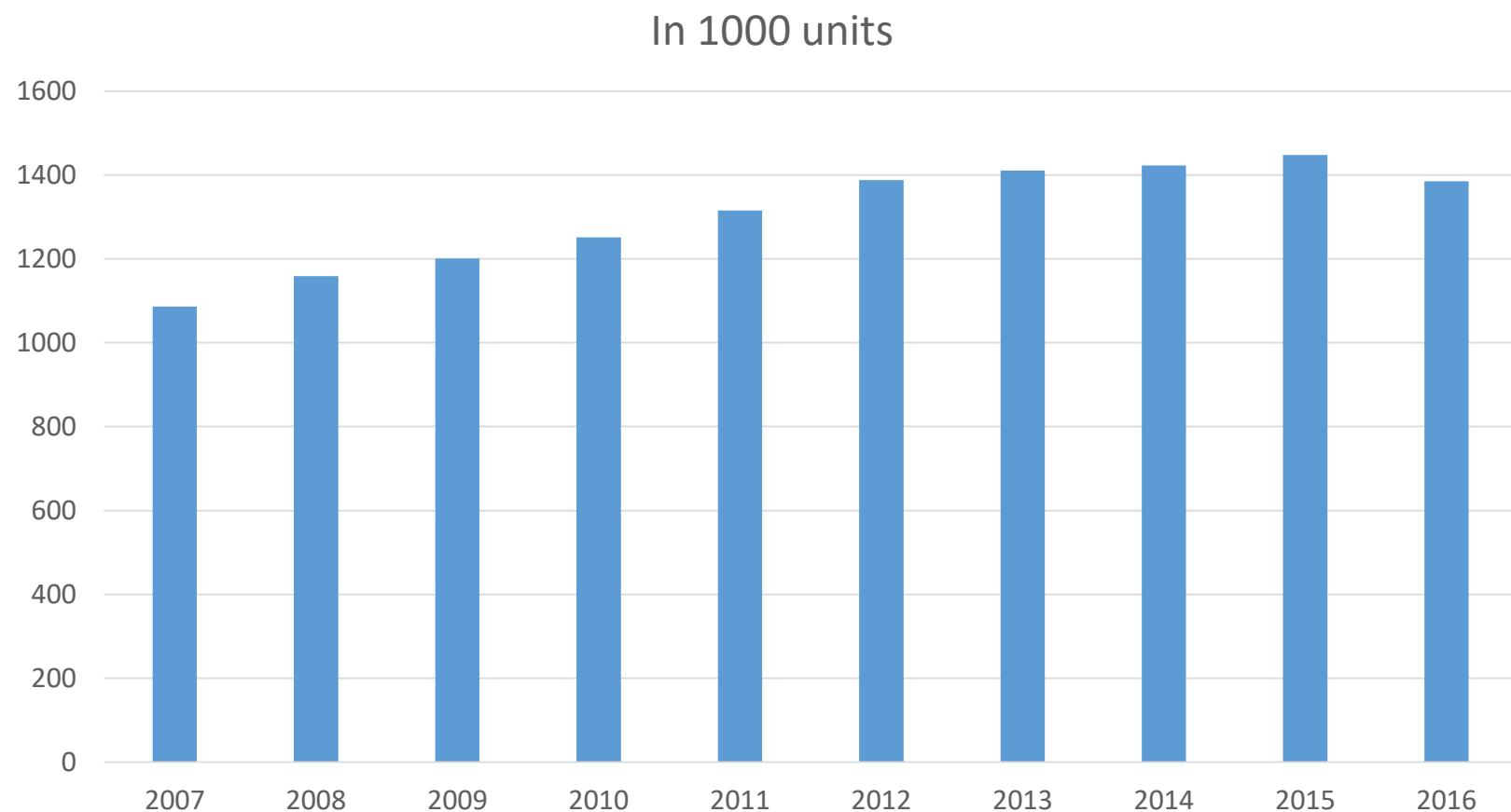
SOURCE: Wayne County Medical Examiner. PROVISIONAL DATA

Black decedents were older than White decedents in 2016



SOURCE: Wayne County Medical Examiner.
PROVISIONAL DATA

Total units of scheduled medications dispensed in Michigan: 2007-2016



SOURCE: Michigan Department of Licensing and Regulatory Affairs



GREATER DETROIT AREA HEALTH COUNCIL

2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit



**Lieutenant Governor
Brian Calley
State of Michigan**



GREATER DETROIT AREA HEALTH COUNCIL

2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit



Dr. Debra A. Pinals
Medical Director of Behavioral Health
and Forensic Programs
Michigan Department of Health
and Human Services (MDHHS)

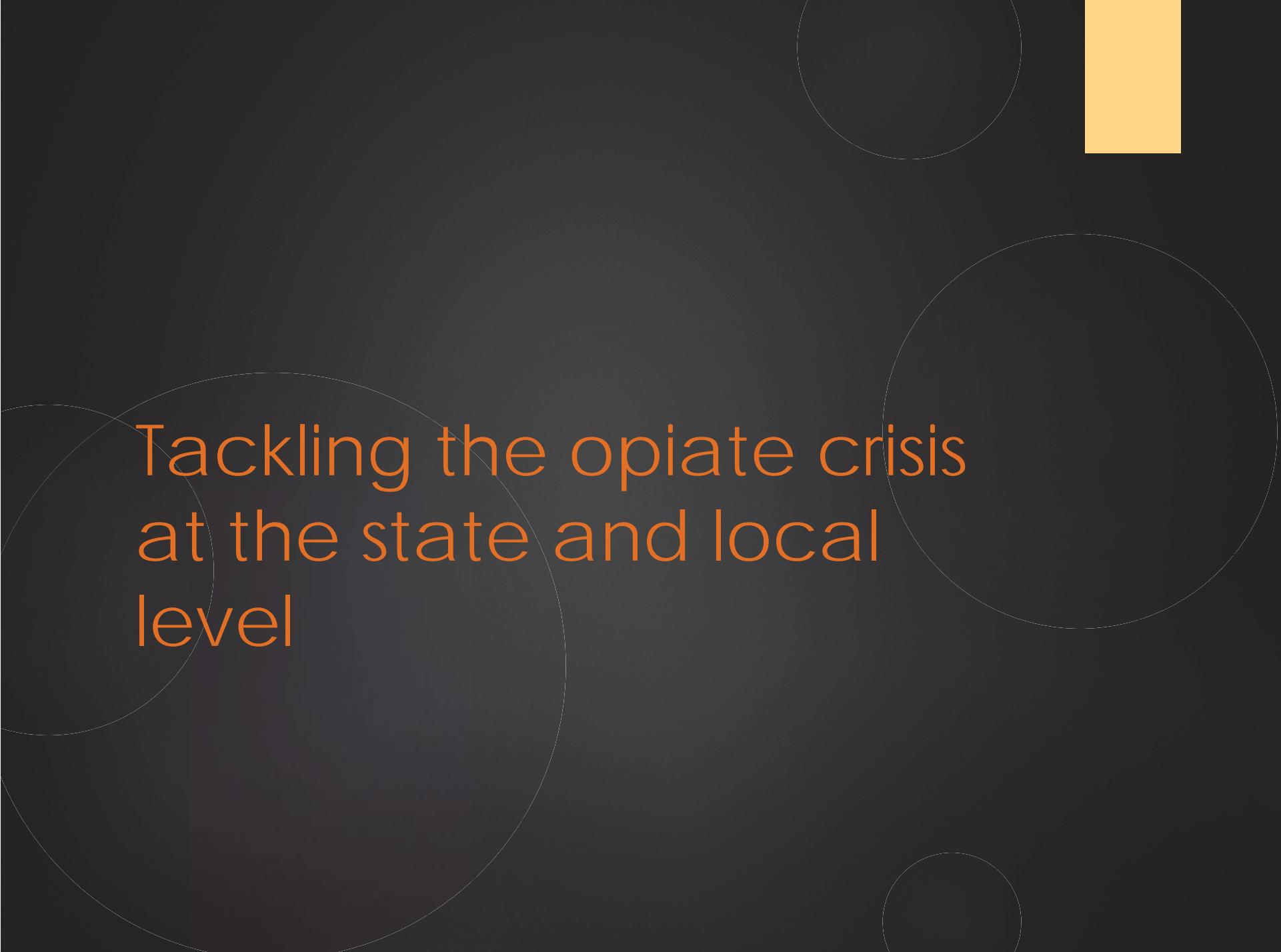
Substance Use Disorders: A Path Forward for Michigan

DEBRA A. PINALS, M.D.

MEDICAL DIRECTOR

BEHAVIORAL HEALTH AND FORENSIC PROGRAMS

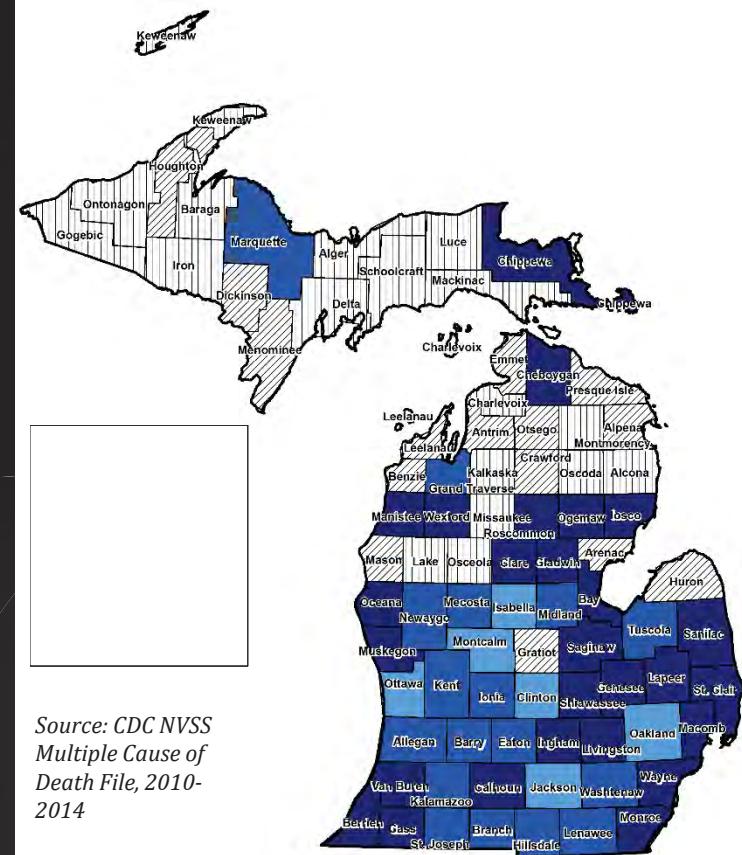
MICHIGAN DEPARTMENT OF HEALTH AND HUMAN SERVICES



Tackling the opiate crisis
at the state and local
level

MICHIGAN

Drug Poisoning Death Rate per 100,000, by County, 2010-2014

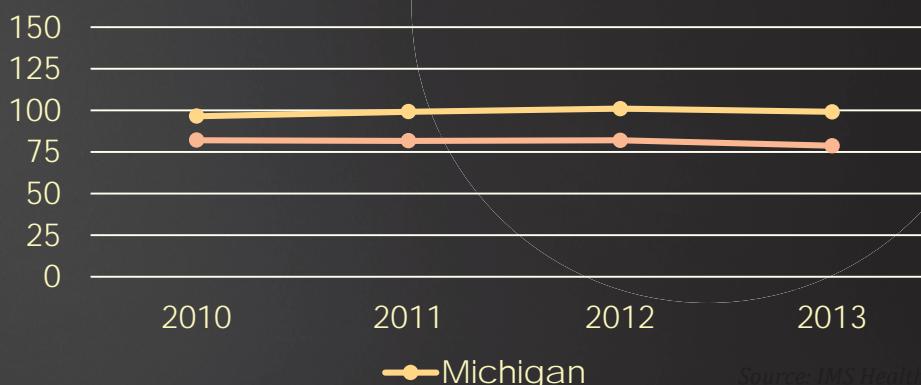


Based on information available as of March 21, 2016

Drug Poisoning Death Rate by State and National (age-adjusted per 100,000 population)



Annual rate of opioid pain reliever prescriptions dispensed by retail pharmacies (per 100 population)



Michigan's Status:

Age-Adjusted Drug Poisoning Death Rate (2014) (Avg. National Rate: 13.5)

18.0 per 100K population

National Rank in Drug Poisoning Death Rate (2014)

16th

Requires ALL Prescribers Receive Appropriate Opioid Prescribing Training

NO

Established a Prescription Drug Monitoring Program (PDMP)

YES [PDMP TTAC State Profiles]

Requires Pharmacy to Submit Data to PDMP within 24 hours

YES [CDC Prevention Status Reports]

Requires PDMP use by ALL Prescribers

NO [CDC Prevention Status Reports]

PDMP Interoperable with other States

Shares info with 20 states [National Association of Boards of Pharmacy]

State Law Explicitly Allows Syringe Service Programs

NO

Permits Distribution of Naloxone by Pharmacists*

NO

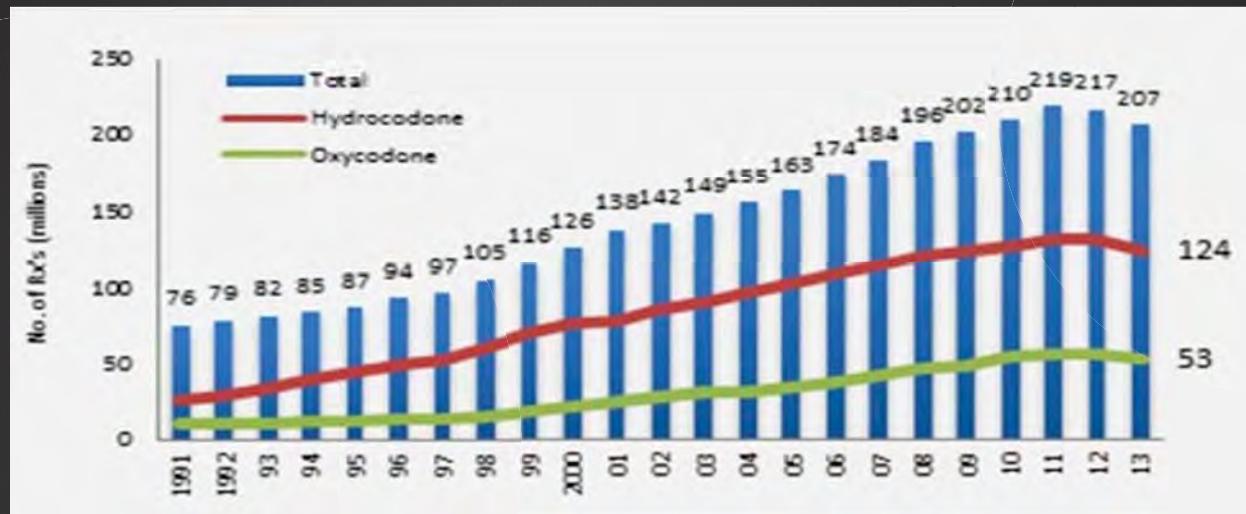
Permits Third Party Prescriptions of Naloxone (eg. Family member, caregiver)

YES [Mich. Comp. Laws § 333.17744b]

*Under a standing order, collaborative practice agreement, or prescriptive authority.

Increase in Prescription of Opioids

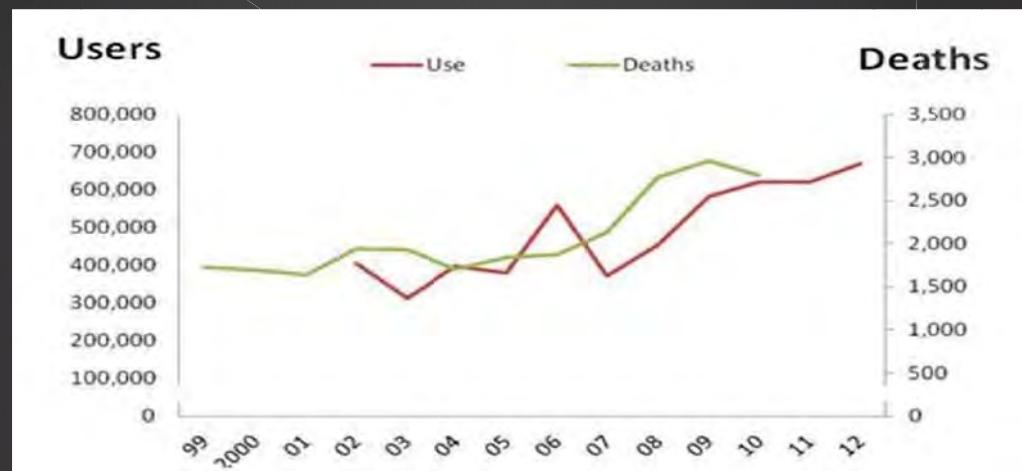
- Hydrocodone and Oxycodone prescribing has increased nearly 300% nationwide since 1991



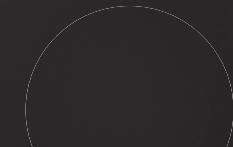
Source: <http://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2014/americas-addiction-to-opioids-heroin-prescription-drug-abuse>

Increase in Heroin Use

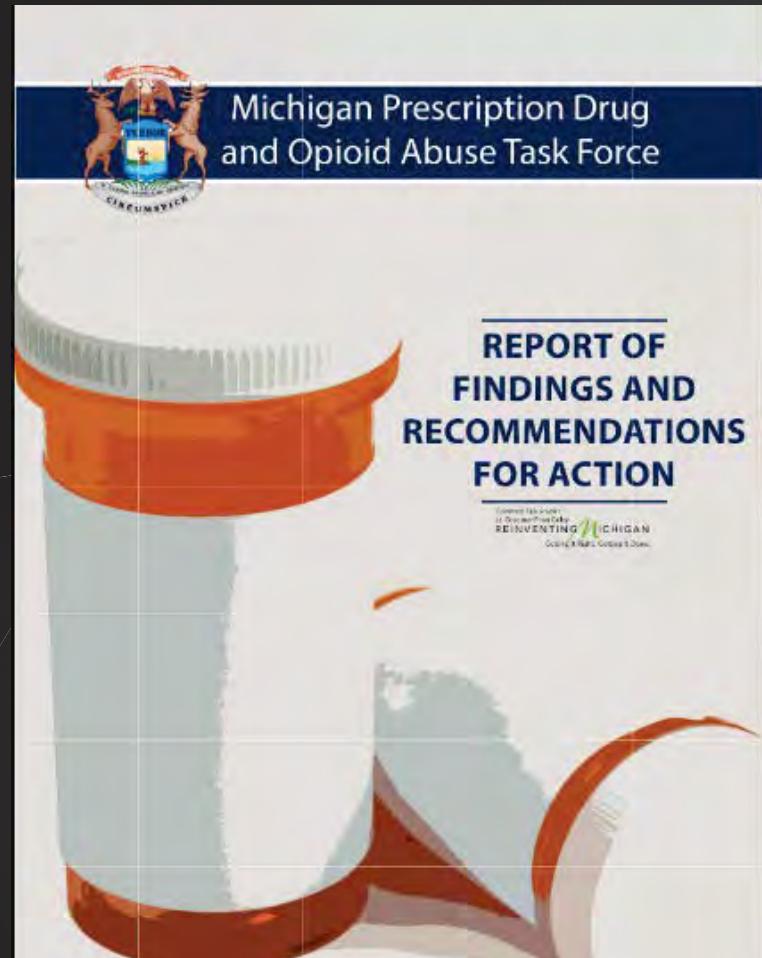
- ▶ Heroin use increased approximately 50% from 2005 to 2010
- ▶ Heroin deaths increased approximately 50% from 2005 to 2010



Source: <http://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2014/americas-addiction-to-opioids-heroin-prescription-drug-abuse>



The State Responds



The 2015 Task Force

- On June 18, 2015, Governor Rick Snyder appointed a task force to address prescription drug and opioid abuse
- Governor Snyder appointed Lt. Governor Brian Calley to lead this effort
- Lt. Governor Calley said "prescription drug and opioid addiction has quadrupled the number of unintentional drug deaths in our state since 1999 and we must come together to reverse this trend before more Michiganders are hurt."

Task Force Recommendations

- ▶ The Task Force report includes 25 primary recommendations and 7 contingent recommendations grouped into the following categories:
 - ▶ Prevention
 - ▶ Treatment
 - ▶ Regulation
 - ▶ Policy and Outcomes
 - ▶ Enforcement

Implementation: Working within and across systems

- ▶ 5 different state agencies are responsible for the implementation of these recommendations:
 - ▶ Department of Health and Human Services
 - ▶ Department of Licensing and Regulatory Affairs
 - ▶ Michigan State Police
 - ▶ Attorney General
 - ▶ Department of Insurance and Financial Services

Prevention

Prevention

Increase drop-off bins

- ▶ Drop-off bins at all Michigan State Police posts throughout the state
- ▶ Many Law enforcement offices, pharmacies, and other locations maintain drop-off bins
- ▶ Maps of locations can be found here:
http://www.michigan.gov/deq/0,4561,7-135-3312_4118_74618-370212--,00.html and here:
<http://ihpi.umich.edu/our-work/strategic-initiatives/michigan-open/protect-your-community>

Prevention

Benefits Monitoring Program

Medicaid improving "Lock In" program that prevents doctor and pharmacy shopping by locking a beneficiary to one doctor and one pharmacy

- ▶ Health Plan contract language strengthened to increase use of benefits monitoring program
- ▶ Beneficiaries are connected to treatment resources
- ▶ Software improvements are ongoing

Prevention

Awareness Efforts

- ▶ In July, MDHHS launched a statewide media campaign on You Tube to raise awareness among teens about the health and personal consequences of drug use
- ▶ MDHHS posted a web based campaign "Do Your Part" to prevent prescription drug and opioid abuse. The campaign can be accessed at www.michigan.gov/bhrecovery
- ▶ MDHHS will soon launch a statewide public awareness campaign on dangers of prescription drug abuse

Prevention

Federal Grant Funded Efforts

- ▶ MDHHS Violence and Injury Division received a \$2.25 million grant to combat opioid misuse from the Centers for Disease Control and Prevention (CDC)
- ▶ The CDC grant enable Michigan to: improve data collection and analysis around misuse and overdose; develop a strategy to combat the epidemic; and work with communities to develop opioid overdose prevention programs

Prevention

Federal Grant Funded Efforts

- ▶ MDHHS is in the second year of a 5-year grant Substance Abuse and Mental Health Services Administration (SAMHSA) grant to prevent prescription drugs opioid abuse among youth and young adults
- ▶ The grant provides eight communities (Macomb, Muskegon, Lake, Mason, Bay, Cass, Genesee and Wayne Counties) resources to integrate evidence-based prevention programming, including Screening, Brief Intervention and Referral to Treatment (SBIRT) in primary care settings

Treatment

Treatment

Increase access to Naloxone

- ▶ Standing Order legislation to improve access to naloxone to family, friends, and others signed in 2016
- ▶ Rule promulgation in progress for Standing Order
- ▶ MDHHS provided 5,800 Naloxone kits to first responders along with information on where to access treatment by five Prepaid Inpatient Health Plans (PIHPs)

Treatment

Increase access to care

- ▶ Medicaid established reimbursement policy regarding Vivitrol in residential treatment services
- ▶ Physicians and non-physician practitioner services related to opioid dependence may be reimbursed through Fee-For-Service Medicaid

Treatment

Good Samaritan Law

- ▶ The Task Force recommended passing a Good Samaritan law to encourage people to seek medical assistance during an overdose
- ▶ In 2016, Governor Snyder signed Michigan's Good Samaritan law that will protect individuals from criminal liability if they seek medical assistance for an overdose

Treatment

Neo-Natal Abstinence Syndrome

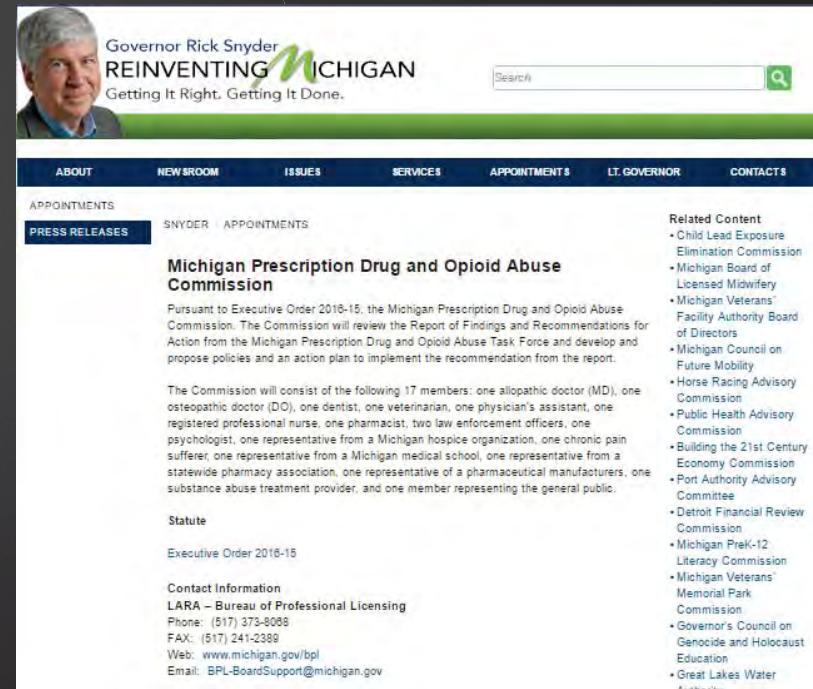
- ▶ Michigan participating in a Policy Academy focused on improving outcomes for pregnant and postpartum women with opioid use disorders and their infants and families who are involved or at risk of being involved with child welfare services
- ▶ MDHHS NAS Project – Substance Abuse Prevention and Treatment Block Grant Funding
 - Each PIHP region submitted a proposal aimed at reducing the incidence of NAS affected births
 - Involves building relationships with NICUs, Hospitals and other agencies such as CPS

Task Force Recommendations

- ▶ Policy and Outcomes
 - ▶ Create ongoing Task Force
- ▶ Enforcement
 - ▶ Improve the MI Automated Prescription System (MAPS)
 - ▶ Increase access to MAPS
 - ▶ Increase sanctions

Implementation: Process and Direction

- ▶ In 2016, an ongoing Prescription Drug and Opioid Abuse Commission (PDOAC) was established by Executive Order
- ▶ First meeting: December 2016
(Chair: Judge Linda Davis)
- ▶ The Commission will further support implementation of the Task Force's recommendations



The screenshot shows the official website of Governor Rick Snyder's office. At the top, there is a portrait of Governor Rick Snyder and the text "REINVENTING MICHIGAN" with the tagline "Getting It Right. Getting It Done." Below the header, there is a navigation menu with links for "ABOUT", "NEWS ROOM", "ISSUES", "SERVICES", "APPOINTMENTS", "LT. GOVERNOR", and "CONTACTS". A "PRESS RELEASES" link is highlighted. The main content area features a section titled "Michigan Prescription Drug and Opioid Abuse Commission" with a brief description of its purpose and members. To the right, there is a "Related Content" sidebar listing various other state commissions and committees.

Michigan Prescription Drug and Opioid Abuse Commission

Pursuant to Executive Order 2016-15, the Michigan Prescription Drug and Opioid Abuse Commission. The Commission will review the Report of Findings and Recommendations for Action from the Michigan Prescription Drug and Opioid Abuse Task Force and develop and propose policies and an action plan to implement the recommendation from the report.

The Commission will consist of the following 17 members: one allopathic doctor (MD), one osteopathic doctor (DO), one dentist, one veterinarian, one physician's assistant, one registered professional nurse, one pharmacist, two law enforcement officers, one psychologist, one representative from a Michigan hospice organization, one chronic pain sufferer, one representative from a Michigan medical school, one representative from a statewide pharmacy association, one representative of a pharmaceutical manufacturers, one substance abuse treatment provider, and one member representing the general public.

Statute
Executive Order 2016-15

Contact Information
LARA – Bureau of Professional Licensing
Phone: (517) 373-5088
FAX: (517) 241-2389
Web: www.michigan.gov/bpl
Email: BPL-BoardSupport@michigan.gov

Related Content

- Child Lead Exposure Elimination Commission
- Michigan Board of Licensed Midwifery
- Michigan Veterans' Facility Authority Board of Directors
- Michigan Council on Future Mobility
- Horse Racing Advisory Commission
- Public Health Advisory Commission
- Building the 21st Century Economy Commission
- Port Authority Advisory Committee
- Detroit Financial Review Commission
- Michigan Pre-K-12 Literacy Commission
- Michigan Veterans' Memorial Park Commission
- Governor's Council on Genocide and Holocaust Education
- Great Lakes Water Authority

Legislation

Legislation

On March 23, Governor Snyder and several legislators announced a package of bills to combat opioid and prescription drug abuse

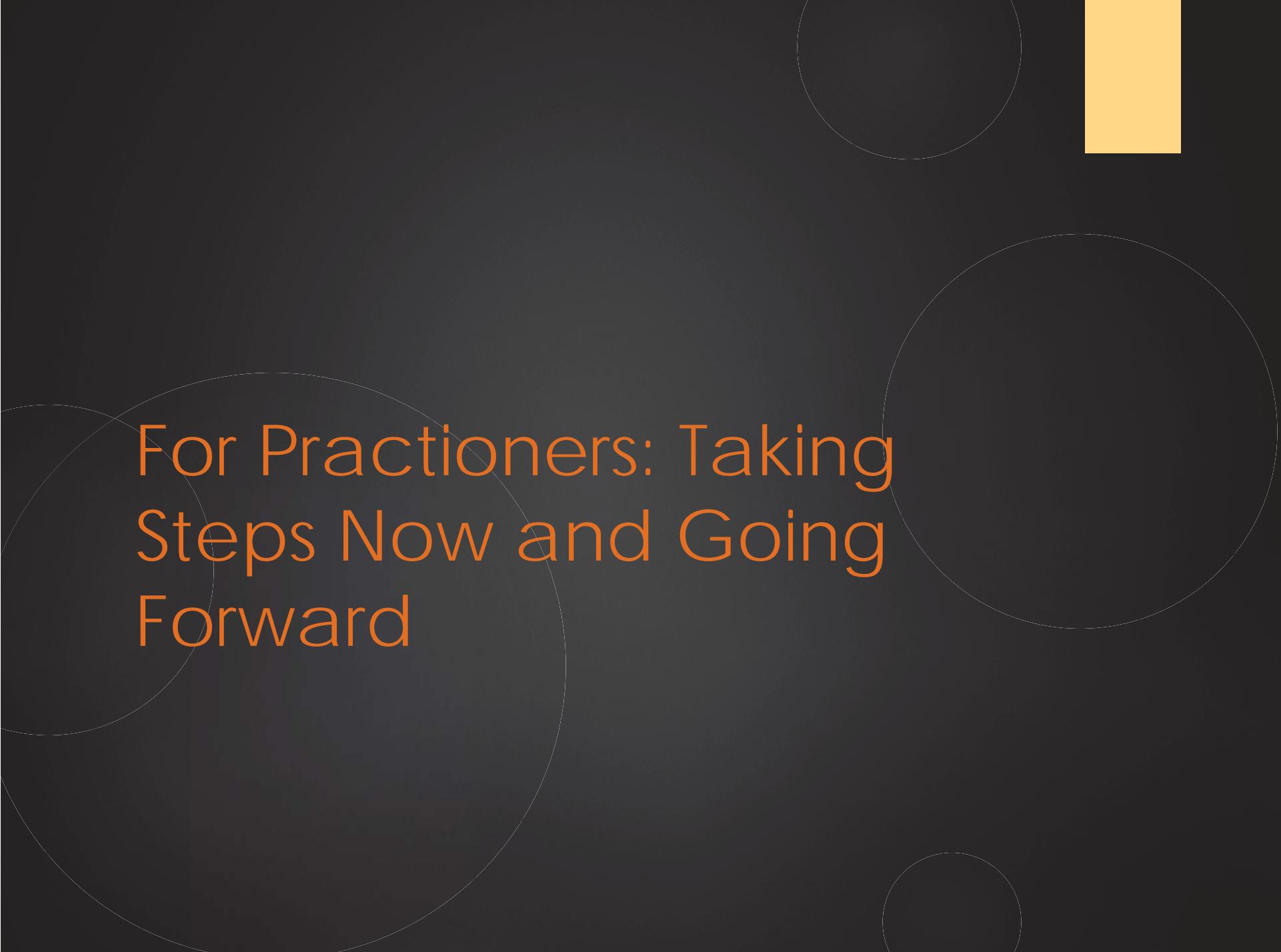
Some bills are Task Force recommendations:

- ▶ Bona-fide doctor-patient relationship
- ▶ Licensing of pain clinics
- ▶ Good faith exemption for pharmacists

Potential for More Legislation

Other legislation includes:

- ▶ 7 day prescribing limit
- ▶ MAPS mandate
- ▶ Develop prescription drug education curriculum in schools
- ▶ Greater patient education requirements
- ▶ Greater provider sanctions



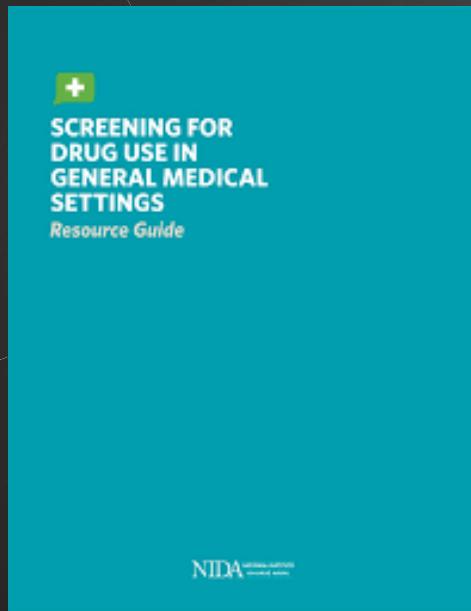
The background of the slide features a dark gray or black gradient. Overlaid on this are several thin, light gray dashed circles of varying sizes and positions. In the top right corner, there is a solid yellow rectangular bar. The main title text is centered within the slide area, with the circles partially obscuring it from the sides.

For Practitioners: Taking
Steps Now and Going
Forward

Screening Tools

43

- ▶ Increasingly recognized and further developed
- ▶ Separate screening tools for specific populations (e.g., Youth, Justice-involved)



The CRAFFT Screening Interview

Begin. I'm going to ask you a few questions that I ask all my patients. Please be honest; I will keep your answers confidential.

Part A

During the PAST 12 MONTHS, did you:

1. Drive any vehicle (car, boat, plane, etc.)?
2. Smoke any marijuana or hashish?
3. Use anything else to get high? (anything else: illegal drugs, over-the-counter and prescription drugs, and things that you sniff or "huff")

No	Yes
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

For clinic use only: Did the patient answer "yes" to any questions in Part A?

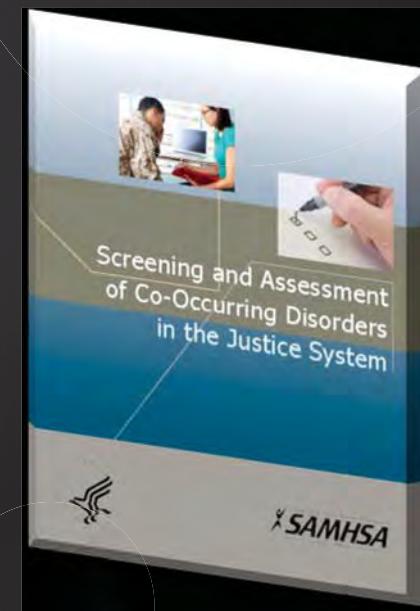
No Yes

Ask CAR question only, then stop. Ask all 6 CRAFFT questions.

Part B

1. Have you ever been in a CAR-driven by someone (including yourself) into "high" or been with "using alcohol or drugs"?
2. Do you think about or want to RELAX (either with alcohol or drugs)?
3. Do you ever use alcohol or drugs while you are by yourself or ALONE?
4. Do you ever FORGET things you did while you're alcohol or drugs?

No	Yes
<input type="checkbox"/>	<input type="checkbox"/>



Screening and Brief Intervention in Primary Care Settings

- ▶ *Ask*: Screen and Assess Risk, with follow up Brief Intervention
- ▶ *Advise*: Provide direct personal advice about substance use
- ▶ *Assess*: Evaluate the patient's willingness to quit or reduce use
- ▶ *Assist*: Help interested patients develop a treatment plan
- ▶ *Arrange*: Help patient arrange follow up appointment if desired

Amaza et al 2015, ASAM

"SBIRT"

- ▶ Screening
- ▶ Brief Intervention
- ▶ Referral to treatment
- ▶ Primary Use for Alcohol and Tobacco
- ▶ Impact on other substance use requires further study

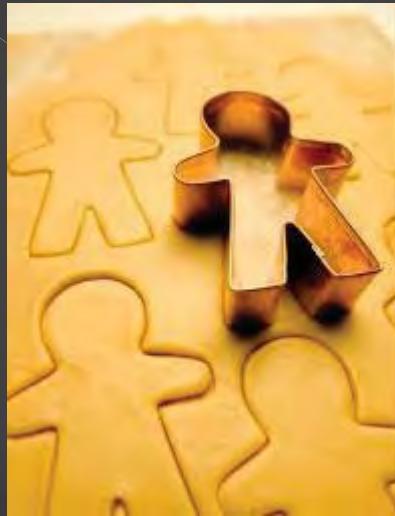




The background features a dark gray or black field with several white-outlined circles of varying sizes. One large circle is positioned at the bottom left, another large circle is on the right side, and a smaller circle is at the top center. A solid yellow vertical rectangle is located in the upper right corner. The text is centered within the composition.

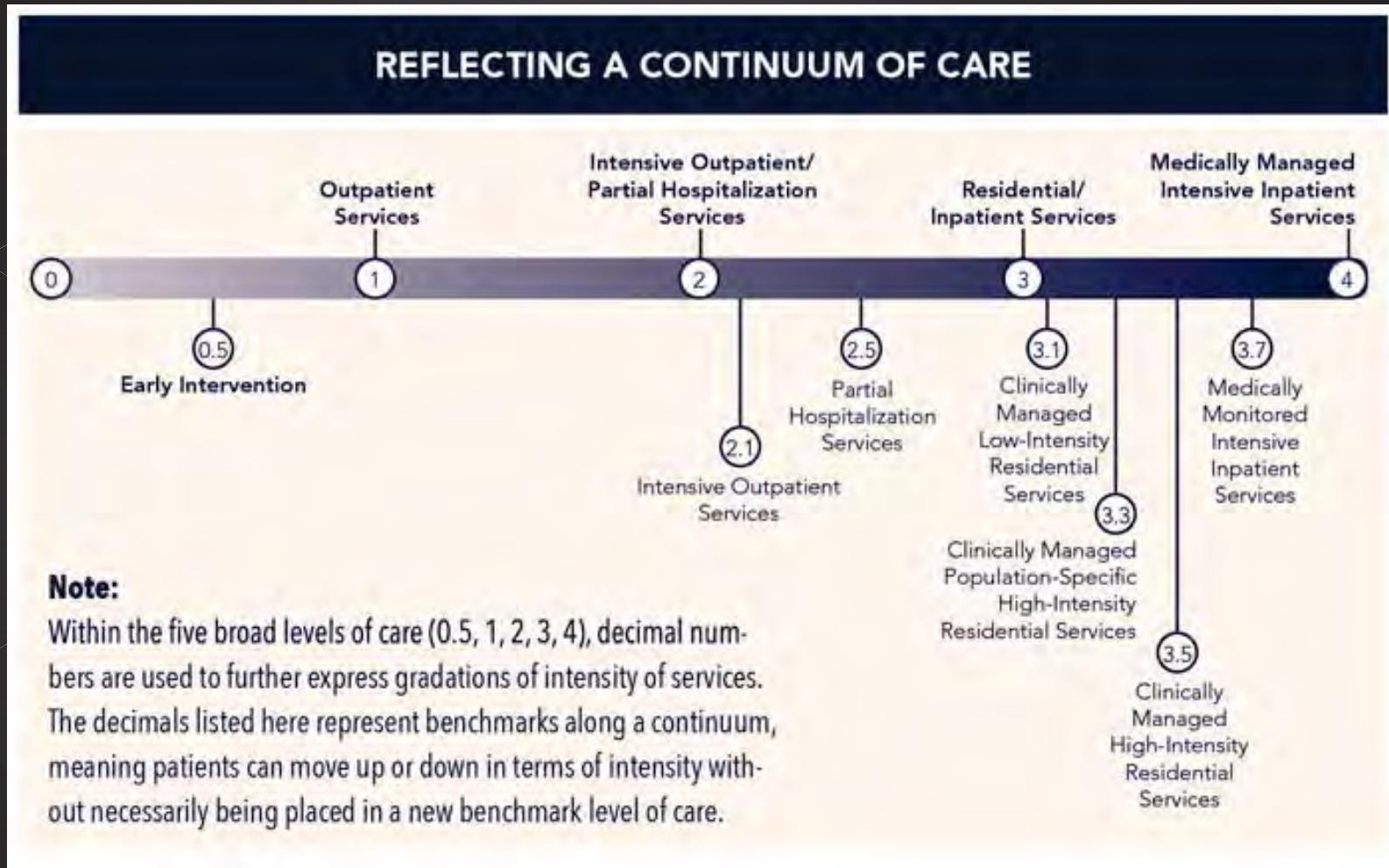
Substance Use Assessment and Treatment Services

ASAM Criteria:
Moving away from the cookie cutter approach



ASAM Continuum of Care

48



Medication Assisted Treatments

FDA-Approved Medications for Substance Abuse Treatment and Tobacco Cessation

Medications for Alcohol Dependence

Naltrexone (ReVia®, Vivitrol®, Depade®)
Disulfiram (Antabuse®)
Acamprosate Calcium (Campral®)

Medications for Opioid Dependence

Methadone
Buprenorphine (Suboxone®, Subutex®, and Zubsolv®)
Naltrexone (ReVia®, Vivitrol®, Depade®)

Medications for Smoking Cessation

Varenicline(Chantix®)
Bupropion (Zyban® and Wellbutrin®)
Nicotine Replacement Therapy (NRT)

Integrated Behavioral Health

Table 1. Six Levels of Collaboration/integration (Core Descriptions)

COORDINATED KEY ELEMENT: COMMUNICATION		CO-LOCATED KEY ELEMENT: PHYSICAL PROXIMITY		INTEGRATED KEY ELEMENT: PRACTICE CHANGE	
LEVEL 1 Minimal Collaboration	LEVEL 2 Basic Collaboration at a Distance	LEVEL 3 Basic Co-located Practice	LEVEL 4 Close Collaboration with Some System Integration	LEVEL 5 Close Collaboration Approach in Integrated Practice	LEVEL 6 Full Collaboration in a Transformed/Merged Integrated Practice
Behavioral health, primary care and other healthcare providers work:					
In separate facilities, where they:	In separate facilities, where they:	In same facility not necessarily same offices, where they:	In same space within the same facility, where they:	In same space within the same facility (same shared space), where they:	In same space within the same facility, sharing all practice space, where they:
<ul style="list-style-type: none"> ▪ Have separate systems ▪ Communicate about cases only rarely and under compelling circumstances ▪ Communicate, driven by provider need ▪ May never meet in person ▪ Have limited understanding of each other's roles 	<ul style="list-style-type: none"> ▪ Have separate systems ▪ Communicate periodically about shared patients ▪ Communicate, driven by specific patient issues ▪ May meet as part of larger community ▪ Appreciate each other's roles as relatives 	<ul style="list-style-type: none"> ▪ Have separate systems ▪ Communicate regularly about shared patients, by phone or e-mail ▪ Collaborate, driven by need for each other's services, and more reliable referral ▪ Meet occasionally to discuss cases due to close proximity ▪ Feel part of a larger yet ill-defined team 	<ul style="list-style-type: none"> ▪ Share some systems, like scheduling or medical records ▪ Communicate in person as-needed ▪ Collaborate, driven by need for consultation and coordinated plans for difficult patients ▪ Have regular face-to-face interactions about same patients ▪ Have a basic understanding of other culture 	<ul style="list-style-type: none"> ▪ Actively seek opportunities together to develop work-a-rounds ▪ Communicate frequently in person ▪ Collaborate, driven by desire to be a member of the care team ▪ Have regular team meetings to discuss overall patient care and specific patient issues ▪ Have an in-depth understanding of other culture 	<ul style="list-style-type: none"> ▪ Often involved read all system issues, functioning as one integrated system ▪ Communicate consistently at the system, team and individual levels ▪ Collaborate, driven by shared concept of team care ▪ Have formal and informal meetings to support integrated model of care ▪ Their roles and cultures blur/tier or blend

Heath B, Wise-Romero P, and Reynolds K. A Review and Proposed Standard Framework for Levels of Integrated Healthcare. Washington, D.C.: SAMHSA-HRSA Center for Integrated Health Solutions; March 2013.

Required SUD Services Funded and Administered by the PIHP

- ▶ Access Management System – Screening, assessment and referral to appropriate treatment
- ▶ Receiving and placing referrals from the Department of Corrections
- ▶ Data System to track performance relative to National Outcome Measures
- ▶ Prevention Data System – To capture number of persons served by evidence-based practices and population type, i.e., universal, selective and indicated populations.



Required Treatment Services

- ▶ The PIHP must assure use of a standardized assessment process, including the American Society of Addiction Medicine (ASAM) Patient Placement Criteria, to determine clinical eligibility for services based on medical necessity.
- ▶ Treatment services at all levels: outpatient, case management, residential
- ▶ Inclusion of peer recovery supports and access to MAT

STR Grant

STR Grant

- ▶ The MDHHS applied for and received a \$16M State Targeted Response to the Opioid Crisis Grant from SAMHSA
- ▶ The grant is a two year grant and grant activity is expected this fiscal year
- ▶ The purpose of the Michigan Opioid STR project is to increase access to treatment and reduce unmet treatment need; and reduce opioid overdose related deaths through the provision of prevention, treatment and recovery activities for Opioid Use Disorders (OUDs)

STR Grant: Highlights

To achieve our purpose for the project, MDHHS will:

- ▶ Improve the state infrastructure for individuals with an OUD;
- ▶ Train PIHP and provider administration on infrastructure improvements, and train provider staff on evidence based interventions and fidelity measures;
- ▶ Implement evidence based prevention and treatment interventions with accompanying fidelity instruments to ensure that the quality of the intervention is consistent across the provider network;
- ▶ Improve access to psychiatric services and psychotropic medications to individuals with an OUD;

STR Grant

- ▶ Expand the availability and use of specially trained peers for MAT and drug free programming;
- ▶ Expand outreach and engagement activities to primary care and law enforcement sites;
- ▶ Increase supports to the prisoner re-entry population with an OUD;
- ▶ Expand the use of peers in emergency departments and primary care settings;
- ▶ Expand overdose education and naloxone distribution; and
- ▶ Disseminate a statewide media campaign for the purpose of public education.

STR Grant

The Michigan Opioid STR initiative will:

- ▶ Improve awareness of the risks associated with using opioid based medications, as well as illegal opioids;
- ▶ Increase the availability of prevention focused evidence based practices for individuals considered to be part of the selected or indicated portion of the population;
- ▶ Educate physicians on the CDC Prescriber Guidelines for responsible opioid prescribing;
- ▶ Increase access to Medication Assisted Treatment, withdrawal management, and residential treatment services for individuals with OUDs

STR Grant

- ▶ Increase availability of treatment and recovery support services to individuals with OUDs, improve the quality of services for individuals with OUDs;
- ▶ Increase treatment and support services available to individuals re-entering the community from prison; and
- ▶ Revise policy and contractual language to reflect standards of care as identified in Michigan's MAT Guidelines for OUDs

RECOVERY

a process of change through which individuals improve their health and wellness, live a self-directed life, and strive to reach their full potential (SAMHSA 2014)

E.G., SYMPTOM RESOLUTION, SOBRIETY, REDUCED RECIDIVISM, SOCIAL CONNECTEDNESS, EMPLOYMENT, EDUCATION, INDEPENDENT LIVING, SELF-RELIANCE

Lessons and Opportunities

- ▶ No one system or agency has the resources to meet all the needs of their clients.
- ▶ Service systems need to be aligned with what we know is true.
 - ▶ Addiction is a chronic illness.
 - ▶ Healthy communities help to sustain recovery and promote wellness for all.

Websites and Resources

- ▶ SAMHSA - www.samhsa.gov
- ▶ PCSS- Provider Clinical Support Services for Opioid Therapies -www.pcss-o.org
- ▶ NIDA - www.drugabuse.gov
- ▶ AAAP - www.aaap.org
- ▶ ASAM - www.asam.org
- ▶ APA- www.psych.org

Resource and Contact Information

- ❖ Michigan Department of Health and Human Services,
Office of Recovery Oriented Systems of Care at
www.michigan.gov/bhrecovery



GREATER DETROIT AREA HEALTH COUNCIL

2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit



15 MINUTE BREAK



GREATER DETROIT AREA HEALTH COUNCIL

2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit





GREATER DETROIT AREA HEALTH COUNCIL

2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit



Dr. Chad Brummett
Director
Clinical Anesthesia Research & Pain Research,
Dept. of Anesthesiology
University of Michigan



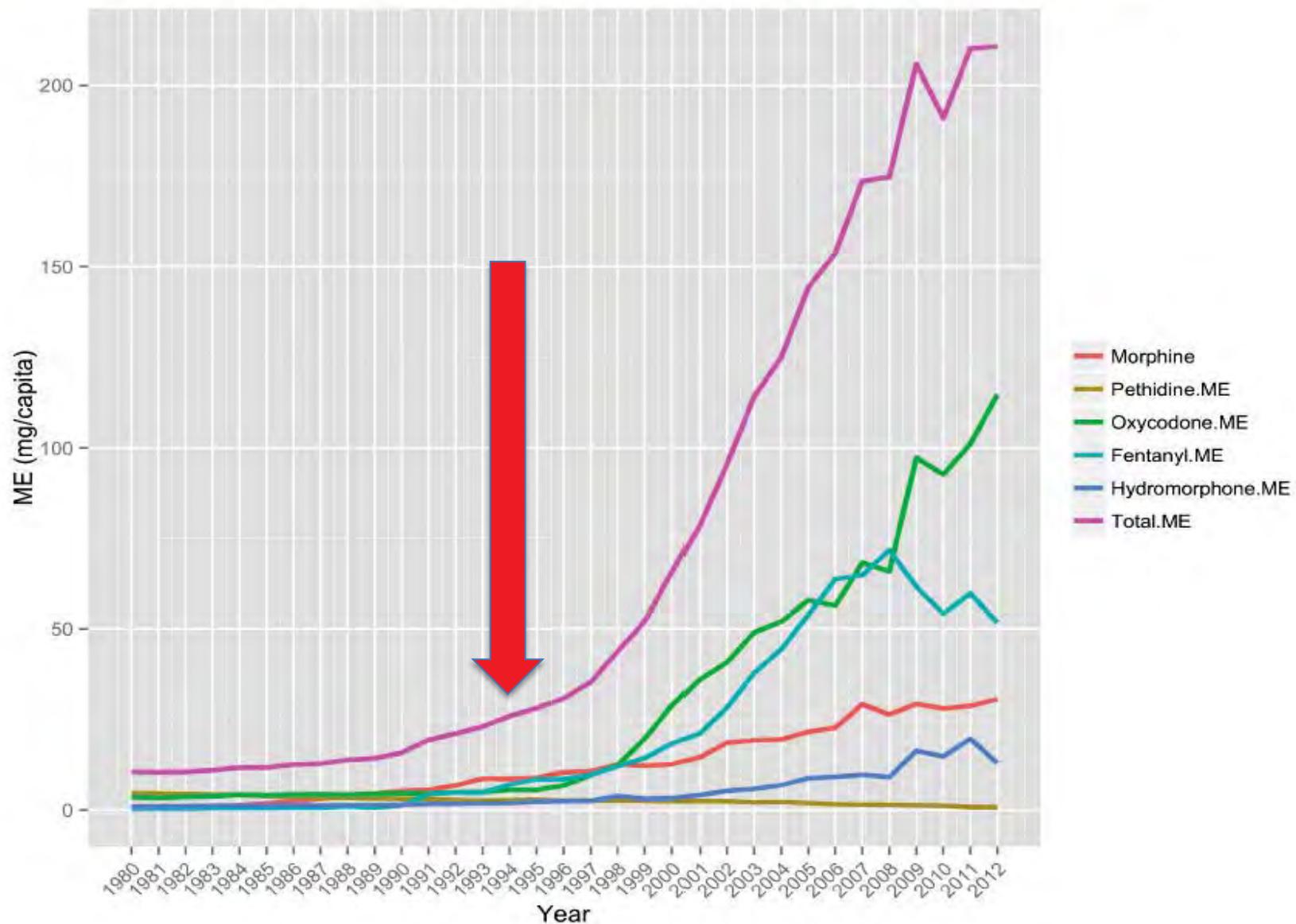
Dr. Jennifer Waljee
Assistant Professor
Section of Plastic and Reconstructive Surgery
University of Michigan
School of Medicine

The Opioid Epidemic:

What is the Role of Acute Pain Prescribing?



AMRO Regional Opioid Consumption in Morphine Equivalence (ME) minus Methadone, mg/person



How did we get here?



2012: 259 million opioid prescriptions



Levy B, Paulozzi L, Mack KA, Jones CM. Trends in Opioid Analgesic-Prescribing Rates by Specialty, U.S., 2007-2012. Am J Prev Med. 2015;49(3):409-413.

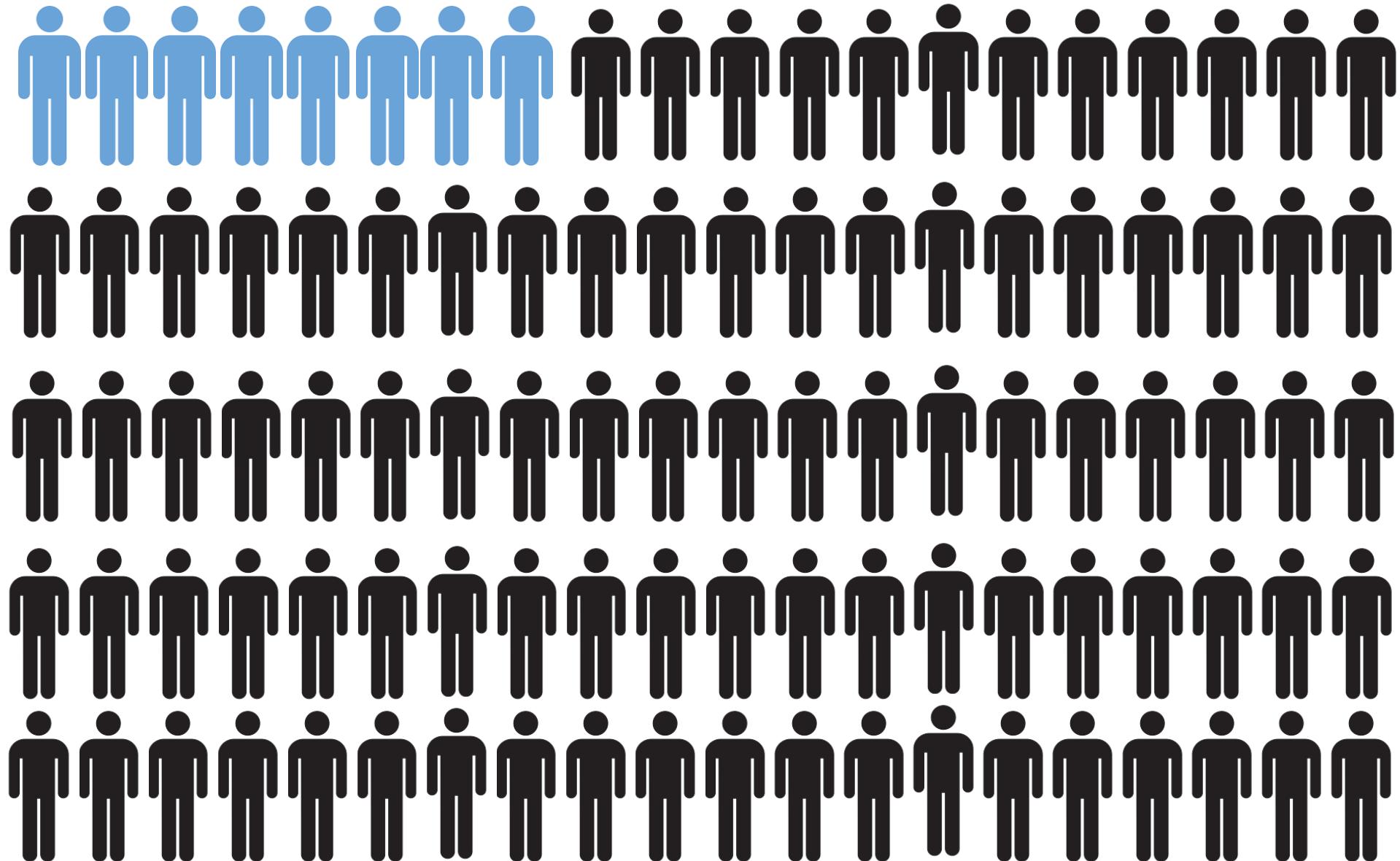
Our Patients

Will I get addicted
to painkillers?

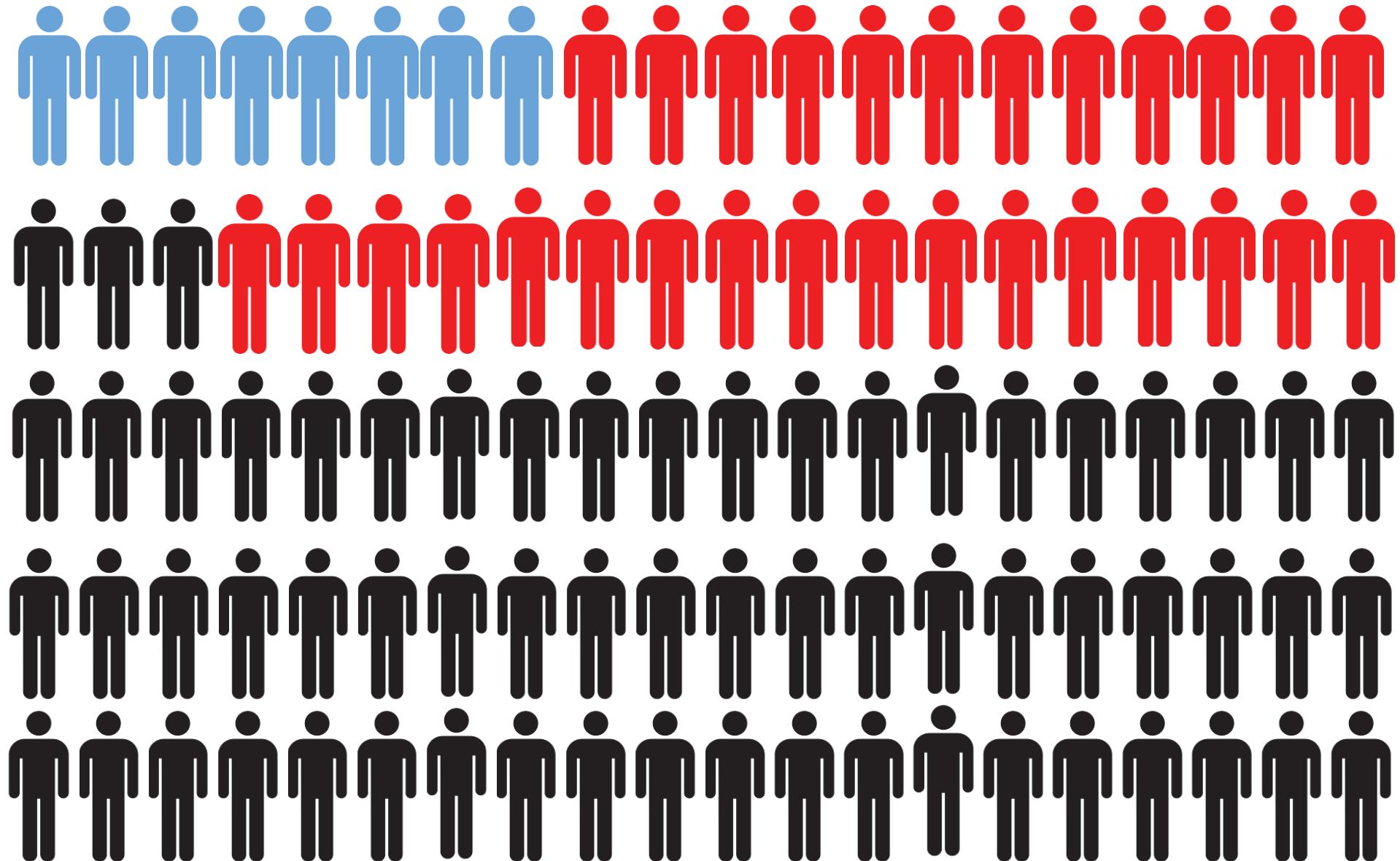




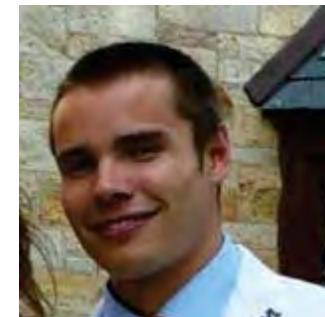
Chronic Opioid Users ~8%



Intermittent Opioid Users ~30%



Pre-Operative Opioid Use and Associated Outcomes after Major Abdominal Surgery



Increased Costs Per Hospitalization



+\$2,341

(avg. additional cost / patient)

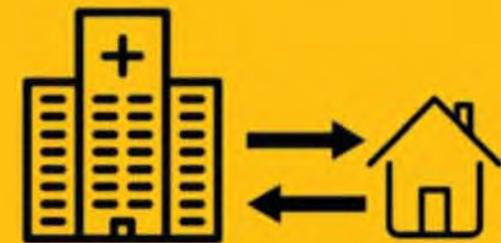
Increased Rate of Complications



16% → 20%

(% of patients)

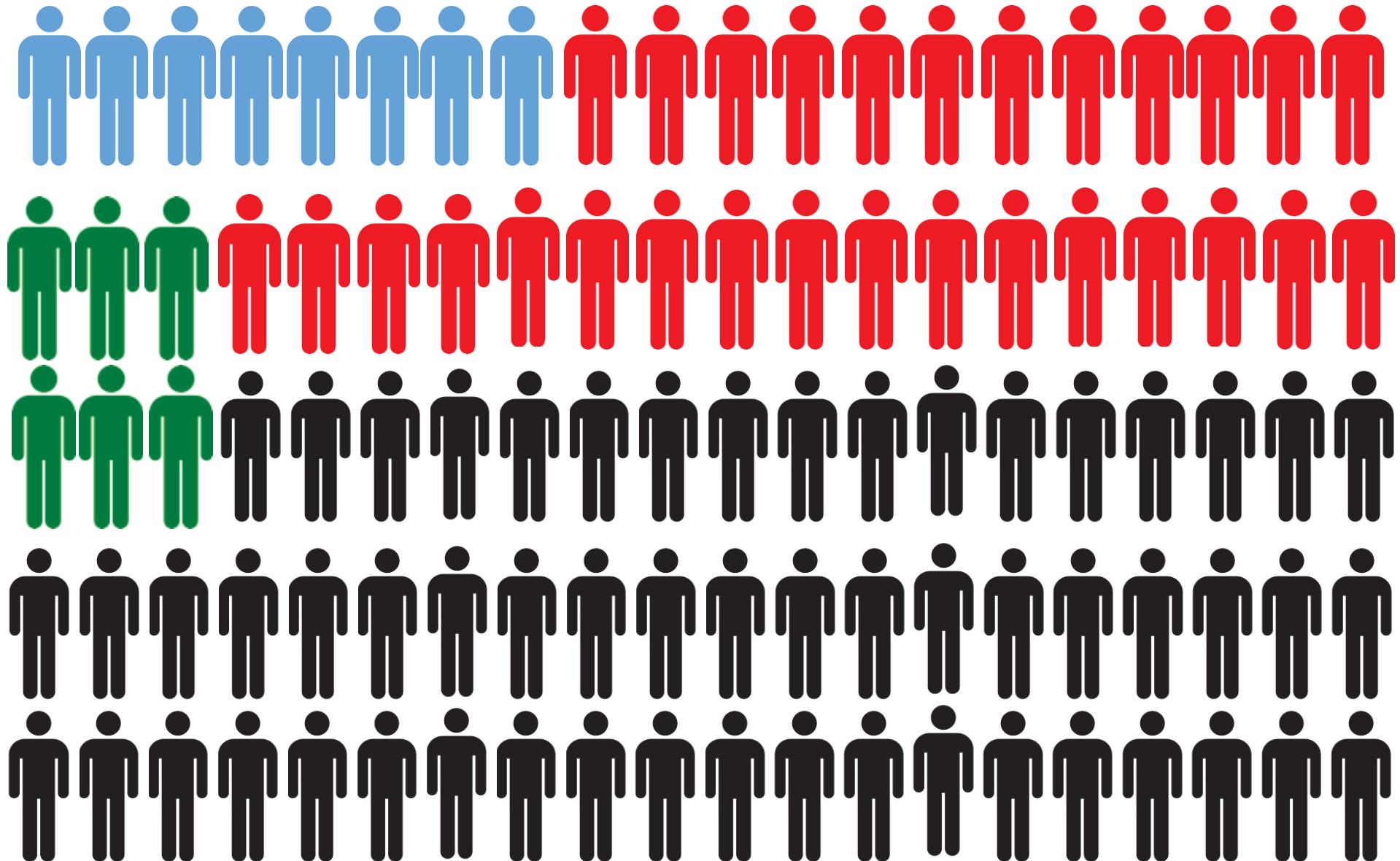
Increased Rate of Readmissions



6% → 10%

(% of patients)

New Persistent Users ~6%

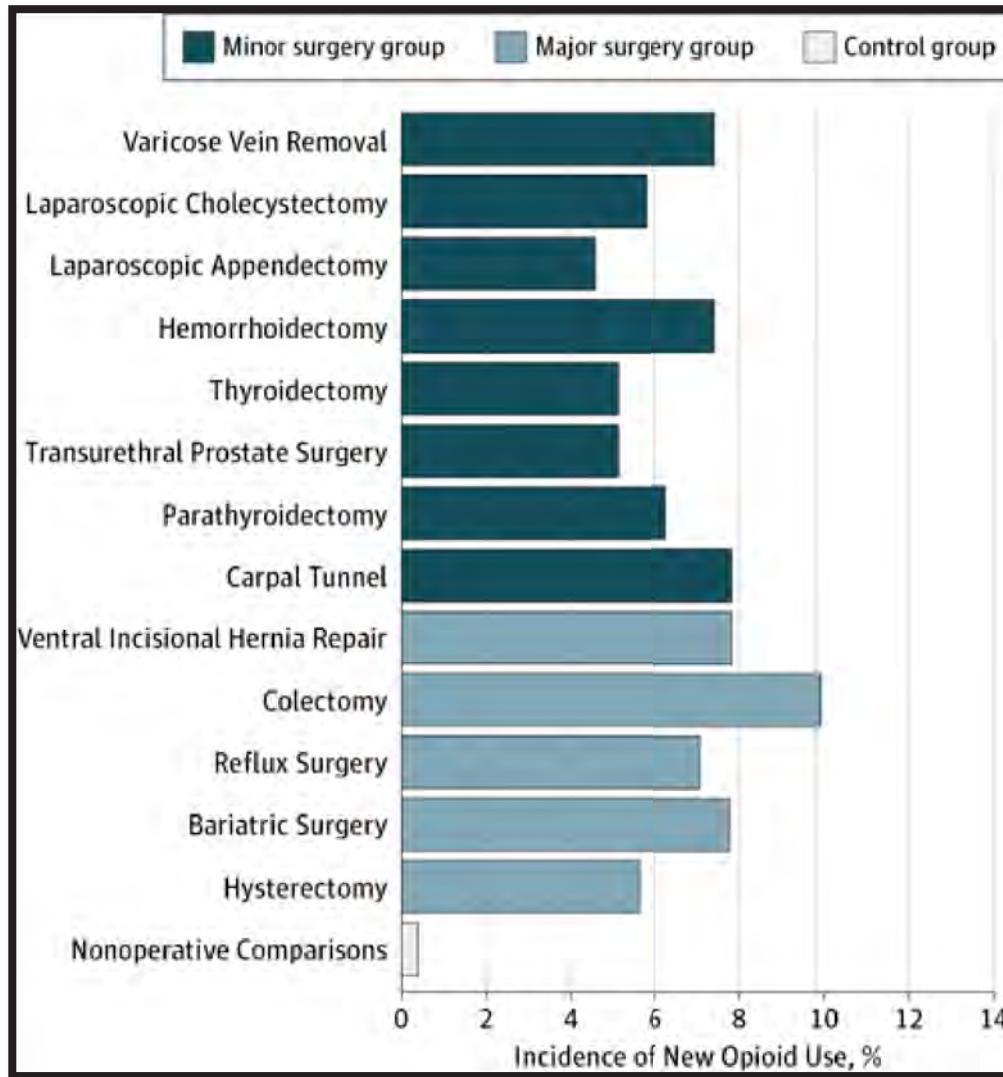


New persistent opioid use

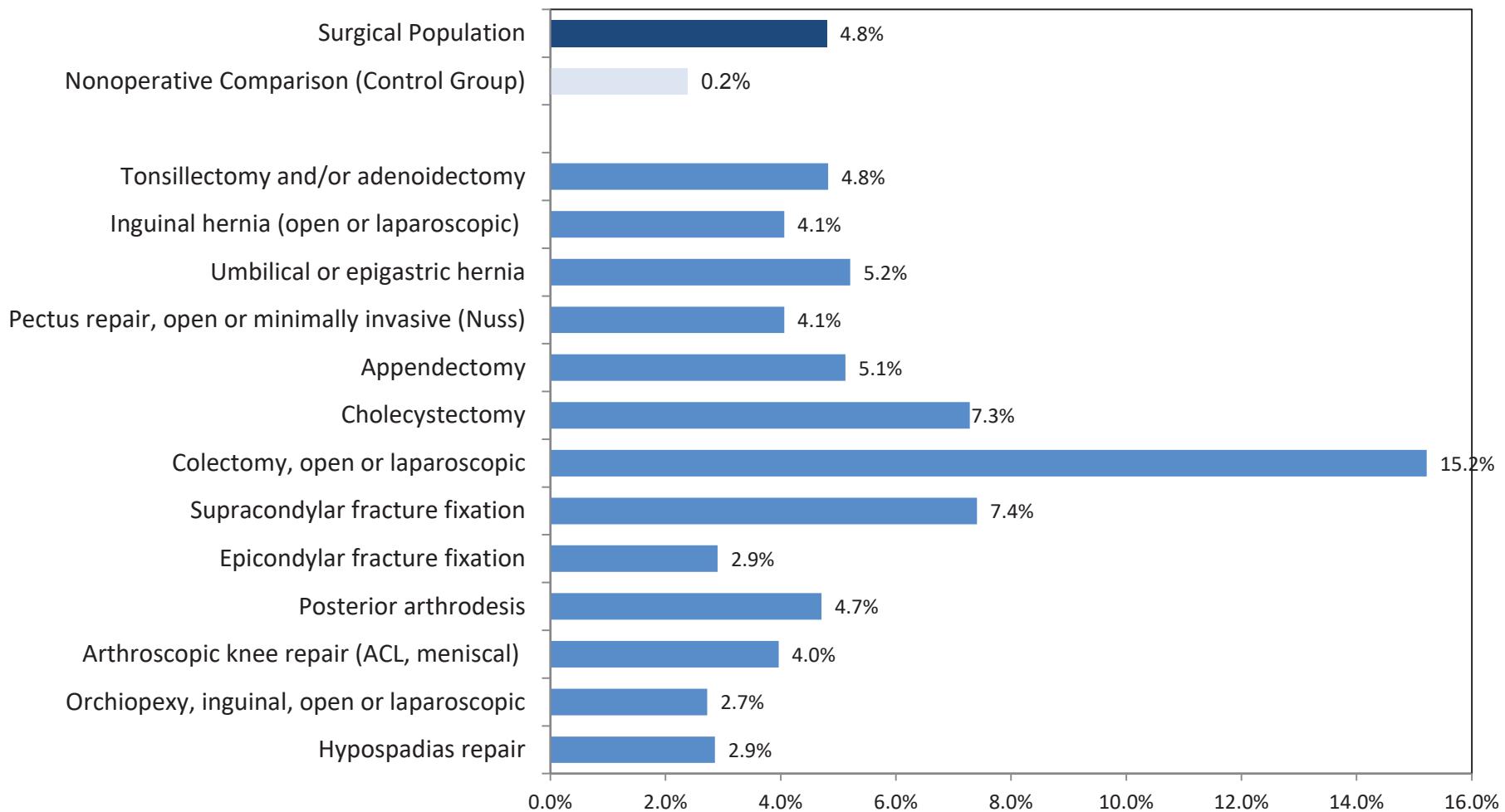
- Previously opioid naïve patient still filling opioid Rx's 3 mo postop¹
- What is the risk after surgery?

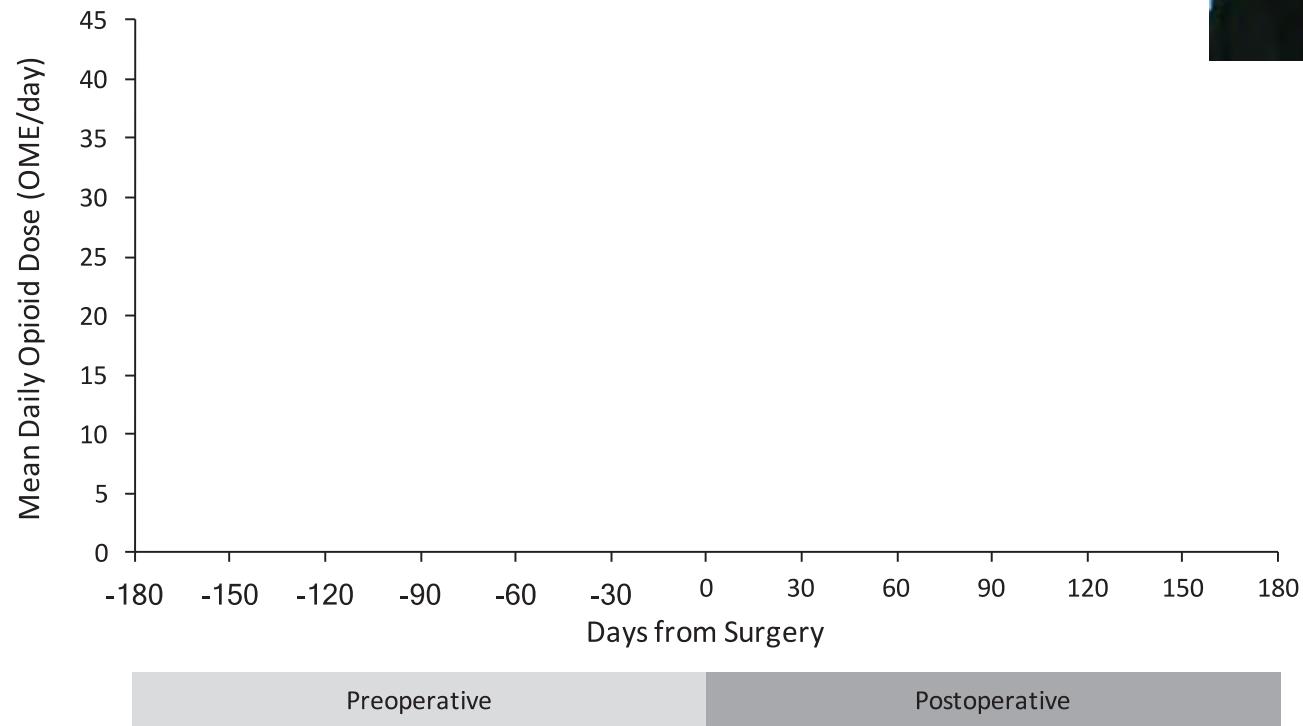
Kehlet H, Rathmell JP. Persistent postsurgical pain: the path forward through better design of clinical studies. Anesthesiology. 2010;112(3):514-515.

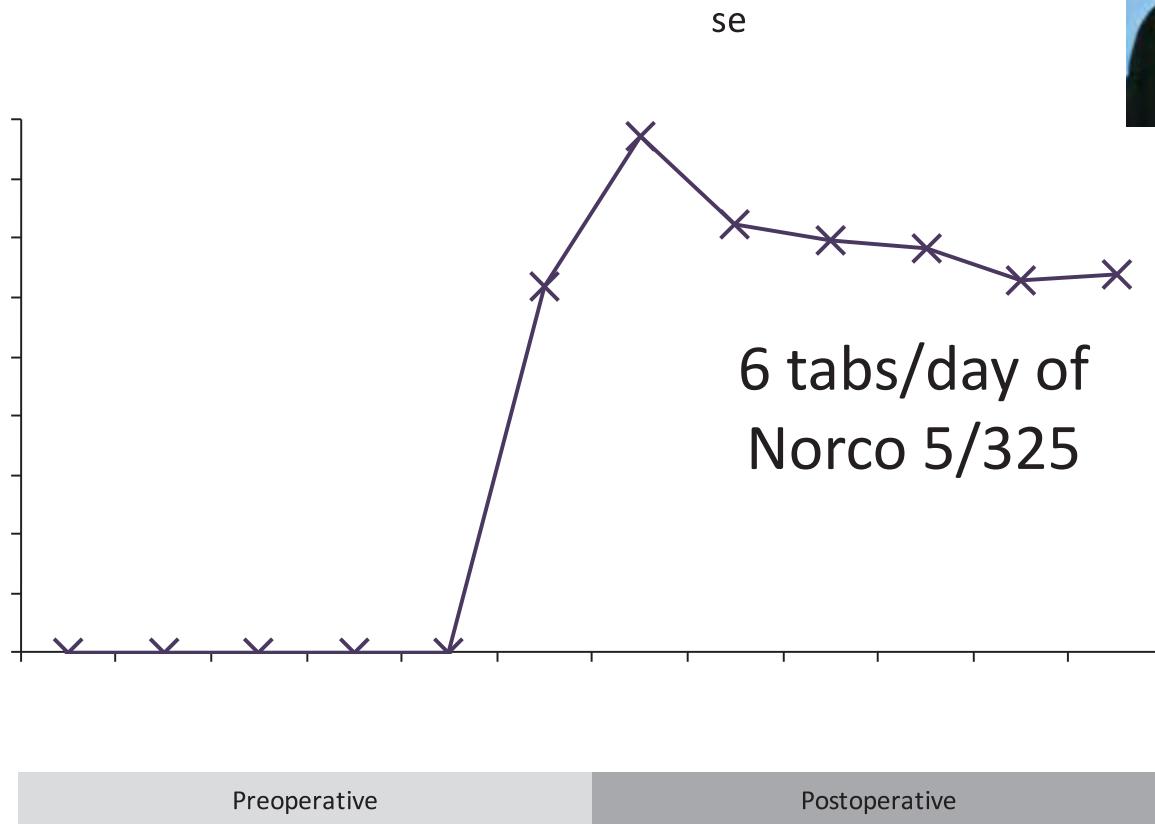
New chronic use of opioids after surgery was 6% and did not differ between major and minor surgeries

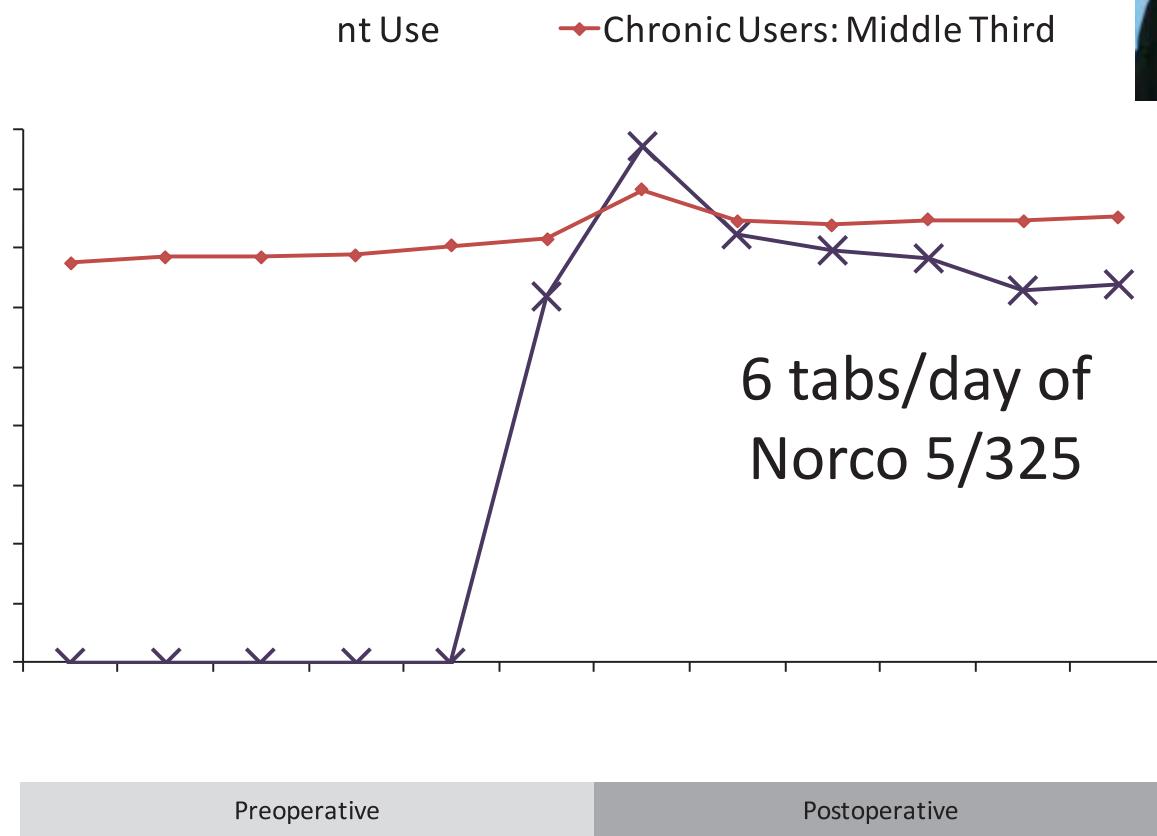


Postoperative opioid dependence happens in pediatric patients









Pain Management Is Not Uniformly Taught



AMERICAN BOARD
OF PLASTIC SURGERY
ABMS

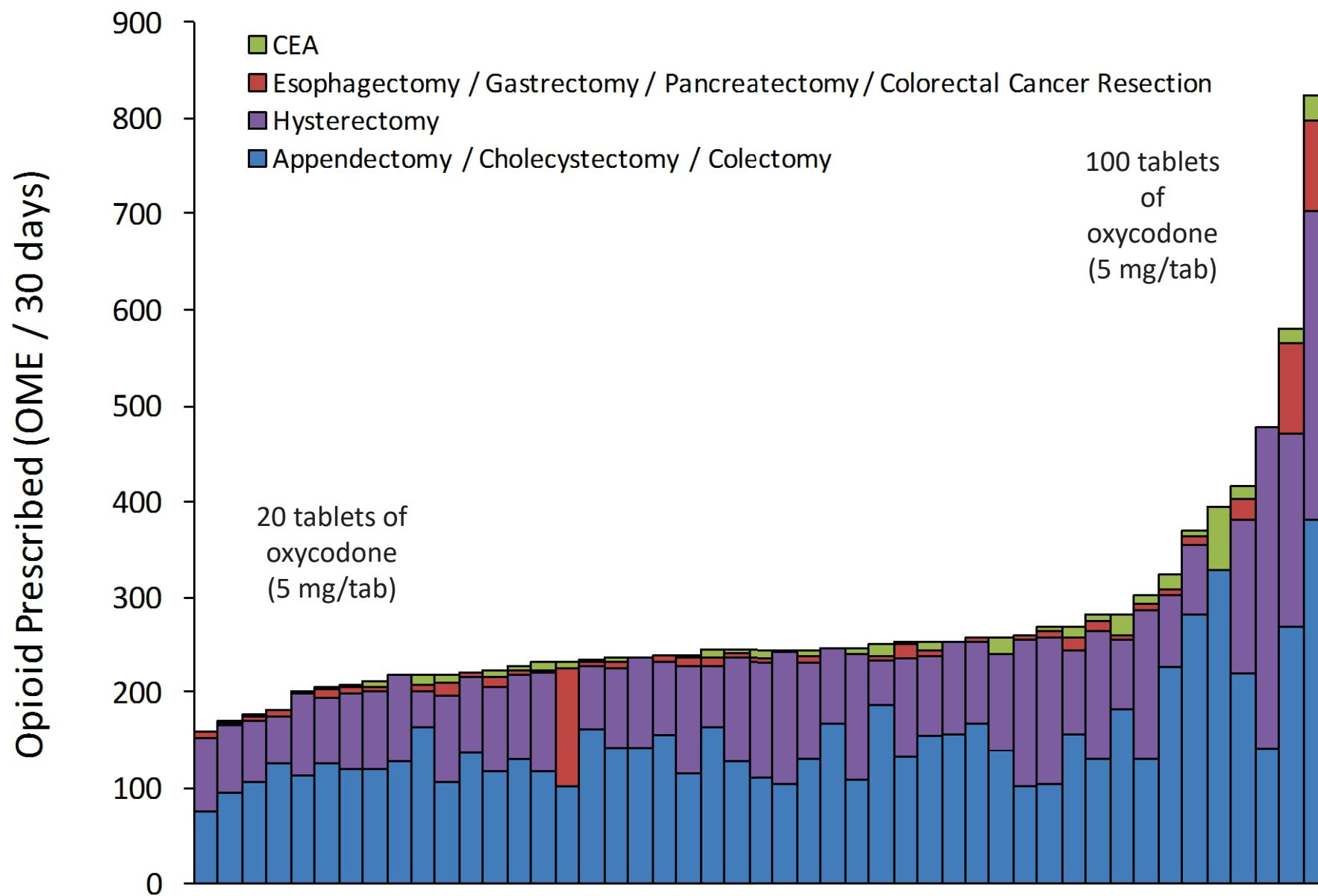
Certification Matters.

SE SAP[®] 15
SURGICAL EDUCATION and SELF-ASSESSMENT PROGRAM

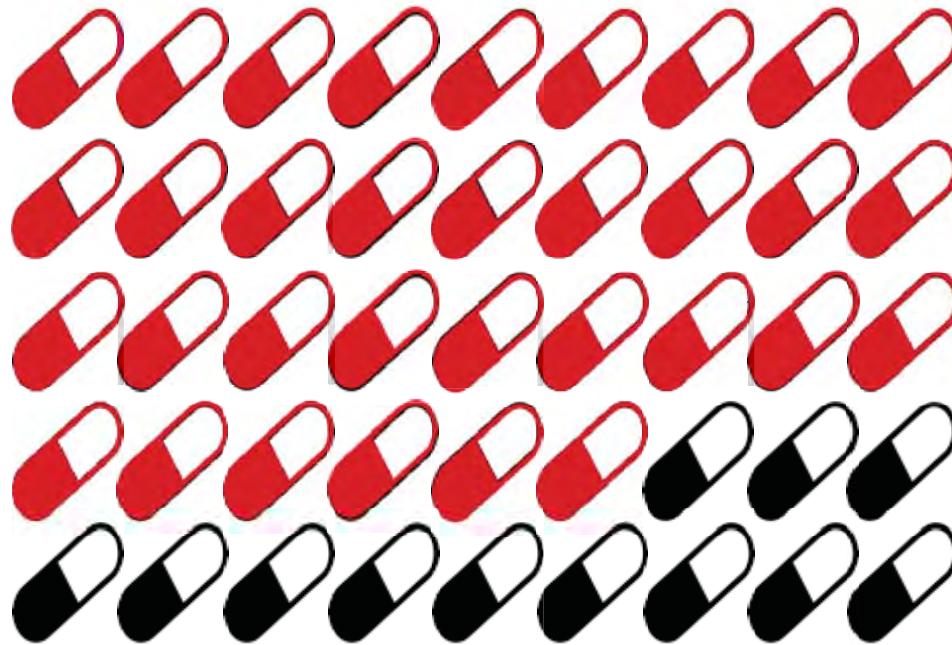


AMERICAN COLLEGE OF SURGEONS
*Inspiring Quality:
Highest Standards, Better Outcomes*

OPEN 
Opioid Prescribing Engagement Network
engaging patients, educating providers, protecting communities



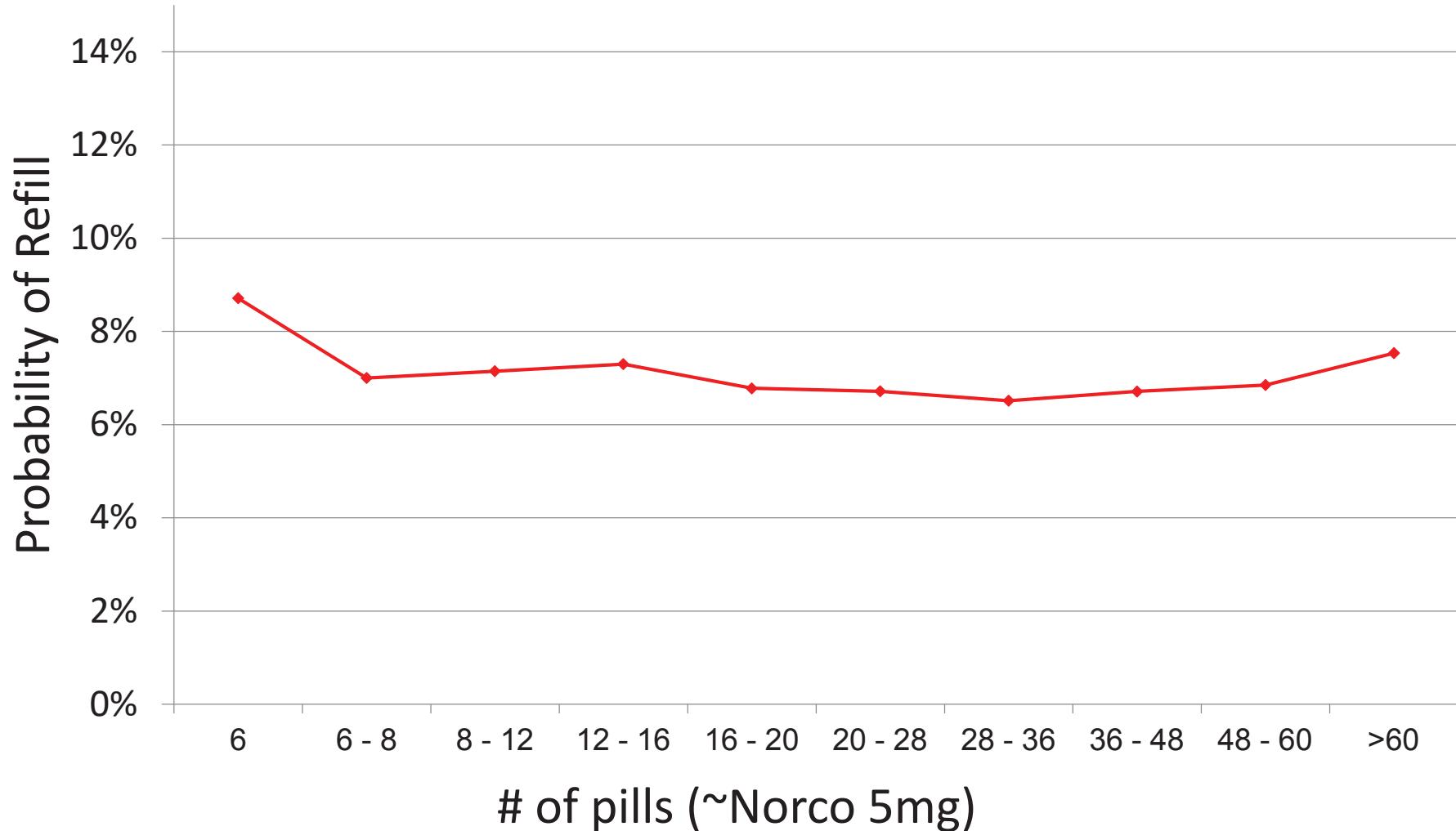
45 tablets of Norco (5/325)



70 – 75% unused

Hill MV, McMahon ML, Stucke RS, Barth RJ, Jr. Wide Variation and Excessive Dosage of Opioid Prescriptions for Common General Surgical Procedures. Ann Surg. 2017;265(4):709-714.

Quantity Does Not Predict Refill

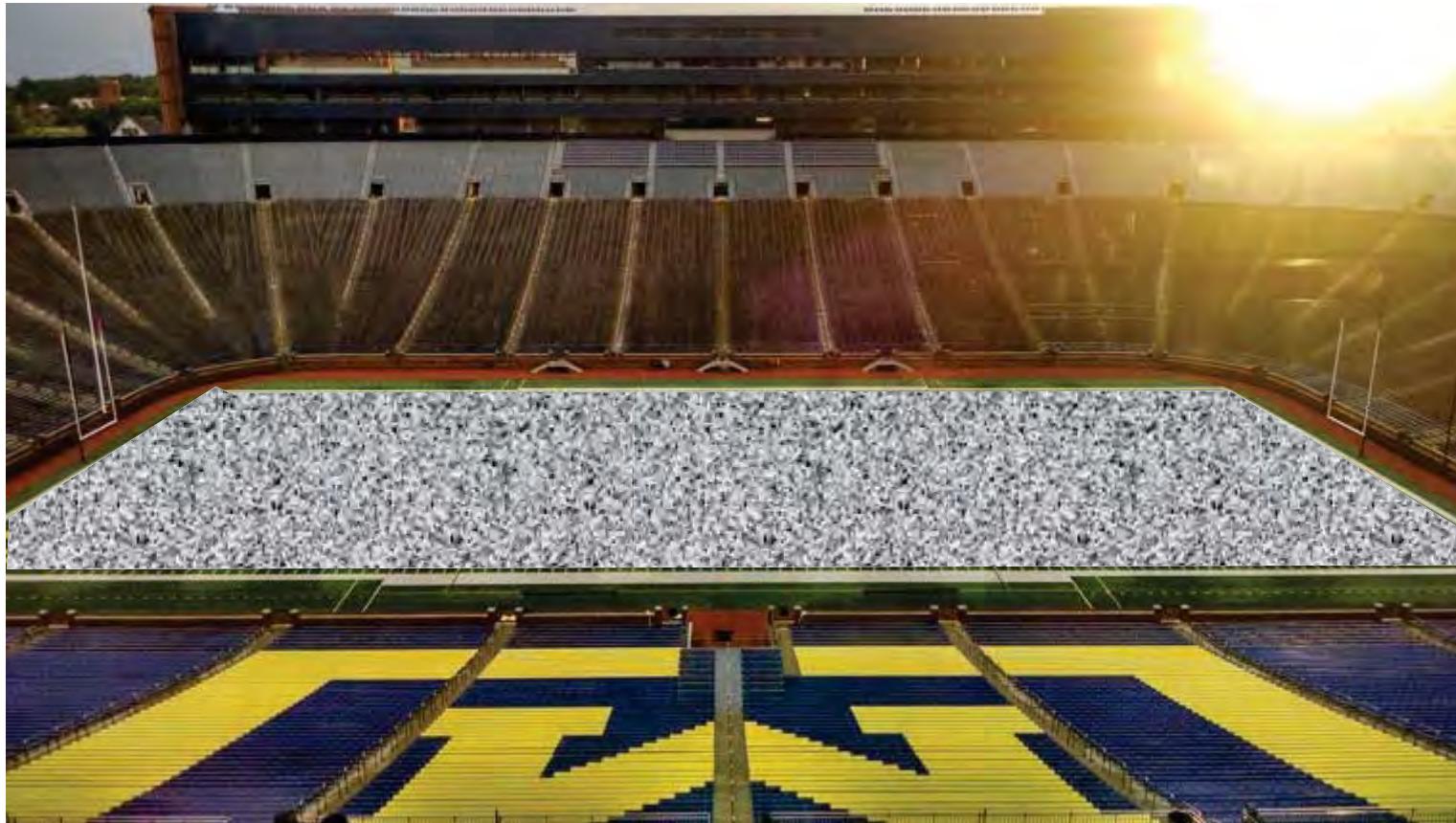


33 extra pills per prescription

62 million
X
unused pills/year

1,881,481 operations / year ^{1,2}

1. HCUP Fast Stats. Healthcare Cost and Utilization Project (HCUP). March 2017. Agency for Healthcare Research and Quality, Rockville, MD.
2. HCUP Central Distributor SASD File Composition. Healthcare Cost and Utilization Project (HCUP). March 2017. Agency for Healthcare Research and Quality, Rockville, MD.

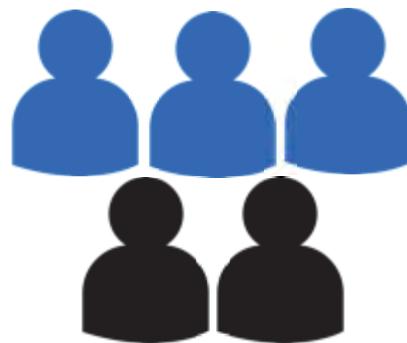




62 million unused pills/year

DIVERSION

Leftover Opioids

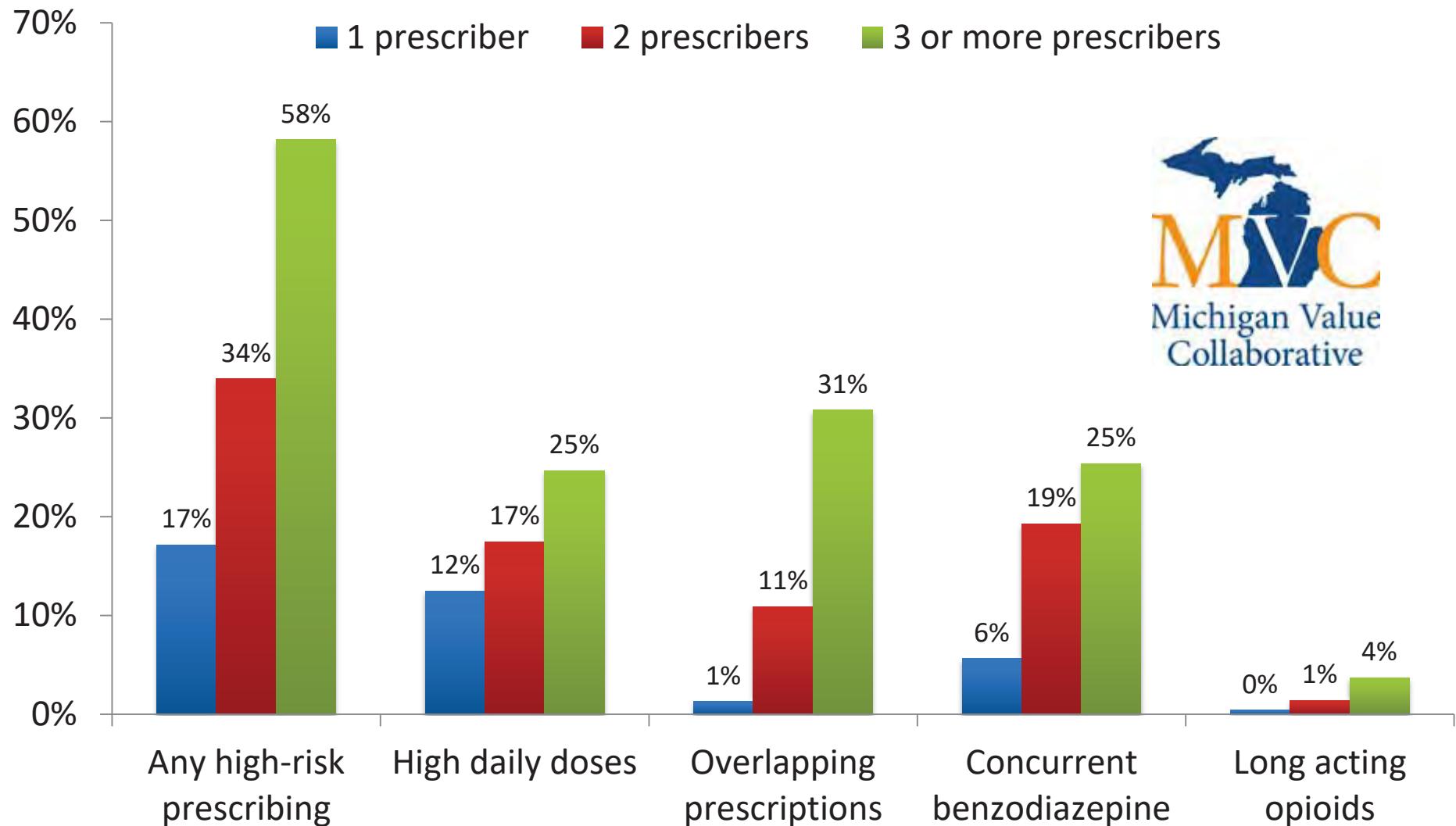


Share Opioids



Kennedy-Hendricks A, Gielen A, McDonald E, McGinty EE, Shields W, Barry CL. Medication Sharing, Storage, and Disposal Practices for Opioid Medications Among US Adults. JAMA Intern Med. 2016;176(7):1027-1029.

High-risk opioid prescribing



Our Role



How Will We Have Impact?



Educate patients and providers about appropriate opioid management for acute care



Create guidelines for postoperative pain management

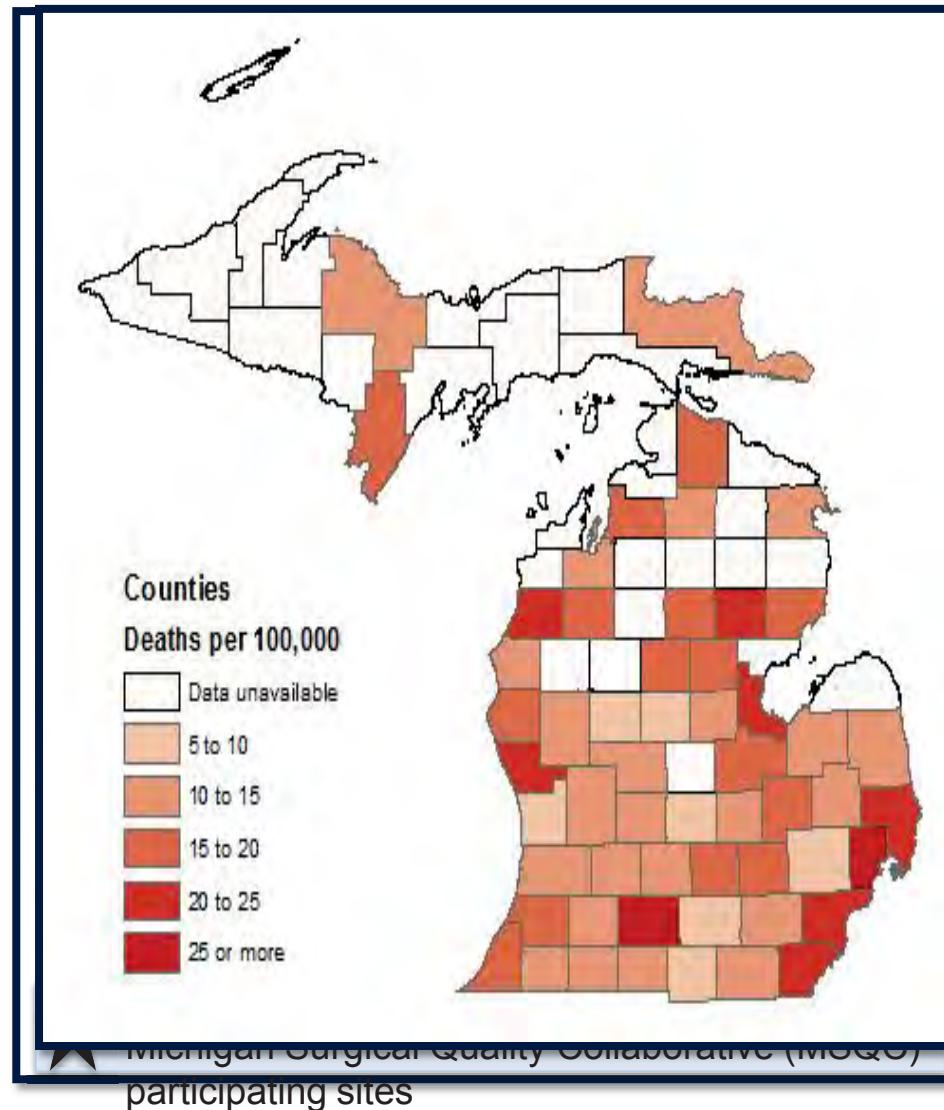


Develop interventions to reduce postoperative opioid prescribing and use



Implement new methods for safe opioid disposal

U-M is Uniquely Positioned to Make a Difference in the Opioid Epidemic



M-TQIP

MSQC

Michigan Surgical Quality
Collaborative



Blue Cross
Blue Shield
Blue Care Network
of Michigan

Nonprofit corporations and independent licensees
of the Blue Cross and Blue Shield Association



VALUE Partnerships
Improving Health Care in Michigan

Blue Cross Blue Shield of Michigan is a nonprofit corporation and independent licensee of the Blue Cross and Blue Shield Association



ASPIRE

Anesthesiology Performance Improvement and Reporting Exchange

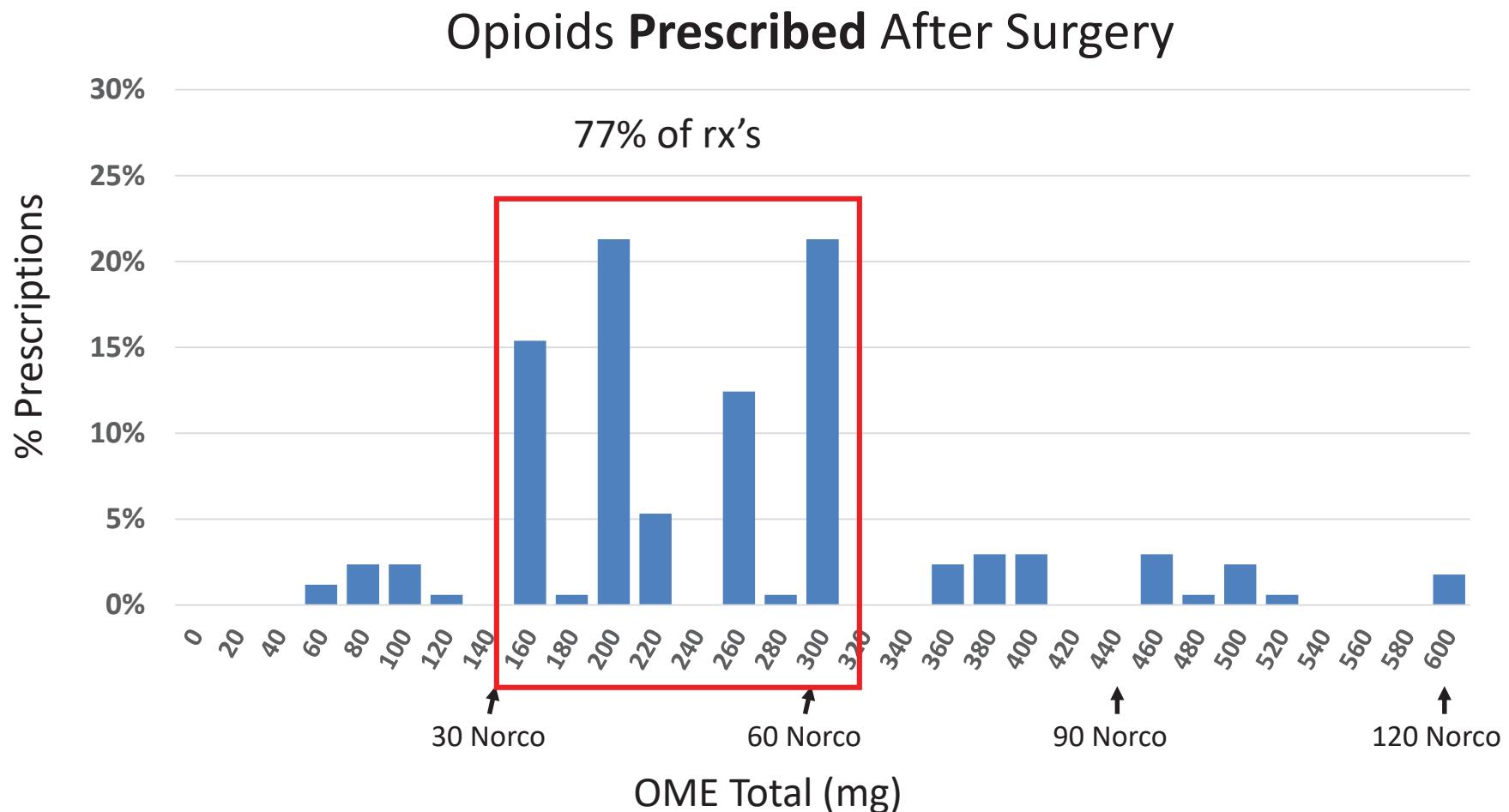
MARCQI
MICHIGAN ARTHROPLASTY
REGISTRY
COLLABORATIVE QUALITY INITIATIVE

The logo features a stylized green outline of the state of Michigan. To the right of the outline, the letters 'MDHHS' are written in large, bold, blue capital letters. Below 'MDHHS', the text 'Michigan Department of Health & Human Services' is written in smaller, green capital letters.
RICK SNYDER, GOVERNOR | NICK LYON, DIRECTOR

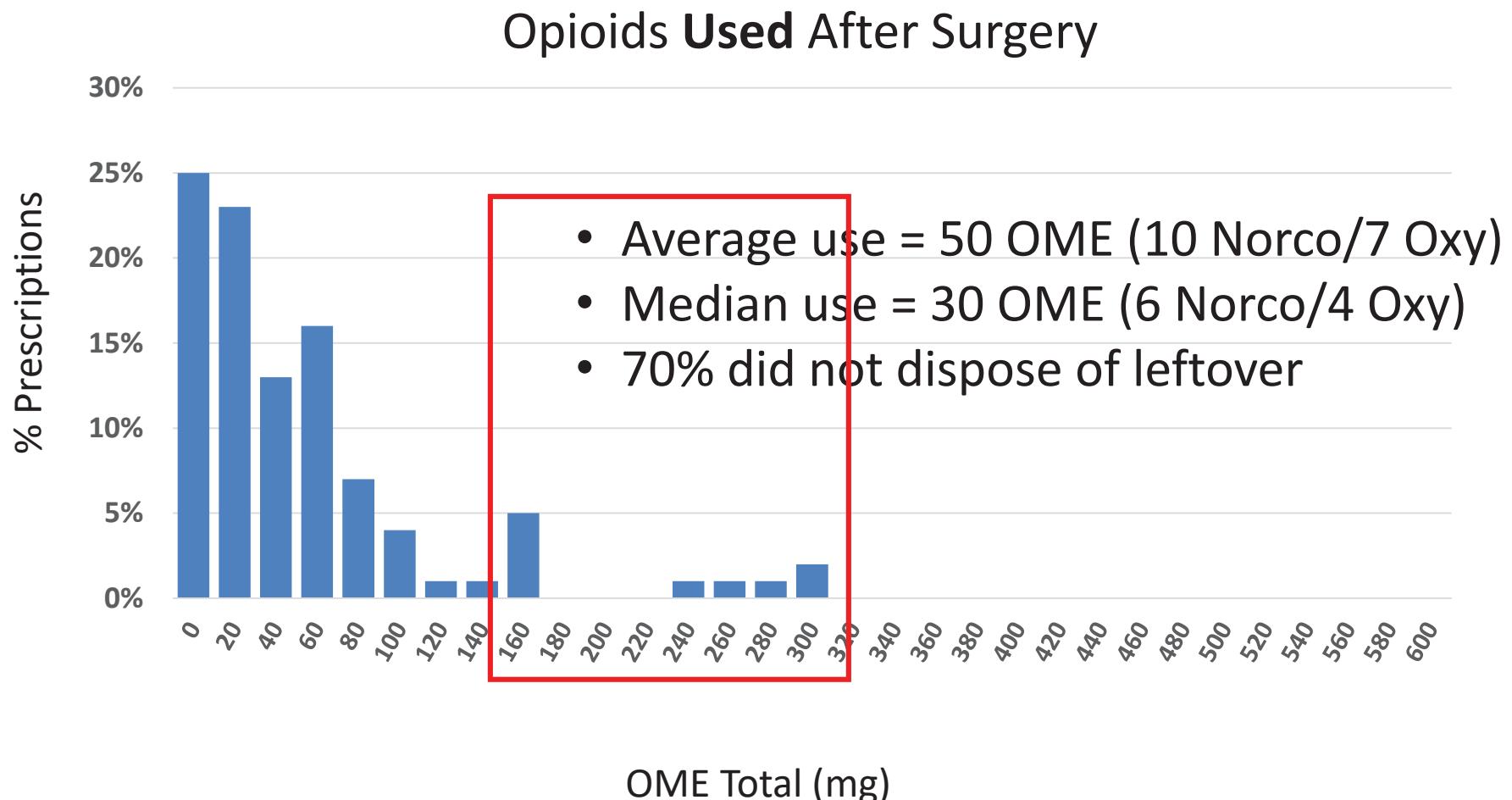
Opioid Prescribing Guidelines: Laparoscopic Cholecystectomy



Laparoscopic Cholecystectomy



Laparoscopic Cholecystectomy

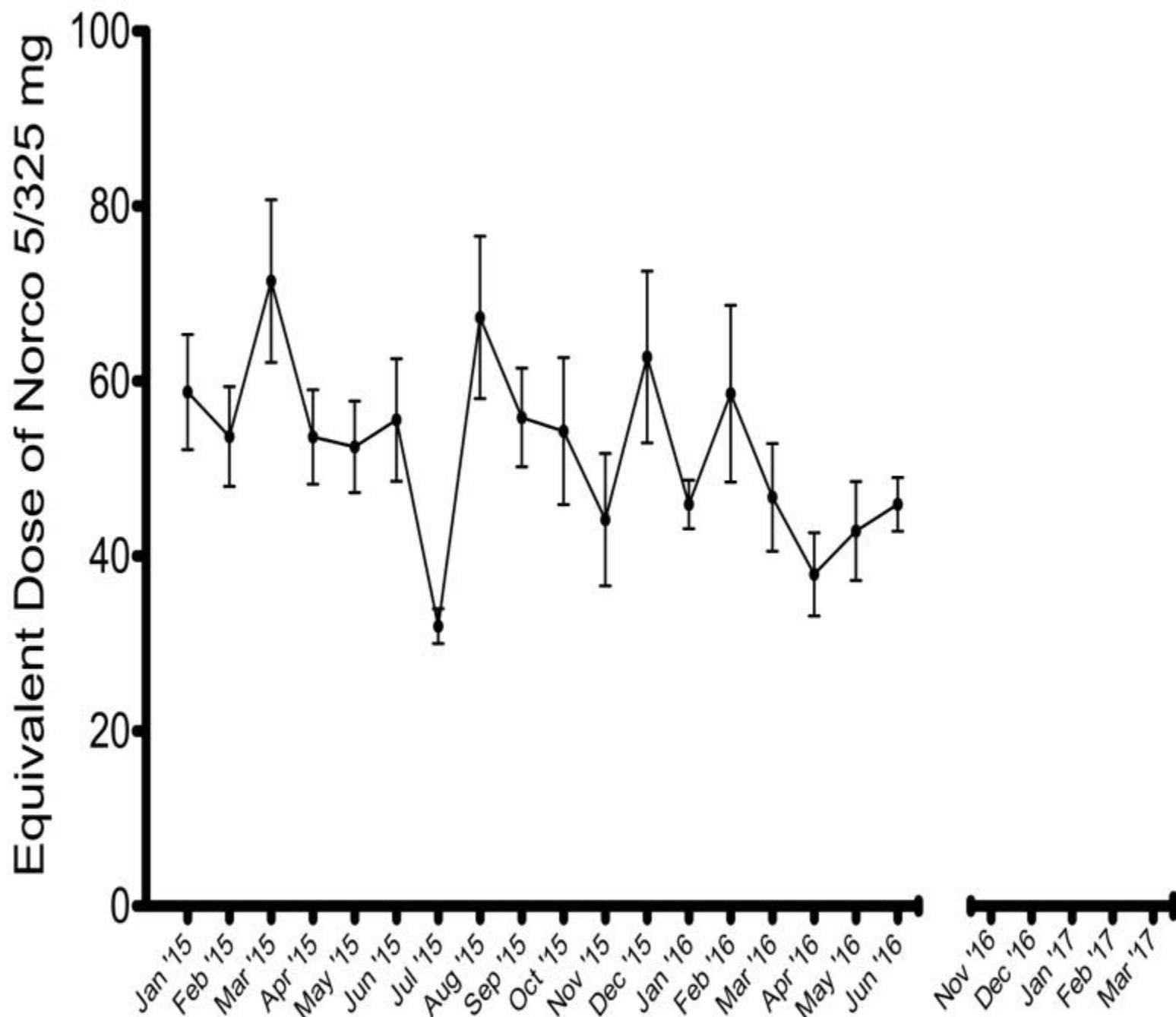


Let's get smart about prescribing

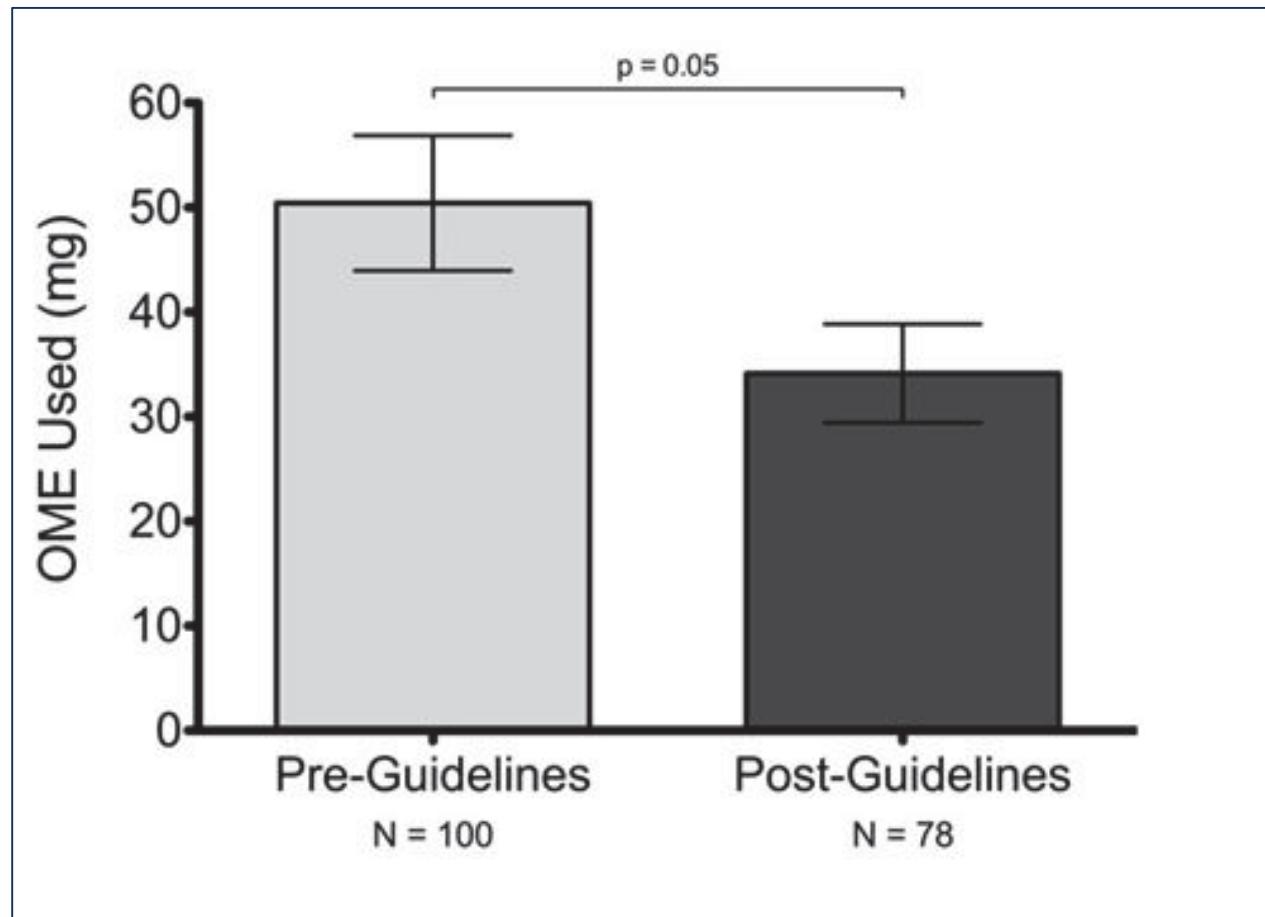
15 Oxycodone 5 mg 1q4-6 PRN

15 Norco 5/325 mg 1q4-6 PRN

+ Tylenol AND Motrin



After the new protocol, patients also reported less opioid use



Supersize it!



David Marchiori, Esther K. Papies, Olivier Klein, The portion size effect on food intake. An anchoring and adjustment process?, *Appetite* (2014), doi: 10.1016/j.appet.2014.06.018

Proposed Prescribing Guidelines

Procedure	Recommendation		
	Oral Morphine Equivalents	Hydrocodone 5 mg (Norco/Vicodin)	Oxycodone 5 mg
Laparoscopic cholecystectomy	75	15	10-15
Laparoscopic appendectomy	75	15	10-15
Laparoscopic inguinal hernia repair	75	15	10-15
Open inguinal hernia repair	75	15	10-15
MIS Hysterectomy (lap, vaginal)	100	20	15
Abdominal Hysterectomy	150	30	20



Opioid Recovery Drives

Medication Take-Back Day

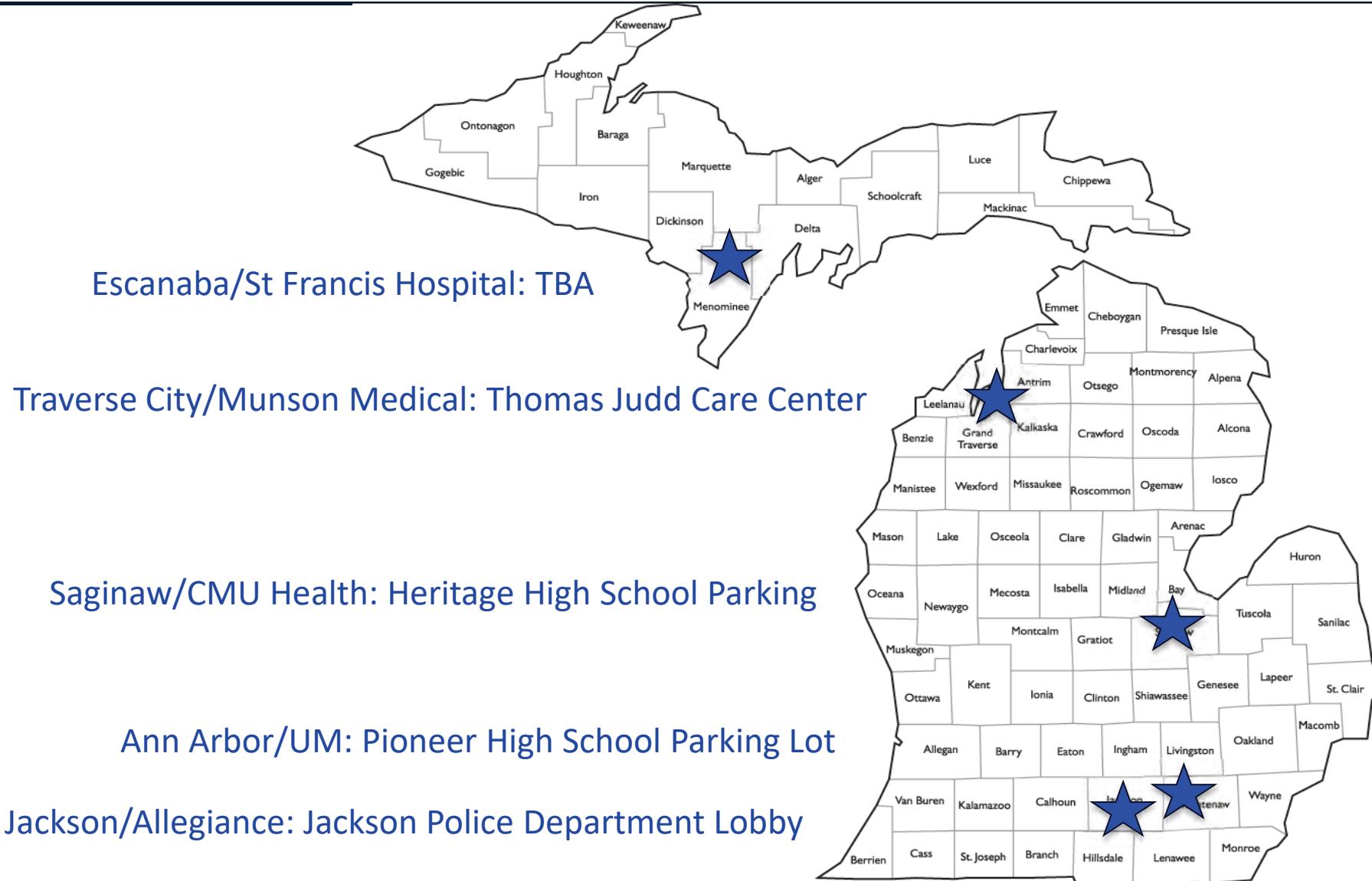
Saturday, May 20, 2017
10 a.m. – 2 p.m.



Total number of people	349
Pills	
Estimated weight of pills	181.6 lb
Estimated total number pills	139,658.5
Opioid pills	13,784
Most common - Hydrocodone	5,714
Other medications of interest	
Benzodiazepines and sedatives	3,002
Anti-depressants	6,401
Stimulants	623
Muscle relaxants	565
Anti-epileptics	4,156
Additional information	
Oldest opioid date (by year)	1981
Second oldest opioid (different person)	1985
Most common reason for opioid	Surgery



Opioid Recovery Drive – May 20



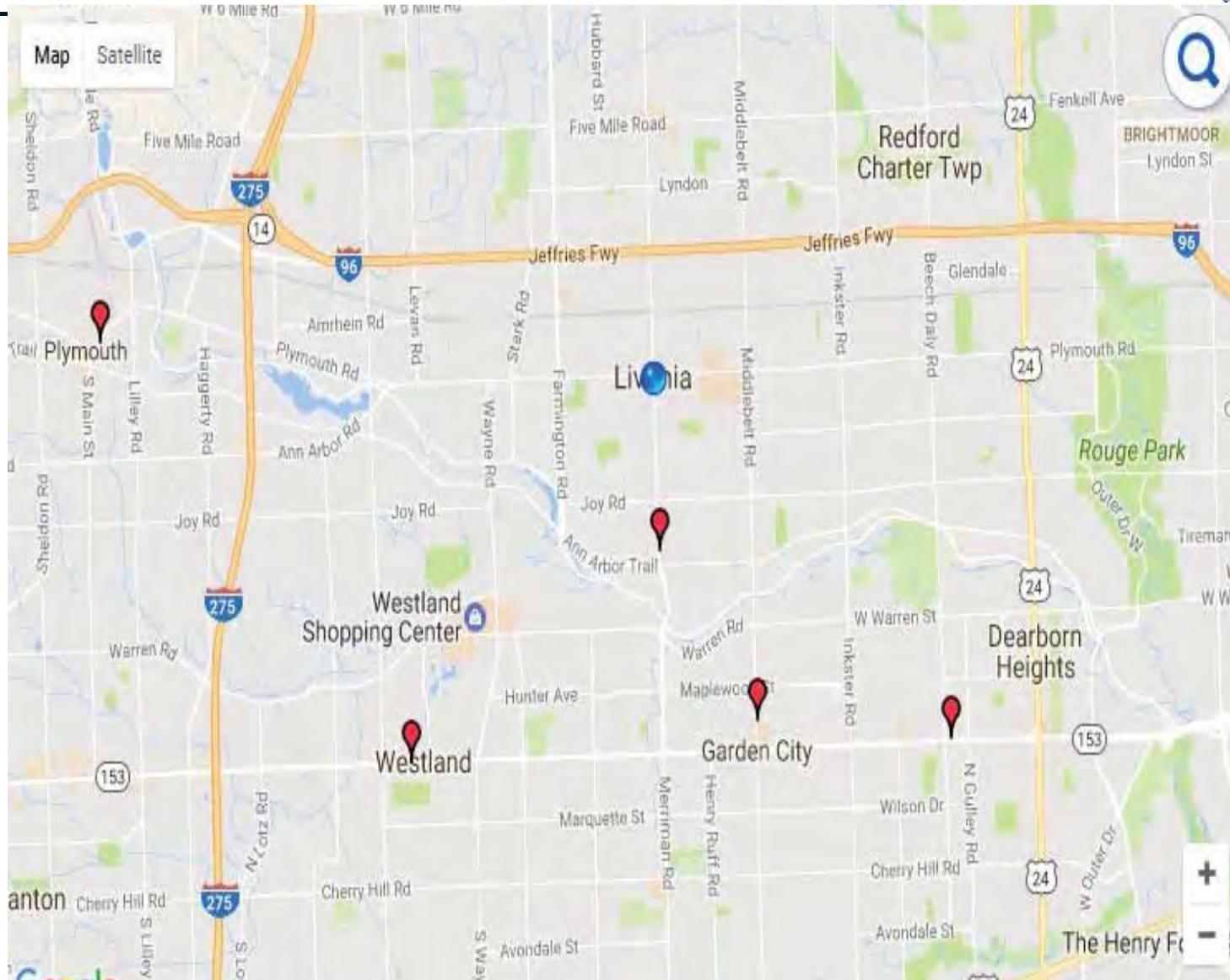


umhealth.me/takebackmap



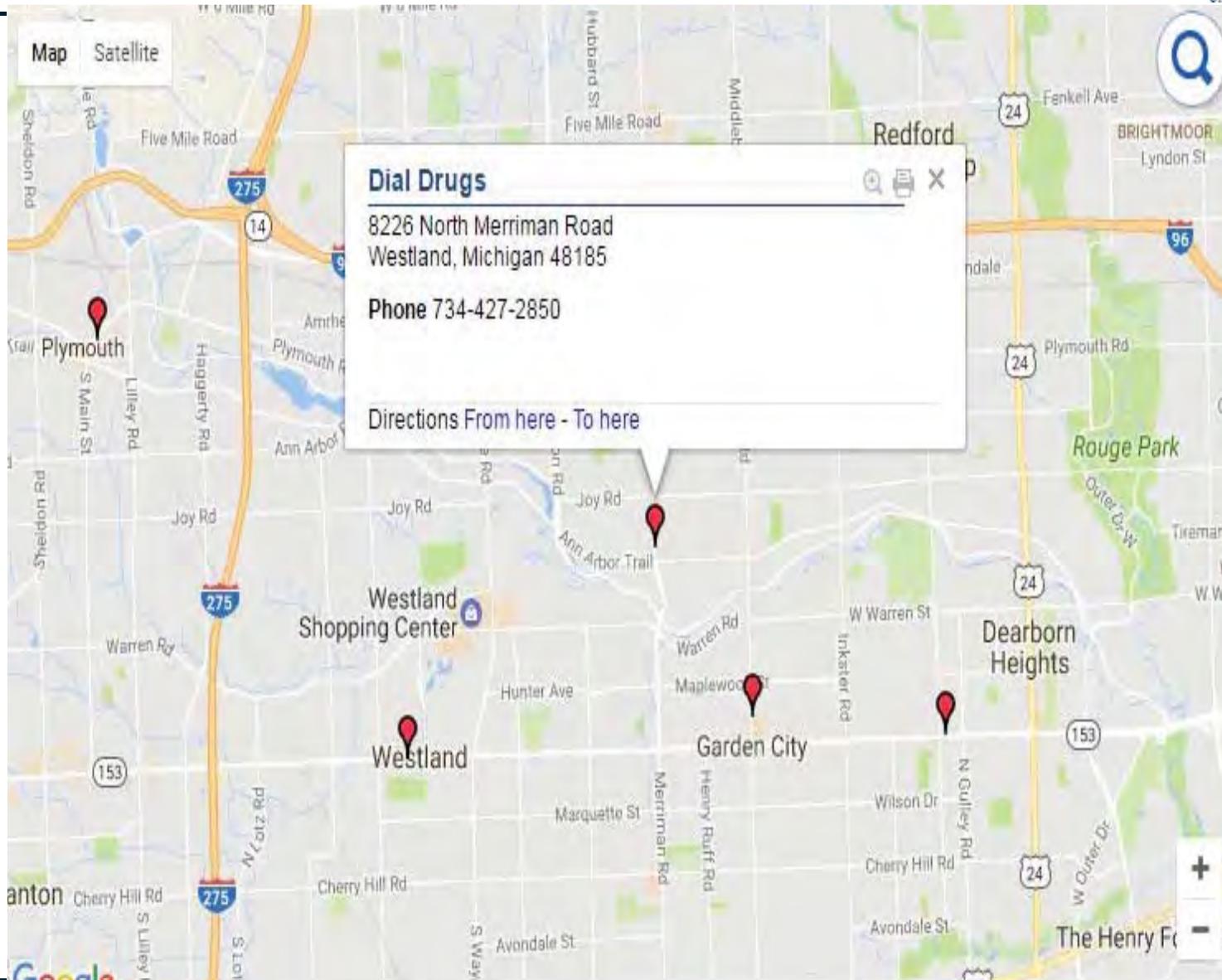


umhealth.me/takebackmap

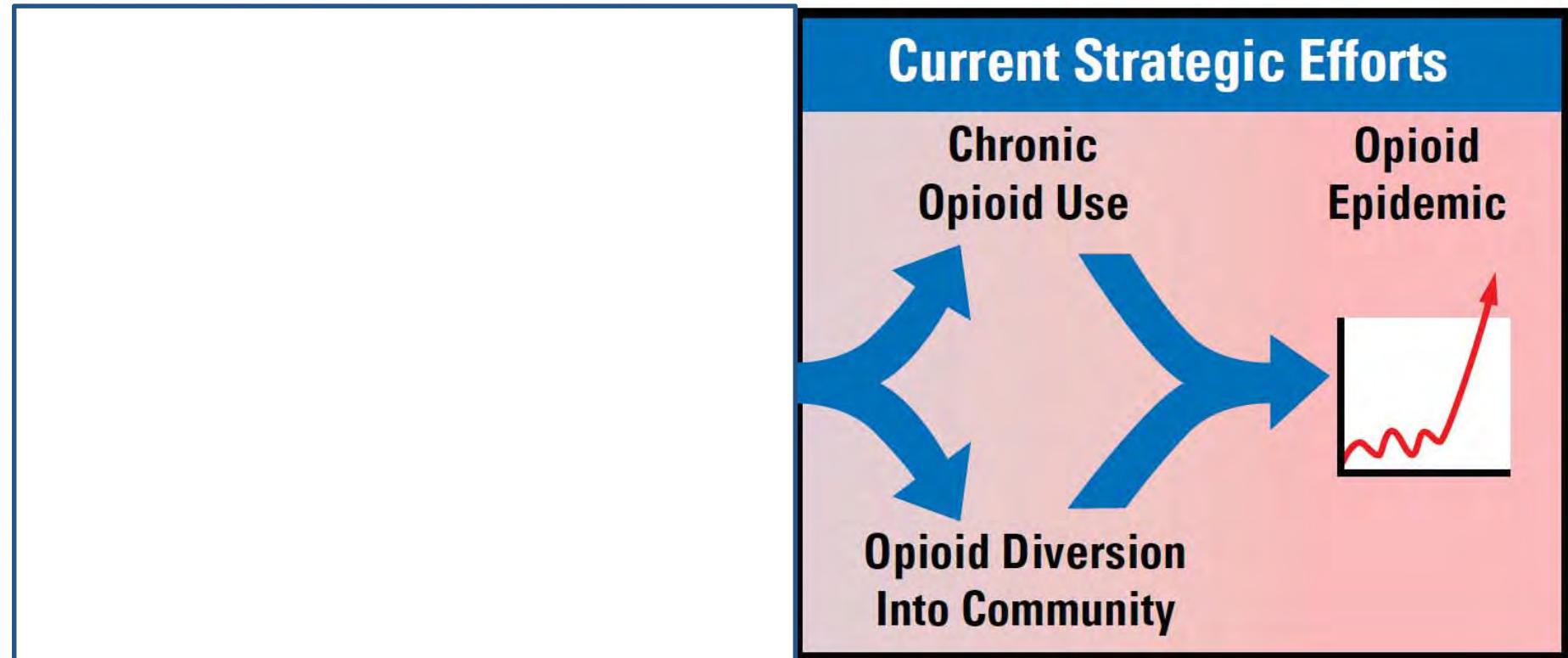




umhealth.me/takebackmap



Moving to a Preventative Model



Surgical Prescribing is Fueling the Opioid Epidemic

6-15%

Incidence of new chronic opioid use after surgery

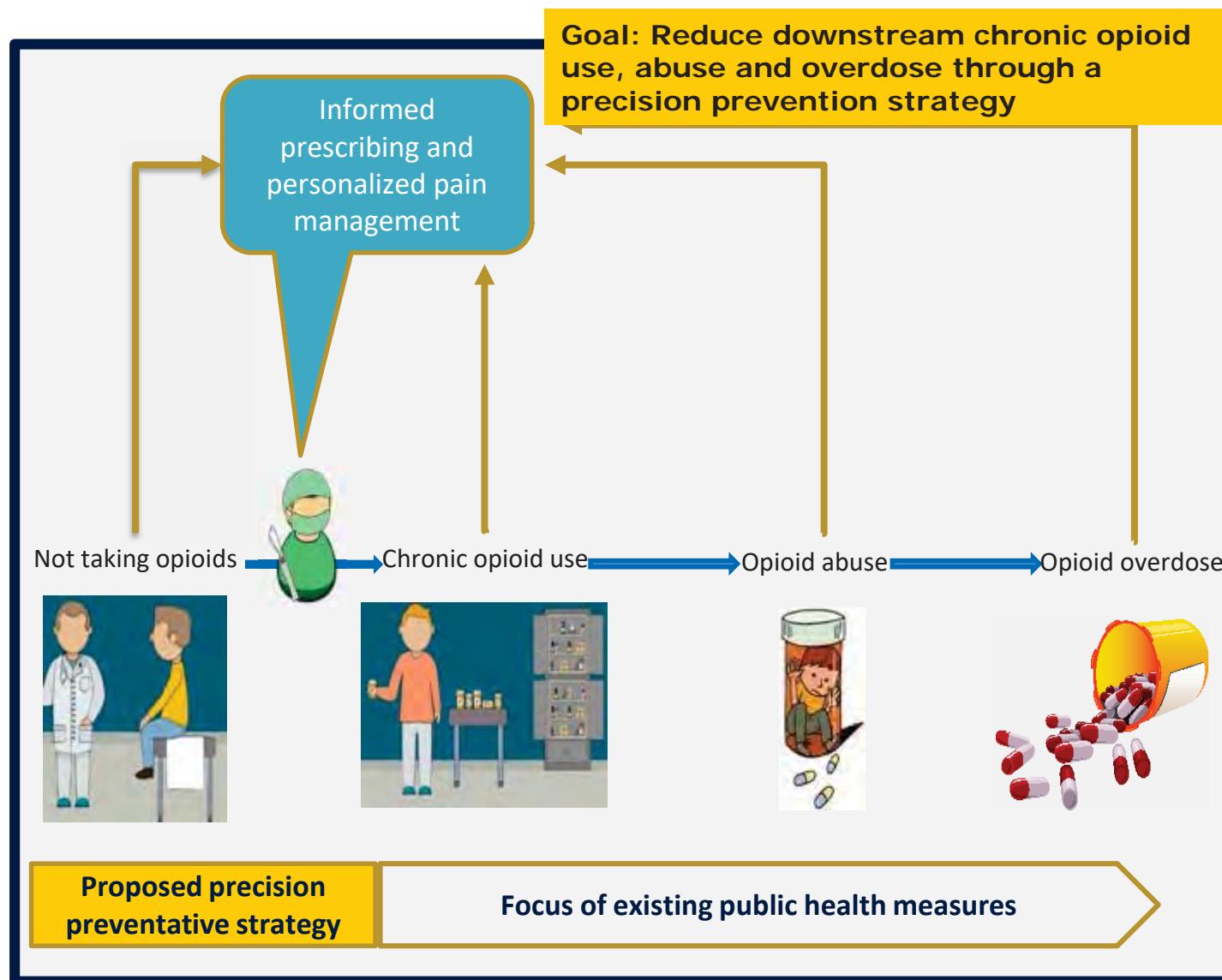


~70%

Opioids prescribed after surgery are unused

Postoperative prescribing is not currently tailored to the individual

Precision Opioid Prescribing



Contact us



cbrummet@umich.edu



caitham@umich.edu



Opioid Pre Engagement Network
engaging patients, protecting providers, protecting communities



filip@umich.edu

englesbe@umich.edu



2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit



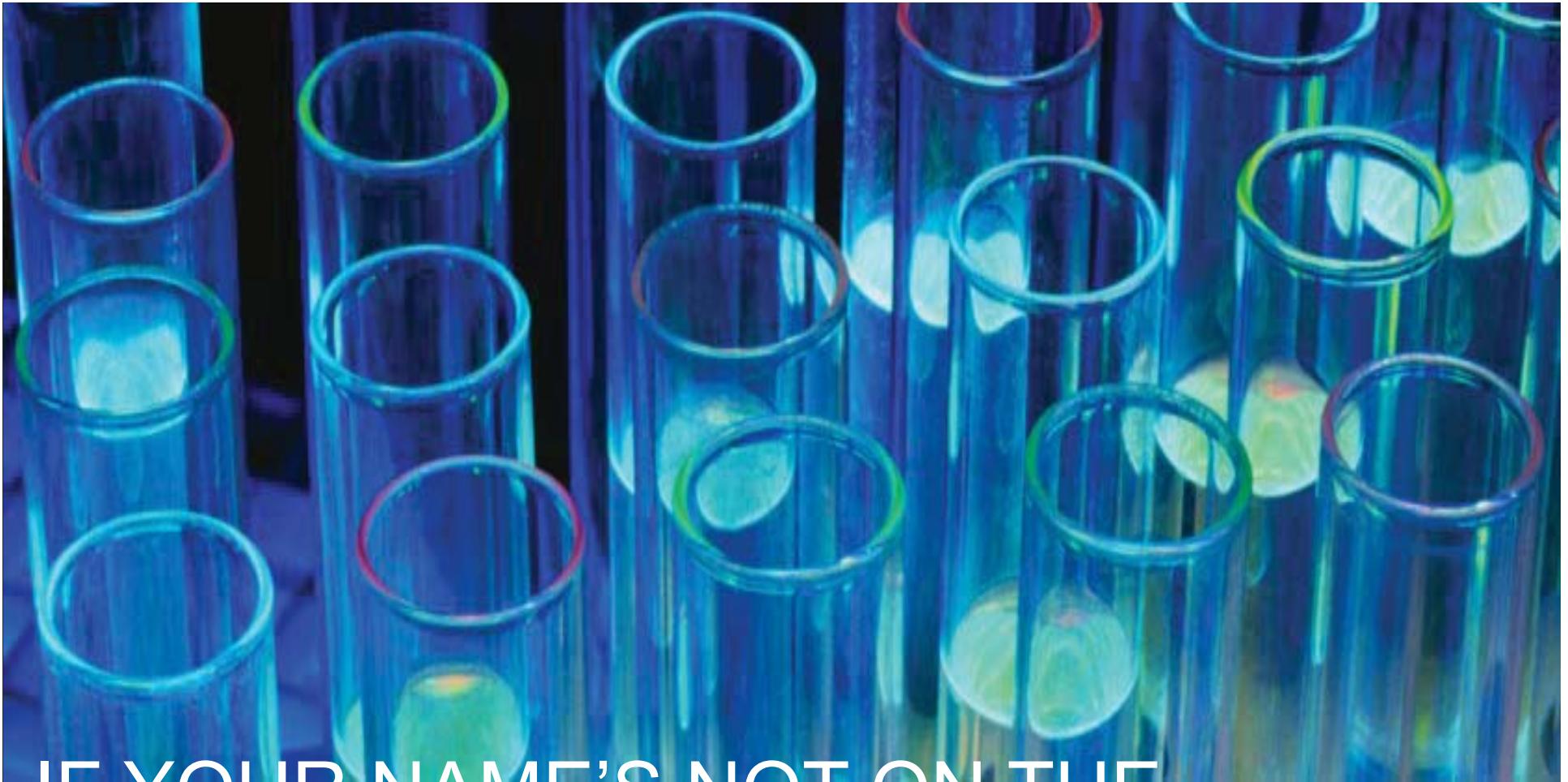
Judge Linda Davis
41B District Court
Macomb County Drug Court



2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit



Grenae Dudley, PhD
President and CEO
The Youth Connection



IF YOUR NAME'S NOT ON THE
BOTTLE...

THEY'RE NOT MEANT FOR YOU TO SWALLOW!

2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit



Presented by:
Grenae Dudley, Ph.D.



The Youth Connection and Love Detroit Prevention Coalition



2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit



Wayne County's Impact
Through Partnership and
Collaboration

May 11, 2017

Who Owns The Problem?

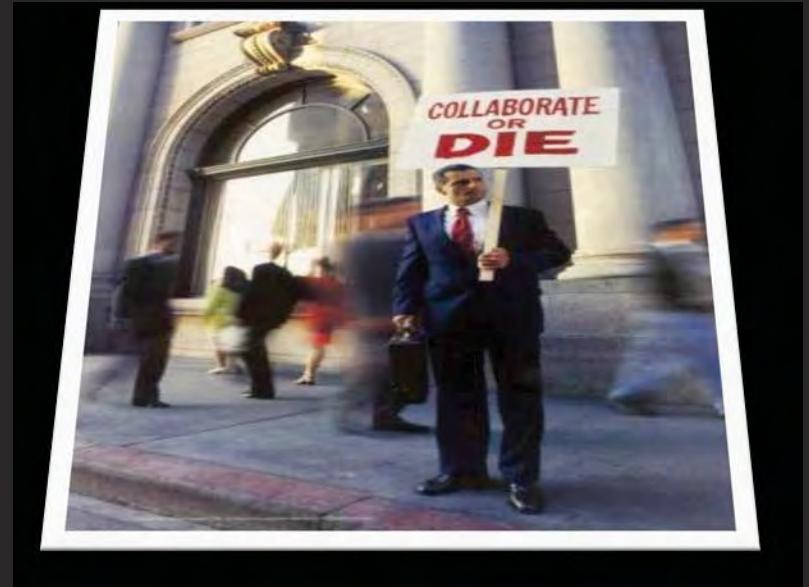
We All Do!

Prescription Drug Abuse And
The Rise Of Heroin Is A Key
Community Problem And It Is
Our Collective
Responsibilities To Address



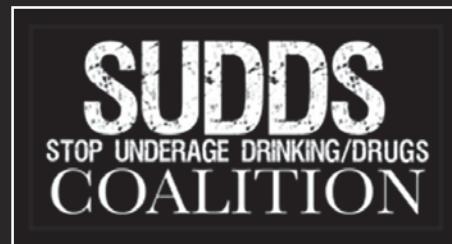
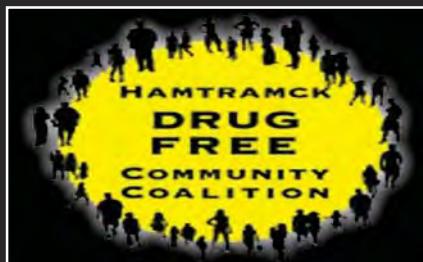
Collaborate Or.....

To Address This
Problem In Wayne
County... In Our
Collective Communities
We Have To
Collaborate!





Wayne County's Coalitions, Task Forces and Collaboratives



Empowerment Zone
Coalition



Beaumont



Detroit Wayne
County Drug
Surveillance Task
Force



NCADD-GDA
STEPS-RADIO (TOPS)



WORKING TOGETHER

The Love Detroit Prevention Coalition Brought
Together Key Leaders Across Sectors to Help
Address Prescription Drug Misuse and Abuse

We have Hosted Three Key Leaders
Roundtables and Planning One for This June

Key Leaders Roundtables Have Included:

The Youth Connection

Detroit Wayne Mental Health Authority

Detroit Recovery Project

Pharmacists

Independent Pharmacist Association

Physicians

DEA

HIDTA

Molina Healthcare

University Professors

WSU Generation Rx

Prescription Drug Companies

Community Based Organizations

Key Leaders Roundtable cont.:

Hospitals

- Children's Hospital
- St. John Providence Health System

University and Hospital Residents

Health Clinics

Substance Abuse Prevention Organizations

SUD Treatment Organizations

Schools (EAA and DPS)

Department of Health and Human Services

Wayne State University

- Eugene Applebaum School of Pharmacy
- School of Nursing
- School of Medicine Family Practice MPH



Key Leaders Recommendations

Systems Change to Impact Diversion and Addiction



Create Awareness Campaigns For Each Sector

Promote The Use Of Naloxone With Police And Families.

Add Quality Standards To Health Plans For The Prescribing And Dispensing Of Narcotics



Key Leaders Recommendations

Systems Change to Impact Diversion and Addiction



- Make MAPS Real Time
- Encourage Use of MAPS among Physicians and Pharmacists
- Change the MAPS Signage to Improve Messaging
- In MAPS allow Physicians and Pharmacist to view their history
- De-Identify the Data Base so it can be Available for Analysis



Key Leaders *Recommendations*

Systems Change to Impact Diversion and Addiction

Key Leaders Round Table Recommendations
Were Shared With

The Governor's Liaison to the Michigan Prescription
Drug and Opioid Abuse Task Force

Chris Priest, Deputy Director of Strategy

Michigan Prescription Drug and Opioid Abuse Task Force Recommendation



Collaboration among local coalitions, pharmacies, health profession boards, state agencies and the **DEA** to increase the availability of prescription drop-off bins.

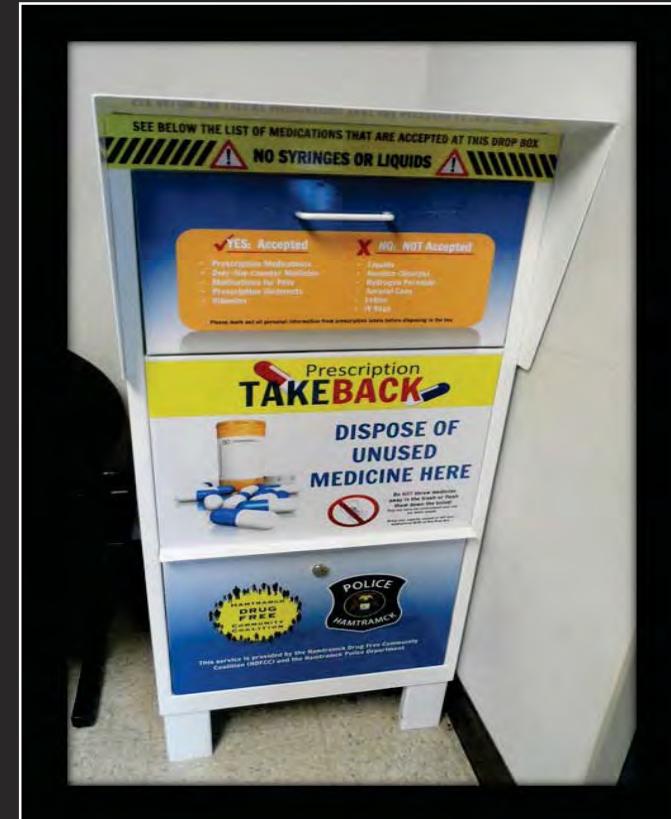
A review of successful state and local collection programs for possible replication and expansion

WAYNE COUNTY'S RESPONSE!



Take Back Boxes:

Allen Park Police Department
City of Grosse Pointe Park Public Safety
Flat Rock Police Department
Gibraltar Police Department
Grosse Ile Police Department
Grosse Pointe Park Public Safety
Grosse Pointe Woods Public Safety
Hamtramck Police Department
Lincoln Park Police Department
Livonia Police Department
Melvindale Police Department
Riverview Police Department
Rockwood Police Department
Romulus Police Department
Southgate Police Department
Taylor Police Department
Westland Police Department
Woodhaven Police Department
Wyandotte Police Department





Appropriate Disposal of Unwanted Pills



Detroit Wayne Mental Health Authority Provided 100's Of DETERRA Bags To Agencies And Coalitions for Distribution To:

- Help Curtail Diversion
- Prevent Improper Disposal Of Prescription Medications



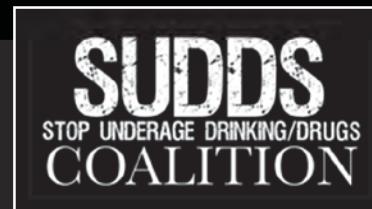
Nancy JW Lewis, PharmD, MPH, A Member Of LDPC Working With Wayne County Pharmacists.
DETERRA Bags Are Now Being Distributed At:

- Andy's Pharmacy
- CVS Pharmacy On Van Dyke And Outer Drive!
- More to Come!





20,370 lbs. Of Prescription Drugs
Collected In Michigan For The April 2017
Take Back Day. 34 Sites In Detroit Wayne
County Participated!



Beaumont





The Youth Connection, TYC'S WSU MPH Intern, Eli Sullivan, LDPC, And The Great Lakes Water Authority Are Working To Include A Prescription Disposal Message On Every Water Bill In Communities GLWA Serve In Southeastern Michigan. It Will Also Include A Link To A Website To Inform Residents Of Why, How and Where To Appropriately Dispose Of Prescription Drugs.



Michigan Prescription Drug and Opioid Abuse Task Force Recommendation



A multifaceted **Public Awareness Campaign** be undertaken to **Inform the Public of the Dangers of Abuse, How to Safeguard and Properly Dispose of Medicine, Publicize Improper Prescribing Practices, and Reduce the Stigma of Addiction**





Wayne County's Response.....

If Your Name ISN'T on the Bottle
They're Not FOR YOU to Swallow!



www.PreventionDetroit.com

 DETROIT RECOVERY PROJECT INC.
(Doing It Together)

 Love Detroit
Prevention Coalition

 DWMHA

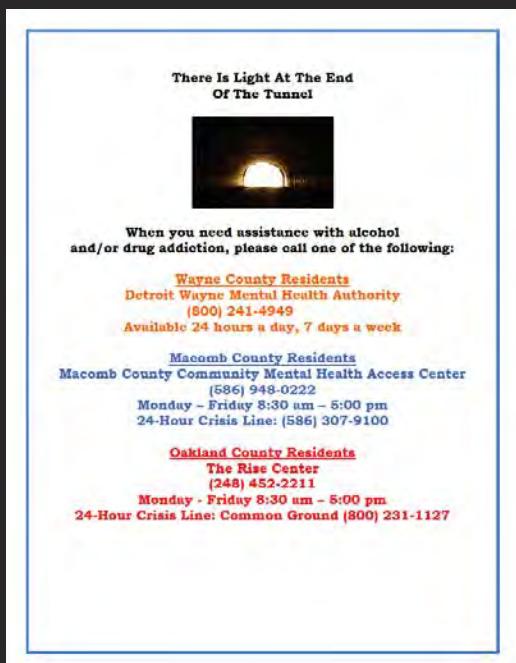
Poster Designed by: Adnan Khalil, The Youth Connection



Wayne County's Response.....



Wayne County's Response.....



Pharmacists Shared Diversion Prevention Best Practices

Several implemented Diversion Prevention Practices in their Pharmacies

Increased Prevention and Treatment Referral Information utilizing kicker cards provided by coalition

Molina Healthcare of Michigan Reviewed their Health Plans Across The Country (Dr. Forshee, the Vice President of Medical Affairs and Chief Medical Officer for Molina Health Care, 2015)

Member Monitoring

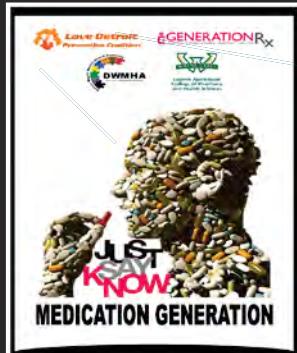
Prescriber Monitoring

Lock-in Program To Promote Monitoring/Prevent Diversion

Drug Formulary Management



Community Engagement





Wayne County's Response.....



EMPOWERMENT ZONE

COALITION

Lock It Up- Think About it Campaign

Community Workshops on Proper Disposal of Rx
Drugs

Designed and Distributed Postcards on Teens
and Prescription Drugs





Wayne County's Response.....

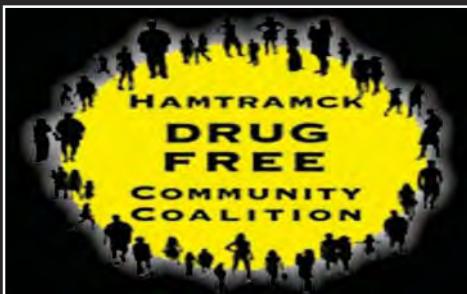
Prevention
Collaborative



Actively Participates In Take Back Days!
Emerging Threat: Prescription Drugs Workshops
Provide Education To Grandparents Raising
Grandchildren



Wayne County's Response.....



Distributed Education Packets And Prescription Take Back Info To:
Hamtramck Police Department
Highland Park Police Department
Hamtramck Fire Department
23 Pharmacies In Hamtramck
Distributed Flyers Of Prescription Takeback Literature In Several Languages



Prescription Medication Committee Including Livonia Police, St. Mary-Mercy-Livonia and LSOY working on implementing a Safe Storage and Disposal Campaign.



LSOY Provides Prescription Medication Awareness to Children at The Livonia Police Passport to Safety Annual Event.

Michigan Prescription Drug and Opioid Abuse Task Force Recommendation



A Review of the Budgetary Requirements for **Updating or Replacing MAPS Mandatory Registration in MAPS by all Licensed Prescribers** be Implemented to Ensure All are Registered When the Updated or New System is Brought on Line

Michigan Prescription Drug and Opioid Abuse Task Force Recommendation



The State of Michigan has replaced the Michigan Automated Prescription System (MAPS) with Appriss, PMP AWARxE software as of April 4, 2017.

Michigan Prescription Drug and Opioid Abuse Task Force Recommendation



Pharmacists be Allowed to
**Dispense Naloxone to the
Public** in Similar Fashion to
How Pseudoephedrine is
Currently Dispensed.

Wayne County's Response.....

Expanded Opioid Training Helps Detroit And Wayne County



The DWMHA Is Partnering With Local Law Enforcement To Create A Holistic Approach To Drug Addiction, Treating Substance Abuse As A Mental Health Issue.

Police Throughout Wayne County Are Trained To Use Opioid Overdose Kits Through The DWMHA, Which Give The Kits To The Police Department For Free.

Wayne County's Response.....



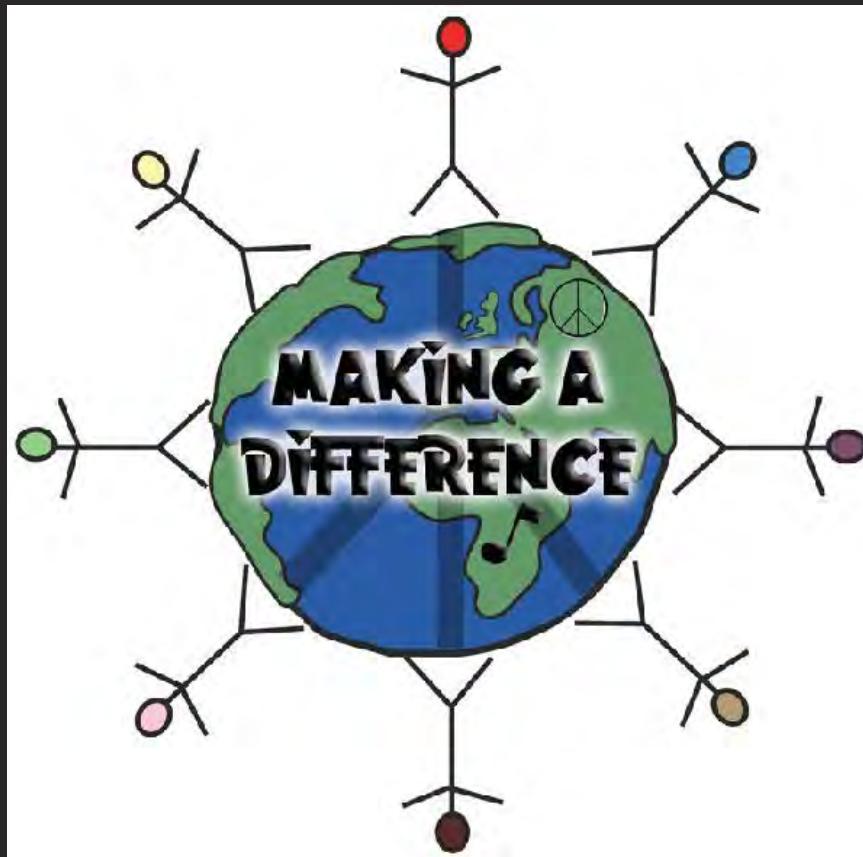
In The Four Months Since The Detroit Wayne Mental Health Authority Began Training Local Law Enforcement On The Use Of The Opioid Antidote Naloxone, Two Lives Have Been Saved By Michigan State Police Troopers.

Dr. Carmen McIntyre, The Authority's Chief Medical Officer, Described Herself As A "Proud Teacher" When She Watched Dash Cam Video Of One Of The Saves. She Saw The Trooper Examine A Man Who Had Passed Out And Administer The Drug Expertly, Just As He'd Been Taught.

Six Months After They Were Trained Dearborn Police Have Already Saved Five Lives With The Kits, Including One Just Two Weeks Ago, A Man Found Unresponsive In A Hotel Parking Lot.



WAYNE COUNTY WE ARE





GREATER DETROIT AREA HEALTH COUNCIL

2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit



Award Presentation

Dr. Carmen McIntyre, Tom Watkins, Kate Kohn-Parrott



2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit



Collin Rose Memorial

Accepting on Behalf of the Family

Captain Patrick Saunders
Coordinator of Line Operations
Wayne State University Police



2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit



Collin Rose Award for Excellence in Saving Lives

Accepting Award

Sargent Jacob Liss
Trooper Mark Bessner
Michigan State Police



GREATER DETROIT AREA HEALTH COUNCIL

2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit



Please Enjoy
Lunch
Vendor Visits
and Networking



GREATER DETROIT AREA HEALTH COUNCIL

2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit



Please Take Your Seats,
The Program is About
to Resume.

Thank You!



2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit





2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit



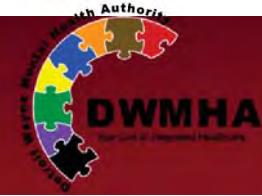
Dr. Benjamin Jones
President and CEO
National Council on Alcoholism and
Drug Dependence

Panel Moderator



GREATER DETROIT AREA HEALTH COUNCIL

BRIDGING SILOS Panel Discussion



Ghada Abdallah
Park Pharmacy



Julia Hitchingham
Michigan Department of Corrections



Andre Johnson
Detroit Recovery Project



Dr. Carmen McIntyre
Detroit Wayne Mental Health Authority



Geno Salomone
23rd District Court



Patty Wagenhofer-Rucker
Genesee Community Health Center



GREATER DETROIT AREA HEALTH COUNCIL

2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit



Cathy Gallagher
Diversion Program Manager
Detroit Division of the
Drug Enforcement Administration



Drug Enforcement Administration

DEA: Combating the Supply 2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit

Cathy Gallagher
Diversion Program Manager
Detroit Division

May 11, 2017

159



SECTIONS

TRAFFIC

WATCH

NEWS

COPS: PHOTOS OF BOY WITH PASSED-OUT ADULTS SHOW DRUG SCOURGE

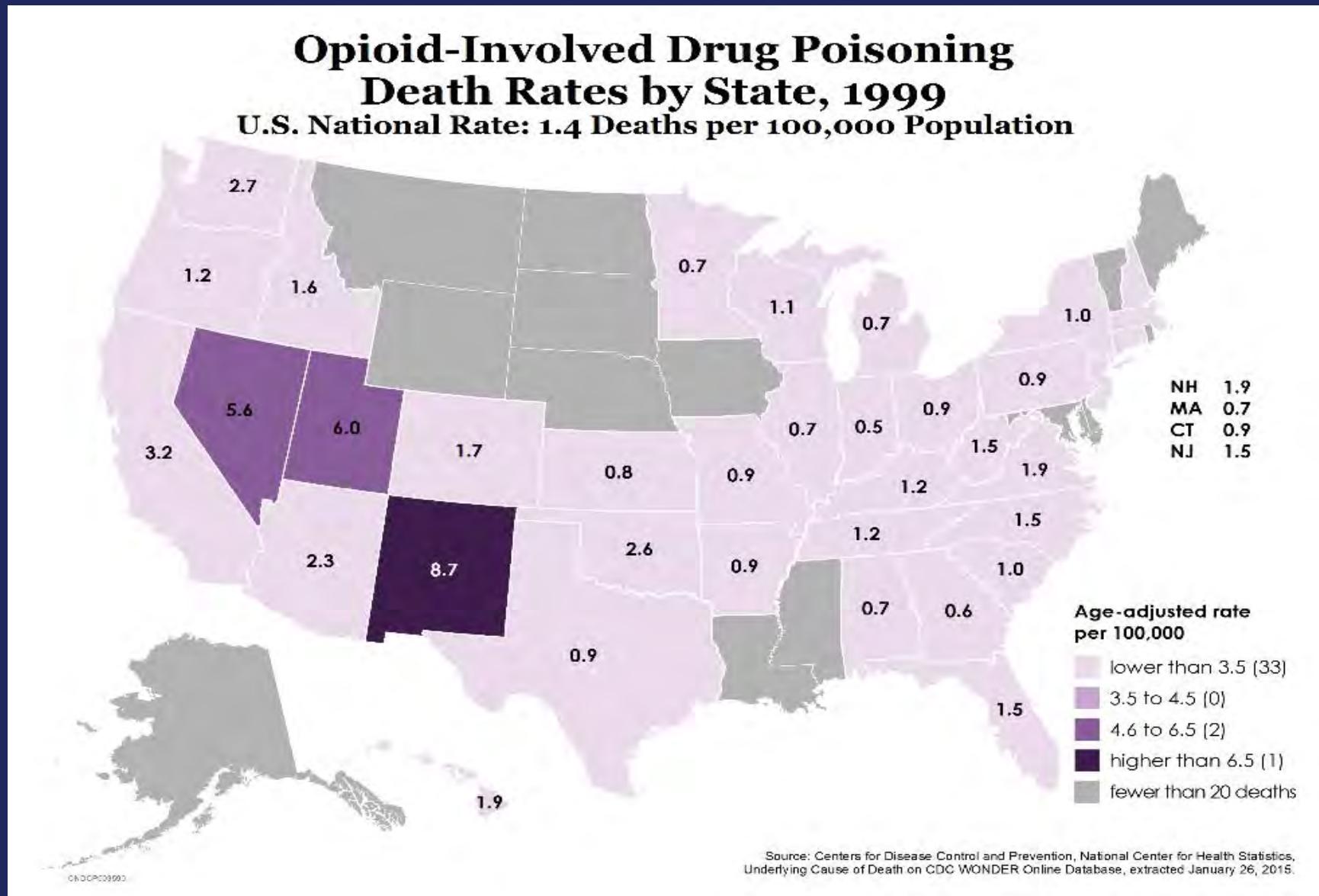
Share

Email



Police in East Liverpool, Ohio released these images they say to illustrate the impact of the heroin and painkiller epidemic. (City of East Liverpool, Ohio/Facebook)

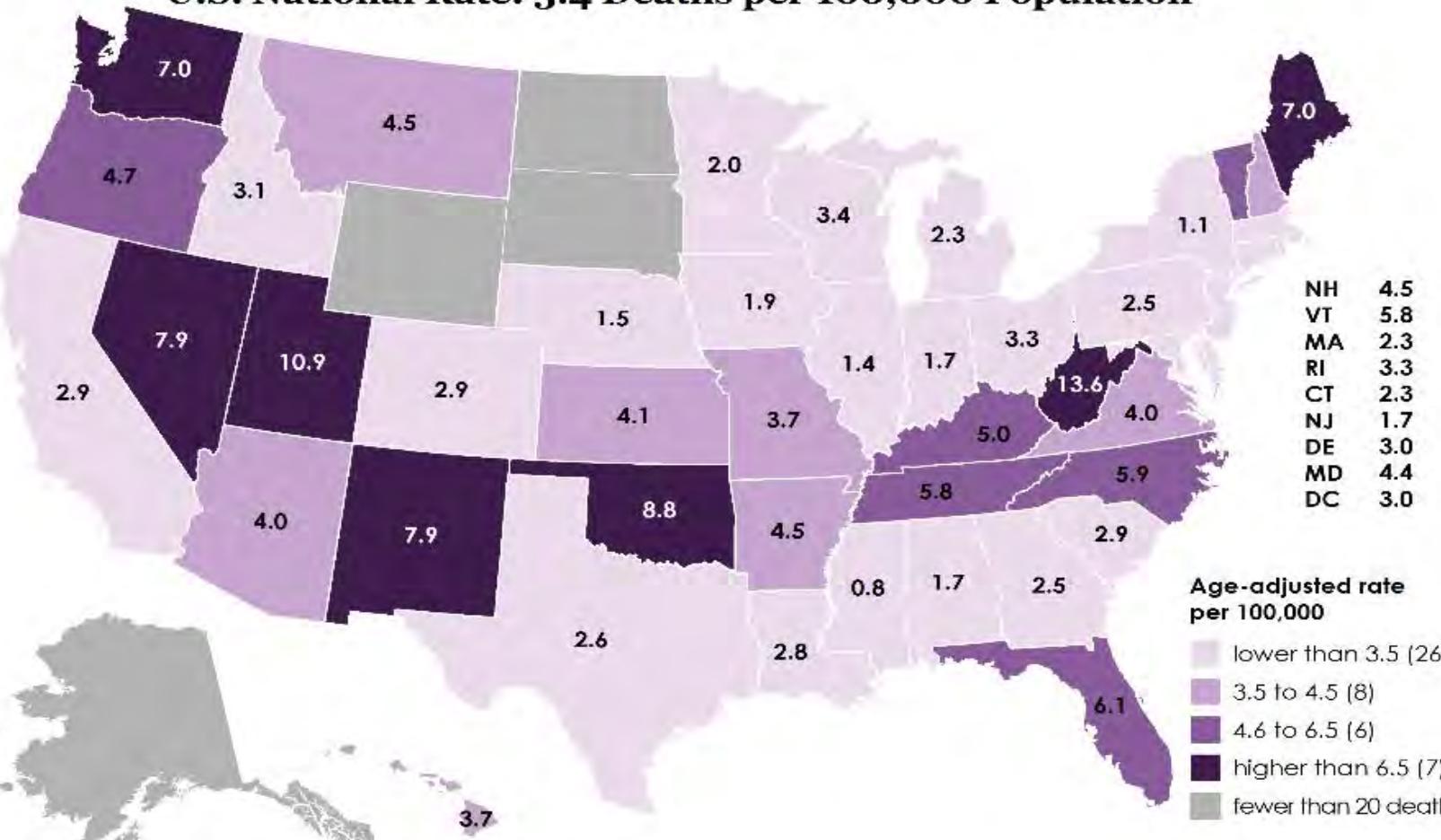
Prescription Opioid Analgesics Poisoning Deaths



Prescription Opioid Analgesics Poisoning Deaths

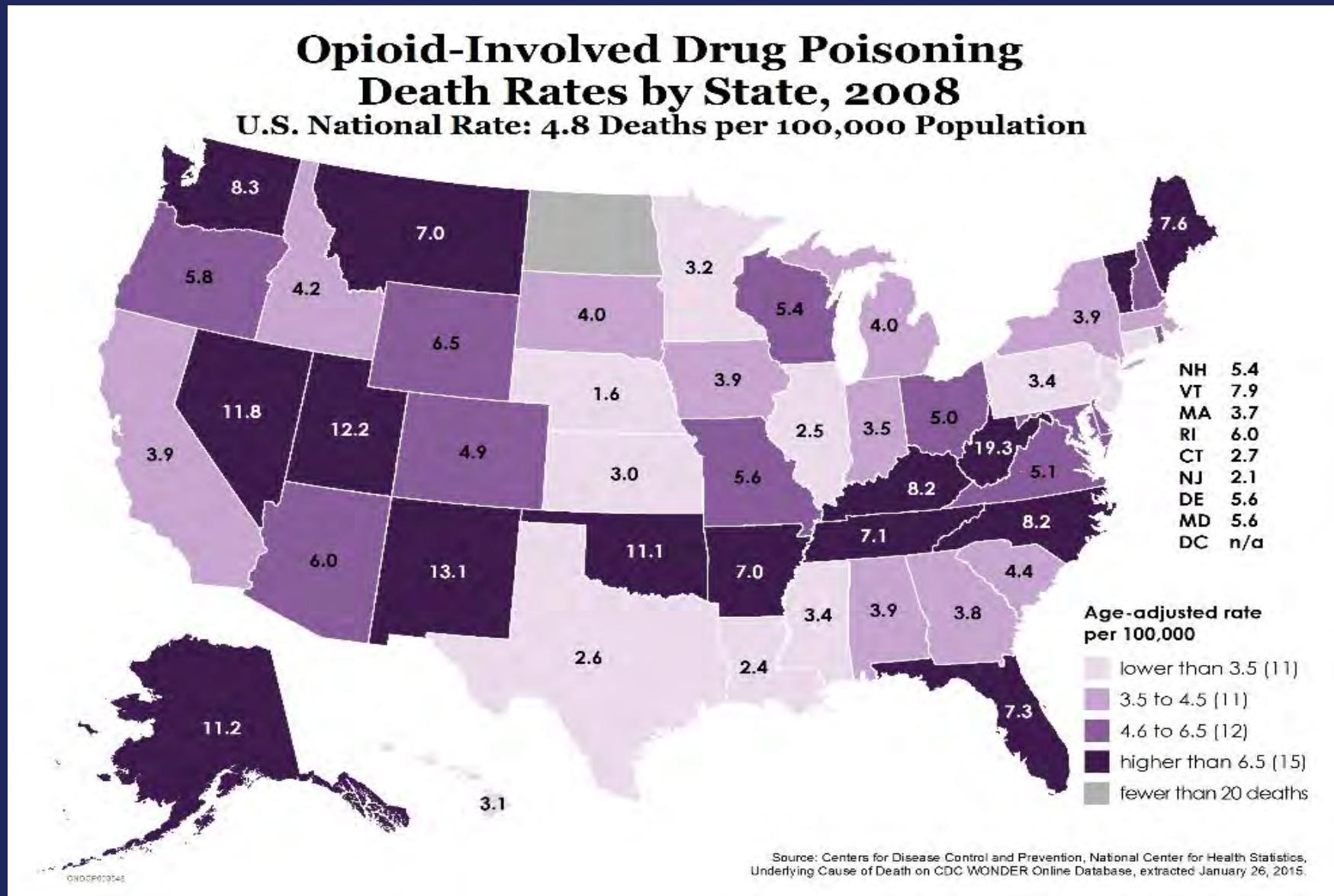
Opioid-Involved Drug Poisoning Death Rates by State, 2004

U.S. National Rate: 3.4 Deaths per 100,000 Population

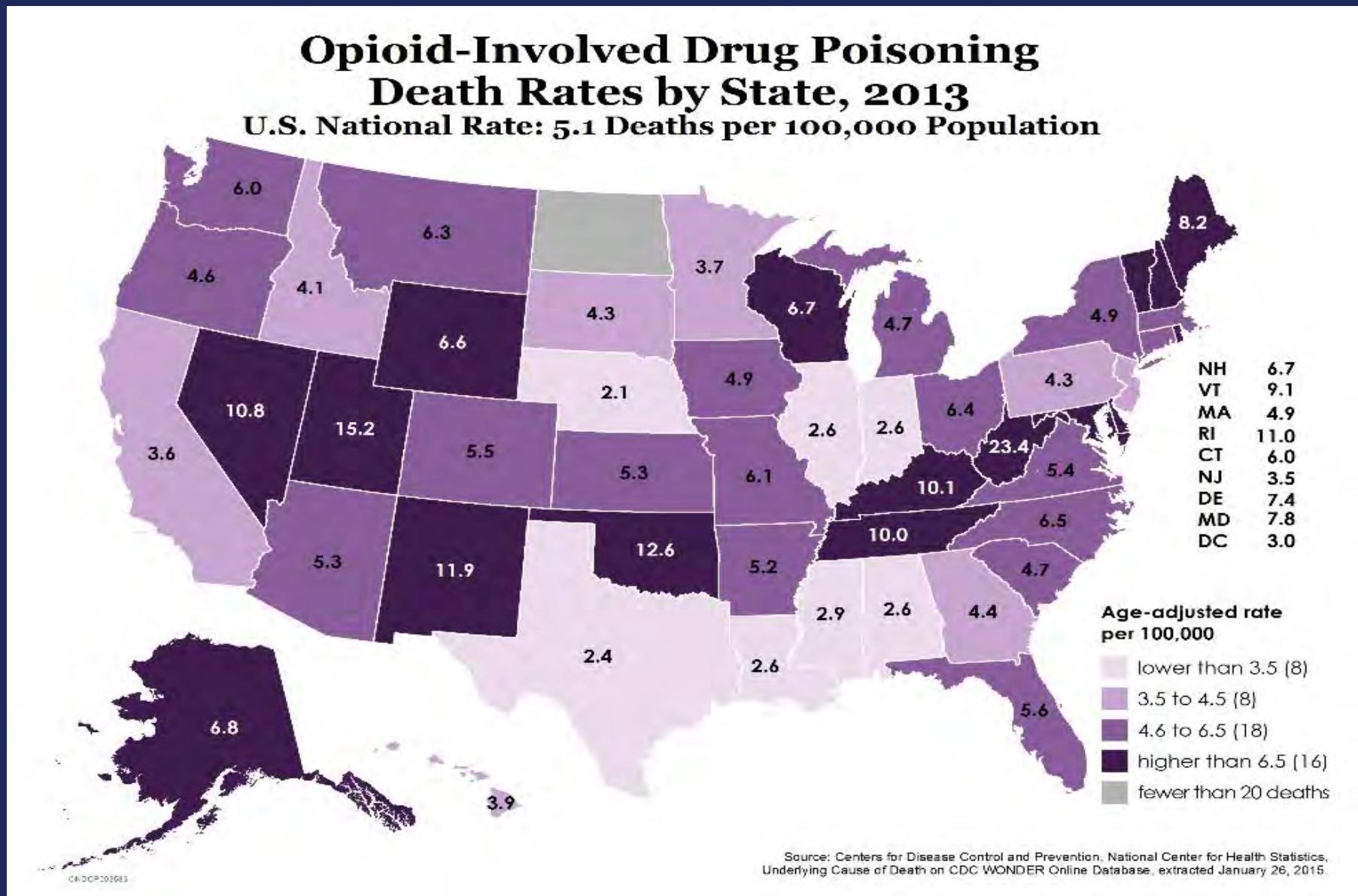


Source: Centers for Disease Control and Prevention, National Center for Health Statistics, Underlying Cause of Death on CDC WONDER Online Database, extracted January 26, 2015.

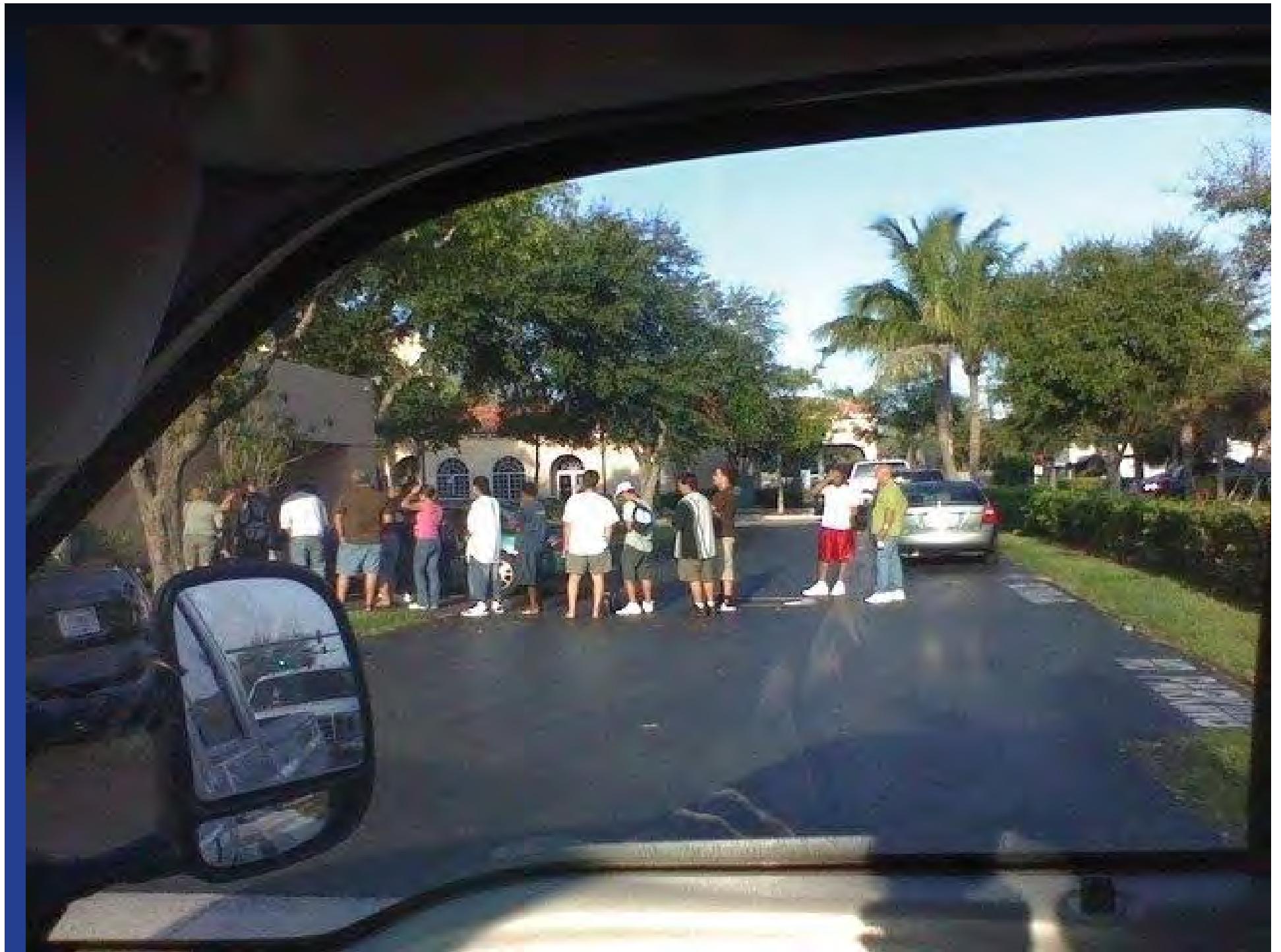
Prescription Opioid Analgesics Poisoning Deaths



Prescription Opioid Analgesics Poisoning Deaths





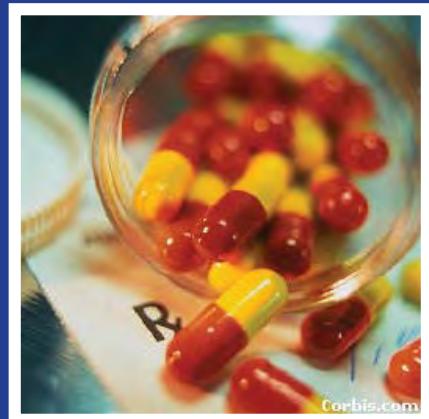


Office of Diversion Control

Mission

To prevent, detect, and investigate the diversion of controlled substances from legitimate sources

while



Ensuring an adequate and uninterrupted supply for legitimate medical and scientific purposes

Diversion Control Functions

- U.S. Competent Authority under U.N. drug and chemical control treaties
- Control of imports / exports of drugs and chemicals
- Domestic and international controlled substances scheduling
- Establishment of drug production quotas

Diversion Control Functions

- Industry Liaison/Policy Development
- Promulgation of regulations
- Registrar to 1.6 million controlled substance registrants and 2,700 listed chemical handlers
- Computerized monitoring, tracking of distribution of certain controlled drugs and chemicals; providing distribution intelligence to the states

The CSA's Closed System of Distribution



Types of Controlled Substances

- Narcotics
- Stimulants
- Depressants
- Hallucinogens
- Anabolic Steroids

Schedules of Controlled Substances

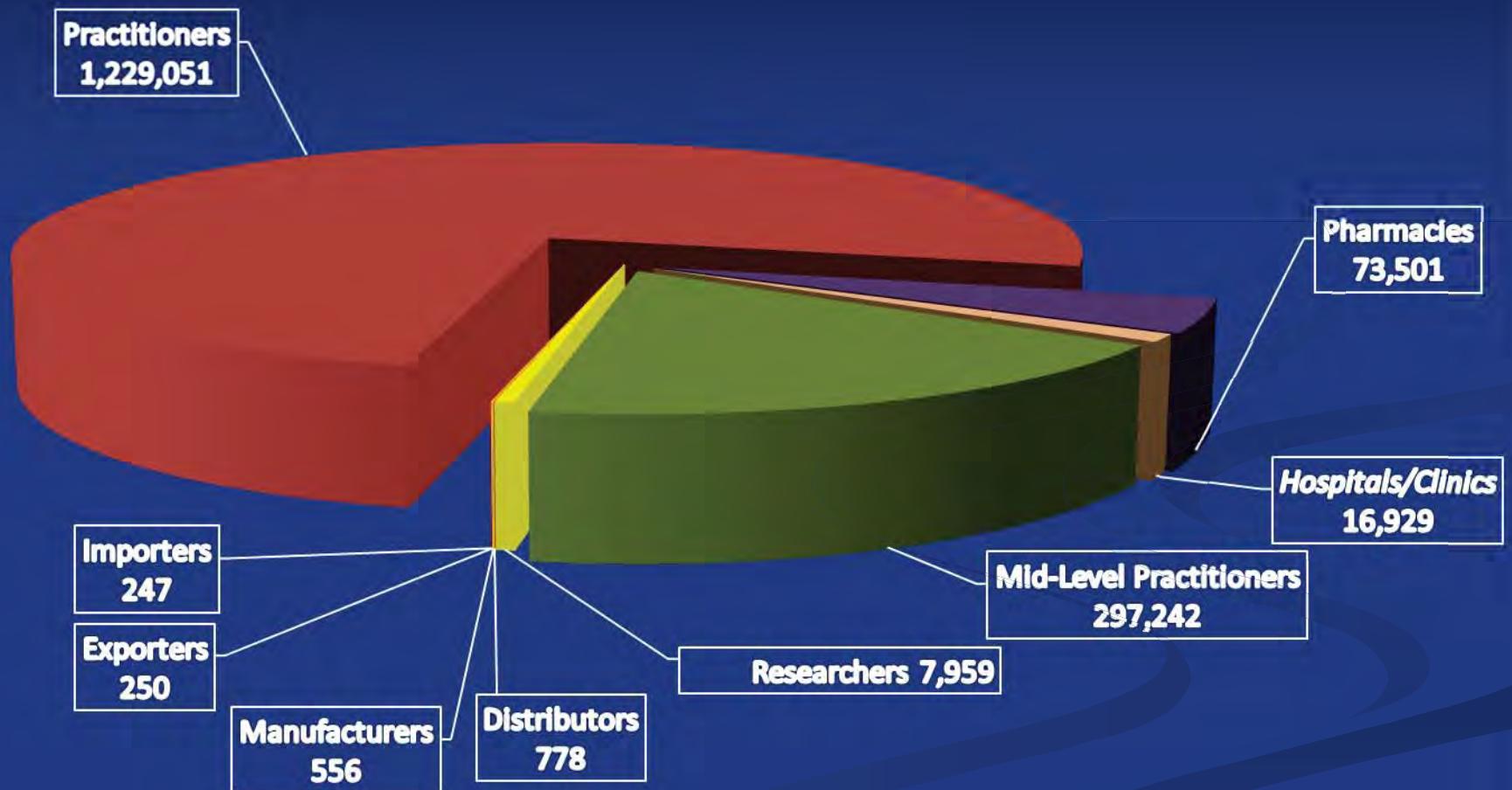
- Schedule I - No accepted medical use/ High potential for abuse/dependency (Heroin, Marihuana, “Bath Salts”)
- Schedule II - Accepted medical use/ High potential for abuse/dependency (Morphine, Oxycodone)
- Schedule III - Accepted medical use/ Less potential for abuse/dependency (Hydrocodone compounds)
- Schedule IV - Accepted medical use/ Less potential for abuse/dependency (Benzodiazepines)
- Schedule V - Accepted medical use/ Less potential for abuse/dependency (Codeine cough syrup)

Maintaining the CSA's Closed System of Distribution



Active Registrants

1,666,501 total (3-3-2017)



Michigan Registrant Population

- Manufacturers: 16
- Distributors: 22
- Practitioners: 37,019
- NPs/PAs: 9,207
- Pharmacies: 2,495
- Opioid Treatment Programs: 44
- DATA-Waived Practitioners: 998

How Do DEA Field Offices Combat the Supply?

- Regulatory Inspections – Record Keeping and Security
- Monitor the chain of distribution/suspicious orders
- Monitor reported thefts and significant losses
- Criminal, Civil and Administrative Action
 - Diversion Groups
 - Tactical Diversion Squads

DEA Action

- Administrative Action:
 - Scheduled Inspections
 - Letters of Admonition
 - Memorandum of Agreements
 - Immediate Suspension Orders (ISO)
 - Order To Show Cause (OTSC) registrations
- Criminal/Civil Investigations Action:
 - Federal and State Level

Prescription Requirements

In order to be legal, a prescription must:

- Be issued by a registered practitioner.
- For a legitimate medical purpose.
- In the usual course of professional practice.

21 CFR §1306.04(a)



Prescription Requirements

- DEA does NOT define nor regulate medical practice standards.
- There are no federal laws or regulations that put limits on the quantity of controlled substances that may be prescribed.
- Some states or insurance providers may limit the quantities of controlled substances prescribed or dispensed.

Pharmacist's Corresponding Responsibility

- Corresponding responsibility rests with the pharmacist who fills the prescription.
21 C.F.R. § 1306.04 (a)

Drugs of Concern

- Hydrocodone (CII)
- Oxycodone (CII)
- Oxymorphone (CII)
- Methadone (CII)
- Fentanyl (Schedule II)
- Adderall® (CII)
- Suboxone (CIII)
- Alprazolam (CIV)
- Carisoprodol/Soma® (CIV)
- Cough Syrup (CV)

State Ranking* - Hydrocodone

January – December 2016

RANK	STATE	TOTAL	RANK	STATE	TOTAL	RANK	STATE	TOTAL	RANK	STATE	TOTAL	RANK	STATE	TOTAL
1	CA	761,524,830	12	KY	167,156,880	23	MS	93,319,730	34	MD	33,623,090	45	WY	10,264,600
2	TX	490,024,170	13	PA	164,632,230	24	OR	90,197,120	35	NJ	33,451,020	46	AK	9,277,300
3	MI	340,090,370	14	MO	160,127,350	25	WI	82,866,264	36	MA	32,595,900	47	NH	9,158,690
4	FL	291,256,130	15	NY	157,669,940	26	NV	73,346,530	37	NE	31,776,250	48	ND	8,138,030
5	IL	263,273,500	16	OK	137,166,930	27	KS	69,862,710	38	NM	31,223,910	49	DE	5,938,440
6	IN	200,457,150	17	LA	126,294,860	28	IA	57,332,210	39	MT	20,872,990	50	VT	5,030,470
7	OH	200,405,880	18	WA	123,108,310	29	CO	56,365,150	40	CT	19,790,230	51	DC	1,400,090
8	TN	200,348,680	19	SC	117,214,080	30	WV	53,773,800	41	ME	17,946,020	52	PR	532,450
9	GA	196,802,830	20	AR	103,551,640	31	MN	50,004,380	42	HI	14,385,450	53	VI	290,920
10	AL	192,898,540	21	VA	101,240,330	32	UT	48,752,040	43	SD	13,094,290	54	GU	141,700
11	NC	168,661,440	22	AZ	95,911,090	33	ID	44,712,660	44	RI	11,447,000	55	AS	0

* *Business Activity – Retail Pharmacies*

State Ranking* - Oxycodone

January – December 2016

RANK	STATE	TOTAL	RANK	STATE	TOTAL	RANK	STATE	TOTAL	RANK	STATE	TOTAL	RANK	STATE	TOTAL
1	FL	327,396,960	12	MD	125,735,760	23	KY	82,392,630	34	MS	37,881,860	45	MT	14,987,850
2	PA	289,615,310	13	VA	125,223,670	24	AL	81,599,660	35	NM	37,587,670	46	PR	12,343,940
3	CA	283,323,420	14	MO	110,174,930	25	MN	72,078,260	36	WV	34,522,500	47	AK	11,106,040
4	NY	274,724,480	15	MA	109,525,870	26	OK	70,780,960	37	ME	24,677,180	48	WY	9,734,720
5	OH	240,022,630	16	MI	97,933,810	27	LA	67,844,460	38	NH	24,281,880	49	VT	8,974,030
6	NC	236,168,260	17	WI	94,207,800	28	CT	62,070,650	39	IA	24,180,470	50	SD	7,231,450
7	NJ	174,379,890	18	IN	91,166,180	29	NV	60,054,648	40	DE	24,126,160	51	DC	6,682,270
8	AZ	168,119,440	19	OR	90,591,450	30	UT	59,277,520	41	ID	21,551,870	52	ND	6,175,330
9	TN	166,650,300	20	SC	90,410,270	31	IL	53,048,100	42	NE	17,785,620	53	GU	442,000
10	GA	150,552,720	21	CO	85,984,060	32	AR	47,225,630	43	RI	16,602,080	54	VI	328,320
11	WA	135,572,910	22	TX	84,794,340	33	KS	44,555,870	44	HI	15,466,860	55	AS	0

* *Business Activity – Retail Pharmacies*

State Ranking* - Methadone

January – December 2016

RANK	STATE	TOTAL	RANK	STATE	TOTAL	RANK	STATE	TOTAL	RANK	STATE	TOTAL	RANK	STATE	TOTAL
1	CA	49,816,700	12	OR	10,113,900	23	NV	6,053,100	34	ID	3,539,300	45	NM	1,334,600
2	FL	28,320,400	13	IN	9,890,200	24	TN	5,634,000	35	CT	3,157,100	46	MT	1,150,100
3	MI	19,721,100	14	MA	9,143,400	25	UT	5,248,600	36	NH	3,018,700	47	RI	845,300
4	NY	19,545,240	15	VA	9,097,000	26	SC	5,055,760	37	IA	2,385,600	48	SD	679,800
5	TX	19,378,820	16	MD	8,523,200	27	AR	4,998,000	38	MS	2,342,500	49	WY	584,500
6	PA	16,915,200	17	AZ	7,231,900	28	LA	4,638,100	39	WV	2,293,100	50	ND	513,300
7	WA	15,801,800	18	MO	6,862,200	29	CO	4,537,400	40	AK	2,054,100	51	DC	191,100
8	NC	14,976,160	19	KY	6,761,600	30	ME	4,536,300	41	DE	1,928,800	52	PR	32,400
9	OH	12,759,600	20	IL	6,455,200	31	MN	4,518,900	42	VT	1,859,700	53	GU	21,800
10	GA	12,545,300	21	WI	6,264,800	32	OK	4,457,600	43	HI	1,761,400	54	VI	18,700
11	AL	10,739,100	22	NJ	6,101,200	33	KS	3,836,000	44	NE	1,644,700	55	AS	0

* *Business Activity – Retail Pharmacies*

Methods of Diversion

- Practitioners / Pharmacists
 - Illegal distribution
 - Self abuse
 - Trading drugs for sex
- Employee pilferage
 - Hospitals
 - Practitioners' offices
 - Nursing homes
 - Retail pharmacies
 - Manufacturing / distribution facilities
- Pharmacy / Other Theft
 - Armed robbery
 - Burglary (Night Break-ins)
 - In Transit Loss (Hijacking)
 - Smurfing
- Patients
 - Drug rings
 - Doctor-shopping
 - Forged / fraudulent / altered prescriptions
- Internet availability

Violence



Starting the year with a bang

Sarahac Hale Spencer, The News Journal

12:36 a.m. EST January 4, 2016



18



3



(Photo: DELAWARE STATE POLICE)

A 26-year-old Lewes man threatened to detonate explosives he said were strapped to his body if a pharmacist at a Walgreens near Magnolia didn't give him prescription drugs, according to state police.

The man, Curtis Kuhn, didn't actually have explosives strapped to his body, according to police.

Kuhn went into the pharmacy at about 9:30 a.m. on Saturday and put a note on the counter demanding Percocet and Xanax – he told the pharmacist that he had explosives strapped to his body and he was being forced to commit the robbery by someone who was sitting in a car in the parking lot, according to police.

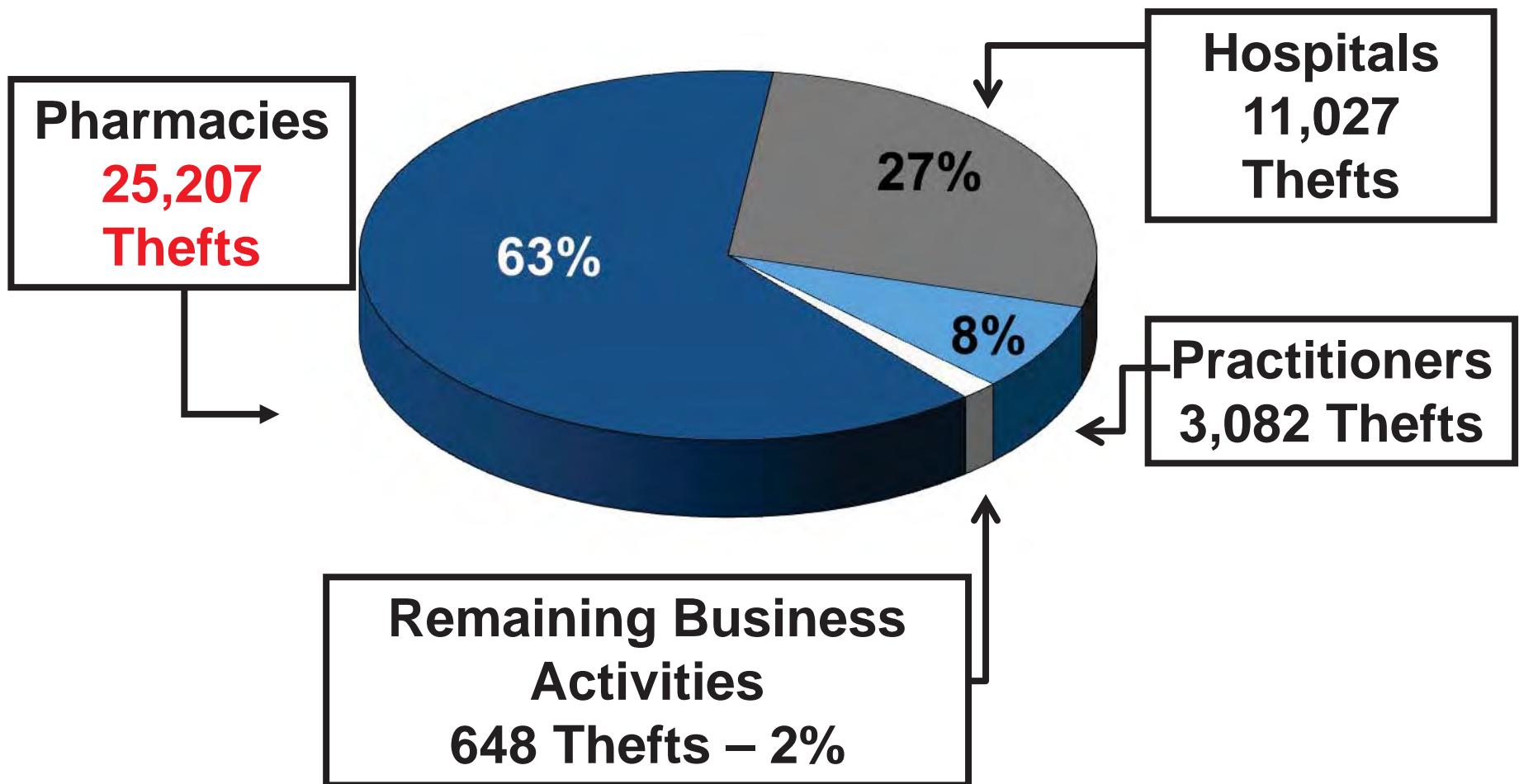
When officers arrived shortly after that, they took Kuhn into custody without incident and found that he had no explosives and there was no car fitting his description in the parking lot, according to police.

Kuhn was charged with first-degree attempted robbery, attempted theft of a controlled substance and two counts of terroristic threatening. He was arraigned and sent to Vaughn Correctional Center near Smyrna for lack of \$27,000 secured bond and

Nationwide Reported Thefts

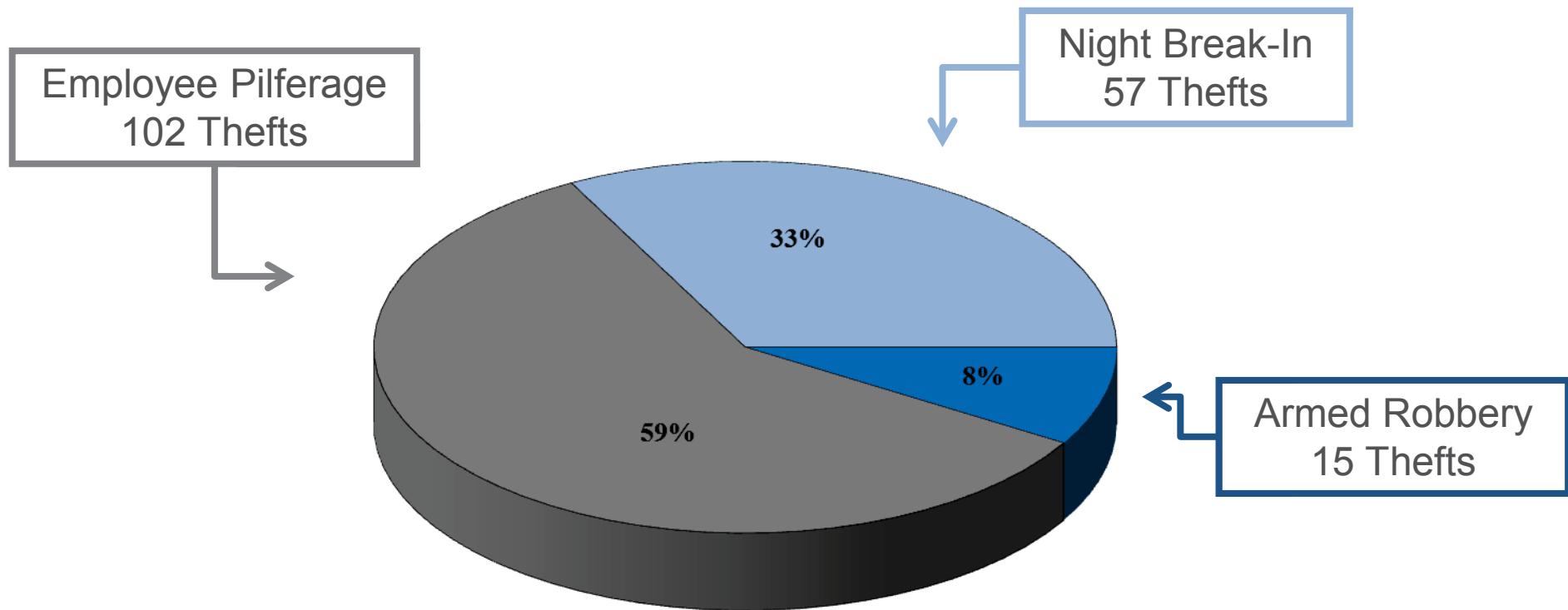
(Armed Robbery, Employee Pilferage and Night Break-In Only)

January 1, 2009 – December 31, 2016



Number of Pharmacy Thefts in Michigan

January 1, 2015 – December 31, 2015



Pharmacy Armed Robberies

January 1 thru December 31, 2016

- U.S. (Nationwide) – 815
- State of Michigan – 12



Michigan Counties	Number of Pharmacy Thefts
WAYNE	4
KENT	2
OAKLAND	2
ALCONA	1
CALHOUN	1
MALCOMB	1
MONROE	1
No Reported Armed Robberies in remaining counties	

Oxycodone v. Heroin

Circle of Addiction & the Next Generation

Oxycodone
Combinations

Percocet®

\$7-\$10/tab

Hydrocodone
Lorcet®
\$5-\$7/tab

OxyContin®
\$80/tab

Roxicodone®

Oxycodone IR
15mg, 30mg
\$30-\$40/tab

Heroin
\$15/bag

Collaboration is the Key

How do you stop it?
Don't let it start.

Collaboration is the Key

We can't arrest our way out of this epidemic.

Collaboration is the Key

- Hold pharmaceutical industry accountable
- Ensure compliance (Educate & Enforce)
- Effective state laws on prescribing and dispensing controlled substances
- Teach patients to secure their medications
- Encourage patients to dispose of medications
- Access to treatment
- Demand Reduction programs – Grade School



National Take Back Initiative (NTBI)

Got Drugs?

Turn in your unused or expired medication for safe disposal Saturday.

Click here for a collection site near you.

#13
APRIL 29, 2017



The poster features a large blue prescription bottle lying on its side. The word "dispose" is written across it, and "unused" is printed below. In the background, there is a circular seal for the DEA. At the bottom of the poster, there are several small logos for various organizations involved in the initiative, including the DEA, the National Association of State Pharmacy Boards, the U.S. Pharmacopeia, and the National Council of State Medical Boards.

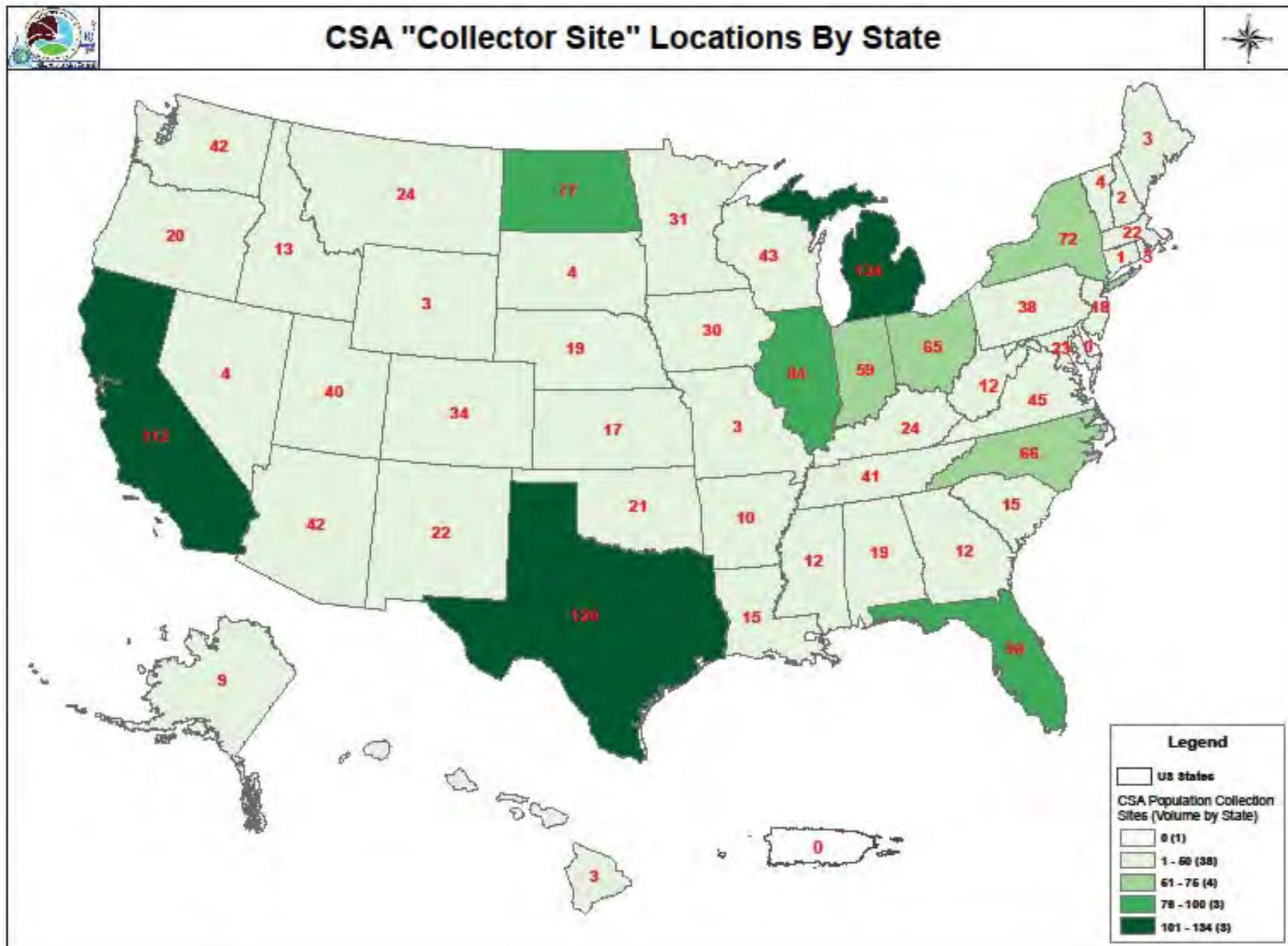
Regional Totals from NTBI

April 29, 2017

- Michigan: 20,370 lbs
- Ohio: 33,261 lbs
- Kentucky: 11,439 lbs

Collection Receptacle Locations

- Pharmacies
- LTCF
- Hospital/clinic
- Opioid Treatment Program
- Police Departments



Mail-Back Program

- Mostly pharmacies provide mail-back envelopes for purchase.



Drug Enforcement Administration

360 Degree Strategy





Drug Enforcement Administration

Community Partnerships



- DEA recognizes we cannot arrest our way out of the drug problem – our goal is lasting success in the communities we serve.
- Education and Prevention are key elements for a true 360 Strategy.
- Law enforcement operations provide an opportunity for community empowerment and a jumping off point for education and prevention efforts.



DEA Web-based Resources

Office of Diversion Control

www.deadiversion.usdoj.gov

The screenshot shows the official website for the U.S. Department of Justice, Drug Enforcement Administration, Office of Diversion Control. The header features the DEA logo and the text "U.S. Department of Justice | Drug Enforcement Administration" and "Office of Diversion Control". Below the header, there's a large banner for reporting illicit pharmaceutical activities with the phone number 1-877-RX-ABUSE and 1-877-792-2873. To the left, there's a sidebar with links like "Home", "Registration", "Reporting", "Info & Legal Resources", and "Media Diversion Control". A "Got Drugs?" section includes an "EMERGENCY Disaster Relief RX" button. Another sidebar on the left lists various news items under "What's New". The main content area has sections for "Report Illicit Pharmaceutical Activities", "Registration Support" (with a "Registration Number Toll Free: 1-800-882-9539 (8:30 am-6:00 pm EST)"), "Upcoming Meetings", and "FAQ". The footer contains links to various DEA programs and resources.

Report Illicit Pharmaceutical Activities
1-877-RX-ABUSE
1-877-792-2873

What's New

- Lia A. Farina, M.D., Discussed and Other May 13, 2013.
- John G. Zdziarski, M.D., Discussed and Other May 10, 2013.
- Substances of Controlled Substances That Cannot Be Placed on Schedule II (May 8, 2013)
- Top 50 Prescribers, Discussed and Other (May 8, 2013)
- Licensed (April 25, 2013)
- Healthcare Group Services, Inc. (April 23, 2013)
- Research Therapeutics Institute (April 23, 2013)
- USA Laboratories, Inc. (April 23, 2013)
- U.S. Pharmacopeia (April 23, 2013)
- Alaris Associates, Inc. (April 18, 2013)
- PCKs Network, LLC (April 23, 2013)
- Cyber Therapeutic Company (April 23, 2013)
- Resale Therapeutics (April 19, 2013)
- Genentech, Inc. (April 19, 2013)
- Healthcare Group Services, Inc. (April 19, 2013)
- GE Healthcare (April 19, 2013)
- Hologic Therapeutics (April 19, 2013)
- Hologic Corporation (April 19, 2013)
- Artemesia Biopharmaceutical Chemical, Inc. (April 19, 2013)
- Hauke, LLC (April 19, 2013)
- HealthCare Rx Retail Products Research/DEA Microtest (April 19, 2013)
- Regulations of Controlled Substances: Temporary Placement of Trade Names/Proprietary Names into Schedule I (April 19, 2013)
- Schedule II Controlled Substances: Placement of Methylene into Schedule I (April 19, 2013)
- Good Manufacturing Practice Requirements: Human Drug Product Safety, Linkages With Changes in a Preexisting Assessment, and the Impact on the Industry (April 19, 2013)
- 60-Day Notice - Compliance Requirements for Importers of Prescription Drugs (April 19, 2013)
- Final Rule: Importation of Prescription Drugs (March 26, 2013)

Registration Support
Registration Number Toll Free: 1-800-882-9539 (8:30 am-6:00 pm EST)
Sale form by applying for assistance renewing your DEA Registration online. Only individuals or entities that have a valid connection to the ODMR can apply for registration.
Individuals/Entities: Credit Card and A secure connection that supports 128-bit encryption.
Cybernetic Services Plus for Hospitals
Email Registration Questions to: USA.Registrations@doj.dhs.gov
Call Us with Questions: 1-800-882-9539
FAQ

Upcoming Meetings

Hurricane Sandy
Messages to New Jersey and New York Area Registrants - As you know Hurricane Sandy impacted the New Jersey and New York areas significantly last October. Some of the DEA's offices in these two states have also been affected by Hurricane Sandy. If you are able to contact your local DEA Post, Division you may direct any questions or problems you may have to your local DEA's main call center at 1-800-882-9539 hours of operation or from 8:00 to 10:00 EST. Thank you for your patience.



DEA Web-based Resources

www.DEA.gov

A screenshot of the DEA website homepage (www.dea.gov). The page features a large "DEA" logo and the tagline "TOUGH WORK, VITAL MISSION". The navigation menu includes links for HOME, ABOUT, CAREERS, OPERATIONS, DRUG INFO, PREVENTION, and PRESS ROOM. A sidebar on the left highlights "The Facts About DEA" and "Tough Work, Vital Mission". The main content area includes a "TOP STORY" about a cocaine trafficking conspiracy, "TOPICS OF INTEREST" like DEA Fact Sheet and Drugs of Abuse, and a "RESOURCE CENTER" with links to various programs and acts. A "Wall of Honor" section is also visible.

TOP STORY

Couple Handed Lengthy Sentences in International Cocaine Trafficking Conspiracy

JAN 29 (BROWNSVILLE, TEXAS)

DEA Fact Sheet

Drugs of Abuse: A DEA Resource Guide

Extension of Temporary Placement of Five Synthetic Cannabinoids

The DEA Position on Marijuana

Controlled Substances Act

DEA Museum and Visitors Center

Doing Business with DEA

Drug Disposal

Employee Assistance Program



DEA Web-based Resources

The screenshot displays the homepage of the [Just Think Twice](http://www.justthinktwice.com) website. The header features the title "JUST THINK TWICE" and the tagline "YOU'VE HEARD THE FICTION. NOW LEARN THE FACTS." Below the header is a navigation bar with links for "HOME", "DRUG FACTS", "FACTS & FICTION", "CONSEQUENCES", "TEENS TO TEENS", and "INSIDE DEA". A search bar is also present. The main content area features a large image of a young person and the text "THINK YOU KNOW WHAT METHAMPHETAMINE IS MADE OF?". It includes a "Did You Know?" section about "meth mouth". Other sections visible include "IT'S TIME TO SHATTER THE MYTHS ABOUT DRUGS AND DRUG ABUSE", "FACTS & FICTION", and "TEENS TO TEENS".

www.JustThinkTwice.com

JUST THINK TWICE
YOU'VE HEARD THE FICTION. NOW LEARN THE FACTS.

HOME return home DRUG FACTS learn the truth FACTS & FICTION know the difference CONSEQUENCES life changing events TEENS TO TEENS sharing our experience INSIDE DEA find out more

SEARCH

Parents & Educators | Drug Glossary

THINK YOU KNOW WHAT METHAMPHETAMINE IS MADE OF?

Maybe you've heard it's made of the same stuff as cold medicine. Well, that's not all. Some of the ingredients used to make meth include battery acid, gasoline, and drain cleaner.

GET THE FACTS ABOUT METHAMPHETAMINE »

MARIJUANA COCAINE METH

Did You Know? Combine toxic chemicals with neglected hygiene, and you get a condition called "meth mouth"—rotten and decaying teeth.

IT'S TIME TO SHATTER THE MYTHS ABOUT DRUGS AND DRUG ABUSE

Learn More

FACTS & FICTION

Get the Facts

TEENS TO TEENS

Advice from teens on the D.A.R.E. Youth Advisory Board

READ MORE »

KEY WORKS



DEA Web-based Resources

[www.GetSmartAboutDrugs.com](http://www.getsmartaboutdrugs.com)

The screenshot displays the homepage of the Get Smart About Drugs website. At the top, there's a navigation bar with links for Home, Identify, Prevent, Help, Hot Topics, DEA in the Community, and Communities of Practice. On the left, a sidebar highlights the new Communities of Practice section, featuring three PowerPoint presentations and a Train the Trainer module. The main content area includes sections for Latest News (Drug Court Offers Hope for the Future, ER Visits Tied to Energy Drinks Double Since 2007), Voices (Irma Perez's Story), and Inside DEA. A sidebar on the right provides links to DEA Publications and Videos.

The new Communities of Practice section includes three PowerPoint presentations about drug abuse and awareness and an online Train the Trainer module that provides presenters with techniques to effectively deliver the presentations.

[Learn more >](#)

BACK STOP NEXT

Latest News

See All News Stories

Drug Court Offers Hope for the Future
Jan 22, 2013 The Columbia River Partnerships for Change, a nonprofit in Oregon, is seeing tremendous success with its three drug court programs: adult treatment, juvenile treatment, and families restored.

ER Visits Tied to Energy Drinks Double Since 2007
Jan 16, 2013 Hospitals around the country have seen a gradual uptick in the number of emergency room visits involving energy drinks.

Voices

Irma Perez's Story

Irma was a 14 year old girl from Belmont, California who took an Ecstasy pill on April 23, 2004. She became sick immediately—vomiting and writhing in pain—yet her friends did not seek medical help for her. Instead, they gave

Inside DEA

The men and women of DEA aren't just drug enforcement agents—we're parents, grandparents, brothers and sisters. We've seen how drugs rob young people of their promise and dreams, and how entire families are affected by a child's drug abuse.

DEA Diversion Control Program :: Welcome :: - Mozilla Firefox

File Edit View History Bookmarks Tools Help

http://www.deadiversion.usdoj.gov/ Google

Most Visited Getting Started Latest Headlines

DEA Diversion Control :: Wel...

 U.S. Department of Justice Drug Enforcement Administration
Office of Diversion Control

Office of Diversion Control

Contact Us | Site Map | Search

Quick Links

- [Renew Applications Online](#)
- [New Application Online](#)
- [Duplicate Certificate Request](#)
- [Registration Validation](#)
- [Registration Change Request](#)
- [Order Forms](#)
- [CSOS](#)
- [DEA Form 106: Report Theft or Loss of Controlled Substance](#)
- [Combat Meth Act 2005](#)
- [Cases Against Doctors](#)
- [Mailing Addresses for Topics Related to Title 21 CFR](#)

What's New

- [30-Day Notice of Information Collection Under Review \(January 8, 2010\)](#)
- [Mylan Technologies Inc. \(January 4, 2010\)](#)

Registration Support

Registration Number
Toll Free:
1-800-882-9539

Save time by applying for and/or renewing your DEA Registration online. Data will be entered through a secure connection to the ODWIF online web application system.

Minimum requirements:
Credit Card and a web browser that supports 128-bit encryption.

Email Registration Questions to DEA.Registration.Help@usdoj.gov

[Field Offices with Registration Specialists](#)

FAQ

- [ARCOS](#)
- [Controlled Substance Ordering System \(CSOS\)](#)
- [General Information](#)
- [DEA Form 222 Order Forms](#)
- [Prescription Drug Monitoring Program](#)
- [Registration Procedures](#)

To view PDF documents [Get ADOBE® READER®](#)

External links included in this website should not be construed

www.DEAdiversion.usdoj.gov

Comments / Questions?





2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit



What's Next?



Kate Kohn-Parrott
President and CEO
Greater Detroit Area Health Council



Tom Watkins
President and CEO
Detroit Wayne Mental Health Authority



GREATER DETROIT AREA HEALTH COUNCIL

2nd Annual Opioid Abuse and Heroin Overdose Solutions Summit



*Thank You for
Your Commitment
To Help*

Moving Forward to Affect Change

EXHIBIT 10

[Access Oakland](#)[Oakland County Home](#)[Account Services](#)[Existing Online Services](#)[Sign In](#)

Prevent Prescription Drug Abuse

Prescription drugs account for nearly 60% of all deaths from drug overdose, and pain relievers such as oxycodone, hydrocodone, and methadone are involved in three of every four prescription drug overdose fatalities. ~ L. Brooks Patterson, Oakland County Executive

Key Statistics for Oakland County

Opioid Prescriptions



743,969

Filled in 2016

Source: [MI Automated Prescription System](#)

National Drug Take Back Day



3,507

Pounds Destroyed on **4/29/17**

Source: [US Drug Enforcement Agency](#)

Outpatient Treatment



6,409

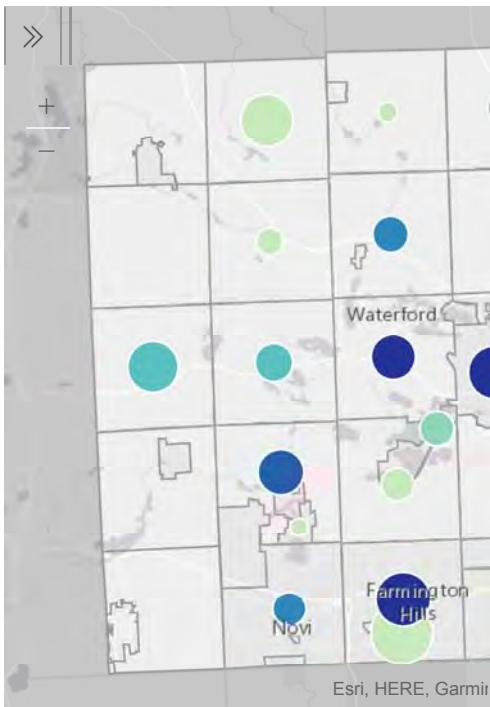
Individuals Treated in 2016

Source: [Oakland Community Health Network](#)

?

Education

Understanding how the opioid epidemic is impacting our community.

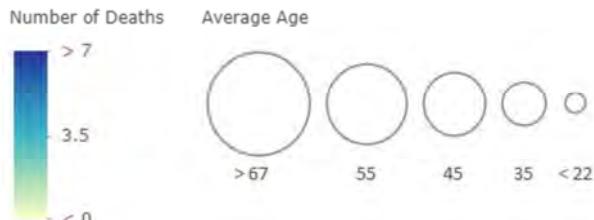


Study of Opioid-Related Deaths

In 2016, 165 people died from opioid-related deaths in Oakland County. The average age of those who died in each community is shown on the right, along with the number of people who lost their lives.

Source: Oakland County Health Division

2016 Potential Opioid Overdose Deaths



Opioid Prescriptions

In 2016, almost 750,000 opioid prescriptions were filled in Oakland County. This is equivalent to 6,035 prescriptions per every 10,000 residents (including children). Compare this to the number of scripts filled in 2014 and 2015 [in this app](#).

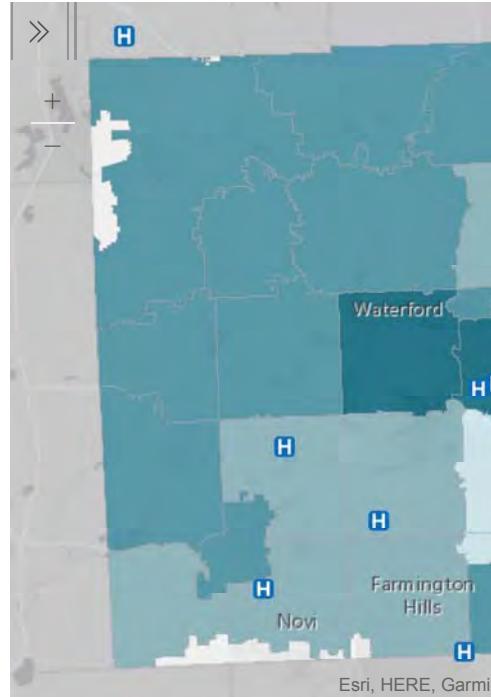
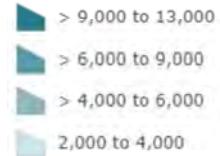
Source: Michigan Automated Prescription System (MAPS). Though this data was originally downloaded from MAPS, further analysis was done. The end result was an analysis of prescription drug quantity information by a residents' zip code, then grouped by city, village, or township.

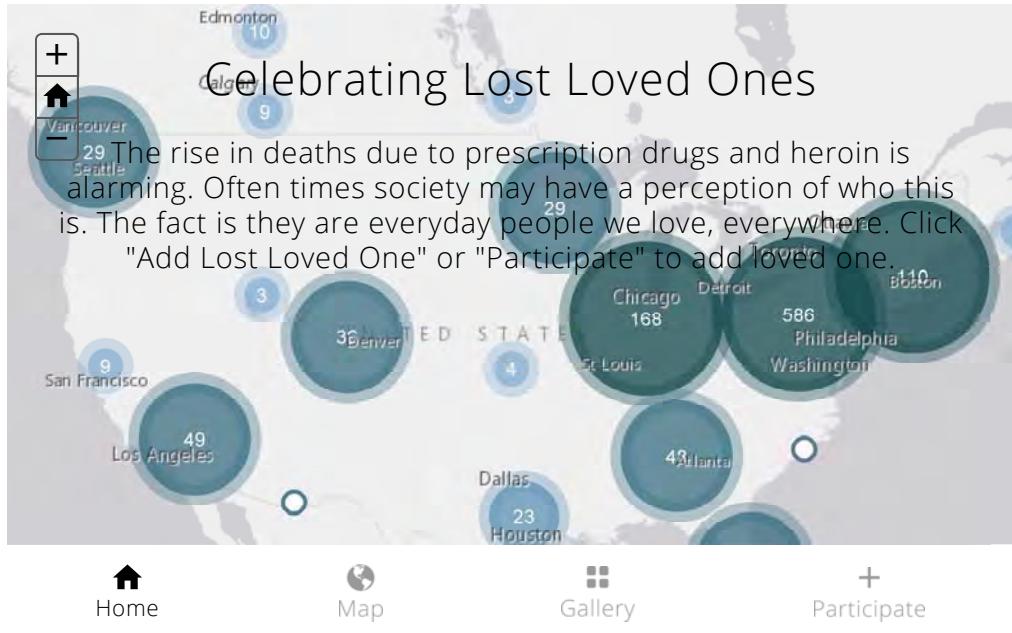
Hospitals



Opioid Prescriptions per 10,000 Residents (2016)

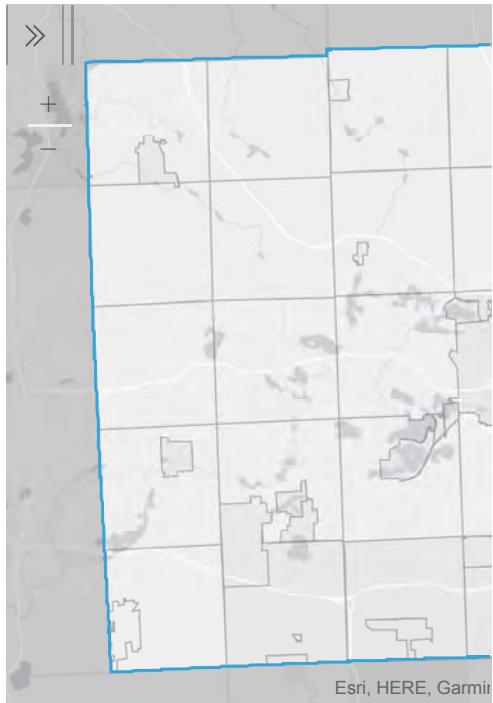
Opiates Scripts per 10,000 residents





🚫 Prevention

Reducing the availability of unused medications.



Dispose of Unused Prescriptions

Operation Medicine Cabinet, sponsored by Oakland County Sheriff's Department, provides safe, anonymous locations for people to bring unneeded medications for disposal. [Use the app](#) to also find pharmacies that accept unneeded medications and locations where Deterra bags (bags that destroy medications) can be picked up for free.

Drug Disposal Bag Pickup



Police Station



County



Local

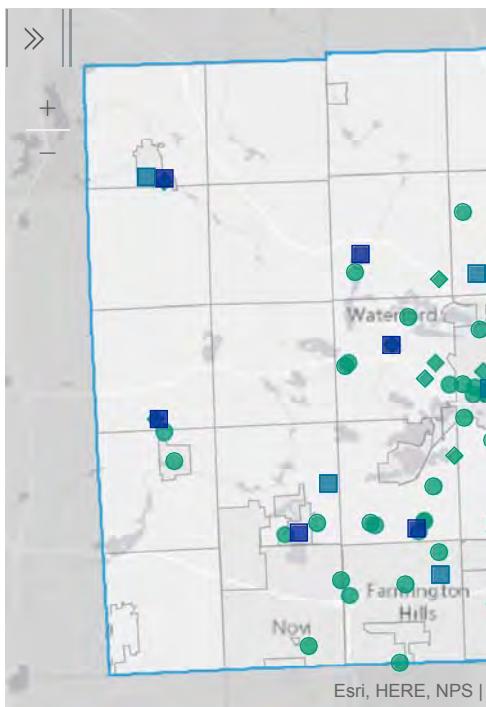
Pharmacy



Prevent Addiction

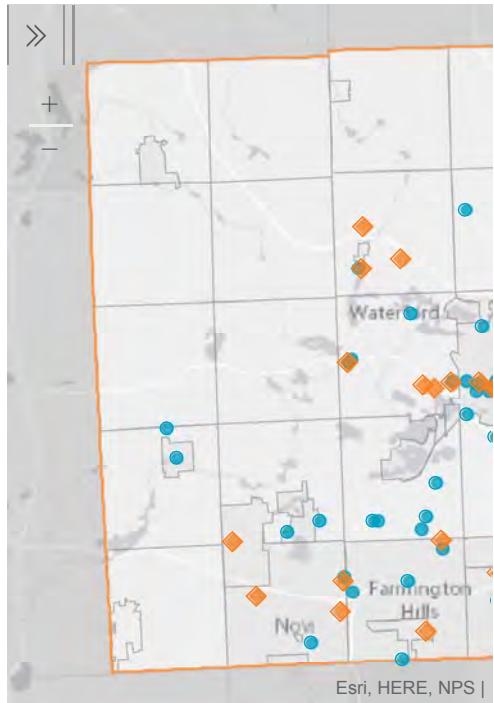
Find places where prevention resources are available.
To look for resources near to you, [open the application](#).

- Families Against Narcotics (FAN) Locations**
- Alliance Of Coalitions For Healthy Communities (ACHC)**
- Licensed Prevention Programs**
 - Prevention 
 - Prevention & Treatment 



Treatment & Recovery

Promoting treatment and recovery alternatives.



Locate Treatment Alternatives

Use our [Opioid Treatment Locator](#) to find providers in the community who can help with substance abuse.

Licensed Treatment Programs

-  Treatment
-  Treatment & Prevention

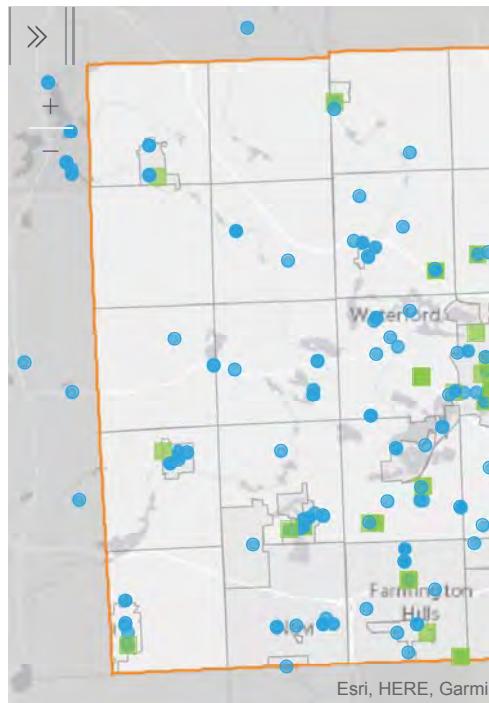
Find Recovery Resources

Find help after treatment. Use our [Recovery Resource Locator](#) to find meetings on certain days of the week.

Recovery Meeting Location

Narcotics Anonymous ■

Alcoholics Anonymous ●



Copyright 2017. Oakland County.

About

- Oakland County
- Oakland County Prescription Drug Abuse Prevention
- Oakland County GIS
- Access Oakland

Contact Us

- [@oakgov](#)
- [Oakland County Health](#)

EXHIBIT 11

Read the Stories ▼
(HTTP://WWW.LATIMES.COM/)



A TIMES INVESTIGATION

OxyContin goes global — “We’re only just getting started”

By HARRIET RYAN (HTTP://WWW.LATIMES.COM/LA-BIO-HARRIET-RYAN-STAFF.HTML), LISA GIRION AND SCOTT GLOVER

DEC. 18, 2016



OxyContin is a dying business in America.

With the nation in the grip of an opioid epidemic that has claimed more than 200,000 lives, the U.S. medical establishment is turning away from painkillers. Top health officials are discouraging primary care doctors from prescribing them for chronic pain, saying there is no proof they work long-term and substantial evidence they put patients at risk.

Prescriptions for OxyContin have fallen nearly 40% since 2010, meaning

billions in lost revenue for its Connecticut manufacturer, Purdue Pharma.

This is the third part of a Los Angeles Times investigation (<http://www.latimes.com/projects/oxycontin-part1/>) exploring the role of OxyContin in the nation’s opioid epidemic.

So the company’s owners, the Sackler family, are pursuing a new strategy: Put the painkiller that set off the U.S. opioid crisis into medicine cabinets around the world.

A network of international companies owned by the family is moving rapidly into Latin America, Asia, the Middle East, Africa and other regions, and pushing for broad use of painkillers in places ill-prepared to deal with the ravages of opioid abuse and addiction.

Visit the site ↗

Mundipharma China

Mundipharma is courting Chinese patients with a campaign encouraging people to take medications as their physicians prescribe.



(<http://www.mundipharma.com.cn/>)

In this global drive, the companies, known as Mundipharma, are using some of the same controversial marketing practices that made OxyContin a pharmaceutical blockbuster in the U.S.

In Brazil, China and elsewhere, the companies are running training seminars where doctors are urged to overcome “opiophobia” and prescribe painkillers. They are sponsoring public awareness campaigns that encourage people to seek medical treatment for chronic pain. They are even offering patient discounts to make prescription opioids more affordable.

U.S. Surgeon General Vivek H. Murthy said he would advise his peers abroad “to be very careful” with opioid medications and to learn from American “missteps.”

“I would urge them to be very cautious about the marketing of these medications.”

— Vivek H. Murthy, U.S. Surgeon General



Surgeon General Vivek H. Murthy has called on U.S. doctors to help end the opioid epidemic. (Charles Dharapak / AP)

“I would urge them to be very cautious about the marketing of these medications,” he said in an interview. “Now, in retrospect, we realize that for many the benefits did not outweigh the risks.”

Former U.S. Food and Drug Administration commissioner David A. Kessler has called the failure to recognize the dangers of painkillers one of the biggest mistakes in modern medicine. Speaking of Mundipharma’s push into foreign markets, he said, “It’s right out of the playbook of Big Tobacco. As the United States takes steps to limit sales here, the company goes abroad.”

“It’s right out of the playbook of Big Tobacco.”

— David A. Kessler, former commissioner of the U.S. Food and Drug Administration



David A. Kessler, a physician, was head of the U.S. Food and Drug Administration from 1990 to 1997.
(Randi Lynn Beach / Los Angeles Times)

Some Mundipharma representatives and promotional material have downplayed the risk that patients will become addicted to their opioid medications. Those claims recall the initial marketing of OxyContin in the U.S. in the late 1990s when Purdue deceived doctors about the drug's addictiveness.

Purdue and three executives pleaded guilty in 2007 to federal charges of misbranding drugs and were ordered to pay \$635 million. The Drug Enforcement Administration said in 2003 that the company’s “aggressive, excessive and inappropriate” marketing “very much exacerbated” abuse and criminal trafficking of OxyContin.

Purdue was a small New York City pharmaceutical firm when brothers Mortimer and Raymond Sackler, both psychiatrists, bought it in 1952. The spectacular success of OxyContin has generated nearly \$35 billion in revenue over the last two decades and made the Sacklers one of the nation’s wealthiest families. Three generations of the family now help oversee Purdue and the Mundipharma associated foreign corporations.

Family members declined to be interviewed for this article, as did executives who run their international companies.

GET INVOLVED

Tell us your story ↗ ([/oxycontin-your-story](#))

I have had an experience with OxyContin
(<http://www.latimes.com/projects/oxycontin-your-story//#my-experience>)

I know someone who has had an experience with OxyContin
(<http://www.latimes.com/projects/oxycontin-your-story/#friend-family-experience>)

In a statement, Mundipharma International, which is based in Cambridge, England and responsible for European operations, said it was “mindful of the risk of abuse and misuse of opioids” and was “drawing on the experiences and insights of the US in tackling this issue.”

Mundipharma said those efforts include seeking regulatory approval in Europe for a formulation of OxyContin already sold in the U.S. that deters certain forms of abuse and introducing another opioid painkiller, Targin, with similar abuse-deterring properties.

“Mundipharma is committed to developing prescription medicines for healthcare professionals to treat patients in pain safely and responsibly,” the statement said.

Promotional videos for Mundipharma, which feature smiling people of many ethnicities, suggest the companies regard OxyContin’s U.S. success as merely a beginning.

“We’re only just getting started,” the videos declare.

“Opiophobia” around the globe

Joseph Pergolizzi Jr. is a Florida doctor with an array of business ventures. He runs a pain management clinic and co-founded a drug research company. He invented a non-prescription pain-relieving cream he sells on cable television and he serves as an expert for a mail-order nutritional supplements company. He also talks up opioids to foreign doctors for Mundipharma.

In April, Pergolizzi was in Rio de Janeiro at a cancer pain seminar sponsored by the company. For an hour, Pergolizzi lectured the gathered physicians in English about the use of opioids in cancer patients and those with what he called “the death sentence of chronic pain.”

Brazil had stepped up its use of painkillers in recent years, he said, but “you are still low” compared with the U.S., Canada and Europe.

“I think unfortunately you may not have all the tools you need to properly address pain,” he said, according to a video of the seminar posted online by Mundipharma.

Consultants like Pergolizzi are key to helping Mundipharma overcome one of its greatest obstacles to selling painkillers abroad: Doctors’ aversion to prescribing narcotics.

Consultants like Pergolizzi are key to helping Mundipharma overcome one of its greatest obstacles to selling painkillers abroad: Doctors’ aversion to prescribing narcotics. For generations, physicians have been taught that opioid painkillers are highly addictive and should be used sparingly and primarily in patients near death.

Mundipharma executives and consultants call this “opiophobia” and top company officials have said publicly that success in new markets depends on defeating this mind-set. Speeches like Pergolizzi’s portray painkillers as a modern approach endorsed by leading experts in the U.S.

Mundipharma presented Pergolizzi to the Brazilian group as a professor at the Johns Hopkins and Temple University medical schools. Medical journal articles published in 2015 and 2016 with funding from Mundipharma or in collaboration with its scientists have identified him variously as a faculty member at Johns Hopkins, Temple and Georgetown University medical schools.

In fact, he is an adjunct professor at Johns Hopkins and he has not been affiliated with Georgetown since 2010 or Temple since 2014, according to school officials.

Asked to explain, Pergolizzi said by email that he was having “paperwork issues” at Temple “which I am rectifying with their full cooperation” and was “in discussions” with Georgetown about an adjunct position.

“I have never intentionally misrepresented ... my university affiliations,” he wrote in another email.



Joseph Pergolizzi addresses an April cancer pain seminar in Brazil sponsored by Mundipharma.
(Mundipharma)

A Temple spokesman said the university had “no reason to believe he will have any future relationship” with the school, and a Georgetown spokeswoman said, “We are not in discussions with that gentleman.”

Government records indicate that Purdue and other U.S. pharmaceutical firms have paid Pergolizzi more than \$1 million since 2013 for consulting work, speaking engagements and other services as well as travel reimbursements. The records do not include any payments he may have received from foreign pharmaceutical firms such as Mundipharma. In his Rio presentation, he clicked quickly past a slide listing 16 drug companies for which he had done work.

After Purdue launched OxyContin in the U.S. in 1996, the company ran similar training seminars for specialists — known in pharmaceutical marketing as “key opinion leaders” — in the pain field. Doctors were invited to all-expenses paid weekends in resort locations like Boca Raton, Fla., and Scottsdale, Ariz. The company found that doctors who attended seminars in 1996 wrote more than twice as many prescriptions as those who didn’t, according to a company analysis.

Several thousand of these specialists signed on to the Purdue “speakers bureau,” which paid them to make speeches about opioids at medical conferences and at hospitals.

JOIN THE CONVERSATION ([HTTP://WWW.LATIMES.COM/OXYAMA](http://WWW.LATIMES.COM/OXYAMA))

Reddit AMA Dec. 20 at noon (<http://www.latimes.com/oxyama>)

Questions? Reporter Harriet Ryan and editor Matt Lait will join us on Reddit once again to answer your questions about how we reported this story. (<http://www.latimes.com/oxyama>)

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Dr. Barry Cole, a Reno psychiatrist and pain management specialist, started giving speeches about OxyContin for Purdue the year the drug hit the market. In recent years, he moved to the company’s international operation in a consulting role he described in an online resume as a “pain ambassador,” teaching the use of opioids to doctors in Colombia, Brazil, South Korea, the Philippines, China and Singapore.

“Any side effect is reversible when treatment is discontinued, and there is no permanent damage to the body,” Cole told a 2014 conference of pain specialists in Veracruz, Mexico, according to an account of the presentation published on Mexican health websites.

In an interview with The Times, Cole said he made the foreign presentations despite having developed deep misgivings about the use of OxyContin and similar drugs in the U.S. Witnessing the opioid epidemic unfold, seeing the effect of opioids on his patients and reading scientific literature about the drugs, he said, led him to conclude by about 2010 that painkillers were too dangerous for most chronic pain patients.

“We thought we could just get away with putting everybody on opioids, and it would be hunky-dory,” Cole said. “And it didn’t work and it had darker consequences than any of us were predicting.”

He defended his work promoting opioids to foreign doctors, saying terminally ill patients were dying in pain in many places he visited. He said he never shied away from questions about abuse and had no way of knowing whether his talks led doctors to prescribe more opioids.

“You show up, do a presentation and then you get back on the plane and are gone,” he said. He said he stopped making appearances for Mundipharma last year.

One “key opinion leader” who attended Cole’s seminars was Ricardo Plancarte Sanchez, a Mexico City pain doctor who holds a position at Mexico’s national cancer institute.

Plancarte now speaks at Mundipharma seminars in Mexico. In an interview, he said his aim was to help “demystify the use of opioids in chronic pain” and that he was not paid for his appearances.

“We need to work more to educate so that people use analgesics more,” Plancarte said.

He said he was not concerned Mexico would see large-scale abuse and addiction.

“If we educate our doctors as well as our patients, there will be better use of the drugs than in the United States,” he said.

‘Talking about big money’

Untreated pain is a global scourge. Each year millions with terminal cancer and end-stage AIDS die in needless agony, according to the United Nations. The problem is most acute in the poorest countries.

Stefano Berterame, an officer of the U.N.-affiliated International Narcotics Control Board in Vienna, works to increase access to opioids in countries with shortages. He said most of the global problem could be solved with “very cheap morphine” but that selling it held little allure for multinational drug companies

“It’s not very profitable,” he said. “Companies prefer to market expensive preparations.”

Purdue charges hundreds of dollars a bottle for a month’s supply of OxyContin in the U.S. Generic morphine, which provides similar pain relief, can cost as little as 15 cents a day.

Mundipharma is not alone in seeking new markets for opioids outside American borders. In the last year, two other manufacturers, Teva and Grunenthal, each bought drug companies in Mexico.

Mundipharma sells drugs for a range of conditions, including asthma, cancer, and arthritis, but the core of its product line is opioid painkillers. In its global expansion, Mundipharma is looking to countries with wealth, health benefits or large emerging middle classes. And it is pursuing patients healthy enough to be customers for a long time.

“If your market is only cases of terminal cancer, then your market is relatively limited...,” Berterame said. “If you enlarge the market to also chronic pain, then you are talking about big money.”

‘Rebel against the pain’

Seeking new patients in Spain, Mundipharma chose ambassadors guaranteed to attract attention: Naked celebrities.

A string of topless actors, musicians and models looked into the camera and told fellow Spaniards to stop dismissing aches and pains as a normal part of life.

“Don’t resign yourself,” Maria Reyes, a model and former Miss Spain, said in the 2014 television spot.

“Chronic pain is an illness in and of itself,” the pop singer Conchita added.

The one-minute ad was part of a nationwide campaign developed and financed by Mundipharma to raise awareness of chronic pain — Rebélate contra el dolor (Rebel against the pain).

Mundipharma Spain ↗

Rebélate contra el dolor

In a 2013 Spanish television spot sponsored by Mundipharma, celebrities wear chains to represent the burden of chronic pain.

(<http://www.mundipharma.es/>)

Rebélate contra el dolor cró...



The ads do not recommend a specific treatment or medication, but do urge sufferers to see a healthcare professional — thousands of whom have been trained by the company in the use of opioids.

The campaign is part of a strategy to redefine back pain, joint aches and other common conditions as a distinct malady — chronic pain — that doctors and patients should take seriously.

Chronic pain patients, who fill prescriptions month after month and often year upon year, have been the driver of billion-dollar sales for Purdue in the U.S. University of North Carolina researchers analyzed the medical records of patients taking OxyContin at strengths of 30 milligrams or more— common doses for the drug — and found that more than 85% were diagnosed with chronic pain of one type or another.

In Spain, painkiller use is on the rise. Company sales were up seven-fold since 2007, a Mundipharma executive said in a 2014 interview with an industry blog.

Spanish pain specialist Cesar Margarit, a consultant for Mundipharma, said the celebrity ads performed a public service by propelling patients who were “shy in recognizing they suffer from pain” to seek treatment.

“You have celebrities saying, ‘I have chronic pain.’ [Patients] say, ‘OK, if they can say that, I can too,’ ” Margarit said. “The impact in Spain was a very big one.”



A Spanish-language promotional video titled “Dolor Cronico Camapana 2014” shows people discussing pain and where it might afflict them with graphic illustrations. (Instituto Mundipharma)

The company removed the “Rebel against the pain” spots from its YouTube channel this fall — after The Times submitted questions to the company about the chronic pain campaign. A spokeswoman said the videos were taken down because the program was inactive.

Around the world, Mundipharma companies cite statistics suggesting there is a great unmet need for their products. Opening an office in Mexico in 2014, Mundipharma officials declared that 28 million citizens were suffering from chronic pain. In Brazil, the company cited a figure of 80

million. In Colombia last year, a company news release said 47% of the population — about 22 million people — were afflicted by “this silent epidemic.”



A 2011 survey in the Philippines designed and paid for by the company concluded that the “government should recognize chronic pain as a specific health problem” and should improve access to pain medications.

Health authorities in the U.S. say opioids are not the solution to chronic pain. The Centers for Disease Control and Prevention said this year there is “insufficient evidence” that the drugs relieve pain in patients who take them for more than three months.

Up to 24% of people on the drugs long-term become addicted, the CDC said.

Up to 24% of patients who take the drugs long-term develop addiction problems, the CDC said.

Some Mundipharma representatives abroad have suggested publicly that painkiller risk is overblown. As public health officials in the U.S. were issuing their latest warning about painkiller abuse last year, a Mundipharma executive was quoted in a Seoul newspaper saying that Korean doctors “worry too much” about addiction.

“But many studies have shown that it’s almost impossible for those with chronic or severe pain to become addicted to narcotics, as long as the drug is used for pain relief,” Lee Jong-ho told the Korea Herald. Lee could not be reached for comment.

Willem Scholten, a retired World Health Organization official Mundipharma has paid to speak at medical conferences, said President Obama, public health officials and the media have “exaggerated” the U.S. prescription opioid crisis. The surge in addiction and death was largely due to recreational abuse, he said.

“The problem is a lot of crime,” Scholten, a Dutch pharmacist, said in an interview. “If [other countries] make good regulations, they won’t have similar problems.”

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He said that “there is hardly any evidence” that pain patients abuse medications.

Sharon Walsh, a University of Kentucky addiction expert who advises the FDA on risks from pain drugs, called the assertions “completely untrue.”

“That is exactly the same thing they were teaching U.S. physicians when they launched OxyContin in this country,” said Walsh, who runs the university’s Center on Drug and Alcohol Research.

‘The Google of the pharma industry’

Mundipharma’s operations in the developing world are run out of a sleek Singapore office with a Silicon Valley feel. There are bean bag chairs, a “chill-out zone” and a tea bar, and employees are encouraged to think of the company as a nimble, creative start-up — “the Google of the pharma industry,” in the words of one executive.

After introducing OxyContin in the U.S., Purdue’s Canadian affiliate and Mundipharma’s Australian company began promoting the painkiller in those countries. In the last decade and a half, both have seen U.S.-style problems, including criminal trafficking, addiction and death.

Mundipharma turned its focus to the developing world in 2011, as U.S. sales began their drop. Rapidly modernizing countries are expected to spend more than \$20 billion on pain medicines by 2020, according to QuintilesIMS Institute for Healthcare Informatics.

Mundipharma expanded first in Asia, then Latin America and then the Middle East and Africa, ultimately having a presence in 122 developing markets.

The high cost of brand-name medications remains a barrier in many developing countries, but Mundipharma has sought ways to adjust. In Brazil, the company started a program this year that offers patients discounts on the cost of pills. Purdue used coupons in the U.S. that offered patients a free initial prescription for OxyContin. About 34,000 coupons were redeemed before the company terminated the program as concerns about abuse grew, according to a Congressional report.

Revenues for Mundipharma Emerging Markets, the Singapore-based company that oversees developing world operations, have risen 800% over the last five years to about \$600 million annually. A Mundipharma spokeswoman said that growth included revenue from deals the companies have made with other manufacturers to sell non-opioid products.

Raman Singh, head of Mundipharma Emerging Markets, has said publicly that pain treatment in Asia is 1/50th of what it should be. Half the company’s worldwide sales in the developing world, which include products other than painkillers, already come from China, according to Mundipharma, and China is central to the Mundipharma’s global strategy.



As the head of Mundipharma Emerging Markets, Raman Singh, right, has overseen 800% sales growth in the developing world. Tennis star Caroline Wozniacki, left, is a Mundipharma brand ambassador for the antiseptic Betadine. (Suhaimi Abdullah / Getty Images)

The Chinese government has pledged that all 1.4 billion citizens will have health insurance by the close of the decade, and the company is working quickly to establish itself as the market leader in pain medications. Since 2011, Mundipharma has hired more than a thousand employees, most of them sales representatives, and now has a presence in 300 cities.

Thousands of Chinese doctors have attended training seminars about Mundipharma’s drugs, and it claims a 60% share of the cancer pain market. Mundipharma has sponsored clinical trials of OxyContin and Targin at hospitals across the country.

There remains, however, a deep-seated fear of opioids stemming from Chinese defeats in the 19th century Opium Wars that left millions addicted. Under strict government regulations, patients can purchase OxyContin

only from a hospital or other medical institution, and can receive no more than a 15-day supply. Relatively few Chinese use Mundipharma’s painkillers for chronic pain because of their high price.



Mundipharma's operation in China, headquartered in a Beijing skyscraper, has expanded rapidly since 2011. (Jonathan Kaiman/Los Angeles Times)

Mundipharma is courting Chinese patients with a campaign encouraging people to take medications as their physicians prescribe. In one animated video on the company's website, an elderly cancer patient who expresses fear about becoming addicted to painkillers is corrected by his nurse.

“You will not be addicted if you follow the doctor’s instructions,” she tells him. The video was removed from the site this fall at around the time The Times asked company officials about it. Asked why, a company spokeswoman said “programs and campaigns change frequently and content is updated often.”

In China, where there are nearly 3 million registered drug abusers, the government has forced addicts into boot-camp style treatment that human rights advocates have described as prisons. Treatment is rudimentary or unavailable in many parts of the developing world.

UNC researcher Nabarun Dasgupta, who has advised federal health authorities and the WHO on prescription opioid abuse, said the wide use of painkillers in those countries “sounds like a recipe for disaster” because “a certain percent [of users] will go on to need addiction treatment.”

“A certain percent [of users] will go on to need addiction treatment.”

— Nabarun Dasgupta, University of North Carolina researcher



Dr. Nabarun Dasgupta of the University of North Carolina has advised U.S. and world health authorities on opioid abuse. (Los Angeles Times)

Mundipharma Emerging Markets said in a statement, “We attach great importance on promoting our pain medicines in a balanced and responsible manner so that the correct physicians are prescribing the correct medicines to the correct patients.”

‘A big deal’

Public health officials in Europe worry far less about painkiller addiction than their American counterparts. Government health systems in many countries track prescriptions, making it more difficult than in the U.S. to obtain large amounts of opioid medication for abuse or criminal trafficking.

But when a team of international researchers recently conducted the first large-scale survey of drug abuse in Europe, they found what the lead investigator described as a significant problem with prescription opioid abuse.

Painkiller abuse rates are similar to the U.S. in the early 2000s “before the epidemic really got going,” Scott Novak, a scientist at the nonprofit RTI International in North Carolina, said in an interview.

In Spain, 18% of those surveyed acknowledged abusing painkillers in the course of their life, according to the study published in August. Across Europe, people with prescriptions were eight times as likely to abuse the drugs.

BEHIND THE STORY

How we reported the investigation ↗
(<http://www.latimes.com/projects/oxycontin-about/>)

“They are potentially at the precipice of a major public health problem if prescribing increases,” Novak said.

Mundipharma International took issue with that conclusion. The company said in a statement that painkiller abuse is less of a problem in Europe than in the U.S., in part because of stricter pharmacy regulation and government health systems. Mundipharma said that it was conducting a study of abuse in Britain and Germany and that initial results “suggest that in these countries abuse of prescription opioids is less than 1%.”

In one European country — Cyprus — OxyContin abuse is an acknowledged problem. Mundipharma began marketing the painkiller in 2008 on the Mediterranean island of 1 million. Government health coverage made the medication cheaper than heroin and addicts began crushing and snorting the pills.

Officers responding to overdoses knew little of the U.S. experience with painkillers. Stelios Sergides, a superintendent with the Cyprus National Police, said that the first time he heard the word OxyContin, he had to look it up online.

Since 2013, authorities have linked six deaths to the drug.

“It’s a big deal, a big deal,” Sergides said.



Police superintendent Stelios Sergides has investigated OxyContin dealing on the small Mediterranean island of Cyprus. (Lisa Girion / Los Angeles Times)

Mundipharma said it was “deeply disturbed” by the deaths in Cyprus and suggested the blame rested with a rehab center which used OxyContin to treat heroin addiction, a practice the company does not recommend.

Police in Cyprus are investigating doctors suspected of overprescribing and working with public health officials to get addicts into rehab. Last year, 59 people requested treatment.

“We are worried, of course, because of the numbers, especially the treatment demand,” Sergides said.

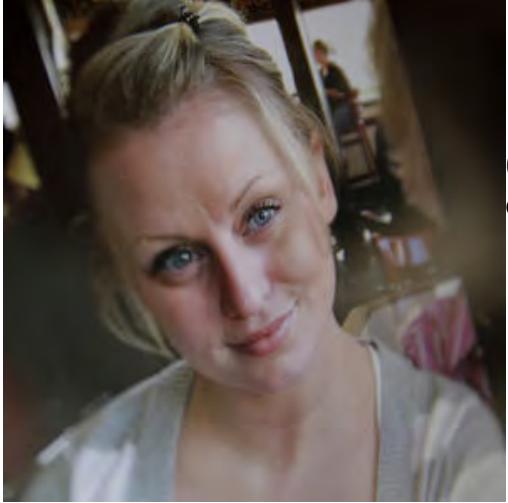
In the Mundipharma’s Cyprus office, managing director, Menicos M. Petrou, called OxyContin “an excellent product” and said he had been honored to meet members of the Sackler family during visits to a factory on the island.

“If people misuse drugs, most of the time there is little a pharmaceutical company can do,” he said.

Times staff writers Hector Becerra, Marisa Gerber and Brittny Mejia in Los Angeles and special correspondent Jessica Meyers and news assistants Nicole Liu and Yingzhi Yang in The Times’ Beijing bureau contributed to this report.

Additional credits: Lily Mihalik and Evan Wagstaff.

Full coverage



How black-market OxyContin spurred a town's descent into crime, addiction and heartbreak

(<http://www.latimes.com/projects/la-me-oxycontin-everett/>)

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EXHIBIT 12



REVIEWS | 16 JANUARY 2007

Systematic Review: Opioid Treatment for Chronic Back Pain: Prevalence, Efficacy, and Association with Addiction

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Abstract

Background: The prevalence, efficacy, and risk for addiction for persons receiving opioids for chronic back pain are unclear.

Purpose: To determine the prevalence of opioid treatment, whether opioid medications are effective, and the prevalence of substance use disorders among patients receiving opioid medications for chronic back pain.

Data Sources: English-language studies from MEDLINE (1966–March 2005), EMBASE (1966–March 2005), Cochrane Central Register of Controlled Clinical Trials (to 4th quarter 2004), PsychInfo (1966–March 2005), and retrieved references.

Study Selection: Articles that studied an adult, nonobstetric sample; used oral, topical, or transdermal opioids; and focused on treatment for chronic back pain.

Data Extraction: Two investigators independently extracted data and determined study quality.

Data Synthesis: Opioid prescribing varied by treatment setting (range, 3% to 66%). Meta-analysis of the 4 studies assessing the efficacy of opioids compared with placebo or a nonopioid control did not show reduced pain with opioids (g , -0.199 composite standardized mean difference [95% CI, -0.49 to 0.11]; $P = 0.136$). Meta-analysis of the 5 studies directly comparing the efficacy of different opioids demonstrated a nonsignificant reduction in pain from baseline (g , -0.93 composite standardized mean difference [CI, -1.89 to -0.03]; $P = 0.055$). The prevalence of lifetime substance use disorders ranged from 36% to 56%, and the estimates of the prevalence of current substance use disorders were as high as 43%. Aberrant medication-taking behaviors ranged from 5% to 24%.

Limitations: Retrieval and publication biases and poor study quality. No trial evaluating the efficacy of opioids was longer than 16 weeks.

Conclusions: Opioids are commonly prescribed for chronic back pain and may be efficacious for short-term pain relief. Long-term efficacy (≥ 16 weeks) is unclear. Substance use disorders are common in patients taking opioids for back pain, and aberrant medication-taking behaviors occur in up to 24% of cases.

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[Opioid Treatment for Chronic Back Pain and Its Association with Addiction](#)

EXHIBIT 13

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The risk of a single 5-day opioid prescription, in one chart

Limiting the length of opioid prescriptions isn't inhumane. It could save lives.

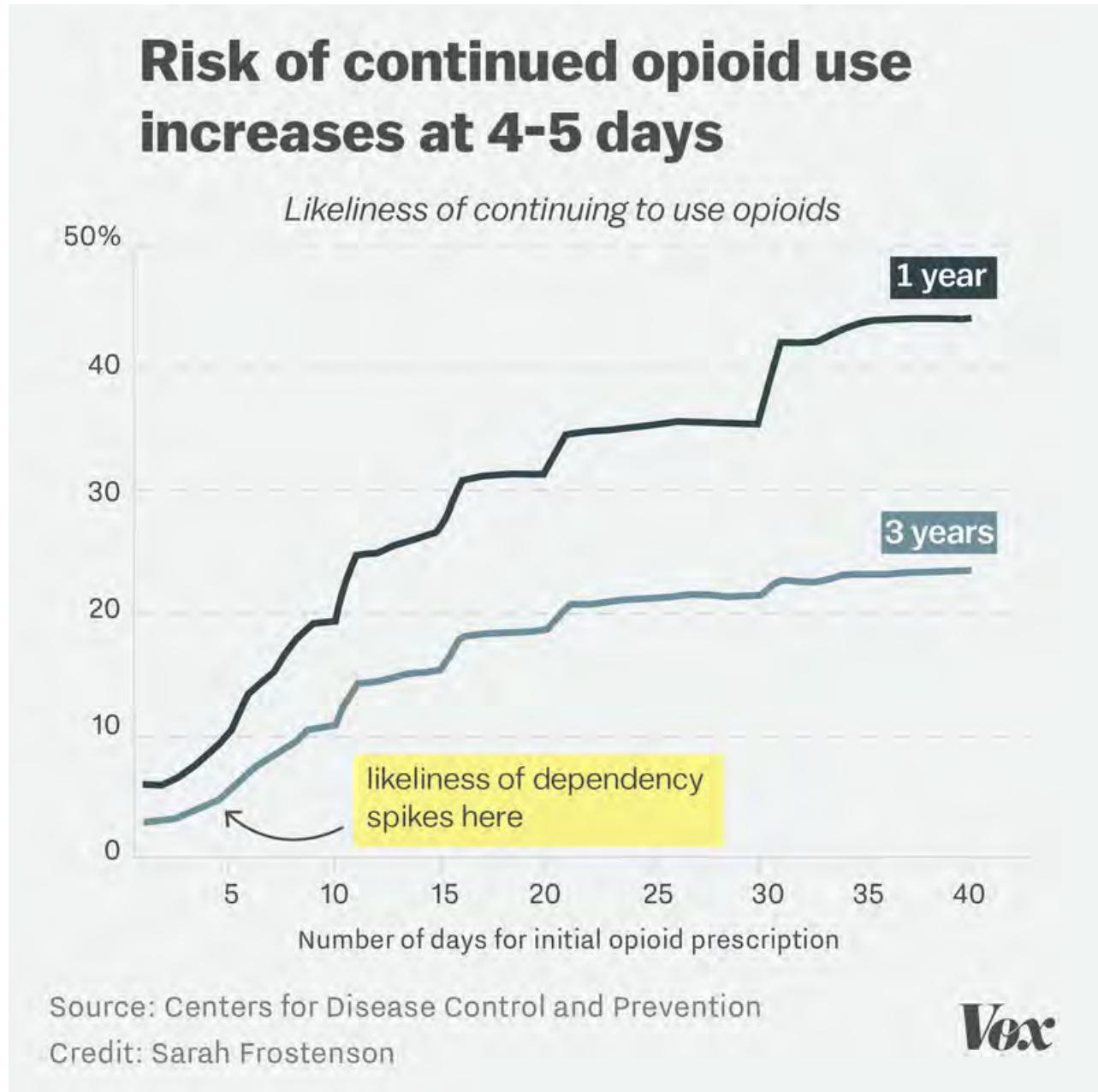
Updated by Sarah Frostenson | @sfrostenson | sarah.frostenson@vox.com | Mar 18, 2017, 7:30am EDT

Now that it's clear opioid painkillers have helped cause the worst drug epidemic in history, health experts are scrambling to figure out when dependency on these powerful prescription drugs starts — and how to prevent it.

A new study from the Centers for Disease Control and Prevention looked at the relationship between the number of days of someone's first opioid prescription and their long-term use. It found that that number has a huge

impact: Patients face an increased risk of opioid dependency in as few as four days of taking the drugs.

As you can see in the chart below, opioid prescriptions longer than five days in length significantly increased the likelihood of continued opioid use both one and three years later.



"There's nothing magical about five days versus six days, but with each day your risk of dependency increases fairly dramatically," said Bradley Martin of the CDC, one of the study authors.



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The study, which analyzed 1.3 million non-cancer patients, also found that only 6 percent of patients prescribed a one-day supply of opioids were still taking the drugs a year later, but that number doubled to 12 percent if patients were prescribed a six-day supply and quadrupled to 24 percent if patients were given a 12-day supply.

Dependency on opioids can develop quickly, and it isn't clear if they are even effective in treating chronic pain

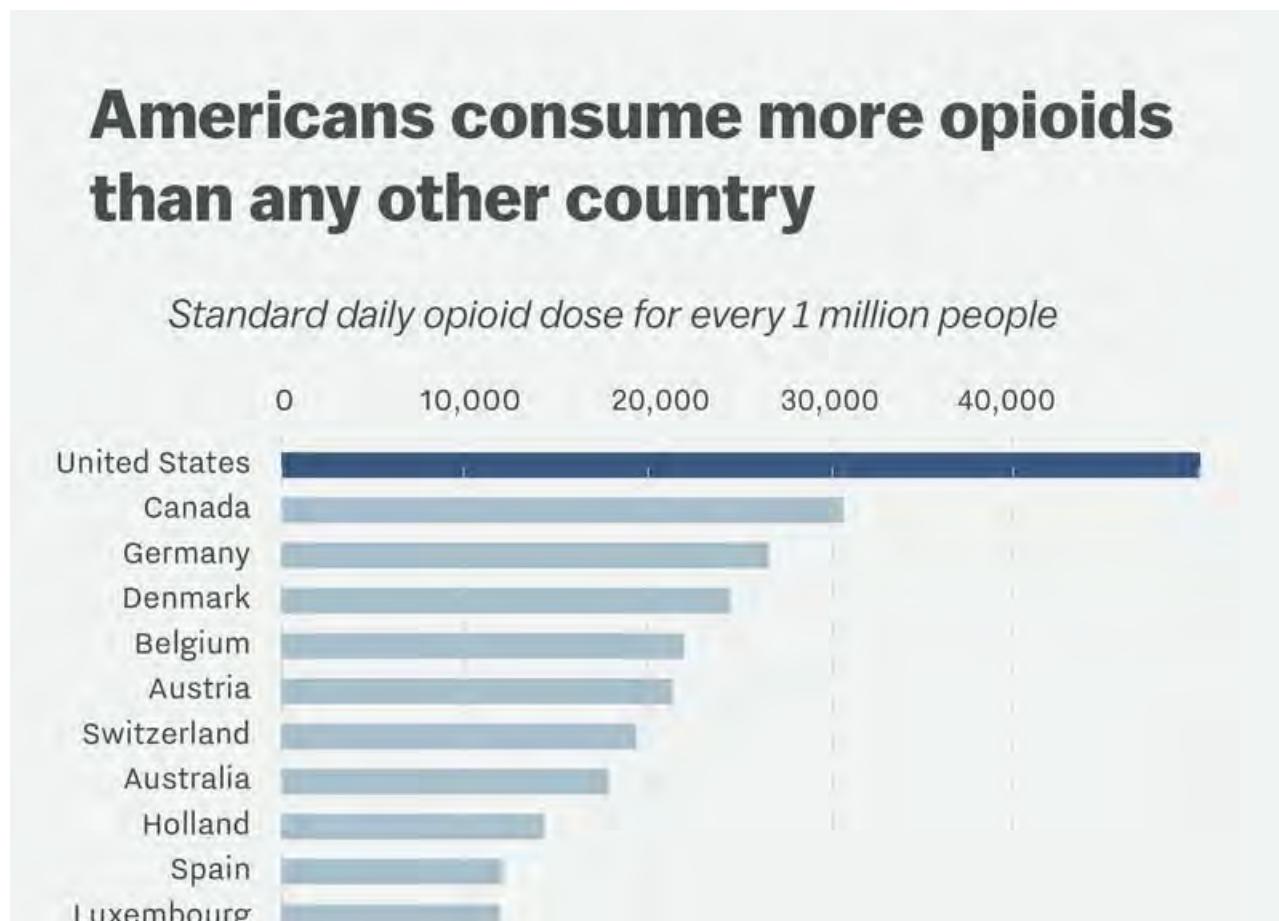
Some in the medical community have pushed back against CDC guidelines released last spring that advise initial opioid prescriptions be limited to seven days or less, arguing that short prescriptions puts patients at risk of "inhumane treatment."

According to Martin, this argument doesn't hold up well since, for one, we don't have good data on the effectiveness of opioids to treat long-term pain.

What's more, Martin is concerned that doctors still don't appreciate just how quickly people can get hooked on these drugs. "[For people who] take an opioid for 10 days, almost one in five will still be taking opioids one year later," said Martin.

To be clear, the researchers are not equating long-term opioid use with addiction in their study. But given that opioid addiction rates and overdose deaths are high, they're hoping physicians will make more careful opioid prescribing decisions to reduce the risk of patients developing long-term issues with the drugs.

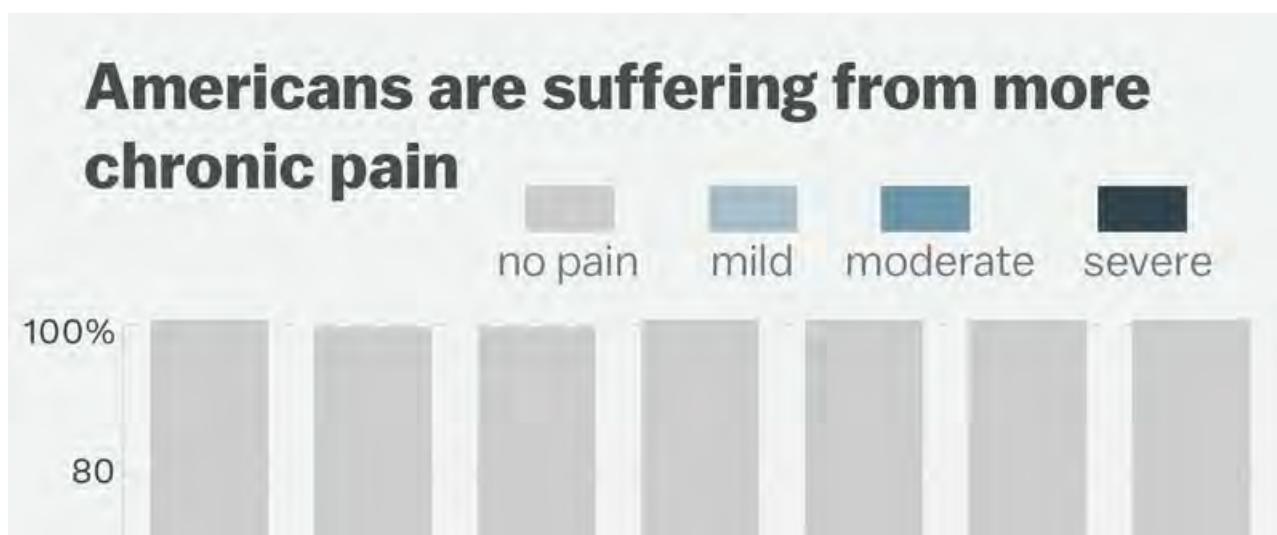
There's no question that America's use of opioids is excessive — we consume far more daily doses per capita than any other country, according to United Nations data of the top 25 countries that use opioids.

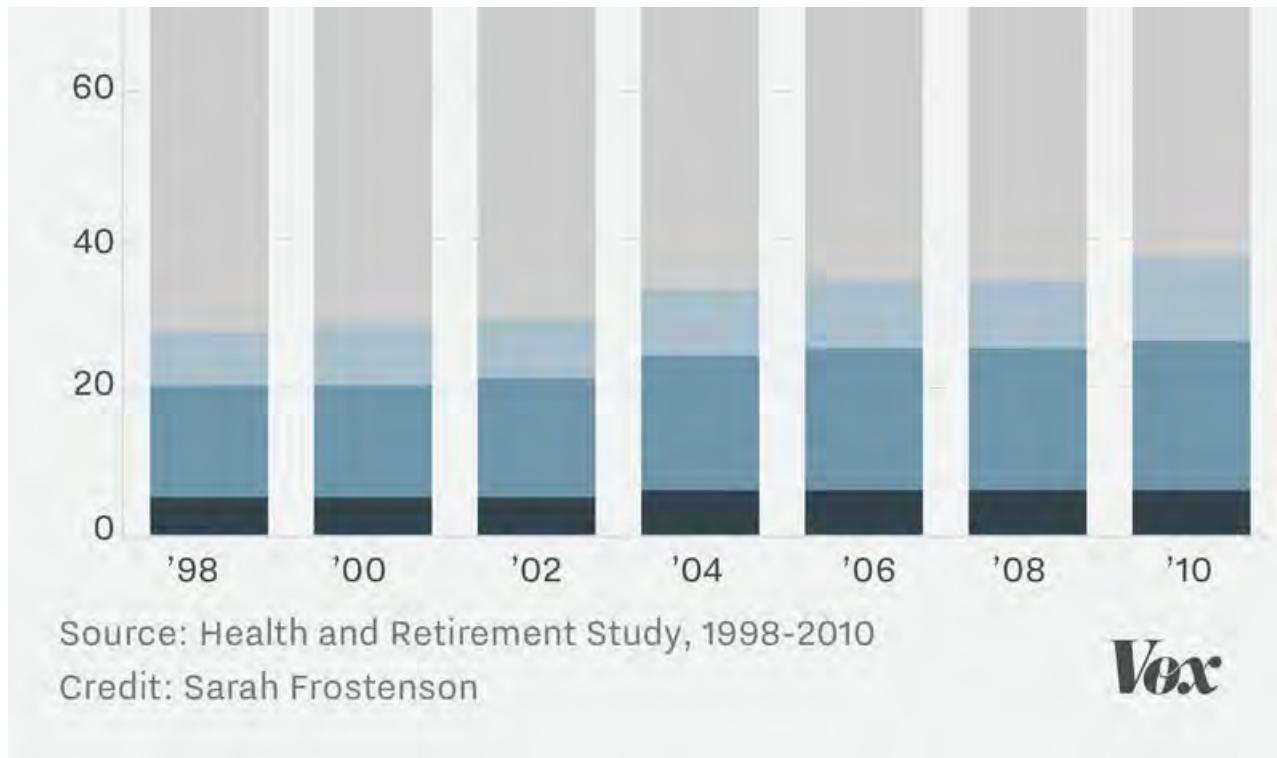




Limiting the length of opioid prescriptions saves lives, but a growing number of people are living in pain

Unfortunately, chronic pain isn't easy to diagnose, measure, or treat. More than a third of Americans now experience chronic pain — more than those who have cancer, heart disease, and diabetes combined. What's more, the severity of pain Americans report is increasing each year.





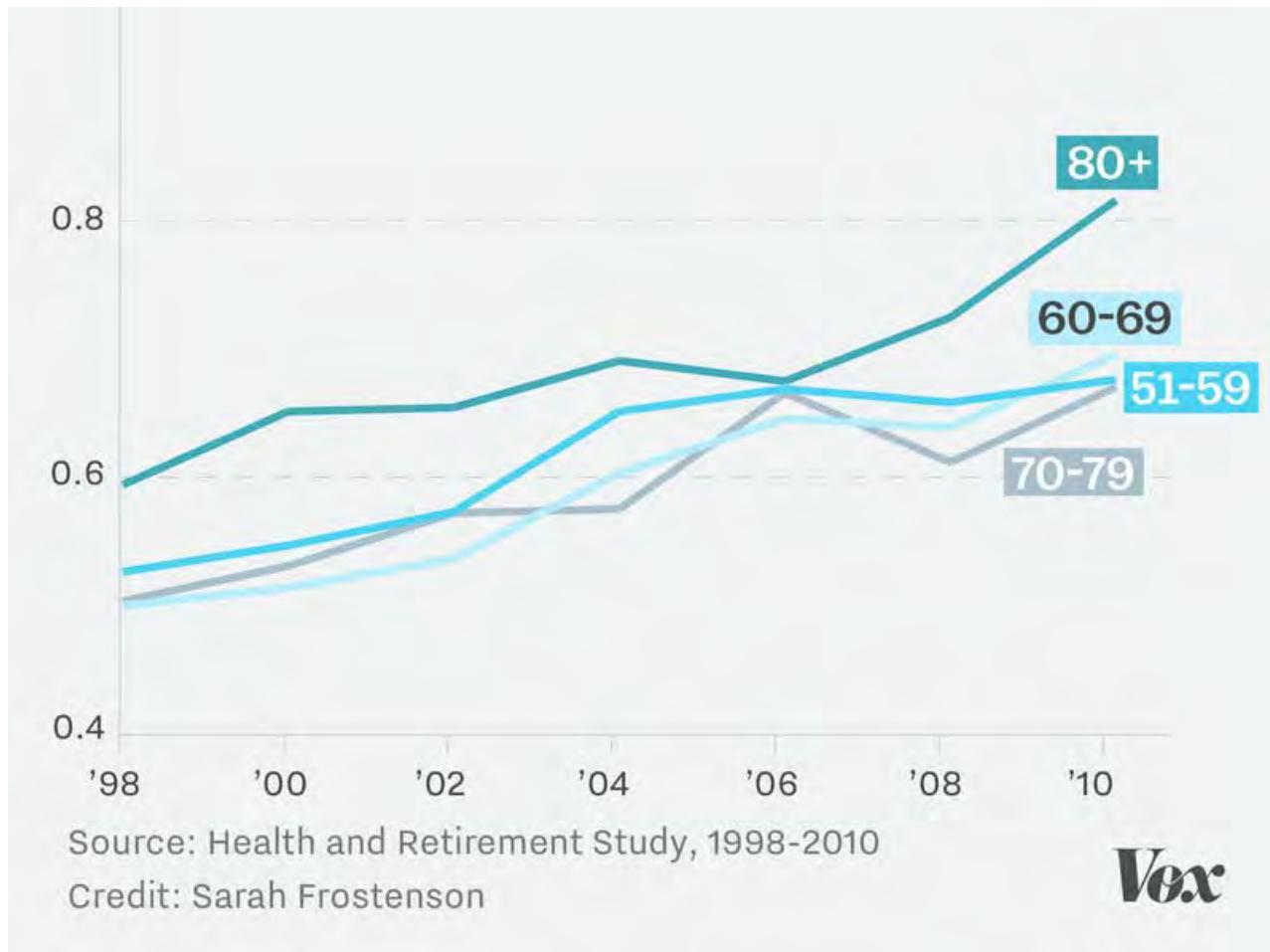
The CDC authors found in their study that patients who continued to use opioids for more than a year were more likely to be older, to be female and to have a preexisting pain diagnosis. This confirms much of what Hanna Grol-Prokopczyk, a medical sociologist at the University at Buffalo, has found in her research on pain.

In a 2016 paper, Grol-Prokopczyk uncovered huge disparities in how Americans experience pain. Examining 12 years of data from the biennial Health and Retirement Study, she found that women were more likely to experience severe pain than men, and that pain doesn't decrease as we age. In fact, it goes up with age, and those over the age of 80 reported experiencing the most pain.

Americans are reporting more chronic pain across all age groups

Median pain score

1.0



Grol-Prokopczyk cautioned me that as we move forward in rethinking our approach to prescribing opioids and how we treat chronic pain, we can't forget there is a sizable minority of Americans living in pain.

"Let's recognize that we need to invest in either figuring out how to prevent chronic pain or treat[ing] it in a way that doesn't have all the deleterious effects of opioids," she said. "Unfortunately, I don't have a great answer for what the alternative is, but I want to make sure that we don't just think, 'Okay, let's limit opioid prescriptions, and we're all done.'"

Was this article helpful? thumb up thumb down

IN THIS STORYSTREAM

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The deadliness of the opioid epidemic has roots in America's failed response to crack

The risk of a single 5-day opioid prescription, in one chart

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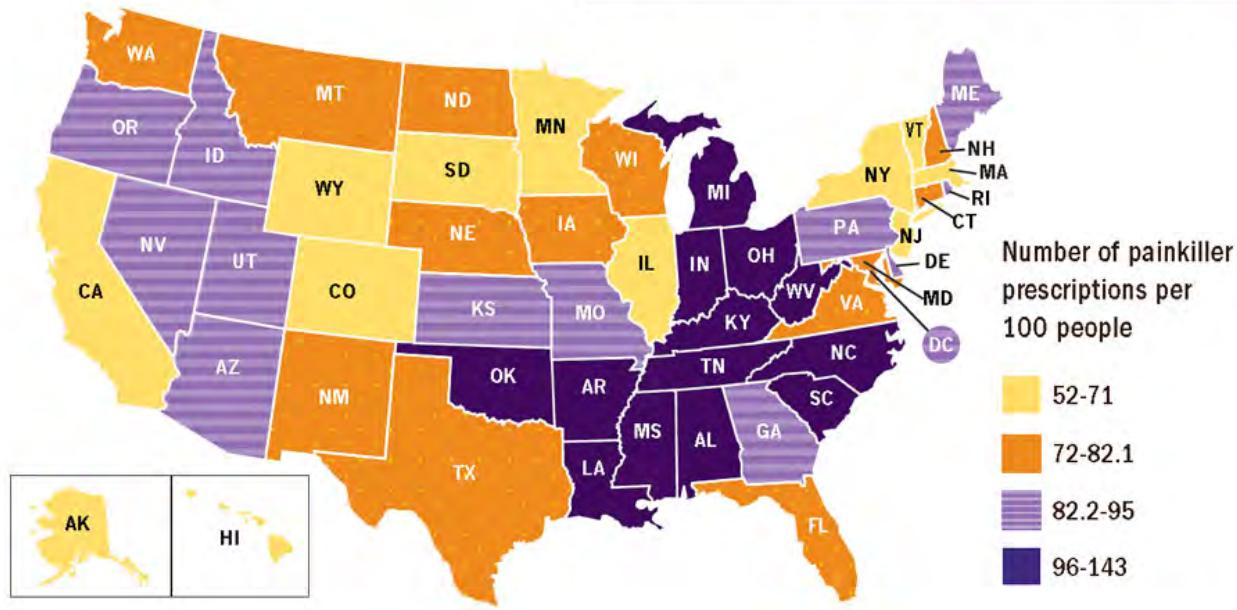
EXHIBIT 14

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Opioid Painkiller Prescribing infographic

Some states have more painkiller prescriptions per person than others.



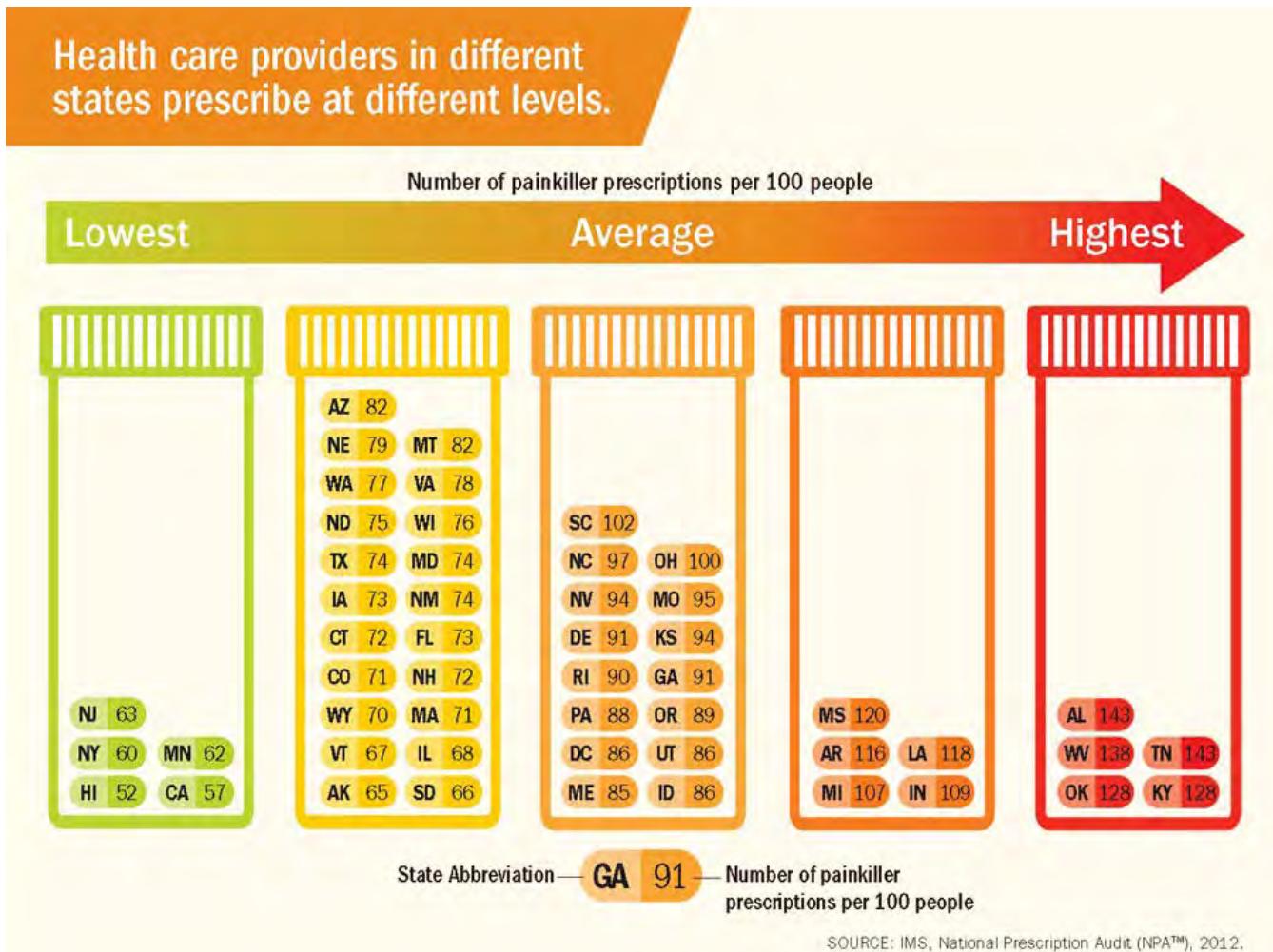
SOURCE: IMS, National Prescription Audit (NPA™), 2012.

Some states have more painkiller prescriptions per person than others.

This color-coded U.S. map shows the number of painkiller prescriptions per 100 people in each of the fifty states plus the District of Columbia in 2012. Data from IMS, National Prescription Audit (NPA™), 2012.

Quartile (Painkiller Prescriptions per 100 People)	States
52-71	HI, CA, NY, MN, NJ, AK, SD, VT, IL, WY, MA, CO
72-82.1	NH, CT, FL, IA, NM, TX, MD, ND, WI, VA, NE, MT

82.2-95	AZ, ME, ID, DC, UT, PA, OR, RI, GA, DE, KS, NV, MO
96-143	NC, OH, SC, MI, IN, AR, LA, MS, OK, KY, WV, TN, AL



Health care providers in different states prescribe at different levels.

This graphic orders the fifty states plus the District of Columbia by the number of painkiller prescriptions per 100 people. There are five pill bottles:

- The green bottle contains states that have the lowest number of prescription painkillers per 100 people: 52-63 (5 states).
- The yellow bottle contains states that have 65-82 prescription painkillers per 100 people (21 states).
- The orange bottle contains states that have 85-102 prescription painkillers per 100 people (15 states).

- The red-orange bottle contains states that have 107 to 120 prescription painkillers per 100 people (5 states).
- The red bottle contains states that have the highest number of prescription painkillers per 100 people: 128-143 (5 states).

[View larger image and text. \(infographic.html#infographic1\)](#)

State	Painkiller Prescriptions per 100 People
HI	52
CA	57
NY	60
MN	62
NJ	63
State	Painkiller Prescriptions per 100 People
AK	65
SD	66
VT	67
IL	68
WY	70
MA	71
CO	71
NH	72
CT	72
FL	73
IA	73
NM	74
TX	74
MD	74
ND	75

WI	76
WA	77
VA	78
NE	79
MT	82
AZ	82
State	Painkiller Prescriptions per 100 People
ID	86
DC	86
UT	86
PA	88
OR	89
RI	90
GA	91
DE	91
KS	94
NV	94
MO	95
NC	97
OH	100
SC	102
State	Painkiller Prescriptions per 100 People
MI	107
IN	109
AR	116
LA	118
MS	120

State	Painkiller Prescriptions per 100 People
OK	128
KY	128
WV	138
TN	143
AL	143

Making a Difference: State Successes



New York down 75%

2012 Action:

New York required prescribers to check the state's prescription drug monitoring program before prescribing painkillers.

2013 Result: Saw a 75% drop in patients who were seeing multiple prescribers to obtain the same drugs, which would put them at higher risk of overdose.

Florida down 50%

2010 Action:

Florida regulated pain clinics and stopped health care providers from dispensing prescription painkillers from their offices.

2012 Result: Saw more than 50% decrease in overdose deaths from oxycodone.

Tennessee down 36%**2012 Action:**

Tennessee required prescribers to check the state's prescription drug monitoring program before prescribing painkillers.

2013 Result: Saw a 36% drop in patients who were seeing multiple prescribers to obtain the same drugs, which would put them at higher risk of overdose.

SOURCES: NY, TN: PDMP Center of Excellence at Brandeis University, 2014. FL: Vital Signs Morbidity and Mortality Weekly Report, July 1, 2014.

[View larger image and text. \(infographic.html#infographic2\)](#)

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Page last reviewed: July 1, 2014

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EXHIBIT 15

**shots**

HEALTH INC.

Drug Distributors Penalized For Turning Blind Eye In Opioid Epidemic

January 27, 2017 · 5:00 AM ET

CHARLES ORNSTEIN

FROM



McKesson Corp. agreed to pay a \$150 million fine to settle claims that it failed to report suspicious orders for controlled substances.

Paul Sakuma/AP

manufacturers are under investigation and face new rules from regulators.

But penalties against companies that serve as middlemen between drug companies and pharmacies have been relatively scarce — until recently.

In the past month, two major drug distributors, also known as wholesalers, have formally agreed to pay millions of dollars to settle claims that they failed to report suspicious orders for controlled substances to the Drug Enforcement Administration, as required by law.

McKesson Corp., the largest such company in the U.S., agreed Jan. 17 to pay a \$150 million fine. And in late December, Cardinal Health reached a \$44 million settlement with the federal government. That's on top of another \$20 million that Cardinal Health agreed this month to pay the state of West Virginia, which has been among the hardest hit by opioid overdoses. Other distributors have also agreed to pay smaller amounts to West Virginia within the past few months. AmerisourceBergen, for instance, will pay \$16 million.

"Have the distributors gotten the message? I would hope so," said Frank Younker, who worked at the DEA for 30 years and retired as a supervisor in its Cincinnati field office in 2014. "The distributors are important. They're like the quarterback. They distribute the ball. ...There's plenty of blame to go around."

The death toll from drug overdoses topped 52,000 in 2015, including 33,000 involving an opioid, according to the Centers for Disease Control and Prevention. Although the epidemic began with prescription pills, it is now being driven largely by heroin and various synthetic opioids.

The fines, some of which had been in the works for years, come as news organizations have raised questions about the significant role distributors have played by failing to stop or report pharmacies that appeared to be dispensing more pills than seemed reasonable.

The *Charleston Gazette-Mail* reported in December how drug companies shipped

Kermit, W. Va., population 392. All told, the newspaper reported, drug wholesalers distributed 780 million pills of oxycodone and hydrocodone in the state over six years. "The unfettered shipments amount to 433 pain pills for every man, woman and child in West Virginia," the story said.

The Washington Post reported in October how DEA leadership delayed and blocked enforcement actions as the overdose epidemic grew. Civil case filings against distributors, manufacturers, pharmacies and doctors dropped from 131 in fiscal 2011 to 40 in fiscal 2014, the *Post* reported. Immediate suspension orders (the toughest sanction the DEA has) fell from 65 to 9.

Later, the *Post* reported why that may have been: The drug industry had hired dozens of officials from the DEA, leading some current and former officials to ask whether the industry sought to hire away those who presented "the biggest headaches for them."

In response to written questions for this story, the DEA said it has always held distributors "accountable for preventing the diversion of controlled and abused prescription drugs, including the opioid painkillers."

Asked if its recent fines were too little, too late, the agency replied, "We don't think so. We hope large fines such as this one [against McKesson] will get the attention of the companies' leaders and stockholders and prompt them to be responsible corporate citizens, because people are dying as a result of the diversion of the opioid drugs they sell, and that can't continue."

In statements released when the distributors finalized their settlements, the companies said they have improved their performance in recent years. McKesson noted that the settlement covers reporting practices dating back to 2009. "Since 2013, McKesson has implemented significant changes to its monitoring and reporting processes," the company said in a statement.

As part of the settlement, the DEA will suspend the registrations of four of McKesson's distribution centers, on a staggered basis, blunting the effect of the punishment.

"Pharmaceutical distributors play an important role in identifying and combating prescription drug diversion and abuse," John H. Hambergren, chairman and chief executive officer, said in the statement. "McKesson, as one of the nation's largest distributors, takes our role seriously."

The DEA had previously taken action against McKesson in 2008 for failing to report suspicious orders, a factor cited in the latest fine.

Cardinal Health's fine was the last aspect of a 2012 settlement with the DEA, which included a two-year suspension of its Lakeland, Fla., distribution center. "These agreements allow us to move forward and continue to focus on working with all participants in addressing the epidemic of prescription drug abuse," Craig Morford, its chief legal and compliance officer, said in a statement last month.

Federal prosecutors who worked on the McKesson case said that distributors play an important role in the overall system in which controlled substances get distributed. "What Congress envisioned is that there would be gatekeepers along the way in this closed system," said Kurt Didier, an assistant U.S. attorney in Sacramento, in an interview. "It starts with the physician writing the prescription and the pharmacist filling the prescription. In between, you have entities like the distributors.

"In this overall scheme, a distributor is obligated to report to DEA prescriptions or orders that it views are suspicious," Didier said.

The agencies regulating the industry have had their own problems. The *Gazette-Mail* reported that the West Virginia pharmacy board didn't pay much attention to its own rules requiring that wholesalers report such orders. The board also had not examined reports from distributors regarding suspicious orders by pharmacies, nor had it shared those with law enforcement.

For its part, the DEA also has been faulted several times by the Government Accountability Office for, among other things, how it sets annual quotas for the amount of controlled substances that can be produced, the information and guidance

Jim Geldhof, who retired in January 2016 after more than 40 years with the DEA, most recently as a manager in the Detroit field office, said the recent fines are important, but he wonders if they will make any difference. "It's going to be pretty hard to undo the damage that's been done," said Geldhof. "Do they get it? I don't know. I don't have a real lot of faith in industry frankly."

ProPublica is a nonprofit newsroom based in New York. You can follow Charles Ornstein on Twitter: @charlesornstein.

opioid abuse west virginia dea pharmaceuticals

EXHIBIT 16

BUSINESS INSIDER

This one-paragraph letter may have launched the opioid epidemic



HARRISON JACOBS

MAY 26, 2016, 12:06 PM

Over the past decade, the US has undergone an opioid epidemic. Prescriptions for opioid painkillers like oxycodone, hydrocodone, fentanyl, and morphine have skyrocketed and, with them, the number of overdoses related to opioids.

In 2014, deaths from opioid-related drug overdoses [reached a new high of](#) 28,647, according to a January report from the US Centers for Disease Control and Prevention (CDC).

But the trend has been [decades in the making](#).

This explosion in opioid prescriptions began in the early 1990s with "a big push" from medical groups that doctors were under-treating pain, according to Dr. Ted Cicero, a professor of psychiatry at Washington University in St. Louis and an opiate-use researcher.

One of the primary justifications for this increase, used by doctors, pharmaceutical companies, and researchers alike, was a single paragraph printed [in the January 10, 1980, issue of the New England Journal of Medicine](#):

ADDICTION RARE IN PATIENTS TREATED WITH NARCOTICS

To the Editor: Recently, we examined our current files to determine the incidence of narcotic addiction in 39,946 hospitalized medical patients' who were monitored consecutively. Although there were 11,882 patients who received at least one narcotic preparation, there were only four cases of reasonably well documented addiction in patients who had a history of addiction. The addiction was considered major in only one instance. The drugs implicated were meperidine in two patients, Percodan in one, and hydromorphone in one. We conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction.

JANE PORTER

HERSHEL JICK, M.D.



The explosion in opioid prescriptions has been decades in the making.

Abid Katib/Getty Images

Boston Collaborative Drug

Surveillance Program

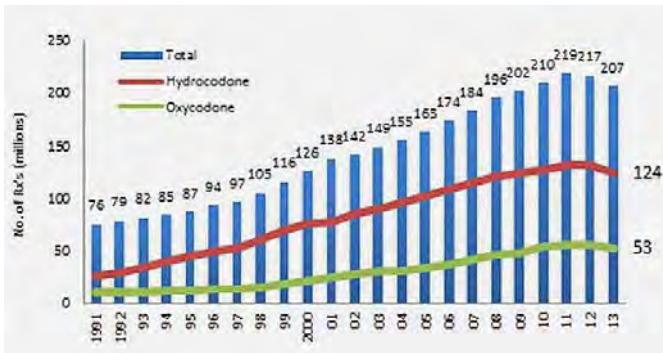
Boston University Medical Center

Waltham, MA 02154

The analysis mentioned in the letter, which was authored by Dr. Hershel Jick, was not included.

In the years that followed, the letter was used by pain specialists, nurses, and pharmaceutical representatives in conventions, seminars, and workshops as evidence that opiate painkillers had the low risk of addiction. Specifically, the letter was used to support the assertion that "less than 1%" of opioid users become addicted to the drugs.

Jick's analysis proved no such thing. The study analyzed a database of hospitalized patients at Boston University Medical Center who were given small doses of opioids in a controlled setting to ease suffering from acute pain. These patients were not given long-term opioid prescriptions, which they'd be free to administer at home.



The number of opioid prescriptions has increased dramatically since the early 1990s.

National Institute on Drug Abuse

Nevertheless, medical groups like the American Pain Society and the American Pain Foundation used the letter as a jumping-off point and began calling pain the "fifth vital sign" that doctors should attend to.

Pharmaceutical companies like Purdue Pharma introduced powerful new painkillers such as [MS Contin](#) and [OxyContin](#), extended-release pills with a very large dose of morphine or oxycodone, respectively, that is designed to be released slowly into a person's body over a 12- or 24-hour period. Major pain specialists began encouraging doctors to prescribe opioids liberally to their pain patients, despite long-held fears of addiction.

As detailed by investigative journalist Sam Quinones in "[Dreamland: The True Tale of America's Opiate Epidemic](#)," his investigation into the causes of the heroin crisis, the Porter and Jick letter was referenced repeatedly to justify the increase in liberal prescriptions of opioid painkillers, including in the following:

- A 1990 article in *Scientific American*, where it was called "an extensive study"
- A 1995 article in *Canadian Family Physician*, where it was called "persuasive"
- A 2001 *Time* magazine feature, which said that it was a "landmark study" demonstrating that the "exaggerated fear that patients would become addicted" to opiates was "basically unwarranted"
- A 2007 textbook, "[Complications in Regional Anesthesia and Pain Medicine](#)," which said that it was "a landmark report" that "did much to counteract" fears that pain patients treated with opioids would become addicted.
- A 1989 monograph for the National Institutes of Health, which asked readers to "consider the work" of Porter and Jick.

As of May 24, 2016, the Porter and Jick letter has been cited 901 times in scholarly papers, according to a Google Scholar search.

The most influential citation of the Porter and Jick letter was in a 1986 paper on the "[chronic use of opioid analgesics in non-malignant pain](#)" by Dr. Russell Portenoy and Kathy Foley in Pain, the official journal of the American Pain Society. In the paper, Portenoy and Foley reviewed the cases of 38 cancer patients with chronic pain who used opioids. Only two became addicted.

"We conclude that opioid maintenance therapy can be a safe, salutary and more humane alternative to the options of surgery or no treatment in those patients with intractable non-malignant pain and no history of drug abuse," Portenoy and Foley wrote.

Their paper, bolstered by the Porter and Jick letter, became an even broader justification for doctors to prescribe opioids liberally for common injuries such as back pain.



Dr. Russell Portenoy.

YouTube/Andrew Kolodny

Over time, the Porter and Jick letter, and its claim that "less than 1%" of opioid users became addicted, became "gospel" for medical professionals, Dr. Marsha Stanton told Quinones.

"I used [Porter and Jick] in lectures all the time. Everybody did. It didn't matter whether you were a physician, a pharmacist, or a nurse; you used it. No one disputed it. Should we have? Of course we should have," Stanton said.

In 1996, the American Pain Society and the American Academy of Pain Management issued a "[landmark consensus](#)," [written in part by Portenoy](#), saying that there is little risk of addiction or overdose in pain patients. The consensus cited the "less than 1 percent" addiction figure and the Porter and Jick letter.

In an interview released by Physicians for Responsible Opioid Prescribing in 2011, Portenoy admitted that he used the Porter and Jick letter, along with other similar studies on opioid use, to encourage more liberal prescribing of opioids:

None of [the papers] represented real evidence, and yet what I was trying to do was to create a narrative so that the primary care audience would look at this information ... and feel more comfort about opioids in a way they hadn't before. In essence this was education to destigmatize [opioids] and because the primary goal was to destigmatize, we often left evidence behind.

Here's the full video:



When asked by Quinones years later about the letter, Jick called it "an amazing thing":

That particular letter, for me, is very near the bottom of a long list of studies that I've done. It's useful as it stands because there's nothing else like it on hospitalized patients. But if you read it carefully, it does not speak to the level of addiction in outpatients who take these drugs for chronic pain.

×

EXHIBIT 17

Vox

A 5-sentence letter helped trigger America's deadliest drug overdose crisis ever

All it took was one paragraph.

Updated by German Lopez | @germanrlopez | german.lopez@vox.com | Jun 1, 2017, 10:50am EDT



In 1980, a pair of doctors published a brief letter in the *New England Journal of Medicine*. Spanning a total of five sentences, the letter claimed, with little substantial evidence, that the development of addiction was very rare in hospitalized patients who briefly received opioids and had no prior history of addiction.

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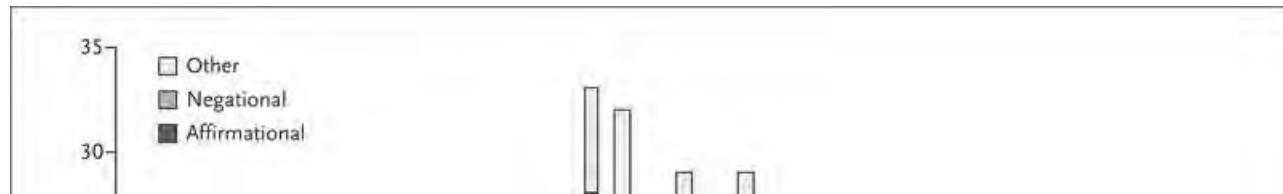
Ad Best Western Hotels Resorts

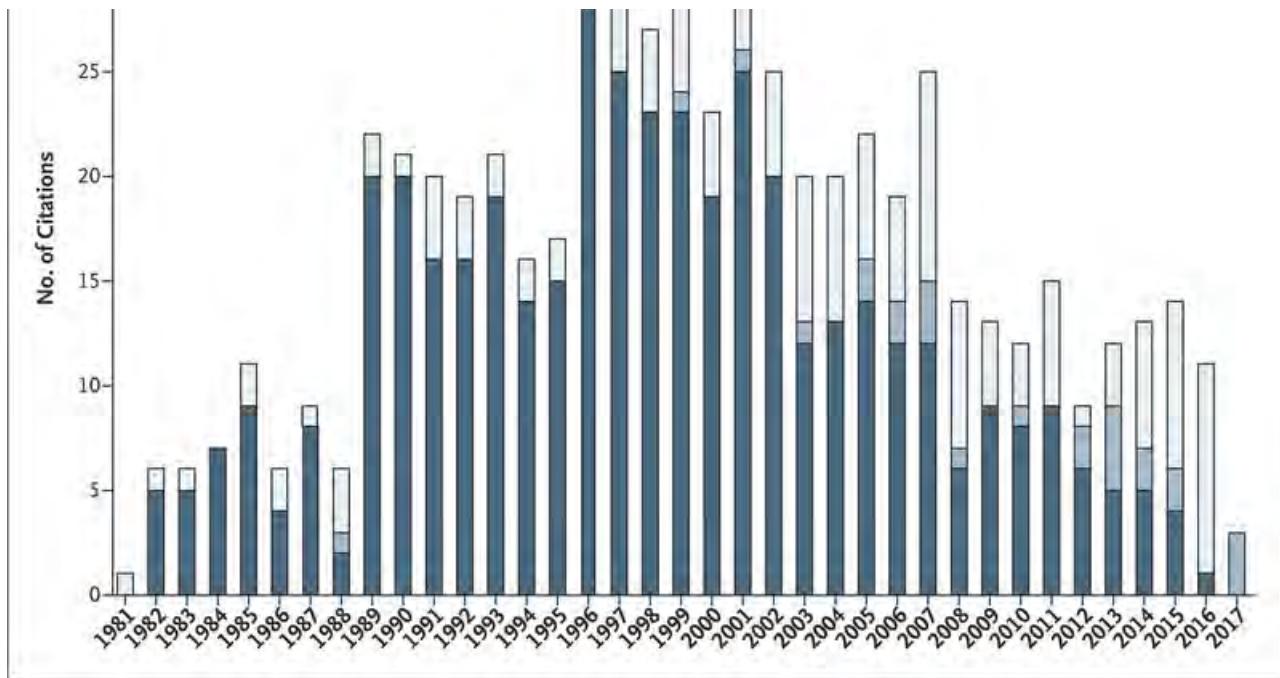
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Drugmakers quickly latched onto the letter, fueling the beginning of the opioid epidemic — to the point that the results have horrified one of the letter's authors. “I'm essentially mortified that that letter to the editor was used as an excuse to do what these drug companies did,” Hershel Jick told the Associated Press. “They used this letter to spread the word that these drugs were not very addictive.”

Now a new study in the NEJM has looked at just how much of a reach the letter had.

Researchers Pamela Leung, Erin Macdonald, Irfan Dhalla, and David Juurlink found that the letter was cited more than 600 times since it was published, with a sharp increase after the opioid maker Purdue Pharma introduced OxyContin in the mid-1990s.





New England Journal of Medicine

The researchers concluded, “[W]e found that a five-sentence letter published in the *Journal* in 1980 was heavily and uncritically cited as evidence that addiction was rare with long-term opioid therapy. We believe that this citation pattern contributed to the North American opioid crisis by helping to shape a narrative that allayed prescribers’ concerns about the risk of addiction associated with long-term opioid therapy.”

Juurlink further elaborated on his findings in a series of tweets shortly after his *NEJM* piece was published. He pointed out that even though the letter was a mere five sentences, some of the people citing the letter didn’t appear to actually read it.

The citations often claimed, for example, that the letter found zero cases of addiction among patients with no prior history of addiction — when the letter cited four cases. And the citations often argued that the findings proved that opioid painkillers could be prescribed safely in an outpatient setting — when the letter, as one author told the Associated Press, only

looked at hospital patients who briefly received opioids, and its findings couldn't be extrapolated to opioids' long-term use in an outpatient setting.

Juurlink and his team aren't the first to draw the connection between the opioid crisis and the 1980 letter. It was a focus of Sam Quinones's *Dreamland*, a groundbreaking book highlighting the opioid epidemic and its causes.

But the new study shows how prominent the letter was: With hundreds of citations, it quickly became instrumental in spreading the myth that opioids could be prescribed safely without the risk of addiction. Decades later, the opioid epidemic is the deadliest drug overdose crisis in US history.

The opioid epidemic, explained

In 2015, more Americans died of drug overdoses than any other year on record — more than 52,000 deaths in just one year. That's higher than the more than 38,000 who died in car crashes, the more than 36,000 who died from gun violence, and the more than 43,000 who died due to HIV/AIDS during that epidemic's peak in 1995.

This latest drug epidemic, however, is not solely about illegal drugs. It began, in fact, with a legal drug.

Back in the 1990s, doctors were persuaded to treat pain as a serious medical issue. There's a good reason for that: About one in three Americans suffer from chronic pain, according to a 2011 report from the Institute of Medicine.

Pharmaceutical companies took advantage of this concern. Through a big marketing campaign, they got doctors to prescribe products like OxyContin and Percocet in droves — even though the evidence for opioids treating long-term, chronic pain is very weak (despite their effectiveness for short-term, acute pain), while the evidence that opioids cause harm in the long term is very strong.

So painkillers proliferated, landing in the hands of not just patients but also teens rummaging through their parents' medicine cabinets, other family members and friends of patients, and the black market.

As a result, opioid overdose deaths trended upward — sometimes involving opioids alone, other times involving drugs like alcohol and benzodiazepines (typically prescribed to relieve anxiety). By 2015, opioid overdose deaths totaled more than 33,000 — close to two-thirds of all drug overdose deaths.



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Drug overdose deaths in America

*The numbers for 2016 are preliminary estimates

**Some deaths on this chart may overlap if they involve multiple drugs

70K +

Seeing the rise in opioid misuse and deaths, officials have cracked down on prescriptions painkillers. Law enforcement, for instance, threatened doctors with incarceration and the loss of their medical licenses if they prescribed the drugs unscrupulously.



Ideally, doctors should still be able to get painkillers to patients who truly need them — after, for example, evaluating whether the patient has a history of drug addiction. But doctors, who weren't conducting even such basic checks, are now being told to give more thought to their prescriptions.

Yet many people who lost access to painkillers are still addicted. So some who could no longer obtain prescribed painkillers turned to cheaper, more potent opioids: heroin and fentanyl, a synthetic opioid that's often manufactured illegally for nonmedical uses.

Not all painkiller users went this way, and not all opioid users started with painkillers. But statistics suggest many did: A 2014 study in *JAMA Psychiatry* found many painkiller users were moving on to heroin, and a 2015 analysis by the Centers for Disease Control and Prevention found that people who are addicted to prescription painkillers are 40 times more likely to be addicted to heroin.

So other types of opioid overdoses, excluding painkillers, also rose.

That doesn't mean cracking down on painkillers was a mistake. It appeared to slow the rise in painkiller deaths, and it may have prevented doctors from prescribing the drugs to new generations of people with drug use disorders.

But the likely solution is to get opioid users into treatment. According to 2014 federal data, at least 89 percent of people who met the definition for a drug use disorder didn't get treatment. Patients with drug use disorders also often complain of weeks- or months-long waiting periods for care.



FROM OUR SPONSOR CONTINUE FOR MORE CONTENT



So federal and state officials have pushed for more treatment funding, including medication-assisted treatment like methadone and buprenorphine.

Some states, such as Louisiana and Indiana, have taken a "tough on crime" approach that focuses on incarcerating drug traffickers. But the incarceration approach has been around for decades — and it hasn't stopped massive drug epidemics like the current crisis.

EXHIBIT 18



CURRENCY

WHO IS RESPONSIBLE FOR THE PAIN-PILL EPIDEMIC?

By Celine Gounder November 8, 2013



How did doctors, who pledge to do no harm, let the use of prescription narcotics get so out of hand?

Photograph by Roberto Machado Noa / LightRocket via Getty

When I started working as a medical resident, in 2004, I heard from a patient I had inherited from a graduating resident. The patient had an appointment scheduled in a couple weeks. “But I need your help now,” he said.

He was a former construction worker who had hurt himself on the job a couple of years earlier. He told me, “I also need some more OxyContin to tide me over until I can see you.” The hospital computer system told me that he had been taking twenty milligrams of OxyContin, three times a day, for at least the last couple of years. I had rarely seen such high doses of narcotics prescribed for such long periods of time. I’d seen narcotics prescribed in the hospital to patients who had been injured, or to those with pain from an operation or from cancer. But I didn’t have much experience with narcotics for outpatients. I figured that if the previous resident—now a fully licensed doctor—was doing this, then it must be O.K.

What I didn’t know was that my time in medical school had coincided with a boom in the prescribing of narcotics by outpatient doctors, driven partly by the pharmaceutical companies that sold those drugs. Between 1999 and 2010, sales of these “opioid analgesics”—medications like Vicodin, Percocet, and OxyContin—quadrupled.

By 2010, the United States, with about five per cent of the world’s population, was consuming ninety-nine per cent of the world’s hydrocodone (the narcotic in Vicodin), along with eighty per cent of the oxycodone (in Percocet and OxyContin), and sixty-five per cent of the hydromorphone (in Dilaudid).

As narcotics prescriptions surged, so did deaths from opioid-analgesic overdoses—from about four thousand to almost seventeen thousand. Studies have shown that patients who receive narcotics for chronic pain are less likely to recover function, and are less likely to go back to work. The potential side effects of prescription narcotics include constipation, sexual dysfunction, cognitive impairment, addiction, and overdosing. When patients receive narcotics for long periods, they can even become more sensitive to pain, a condition called hyperalgesia. (J. David Haddox, the vice-president of health policy at Purdue Pharma—the manufacturer of OxyContin—acknowledged “opioid analgesics have sometimes been associated with diminished pain relief in the face of increasing doses.”)

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And then there are the real-life Walter Whites. I once helped care for a patient with lung cancer who wasn't taking his narcotics, unbeknownst to his doctors. This patient's cancer had spread to his bones and other organs, which can be incredibly painful. But he was selling his prescription narcotics to help support his wife and himself. So when given these high-dose narcotics in the hospital, he overdosed—though not fatally, fortunately.

What's more, no medication reliably eliminates pain in all patients, and narcotics are no exception. And there isn't good evidence that the prescription of narcotics to treat chronic, non-cancer pain is effective over long periods: most studies of prescription narcotics last only twelve to sixteen weeks.

The use of prescription narcotics, and the problems associated with them, are so pervasive that, last month, the Food and Drug Administration recommended tightening regulations for how doctors prescribe some of the most commonly used narcotic painkillers.

How did doctors, who pledge to do no harm, let the use of prescription narcotics get so out of hand?

Not long ago, doctors in the U.S. prescribed narcotics mostly for short-term pain, like the kind that people experience after a surgery, or for pain related to cancer or to the end of life. Then came two small accounts in medical journals that helped lay the groundwork for an expanded role for prescription narcotics. The first, a hundred-word letter to the editor published in 1980 in the *New England Journal of Medicine*, reported that less than one per cent of patients at Boston University Medical Center who received narcotics while hospitalized became addicted. The second, a study published in 1986 in the journal *Pain*, concluded that, for non-cancer pain, narcotics “can be safely and effectively prescribed to selected patients with relatively little risk of producing the maladaptive behaviors which define opioid abuse.” The authors advised caution, and said that the drugs should be used as an “alternative therapy.” They also called for longer-term studies of patients on narcotics; we’re still waiting for those to be performed.

At around the same time, the companies that manufactured these narcotics—including Purdue Pharma, Johnson & Johnson, and Endo Pharmaceuticals—began to aggressively market their products for long-term, non-cancer pain, including neck and back pain. They promoted their prescription narcotics to doctors through ads in highly regarded publications, and through continuing-education courses for medical professionals. They also funded non-profits such as the American Academy of Pain Management and the American Pain Society—the latter previously headed by Dr. Russell Portenoy, a co-author of the *Pain* study and a proselytizer for expanded narcotics prescribing. The American Pain Society published guidelines that advocated for doctors to expand their use of prescription narcotics to relieve pain.

The Joint Commission, which accredits health facilities, issued pain-management standards in 2001 that instructed hospitals to measure pain—you may be familiar with the smiling-to-crying faces scale—and to prioritize its treatment. Elizabeth Zhani, a spokeswoman for the Joint Commission, told me that their standards “were based upon both the emerging and compelling

science of that time, and upon the consensus of a broad array of professionals.” Yet Purdue, according to a report issued by the U. S. Government Accountability Office, helped fund a “pain-management educational program” organized by the Joint Commission; a related agreement allowed Purdue to disseminate educational materials on pain management, and this, in the words of the report, “may have facilitated its access to hospitals to promote OxyContin.”

In a policy drafted by several people with ties to narcotics makers, including Haddox, the Federation of State Medical Boards called on the boards to punish doctors for inadequately treating pain, according to the *Wall Street Journal*. The Federation also reportedly accepted money from pharmaceutical firms to produce and distribute narcotics-prescribing guidelines. In an e-mail, the Federation maintained: “[Our] most recent policy reflects the considerable body of research and experience accrued since our last series of formal policies related to opioid prescribing and addiction were adopted in 2004. Our latest guidelines, adopted this year, acknowledge that evidence for the risk associated with opioids has surged, while evidence for the benefits of opioids for long-term use has remained controversial and insufficient.”

It took a while for authorities to notice what was going on, but once they did, there was a backlash. The Justice Department, the Food and Drug Administration, and the Senate Finance Committee have investigated these questionable marketing practices and financial relationships. Portenoy defended his relationships with pain-pill companies in an interview with the *Wall Street Journal* last year, saying that they “would benefit my educational mission, they benefit in my research mission, and to some extent they can benefit my own pocketbook, without producing in me any tendency to engage in undue influence or misinformation.”

In 2007, Purdue Pharma and three of its top executives pleaded guilty to criminal charges that they had misled the F.D.A., clinicians, and patients about the risks of OxyContin addiction and abuse by aggressively marketing

the drug to providers and patients as a safe alternative to short-acting narcotics. (Doctors had been taught that because OxyContin was time-released, it wouldn't cause a high that would lead to addiction.)

Haddox wrote in an e-mail that "the abuse of prescription medicines has become a serious public-health problem." He added that Purdue works with health-care professionals, law-enforcement bodies, and communities to help curb the abuse. In 2010, Purdue reformulated OxyContin to make it more difficult to inject or snort.

William Foster, a spokesperson for the Janssen Pharmaceuticals subsidiary of Johnson & Johnson, said that the company believes it is "critical for physicians and patients to have multiple treatment options, including opioid analgesics, to help people who need relief from acute and chronic pain," while also recognizing "the potential for misuse of opioid analgesics." Both Purdue and Johnson & Johnson run educational programs on the responsible prescribing of opioid medications, and Janssen Pharmaceuticals has an online database where you can check whether a physician has accepted payment from the company since 2010.

Endo Pharmaceuticals didn't respond to requests for comment.

The rise in prescription narcotics may have been driven partly by the pharmaceutical industry, but many patients also welcomed—and encouraged—it. Many people believe deeply in the power of modern medicine to cure illness, and bristle at the notion that pain is a fact of life. The promise of a set of medicines that could cure pain was appealing to many patients—and, with a customer-is-always-right mentality having pervaded the doctor's office, patients were able to pressure physicians to satisfy their requests for the pain pills they'd begun hearing about.

The pain-pill epidemic has also forced doctors like me to consider our own role. Doctors have a duty to relieve suffering, and many of us became doctors

to help people. But giving that help isn't straightforward, especially when it comes to chronic pain. Try explaining the downsides of narcotics to a patient while declining to give him the medication he wants. He might accuse you of not understanding because you're not the one in pain; he might question why you won't give him what another doctor prescribed; he might give you a bad rating on a doctor-grading Web site. He might even accuse you of malpractice. None of this is rewarding for doctors: we're frustrated that we can't cure the pain, and that our patients end up upset with us.

Doctors have a hard time saying no, whether a patient is asking for a narcotic to relieve pain or an antibiotic for the common cold. We are predisposed to say yes, even if we know it isn't right. Some of us just don't want to take the extra time during a busy day to explain why that prescription for a narcotic isn't a good idea. Some of us also use the promise of prescription narcotics to persuade patients to keep their medical appointments, or to take their other medications.

It's important to take patients' pain seriously. Musculoskeletal disorders like back pain are among the top causes of disability in the U.S. But there are other ways to treat pain. Physical and chiropractic therapy, massage, and acupuncture aren't used enough, in part because they may be more expensive (at least until you take into account the unintended medical, legal, and social costs of overprescribing narcotics); patients also don't want to have to wait for a referral or repeated treatments to get pain relief. Perhaps the best way to address pain is a team approach, in which primary-care doctors, pain specialists, physical therapists, chiropractors, acupuncturists, massage therapists, mental-health providers and addiction specialists work together to find the best solution for a shared patient. Health insurers are part of the problem here: they reliably cover prescription narcotics, but not necessarily these other medical tools. (Foster told me that his company "believes it is critical for physicians and patients to have multiple treatment options, including opioid analgesics," to help patients with acute and chronic pain get better and go back to work.)

Under the F.D.A. proposal, slated to take effect as early as next year, doctors would no longer be allowed to write six-month prescriptions for products like Vicodin that combine hydrocodone with over-the-counter painkillers. Instead, doctors could prescribe only a ninety-day supply of hydrocodone without a return visit. Earlier this year, the F.D.A. also recommended that prescription narcotics be made more abuse-resistant; it is blocking the approval of generic OxyContin that doesn't use this technology. And it is requiring that extended-release and long-acting forms of prescription narcotics be labeled to indicate that these medications are for "around-the-clock" severe pain, and that alternative treatments should be considered first.

Those actions come as states and other local jurisdictions also crack down on the overprescribing of narcotics. Florida, for instance, passed a law making it illegal for anyone other than a doctor in good standing to run a pain clinic, and limiting how much narcotic medication can be dispensed at one time. And many states are also now requiring physicians to police their patients by looking them up in online registries to ensure that they aren't "doctor-shopping" to get narcotics from multiple sources.

I sometimes think of the patient who asked me for OxyContin early in my career; I continued to prescribe the drug. But I also referred him for physical therapy and helped him get bariatric surgery to lose the weight that was putting extra stress on his spine and joints. Unfortunately, even after he lost about a hundred pounds, he wasn't able to stop using narcotics or go back to work.

That wasn't the last time I faced difficult questions about whether and how to prescribe narcotics. Recently, I was tapering one patient's narcotics, then discontinued them completely after three urine tests came up negative for oxycodone but positive for cocaine—suggesting he was selling the former to buy the latter. He warned me that he would give me "one more chance." Since then, he has failed to show up for every appointment, and has lobbied to switch to another provider. I'm torn, because this patient has H.I.V. If he

doesn't take his medications, his H.I.V. won't be controlled, and this will put his health at risk and make him more infectious to others. Again, the perpetual question: How do I do the least harm?

Due to an editing error, an earlier version of this article incorrectly stated that the American Academy of Pain Management published guidelines advocating for doctors to expand their use of prescription narcotics to relieve pain.

Celine Gounder is a physician, public-health specialist, and medical journalist. [Read more »](#)

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Overview

Pain is associated with a wide range of injury and disease, and is sometimes the disease itself. Some conditions may have pain and associated symptoms arising from a discrete cause, such as postoperative pain or pain associated with a malignancy, or may be conditions in which pain constitutes the primary problem, such as neuropathic pains or headaches.

Millions suffer from acute or chronic pain every year and the effects of pain exact a tremendous cost on our country in health care costs, rehabilitation and lost worker productivity, as well as the emotional and financial burden it places on patients and their families. The costs of unrelieved pain can result in longer hospital stays, increased rates of rehospitalization, increased outpatient visits, and decreased ability to function fully leading to lost income and insurance coverage. As such, patient's unrelieved chronic pain problems often result in an inability to work and maintain health insurance. According to a recent Institute of Medicine Report: *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*, pain is a significant public health problem that costs society at least \$560-\$635 billion annually, an amount equal to about \$2,000.00 for everyone living in the U.S. This includes the total incremental cost of health care due to pain from ranging between \$261 to \$300 billion and \$297-\$336 billion due to lost productivity (based on days of work missed, hours of work lost, and lower wages).

Much more needs to be done to meet these challenges and to increase public awareness of them.

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What is Chronic Pain?

While acute pain is a normal sensation triggered in the nervous system to alert you to possible injury and the need to take care of yourself, chronic pain is different. Chronic pain persists. Pain signals keep firing in the nervous system for weeks, months, even years. There may have been an initial mishap -- sprained back, serious infection, or there may be an ongoing cause of pain -- arthritis, cancer, ear infection, but some people suffer chronic pain in the absence of any past injury or evidence of body damage. Many chronic pain conditions affect older adults. Common chronic pain complaints include headache, low back pain, cancer pain, arthritis pain, neurogenic pain (pain resulting from damage to the peripheral nerves or to the central nervous system itself).

A recent market research report indicates that more than 1.5 billion people worldwide suffer from chronic pain and that approximately 3- 4.5% of the global population suffers from neuropathic pain, with incidence rate increasing in complementary to age. (1)

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Incidence of Pain, as Compared to Major Conditions

Pain affects more Americans than diabetes, heart disease and cancer combined. The chart below depicts the number of chronic pain sufferers compared to other major health conditions.

Condition	Number of Sufferers	Source
Chronic Pain	100 million Americans	Institute of Medicine of The National Academies (2)
Diabetes	25.8 million Americans (diagnosed and estimated undiagnosed)	American Diabetes Association (3)
Coronary Heart Disease (heart attack and chest pain)	16.3 million Americans	American Heart Association (4)
Stroke	7.0 million Americans	
Cancer	11.9 million Americans	American Cancer Society (5)

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The Burden of Pain on Every Day Life

- The total annual incremental cost of health care due to pain ranges from \$560 billion to \$635 billion (in 2010 dollars) in the United States, which combines the medical costs of pain care and the economic costs related to disability days and lost wages and productivity. ([2](#))
- More than half of all hospitalized patients experienced pain in the last days of their lives and although therapies are present to alleviate most pain for those dying of cancer, research shows that 50-75% of patients die in moderate to severe pain. ([7](#))
- An estimated 20% of American adults (42 million people) report that pain or physical discomfort disrupts their sleep a few nights a week or more. ([8](#))

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Commonly-Reported Pain Conditions

- When asked about four common types of pain, respondents of a National Institute of Health Statistics survey indicated that low back pain was the most common (27%), followed by severe headache or migraine pain (15%), neck pain (15%) and facial ache or pain (4%). ([6](#))
- Back pain is the leading cause of disability in Americans under 45 years old. More than 26 million Americans between the ages of 20-64 experience frequent back pain. ([6](#))
- Adults with low back pain are often in worse physical and mental health than people who do not have low back pain: 28% of adults with low back pain report limited activity due to a chronic condition, as compared to 10% of adults who do not have low back pain. Also, adults reporting low back pain were three times as likely to be in fair or poor health and more than four times as likely to experience serious psychological distress as people without low back pain. ([6](#))

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Highlights from the National Center for Health Statistics Report: Health, United States, 2006, Special Feature on Pain ([6](#))

- More than one-quarter of Americans (26%) age 20 years and over - or, an estimated 76.5 million Americans - report that they have had a problem with pain of any sort that persisted for more than 24 hours in duration. [NOTE: this number does not account for acute pain].
- Adults age 45-64 years were the most likely to report pain lasting more than 24 hours (30%). Twenty-five percent (25%) of young adults age 20-44 reported pain, and adults age 65 and over were the least likely to report pain (21%).

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Key Findings from the 2006 Voices of Chronic Pain Survey ([9](#))

A 2006 survey conducted for the American Pain Foundation and sponsored by Endo Pharmaceuticals evaluated the impact that chronic pain had on 303 chronic pain sufferers who sought care from their physician and were currently using an opioid to treat their pain.

Control Over Chronic Pain

- More than half of respondents (51%) felt they had little or no control over their pain.
- Six out of ten patients (60%) said they experience breakthrough pain one or more times daily, severely impacting their quality of life and overall well-being.

Impact on Quality of Life

- Almost two-thirds (59%) reported an impact on their overall enjoyment of life.
- More than three quarters of patients (77%) reported feeling depressed.
- 70% said they have trouble concentrating.
- 74% said their energy level is impacted by their pain.
- 86% reported an inability to sleep well.

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Lost Productive Time and Cost Due to Common Pain Conditions in the United States Workforce ([10](#))

Data from the American Productivity Audit, a computer assisted telephone survey of health and work, of 28,902 working adults between August, 2001 and July 2002, was used to estimate lost productive time due to headache, arthritis, back pain, and other musculoskeletal conditions expressed in hours per worker per week and calculated in US dollars.

- Over half (52.7%) of the workforce surveyed reported having headache, back pain, arthritis, or other musculoskeletal pain in the past two weeks, and 12.7% of all workforce lost productive time in a two-week period due to pain.
- Headache (5.4%) was the most common pain condition prompting lost productive time: followed by back pain (3.2%), arthritis pain (2%) and other musculoskeletal pain (2%).
- Overall, workers lost an average of 4.6 hours per week of productive time due to a pain condition.
- Other musculoskeletal pain (5.5 hours/week) and arthritis or back pain (5.2 hours/week) produced the largest amounts of lost productive time.
- Headache produced, on average, 3.5 hours of lost productive time per week.
- Age did not seem to attenuate the findings.
- Lost productive time from common painful conditions was estimated to be \$61.2 billion per year, while 76.6% of lost productive time was explained by reduced work performance, not absenteeism.

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America Speaks: Pain in America ([11](#))

2003 survey conducted by Peter D. Hart Research Associates as a nationwide survey for Research! America. The purpose of this study was to assess the view of Americans about pain in America. The survey's objectives included gauging Americans' perceptions of how pain sufferers and the medical community deal with the problems of chronic pain.

Dealing with Pain

- Among the major adjustments that chronic pain sufferers have made are such serious steps as taking disability leave from work (20%), changing jobs altogether (17%), getting help with activities of daily living (13%) and moving to a home that is easier to manage (13%).

A Visit to the Doctor

- Most pain sufferers (63%) have seen their family doctor for help.
- Forty percent made an appointment with a specialist, such as an orthopedist.
- Twenty-five percent have visited a chiropractor or a doctor that specializes in pain management (15%).
- While 43% of pain sufferers have been to only one type of doctor for their pain, a large proportion (38%) have consulted more than one practitioner in the medical community.
- Treatments for pain have yielded mixed results. Although 58% of those who took prescription medication say that doing so was very fairly effective for their pain, only 41% of those who took over-the-counter

The Pain Gap

- Seven in ten Americans feel that pain research and management should be one of the medical community's top few priorities (16%) or a high priority (55%)
- Almost six in 10 adults (57%) say they would be willing to pay one dollar more per week in taxes to increase federal funding for the scientific research into the causes and treatment of pain.

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Prescription Drug Abuse Facts from the Office of National Drug Control Policy (ONDCP)

- Prescription drugs are the second-most abused category of drugs in the United States, following marijuana.[\(12\)](#).
- Among 12th graders, pharmaceutical drugs used non-medically are six of the ten most-used substances.[\(13\)](#)

- From 1998 to 2008, the proportion of all substance abuse treatment admissions age 12 or older who reported any pain reliever abuse increased more than fourfold.[\(14\)](#)
- Prescription painkillers are considered a major contributor to the total number of drug deaths. In 2007, for example, nearly 28,000 Americans died from unintentional drug poisoning, and of these, nearly 12,000 involved prescription pain relievers.[\(15\)](#)
- Nearly one-third (29 percent) of people age 12 or older who used illicit drugs for the first time in the past year began by using prescription drugs non-medically.[\(12\)](#)
- According to a 2008 Department of Defense survey, about one in nine active-duty service members (11 percent) reported past-month prescription drug misuse.[\(16\)](#)
- The estimated number of emergency department visits linked to non-medical use of prescription pain relievers nearly doubled between 2004 and 2009.[\(17\)](#)
- In 2009, the number of first-time, non-medical users of psychotherapeutics (prescription opioid pain relievers, tranquilizers, sedatives, and stimulants) was about the same as the number of first-time marijuana users.[\(12\)](#)
- Approximately two million adults age 50 and older (2.1 percent of adults in that age range) used prescription-type drugs non-medically in the past year.[\(18\)](#)
- Substance abuse treatment admissions for individuals age 50 or older nearly doubled from 1992 to 2008, climbing from 6.6 percent of all admissions to 12.2 percent. The percentage of primary admissions for prescription drug abuse among older individuals increased from 0.7 percent to 3.5 percent over the same time period.[\(19\)](#)

[To view Prescription Drug Abuse Facts at ONDCP...](#)

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Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education and Research (Institute of Medicine Report)

- In 2011, at least 100 million adult Americans have common chronic pain conditions, a conservative estimate because it does not include acute pain or children. [\(20\)](#)
- Pain is a significant public health problem that costs society at least \$560-\$635 billion annually (an amount equal to about \$2,000.00 for everyone living in the U.S.). [\(20\)](#)
- In 2008 the cost to federal and state governments of medical expenditures for pain was \$99 billion. [\(20\)](#)
- Recent Center for Disease Control and Prevention (CDC) and National Center for Health Statistics (NCHS) data suggest substantial rates of pain from the various causes and that most people in chronic pain have multiple sites of pain. For U.S. adults reporting pain, causes include: severe headache or migraine (16.1%), low back pain (28.1%), neck pain (15.1%), knee pain (19.5%), shoulder pain (9.0%), finger pain (7.6%), and hip pain (7.1%). [\(21\)](#)
- According to the National Health and Nutrition Examination Survey (NHANES) data, 17 percent of U.S. children, aged 4-18, experience frequent or severe headaches, including migraine, over the course of a year. Before puberty, boys and girls have headaches at approximately the same rate, but after 12, the rate of recurrent and severe headaches rises among girls. [\(22\)](#)

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Summary Health Statistics for U.S. Adults: National Health Interview Survey, 2009
Department of Health and Human Services Report [\(23\)](#)

- Women were more likely to experience pain (in the form of migraines, neck pain, lower back pain, or face or jaw pain) than men. Women were twice as likely to experience migraines or severe headaches, or pain in the face or jaw, than men.
- The percentage of person experiencing migraines or severe headaches was inversely related to age. Twenty percent adults aged 18-44 years experienced a migraine or severe headache in the 3 months prior to the interview compared with 15% of adults aged 45-64, 7% of adults aged 65-74, and 6% of adults aged 75 and over.
- Adults aged 18-44 years were less likely to have experienced pain in the lower back during the 3 months prior to the interview compared with older adults.
- When results are considered by single race without regard to ethnicity, Asian adults were less likely to have pain in the lower back compared to white adults, black adults, and American Indian or Alaska Native (AIAN) adults.
- Adults with a bachelor's degree or higher were less likely to have migraine headaches, neck pain, lower back pain, or pain in the face or jaw, compared to adults who did not graduate from high school.
- Adults in poor and near poor families were more likely to experience migraine headaches, neck pain, lower back pain, or pain in the face or jaw in the 3 months prior to the interview than were adults in families that were not poor.
- Among adults under age 65, those covered by Medicaid were more likely to have migraine headaches, neck pain, lower back pain, or pain in the face or jaw than those with private insurance or those who were uninsured. Among adults aged 65 and over, those covered by Medicaid and Medicare were more likely to have migraine headaches, neck pain, lower back pain, or pain in the face or jaw than those with private insurance or only Medicare health care coverage.

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CDC Analysis: Vital Signs: Overdoses of Prescription Opioid Pain Relievers --- United States, 1999--2008 [\(24\)](#)

Overdose deaths involving opioid pain relievers (OPR), also known as opioid analgesics, have increased and now exceed deaths involving heroin and cocaine combined.

- Prescription painkiller overdoses killed nearly 15,000 people in the US in 2008. This is more than 3 times the 4,000 people killed by these drugs in 1999.
- In 2010, about 12 million Americans (age 12 or older) reported nonmedical use of prescription painkillers in the past year.
- One in 20 people in the United States, ages 12 and older, used prescription painkillers nonmedically (without a prescription or just for the "high" they cause) in 2010.
- Nearly half a million emergency department visits in 2009 were due to people misusing or abusing prescription painkillers.
- Sales of OPR quadrupled between 1999 and 2010. Enough OPR were prescribed last year to medicate every American adult with a standard pain treatment dose of 5 mg of hydrocodone (Vicodin and others) taken every 4 hours for a month.
- Nonmedical use of prescription painkillers costs health insurers up to \$72.5 billion annually in direct health care costs.

Certain groups are more likely to abuse or overdose on prescription painkillers:

- Many more men than women die of overdoses from prescription painkillers.
- Middle-aged adults have the highest prescription painkiller overdose rates.
- People in rural counties are about two times as likely to overdose on prescription painkillers as people in big cities.
- Whites and American Indian or Alaska Natives are more likely to overdose on prescription painkillers.
- About 1 in 10 American Indian or Alaska Natives age 12 or older used prescription painkillers for nonmedical reasons in the past year, compared to 1 in 20 whites and 1 in 30 blacks.

Some states have a bigger problem with prescription painkillers than others:

- Prescription painkiller sales per person were more than 3 times higher in Florida (which has the highest rate) than in Illinois (which has the lowest rate).
- In 2008/2009, nonmedical use of painkillers in the past year ranged from 1 in 12 people (age 12 or older) in Oklahoma to 1 in 30 in Nebraska.
- States with higher sales per person and more nonmedical use of prescription painkillers tend to have more deaths from drug overdoses.

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HEADLINE: A Pain-Drug Champion Has Second Thoughts

BYLINE: By Thomas Catan and Evan Perez

BODY:

It has been his life's work. Now, Russell Portenoy appears to be having second thoughts.

Two decades ago, the prominent New York pain-care specialist drove a movement to help people with chronic pain. He campaigned to rehabilitate a group of painkillers derived from the opium poppy that were long shunned by physicians because of their addictiveness.

Dr. Portenoy's message was wildly successful. Today, drugs containing opioids like Vicodin, OxyContin and Percocet are among the most widely prescribed pharmaceuticals in America.

Opioids are also behind the country's deadliest drug epidemic. More than 16,500 people die of overdoses annually, more than all illegal drugs combined.

Now, Dr. Portenoy and other pain doctors who promoted the drugs say they erred by overstating the drugs' benefits and glossing over risks. "Did I teach about pain management, specifically about opioid therapy, in a way that reflects misinformation? Well, against the standards of 2012, I guess I did," Dr. Portenoy said in an interview with The Wall Street Journal. "We didn't know then what we know now."

Recent research suggests a significantly higher risk of addiction than previously thought, and questions whether opioids are effective against long-term chronic pain.

The change of heart among former champions of opioid use has happened quietly, largely beyond the notice of many doctors. New York psychiatrist Joseph Carmody said he was "shocked" after attending a recent lecture outlining the latest findings on opioid risk.

"It goes in the face of everything you've learned," he said. "You saw other doctors come around to it and saying, 'Oh my God, what are we doing?'"

Because doctors feared they were dangerous and addictive, opioids were long reserved mainly for cancer patients. But Dr. Portenoy argued that they could be also safely be taken for months or years by people suffering from chronic pain. Among the assertions he and his followers made in the 1990s: Less than 1% of opioid users became addicted, the drugs were easy to discontinue and overdoses were extremely rare in pain patients.

Many of those experts now say those claims were weren't based on sound scientific evidence. "I gave innumerable lectures in the late 1980s and '90s about addiction that weren't true," Dr. Portenoy said in a 2010 videotaped interview with a fellow doctor. The Journal reviewed the conversation, much of which is previously unpublished.

In it, Dr. Portenoy said it was "quite scary" to think how the growth in opioid prescribing driven by people like him had contributed to soaring rates of addiction and overdose deaths. "Clearly, if I had an inkling of what I know now then, I wouldn't have spoken in the way that I spoke. It was clearly the wrong thing to do," Dr. Portenoy said in the recording.

Speaking to the Journal in September, Dr. Portenoy tempered that statement with cautions about overturning what he sees as the positive change he achieved. He cited his 82-year-old mother, who has taken hydrocodone to control arthritis for 15 years. "If you insist on regulation, then you're consigning my mother and many millions of people like my mother to live in chronic pain," he said.

Virtually no one wants to return to a time when doctors were reluctant to use opioids even for cancer patients. All sides also agree that there is a group of people who do well on opioids long-term, taming their pain while avoiding addiction or excessive sedation, although there is no research on how large this group is or how to identify them before they begin a treatment. There is also widespread agreement that they can be used, with caution, for acute pain, such as after an operation.

But some specialists now question whether the drugs should be prescribed so freely for months or years to people with chronic pain that isn't related to cancer, as Dr. Portenoy proposed 25 years ago. "People lost sight of the fact that these are dangerous drugs that are highly addictive," said Jane Ballantyne, a pain specialist at the University of Washington. She once agreed with Dr. Portenoy and proponents of broad opioid use but now believes they need to be used more selectively.

Opium-derived painkillers have been around for thousands of years. Early in the 20th century, heroin was sold as a cough suppressant. Heroin addiction in the U.S. skyrocketed. Congress banned the drug in 1924 and doctors became deeply wary about using opioids.

Dr. Portenoy set out to change that. As a young doctor at Memorial Sloan-Kettering hospital in New York, he noticed that opioids were effective in cancer patients with terrible pain.

In 1986, at the age of 31, he co-wrote a seminal paper arguing that opioids could also be used in the much larger group of people without cancer who suffered chronic pain. The paper was based on just 38 cases and included several caveats. Nevertheless, it opened the door to much broader prescribing of the drugs for more common complaints such as nerve or back pain.

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Charming and articulate, he became a sought-after public speaker. He argued that opioids are a "gift from nature" that were being forsaken because of "opiophobia" among doctors. "We had to destigmatize these drugs," said Dr. Portenoy.

He rose to chairman of pain medicine and palliative care at Beth Israel Medical Center in New York. His small office is studded with awards and evidence of his offbeat sense of humor. He prominently displays a magazine mock-up that jokingly dubs him "The King of Pain."

At medical conferences, his confident, knowing manner helped smooth the way for his message. Before an audience of government regulators, he once joked that he might tell a patient at low risk of abuse: "Here, [have] six months of drugs. See you later," he said, according to a Food and Drug Administration transcript. Amid laughter, he added, "It's just hyperbole. I don't actually do that."

Steven Passik, a psychologist who once worked closely with Dr. Portenoy and describes him as his mentor, says their message wasn't based on scientific evidence so much as a zeal to improve patients' lives. "It had all the makings of a religious movement at the time," he says. "It had that kind of a spirit to it."

Drug companies took notice. In 1996, Purdue Pharma LP released OxyContin, a form of oxycodone in a patented, time-release form, and rivals followed suit. Today, sales of opioid painkillers total more than \$9 billion a year, according to IMS Health, which tracks sales for drug companies.

In 2007, Purdue Pharma and three executives pleaded guilty to "misbranding" of the drug as less addictive and less subject to abuse than other pain medicines and paid \$635 million in fines.

Purdue Pharma says it has worked to discourage abuse of its drugs, adding that OxyContin is safe and effective when used properly.

In the late 1990s, groups such as the American Pain Foundation, of which Dr. Portenoy was a director, urged tackling what they called an epidemic of untreated pain. The American Pain Society, of which he was president, campaigned to make pain what it called the "fifth vital sign" that doctors should monitor, alongside blood pressure, temperature, heartbeat and breathing.

Dr. Portenoy helped write a landmark 1996 consensus statement by two professional pain societies that said there was little risk of addiction or overdose among pain patients. In lectures he cited the statistic that less than 1% of opioid users became addicted.

Today, even proponents of opioid use say that figure was wrong. "It's obviously crazy to think that only 1% of the population is at risk for opioid addiction," said Lynn Webster, president-elect of the American Academy of Pain Medicine, one of the publishers of the 1996 statement. "It's just not true."

The figure came from a single-paragraph report in the New England Journal of Medicine in 1980 describing hospitalized patients briefly given opioids. Dr. Portenoy now says he shouldn't have used the information in lectures because it wasn't relevant for patients with chronic noncancer pain.

For such a widely used therapy, there is relatively little scientific evidence that opioid drugs are safe and effective for long-term use. "Data about the effectiveness of opioids does not exist," Dr. Portenoy said in his recent Journal interview. To get a painkiller approved, companies must prove that it is better at reducing pain than a sugar pill during short trials often lasting less than 12 weeks.

"Do they work for five years, 10 years, 20 years?" Dr. Portenoy said in the Journal interview. "We're at the level of anecdote." Even so, he says, the drugs can still benefit carefully selected patients.

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Dr. Portenoy's ideas about opioids reached into mainstream medicine and attracted outspoken advocates. In a 1998 talk in Houston, Alan Spanos, a South Carolina pain specialist, said patients with chronic noncancer pain could be trusted to decide themselves how many painkillers to take without risk of overdose. According to a recording, Dr. Spanos said he understood that a patient would simply "go to sleep" before stopping breathing. While asleep, he said, the patient "can't take a dangerous dose. It sounds scary, but as far as I know, nobody anywhere is getting burned by doing it this way."

Dr. Spanos declined to say whether he still agreed with his previous statements. He said opioids can be helpful and safe with proper use.

One of Dr. Portenoy's chief complaints was that doctors were reluctant to prescribe opioids because they feared scrutiny by regulators or law enforcement. In the second half of the 1990s, he and his followers campaigned successfully for policies to change that.

In 1998, the Federation of State Medical Boards released a recommended policy reassuring doctors that they wouldn't face regulatory action for prescribing even large amounts of narcotics, as long as it was in the course of medical treatment. In 2004 the group called on state medical boards to make undertreatment of pain punishable for the first time.

That policy was drawn up with the help of several people with links to opioid makers, including David Haddox, a senior Purdue Pharma executive then and now. The federation said it received nearly \$2 million from opioid makers since 1997. The federation says it derives the majority of its funding from administering medical licensing exams, credential verification, and data services.

A federation-published book outlining the opioid policy was funded by opioid makers including Purdue Pharma, Endo Health Solutions Inc. and others, with proceeds totaling \$280,000 going to the federation. Endo declined to comment.

Purdue Pharma said, "Dr. Haddox was recruited by the FSMB, so he did not have undue or inappropriate influence" on the federation's output. Purdue declined to make Dr. Haddox available to comment.

The federation said it didn't believe its model policy contributed to increased prescriptions and said drug makers didn't influence its guidelines.

In 2001, the Joint Commission, which accredits U.S. hospitals, issued new standards telling hospitals to regularly ask patients about pain and to make treating it a priority. The now-familiar pain scale was introduced in many hospitals, with patients being asked to rate their pain from one to 10 and circle a smiling or frowning face.

The Joint Commission published a guide sponsored by Purdue Pharma. "Some clinicians have inaccurate and exaggerated concerns" about addiction, tolerance and risk of death, the guide said. "This attitude prevails despite the fact there is no evidence that addiction is a significant issue when persons are given opioids for pain control."

Purdue said the booklet emerged from a process that "represented the consensus of a broad range of interested stakeholders." Drug makers regularly pay for educational materials for physicians as an element of their marketing.

The Joint Commission said its standards didn't encourage physicians and hospitals to increase prescriptions. "I think that's a very distorted and not helpful explanation of what's going on," said Ana McKee, the Joint Commission's chief medical officer.

Over his career, Dr. Portenoy has disclosed relationships with more than a dozen companies, most of which produce opioid painkillers. "My viewpoint is that I can have those relationships, they would benefit my educational mission, they benefit in my research mission, and to some extent, they can benefit my own pocketbook, without

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producing in me any tendency to engage in undue influence or misinformation," he said.

Dr. Portenoy and Beth Israel declined to provide details of their funding by drug companies. A 2007 fundraising prospectus from Dr. Portenoy's program shows that his program received millions of dollars over the preceding decade in funding from opioid makers including Endo, Abbott Laboratories, Cephalon, Purdue Pharma and Johnson & Johnson.

Endo, Abbott, Janssen and Purdue declined to comment. Cephalon's current owner, Teva Pharmaceutical Industries Ltd., didn't immediately have a comment.

In May of this year, the Senate Finance Committee opened an investigation into the financial ties between the pharmaceutical makers and the doctors and groups that advocated broader use of opioids. It asked opioid makers to disclose how much they had paid Dr. Portenoy, his program and several organizations he was involved with.

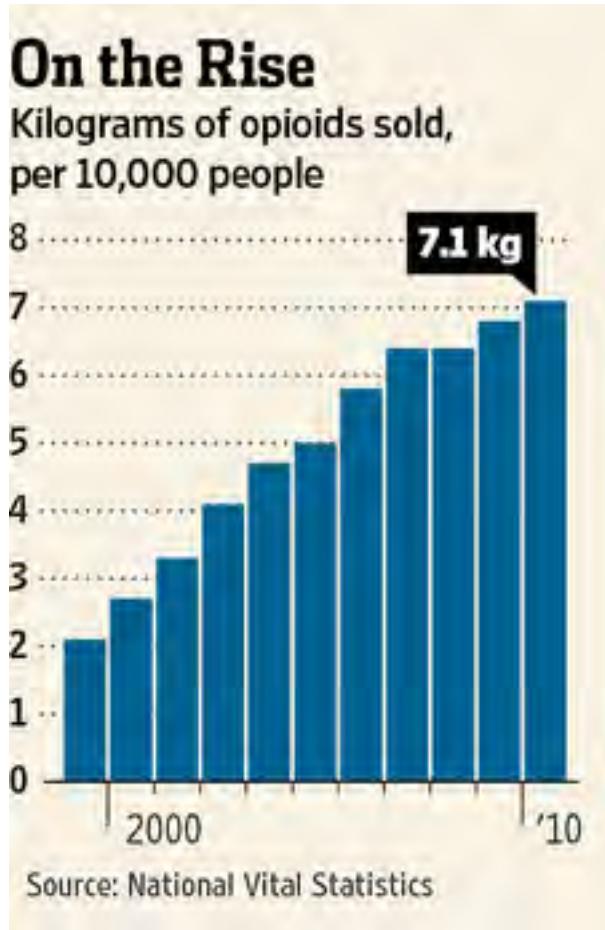
After spending most of his professional life advocating greater use of the drugs, Dr. Portenoy said there is still little research to show whether patients who embark on long-term opioid therapy will ever be able to stop.

Earlier this year, he said, he asked his mother whether she would stop taking her hydrocodone as part of a scientific study. She said no.

"How difficult is it for her to get off these drugs?" Dr. Portenoy asked. "You have no idea and neither do I, because no one knows."

Devlin Barrett contributed to this article.

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EXHIBIT 22



June 8, 2012

The Honorable Max Baucus
United States Senate
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The Honorable Charles Grassley
United States Senate
135 Hart Senate Office Building
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Dear Senators Baucus and Grassley:

The Federation of State Medical Boards (FSMB) is pleased to respond to your letter of May 8, 2012. The FSMB agrees with the Senate Finance Committee that the abuse and misuse of opioids is a serious national problem. We remain committed to raising awareness of the problem among physicians and the public and working to reduce the risk of addiction, abuse and diversion of opioids, while ensuring that patients who suffer from pain have access to needed treatments. In this regard, we respectfully urge you to review the FSMB's Model Policies and *Responsible Opioid Prescribing* publication, described within this letter.

The FSMB is actively addressing the important issues surrounding opioids on multiple levels. These efforts include collaborations with a variety of federal agencies and leading health care organizations. The American Medical Association (AMA), for example, has adopted formal policy specifying that "...states should examine their pain policies and seek to improve them, based on the Federation of State Medical Boards Model Policy..."¹

Gil Kerlikowske, Director of the Office of National Drug Control Policy (ONDCP), said during a recent speech at the 2012 FSMB Annual Conference: "There is a real gap in the amount of education and training that is provided around pain management, addiction, treatment, tolerance and dependence. We know that's an important issue. I could not be more pleased, frankly, and I could not be more proud of the work that you all have done in this area...I was just given the latest edition of the *Clinician's Guide for Responsible Opioid Prescribing* by Dr. Fishman...The second edition of this is just a wonderful, wonderful step in the right direction of putting something that is so well written in the hands of very busy professionals that need that information."²

Background

The problem of prescription drug abuse and related deaths has grown at an alarming pace in the United States. According to the Centers for Disease Control and Prevention (CDC), deaths from prescription painkillers more than tripled between 1999 and 2008, and nearly half a million emergency department visits in 2009 were due to people misusing or abusing prescription painkillers.³

At the same time, the nation faces a serious and related problem: Millions of Americans suffer from debilitating pain – a condition that, for some, can be relieved through the use of opioids.⁴ Studies have concluded that both acute pain and chronic pain are often under-treated in the United States, creating serious repercussions that include the loss of productivity and quality of life.

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Physicians must constantly weigh these dual realities as they consider treatment options for their patients in pain. Similarly, the nation's state boards of medicine must also weigh the risks and advantages of opioid prescribing as they establish the rules and regulations under which medicine is practiced in their jurisdictions – balancing the pressing need for patient safety with the equally important need to ensure that patients have access to treatment.

This dual responsibility – ensuring public safety and access to appropriate medical treatment – is the fundamental mission and purpose of the nation's system of state medical boards. Each of the 50 states, the District of Columbia and the U.S. territories has a medical practice act that delegates to a state medical board the authority to protect the public from the unprofessional, improper, incompetent, unlawful, or fraudulent practice of medicine. With this authority, boards typically establish parameters for the safe practice of medicine, including the prescribing of medicines such as opioid analgesics.

About the Federation of State Medical Boards

Established in 1912, the Federation of State Medical Boards is the national non-profit organization that represents the 70 medical and osteopathic boards of the United States and its territories. The FSMB promotes excellence in medical practice, licensure, and regulation as the national resource and voice on behalf of the boards as they protect the public and ensure access to medical treatment. To assist its efforts, the FSMB launched the Federation of State Medical Boards Research and Education Foundation (FSMB Foundation) in 1980. The FSMB Foundation is a supporting non-profit organization to the FSMB that expands knowledge and awareness of issues of importance to state medical boards, the public and the medical profession.

The FSMB enhances the role of state medical boards in a dynamic health care environment by leading, anticipating and responding to trends in medical regulation; serving as an informational and educational resource for the boards; and assisting the boards in developing and using consistent standards, language, definitions, and tools to regulate the practice of medicine.

The FSMB helps state medical boards adapt and respond as medicine evolves and various new issues emerge that impact the public. In the constantly changing environment of medical practice, the FSMB plays a key role as a thought leader and shaper of policy. In recent years, its work has helped the medical community respond to emerging issues such as outpatient surgery, use of the Internet in medical practice, maintenance of licensure, re-entry to practice, and physician impairment. In addition, the FSMB has been the recipient of multiple license-portability grants, authorized under the Public Health Service Act, and coordinated with the U.S. Department of Health and Human Services Health Resources and Services Administration (HRSA), to develop and expand multi-state cooperation between licensing boards and to create and implement state policies that will also help facilitate telemedicine, and improve access to care.

FSMB Activities Related to Treatment of Pain and the Misuse, Abuse and Diversion of Opioids

Until the mid 1990s, physicians and state medical boards struggled with a lack of consistent policies related to the treatment of pain, which contributed to the dual public health issues of the under-treatment of pain and the improper use of controlled substances in addressing pain. Increased public demand for improvement in the medical management of pain and advances in medical knowledge regarding the use of controlled substances (including opioids), combined with a lack of physician awareness of the laws and regulations governing the prescribing of these substances, led the FSMB to launch a series of initiatives. The FSMB's goal was to provide a policy framework that would bring consistency to differing regulatory processes and to encourage states to clarify their guidelines and laws addressing pain management and appropriate and responsible prescribing.

Since its first major initiative related to pain and opioid prescribing in 1997, the FSMB and its state medical board partners have sought to balance efforts to ensure patient access to appropriate pain care with efforts to reduce the

potential for prescription drug misuse, abuse and diversion. These multi-pronged efforts have included policy-making, educational outreach, and collaboration with key federal and state agencies, physician organizations, foundations, academia, and many other stakeholder groups.

Throughout its work on these issues, the FSMB has sought to raise awareness with physicians and the public of the risks that opioids pose – in addition to their benefits for patients in need – while striving to bolster safeguards for their appropriate use. The FSMB’s policies and educational materials do not advocate for opioid therapy by physicians; rather, they offer a framework to ensure that physicians who choose to prescribe opioids do so responsibly and safely, and remain in compliance with legal regulations regarding their use.

The FSMB has worked vigorously with the physician community to raise awareness of these issues and has worked closely with state and federal policy-making and law enforcement agencies to develop strategies aimed at addressing the misuse, abuse and diversion of all controlled substances.

Model Guidelines for the Use of Controlled Substances for the Treatment of Pain

The FSMB’s efforts began in 1997 with the development of its *Model Guidelines for the Use of Controlled Substances for the Treatment of Pain*. Developed with a grant from the Robert Wood Johnson Foundation, the guidelines were created to address the dual issues of under-treated pain and improper prescribing of controlled substances, providing physicians with best practices to ensure safe and responsible prescribing and public access to appropriate and effective pain relief.

The guidelines represent an extensive effort at achieving consensus on these important topics. They were formulated with input from a diverse group of major stakeholders, ranging from pain and addiction specialists and medical societies to federal law enforcement agencies, many of whom participated in an invitational symposium hosted in March 1998, where they were able to provide formal testimony.

Before the model guidelines were finalized and formally adopted as Federation policy at the FSMB House of Delegates meeting in May 1998, a copy of the draft guidelines were distributed to more than 300 individuals, representing state medical boards, medical professional organizations, other health care regulatory boards, patient advocacy groups, state and federal regulatory agencies, and representatives from pharmacy and nursing regulatory boards for additional review and comment. The result was a set of guidelines that represented consensus from key national stakeholders.

The *Model Guidelines* stressed that all physicians should become knowledgeable about effective methods of pain treatment as well as statutory requirements for prescribing controlled substances. They stipulated that all prescribing must be based on clear documentation of unrelieved pain and in compliance with applicable state and federal law. The *Model Guidelines* set forth state medical boards’ expectations for physicians to incorporate safeguards into their practices to minimize the potential for the abuse and diversion of controlled substances, including thorough examinations; the use of written treatment plans and maintenance of accurate records; the critical importance of discussing both risks and benefits of controlled substances with patients; and the need for periodic review of treatment goals.⁵

Since their adoption, the *Model Guidelines* have been extensively distributed to state medical boards, medical professional organizations, other health care regulatory boards, and patient advocacy groups, as well as state and federal regulatory, law enforcement and other agencies, including the U.S. Department of Health and Human Services Substance Abuse and Mental Health Services Administration (SAMHSA) and U.S. Drug Enforcement Administration (DEA). They have been endorsed or supported by a variety of organizations, including the American Medical Association (AMA) and the National Association of State Controlled Substances Agencies (NASCSA).

In 2004, the *Model Guidelines* were revised and updated at the direction of the FSMB's 70 state member boards, with language intended to ensure they were consistent with emerging medical insights regarding pain management and the use of controlled substances. They were also renamed the *Model Policy for the Use of Controlled Substances for the Treatment of Pain* to better reflect the practical use of the document.⁶

The FSMB subsequently hosted a series of regional educational workshops titled "Promoting Balance and Consistency in the Regulatory Oversight of Pain Care," for members and staff of state medical and pharmacy boards. The objectives of the workshops were to create a regulatory environment that supports accessible and appropriate pain care; to define controlled substances abuse and diversion and the appropriate regulatory responses to these issues; to distinguish between criminality and negligence and acceptable medical practices; and to define key terms and concepts related to pain and addiction. The workshops were accredited by the University of Texas Southwestern Health Science Center.

In March 2012, the FSMB, in collaboration with SAMHSA's Center for Substance Abuse Treatment (CSAT), brought together experts in pain management, addiction medicine, law enforcement, pharmacology, psychiatry, public health, medical regulation and other disciplines to once again review and update the *Model Policy*. The review process will be completed this year, with the goal of an updated and revised policy in 2013.

National Clearinghouse on Internet Prescribing

The FSMB has been a leader in addressing the problem of illegal prescribing through "rogue" Internet pharmacy sites, which operate without appropriate licensing and allow anonymous physicians to prescribe medications based only upon online questionnaires completed by patients never seen by the physician. In 2000, the FSMB launched an initiative creating a clearinghouse for the collection and dissemination of information to state and federal regulatory authorities on the operation of rogue Internet pharmacy sites – leveraging its formal relationship with all state medical boards in the United States and its well established lines of communication with state and federal agencies and the national pharmacist community.

This program gathered valuable information about illegal online activities for state and federal regulatory authorities, identifying more than 1,000 questionable Web sites as a part of its activities. The program received an Award of Excellence from the American Society of Association Executives for its results benefiting the American public. It supplied or assisted with information about 122 illegal prescribing cases on the federal level and 178 cases on the state level. The Clearinghouse was cited in multiple pieces of federal legislation, including: *H.R. 1298/S. 525, Pharmaceutical Market Access and Drug Safety Act of 2009* (March 4, 2009); *S. 3415, Fair Pricing For Prescription Drugs Act* (May 25, 2010); and *S. 319, Pharmaceutical Market Access and Drug Safety Act of 2011* (February 10, 2011). Among their provisions, these federal legislative initiatives called for the Department of Health and Human Services to partner with the FSMB Clearinghouse. Additionally, the FSMB supported a number of federal legislative proposals to address the problem of rogue internet pharmacies by writing endorsement letters and providing testimony at hearings.

Model Policy Guidelines for Opioid Addiction Treatment in the Medical Office

In 2002, the FSMB House of Delegates adopted the *Model Policy Guidelines for Opioid Addiction Treatment in the Medical Office*. These guidelines were intended to directly address the issue of opioid addiction, one of the key components of the FSMB's work related to opioid prescribing.

Developed with substantial funding from SAMHSA, the guidelines encourage state medical boards to adopt consistent standards, promote public health by helping direct opioid-addicted patients to appropriate treatment, and educate physicians and others on new modalities in the treatment of addiction. Following their adoption in 2002, the

FSMB and SAMHSA hosted a series of regional educational programs to help build awareness and visibility of the need for new policies to address opioid addiction treatment.

Responsible Opioid Prescribing: A Physician's Guide

Among the FSMB's educational initiatives has been the development and distribution of a guidebook intended to help physicians recognize the risks of opioids and follow responsible and safe prescribing standards. The first edition of *Responsible Opioid Prescribing: A Physician's Guide* was released in 2007, and later accredited by the University of Wisconsin School Of Medicine and Public Health and designated for *7.25 AMA PRA Category 1 Credits™*. Written by one of the nation's leading experts in pain medicine, Scott M. Fishman, MD, the book offers practical steps for reducing the risk of addiction, abuse and diversion of opioids, and for achieving improved patient outcomes. The book was developed with the assistance of an advisory board, which included a diverse range of physicians, academicians and health-policy experts who reviewed its content.

From its release in 2007 through January 2012, the book has been distributed in each of the 50 states and the District of Columbia. The book has been widely acknowledged and supported in the medical community as an important educational resource for physicians, and has been used extensively by state regulators and others to address the need for safer, more responsible and better-informed opioid prescribing.

The North Carolina Medical Board, for example, has sent a copy of the book to any physician who demonstrated deficits in knowledge of prescribing issues. It has also provided the book at educational seminars given to local physicians, emergency department personnel and county social service workers. The State of Michigan Bureau of Health Professions has made the book available annually, and has distributed more than 40,000 copies to physicians, physician assistants and other prescribers.

In Maine, every practicing physician in the state received a copy. Similarly, in Washington, more than 14,000 copies were distributed to the state's licensed physicians and physician assistants. Virginia distributed 20,000 copies of the book to all of its licensees. In Iowa, physicians seeking renewal of a medical license must complete two hours of accredited training on chronic pain management; the Iowa Board of Medicine provides free copies of the book to help physicians fulfill this requirement. In 2011, the FSMB sent 1,500 copies to the Iowa Board of Medicine, which offered the book free of charge to physicians. Montana received 1,800 copies of the book in 2008 for distribution to all licensed physicians in the state. More than 9,000 copies of the book were sent to Florida for distribution to licensed physicians, and more than 5,000 copies were distributed in West Virginia.

In a letter describing the Virginia Board of Medicine's use of the book to raise awareness of opioid prescribing issues, its executive director stated: "I write on behalf of the Virginia Board of Medicine in support of the Federation's efforts to educate the nation's physicians on the safe prescribing of opioids... From a regulatory board standpoint, education of physicians and other prescribers is first and foremost. Knowing the drugs one is writing, their hazards, and the red flags for abuse, addiction and diversion are critical. The more a prescriber knows, the safer his/her patients will be, and so will the public."⁷

In 2010, Maine Attorney General Janet Mills described the book as "...recommended reading for all primary care doctors and pain specialists." Attorney General Mills also noted: "As a non-physician reading that book, what I found most cogent was the emphasis on measuring progress through documented improvements in life *functions*, if and when prescription opioids are required for treatment of a serious and chronic condition. Documentation of concrete progress in specific areas such as work, sleep and social interaction will improve the patient's life, minimize the risk of addiction and keep your practice within the professional standard of care."⁸

As cited above, Gil Kerlikowske, Director of the ONDCP, has also praised the second edition of the book and the FSMB's efforts to promote responsible opioid prescribing.⁹

In April 2012, recognizing the continuing growth of the nation's prescription drug abuse epidemic, an updated version of the book, now titled *Responsible Opioid Prescribing: A Clinician's Guide*, was published, with new statistics and data on opioid addiction that were not available in 2007. The new edition, funded in part by SAMHSA, is accredited by the University of Nebraska Medical Center and again offers 7.25 AMA PRA Category I Credits™. Copies of the first edition are no longer being distributed; its CME activity expired in March 2012.

The expanded 2012 edition of the book is closely aligned with two important federal initiatives: the U.S. Food and Drug Administration (FDA) proposed Risk Evaluation and Mitigation Strategies (REMS) for Long-Acting/Extended-Release Opioid Class-Wide content guidelines for prescriber education¹⁰ and the ONDCP's action plan to address the national prescription drug abuse epidemic, adopted in 2011.¹¹ Among its recommended strategies, the ONDCP's action-plan calls for a collaborative effort with state medical boards to raise awareness of the safe and appropriate use of opioids to treat pain, while minimizing the risk of addiction and substance abuse, as a part of continuing medical education and instruction in health professional schools. Recommendations in the book are designed to address the key elements of these federal initiatives, including support of prescription drug monitoring programs (PDMPs), more effective disposal methods of unused medications, improved education for healthcare providers and patients, and reducing the prevalence of "pill mills" and doctor shopping through enforcement efforts.

Responsible Opioid Prescribing: A Clinician's Guide reminds physicians that they have vitally important duties when prescribing: to become well versed in the latest guidance on how to evaluate and select patients for whom opioids are appropriate, and to monitor carefully their treatment. It provides a renewed warning to physicians that opioids are potentially dangerous, that the use of opioids for other than legitimate medical purposes poses a threat to the individual and society, and that such medications must be used with great caution. The book is a key supporting resource for the educational efforts of state medical boards as they seek to raise awareness of the risks associated with prescribing opioids.

The Online Prescriber Education Network (OPEN)

In 2006, the FSMB became one of 24 recipients of the Attorney General Consumer and Prescriber Education Grant Program, designed to provide physicians with tools for accessing unbiased sources of information about drugs and to help them recognize improper pharmaceutical industry marketing practices.

As a part of the FSMB's overall efforts to ensure the highest standards of prescribing behavior, the FSMB developed and implemented an internet-based portal, the Online Prescriber Education Network (OPEN). OPEN provides accredited CME courses developed by universities and other educational institutions. Among the nearly 50 CME courses available at the site are modules on clinical practice guidelines for drug therapy, evidence-based medicine, and pharmacologic management of acute pain, as well as modules designed to help physicians recognize improper pharmaceutical marketing practices.

In addition, the portal provides access to relevant state and federal statutes, unbiased databases of information about the safety and efficacy of prescription medicines, and tools and strategies for evidence-based prescribing.

Since its inception in 2006, OPEN has provided guidance to physicians on how to be safer, more responsible prescribers, and how to recognize improper marketing of drugs by pharmaceutical companies. Since 2008, the OPEN modules have been accessed by approximately 10,745 learners with 5,260 completing one or more activity for CME credit.

Policy Brief on Balance, Uniformity and Fairness in Law Enforcement

The FSMB co-produced a policy brief with the Center for Practical Bioethics and the National Association of Attorneys General (NAAG) in 2009, aimed specifically at the issue of prescription drug diversion, titled: "Balance, Uniformity and Fairness: Effective Strategies for Law Enforcement for Investigating and Prosecuting the Diversion of Prescription Pain Medications While Protecting Appropriate Medical Practice."¹²

The brief summarized discussions of the Balanced Pain Policy Initiative Law Enforcement Roundtable, made up of leaders from the law enforcement and health care communities focused on ensuring that patients who need pain medications have access while preventing these drugs from becoming a source of harm and abuse.¹³ The FSMB played a key role as one of the convening organizations, with the goal of helping foster stronger working partnerships between law enforcement and health care on these issues. Among the participants were: Mark Caverly, Chief, Liaison & Policy Section, U.S. Drug Enforcement Administration; Myra Christopher, President and CEO, Center for Practical Bioethics; Adam Clark, PhD, Director of Health Policy, Lance Armstrong Foundation; Drew Edmonson, Attorney General, State of Oklahoma; Cathy Gallagher, Associate Section Chief, Liaison & Policy Section, U.S. Drug Enforcement Administration; Richard Roper, U.S. Attorney, Northern District of Texas; William Sorrell, Attorney General, State of Vermont; Charles Cichon, Executive Director, National Association of Drug Diversion Investigators; Craig Watkins, District Attorney, Dallas County, Texas; and others.

Roundtable participants agreed on six strategies intended to seek balance as law enforcement agencies focus on sources of illegal drug diversion – to ensure that these efforts do not negatively impact appropriate medical practice and patient care. The strategies, ranging from distinguishing between criminal behavior and medical negligence to promoting the use of PDMPs, were publicly distributed in February 2009.

Roundtable participants agreed that the FSMB's *Model Policy for the Use of Controlled Substances for the Treatment of Pain* forms a strong foundation for educating health-care providers about issues related to opioid diversion and that "state boards in all states should learn, study, adopt and promote this Model Policy."¹⁴ Moreover, the brief declared: "the short primer on record keeping and other aspects of pain medicine in Scott Fishman's book, *Responsible Opioid Prescribing: A Physician's Guide*, is another excellent resource for doctors."¹⁵

National Collaboration to Better Utilize Health Information Technology Related to Prescribing

In 2012, the FSMB announced a collaborative effort with the Office of the National Coordinator for Health Information Technology, ONDCP, SAMHSA, major pharmacy chains and other stakeholder organizations to promote the use of health information technology to reduce prescription drug abuse. Under this project, the FSMB will work with partner organizations to improve access to database information on prescribers and dispensers of controlled substances found in PDMPs. The project will put an emphasis on increasing timely access to PDMP data at the point of care, at the point of dispensing, and in hospital emergency departments.¹⁶

Initiatives with Federal Agencies and Other Organizations

An integral component of the FSMB's efforts related to opioid prescribing and the under-treatment of pain is its collaboration with various government agencies and other stakeholder organizations. Among the organizations the FSMB has worked with are SAMHSA's Center for Substance Abuse Treatment, the Drug Enforcement Administration (DEA), the FDA, ONDCP, and the National Institute on Drug Abuse – all of whom are helping the FSMB update and revise its *Model Policy for the Use of Controlled Substances for the Treatment of Pain*.

FSMB leaders continue to meet with their counterparts in federal agencies to assist with the development of national policy, including the ONDCP's new prescription drug abuse plan. Among the FSMB's recent outreach activities:

- In December 2010, FSMB leaders met with Dr. Janet Woodcock, Director, and Douglas Throckmorton, Deputy Director of the FDA's Center for Drug Evaluation and Research (CDER) to discuss REMS, CME, and the FSMB's efforts on behalf of responsible opioid prescribing as they relate to state medical and osteopathic boards.
- In March 2011, the FSMB representatives were invited by U.S. Surgeon General Regina Benjamin, MD, MBA, to participate in the Summit on Prescription Drug Abuse in Youth. Following the conference, the FSMB submitted comments to the U.S. Surgeon General's Office, which sought additional input on ways to reduce prescription drug abuse in the nation's youth population.
- In June 2011, the FSMB participated in the White House Summit on Health Information Technology and Prescription Drug Abuse. The roundtable, hosted by the Office of the Vice President of the United States, ONDCP, Office of the National Coordinator for Health Information Technology, and the Office of Science and Technology Policy, engaged approximately two dozen leaders across the public safety, healthcare, and technology sectors to address a variety of topics, ranging from use of PDMP data at the point of care to facilitate appropriate prescribing to leveraging PDMP data in emergency rooms through health information exchanges. The FSMB is currently serving on the Office of the National Coordinator for Health Information Technology's Law and Policy Work Group for the Enhancing Access to Prescription Drug Monitoring Programs (PDMPs) Project.
- In July 2011, the FSMB CEO met with Thomas Frieden, MD, MPH, Director, Centers for Disease Control and Prevention (CDC) and Administrator of the Agency for Toxic Substances and Disease Registry (ATSDR), in Atlanta, GA. Among items for discussion were opportunities for the CDC and the FSMB to collaborate on opioid prescribing education. Following the meeting with Dr. Frieden, the FSMB's CEO met with other CDC senior leaders to continue the discussion, exploring ways in which the CDC and FSMB can collaborate to address prescription drug abuse, including opportunities available with the promotion of provider and patient education, PDMPs, and identifying state disciplinary trends for opioid prescribing.
- Also in July 2011, the FSMB's senior staff attended a meeting of the FDA Industry Working Group (IWG), which includes the branded and generic manufacturers charged by the FDA to develop REMS for long acting and extended release opioids. As a key component of the REMS, the IWG is required to develop an educational program for prescribers and patients and provide the educational materials either directly or through accredited continuing medical education (CME) providers. In November 2011, the IWG submitted a REMS draft blueprint for prescriber education, to which the FDA requested stakeholder input. The FSMB submitted comments in support of the REMS blueprint.
- In November 2011, FSMB leaders met with ONDCP Director Gil Kerlikowske at the 2011 American Medical Association (AMA) Interim Meeting in New Orleans, LA. ONDCP requested the meeting in order to identify ways in which state medical and osteopathic boards can serve as an education resource to the physician community regarding responsible opioid prescribing. In addition, ONDCP sought to explore mechanisms whereby state boards can be of assistance in monitoring prescribing patterns to identify fraudulent providers and patients who are „doctor shopping.“
- In March 2012, FSMB senior staff served as faculty for a DEA training program, Pharmaceutical Investigations and Prosecution Seminar, in Philadelphia, PA.
- In 2011-2012, the FSMB continued to participate in SAMHSA's Center for Substance Abuse Treatment Open Dialogue Meetings, a forum to discuss the non-therapeutic use of prescription medications, and

strategies to reduce their misuse. Among the participants are experts from the medical community, federal agencies, consumer organizations, and the pharmaceutical industry.

- The FSMB continued to serve as a member of the FDA Opioid Patient Prescriber Pain Treatment Agreement Working Group, assisting with the development of model provider patient agreements for long-term opioid therapy as well as other prescriber resources.
- The FSMB is a sponsor of the DEA's National Prescription Drug Take-Back Day program, promoting the safe disposal of pain medications among state medical and osteopathic boards.

Throughout the last year, the FSMB also maintained an ongoing dialogue and partnership activities regarding prescription drug abuse with a wide variety of other stakeholders, including the National Council of State Boards of Nursing (NCSBN), the National Association of Boards of Pharmacy (NABP), the National Association of State Controlled Substances Agencies (NASCA), the National Council on Patient Information and Education (NCPIE), the Alliance of States with Prescription Drug Monitoring (ASPDM), and the American Pain Society (APS).

Additional Information Regarding the *Responsible Opioid Prescribing* book and the FSMB's Model Policies

As noted earlier, the book *Responsible Opioid Prescribing* educates physicians about FSMB policy on the use of controlled substances for the treatment of pain, seeking to reduce the risk of diversion and abuse of prescription opioids while balancing the need for patient access to these medications. The book distills the principles of FSMB's *Model Policy for the Use of Controlled Substances for the Treatment of Pain*, which were adopted by the FSMB in 2004. The guidelines offer a balanced approach to opioid prescribing, acknowledging the legitimate medical uses of controlled substances for patients in need, while stressing the critical responsibility that physicians have in safeguarding against abuse and diversion.

The first edition of *Responsible Opioid Prescribing* was one of the first books to not only highlight the heightened risks of opioids, but to call upon physicians to measure the efficacy and safety of opioid therapy against tangible and measurable functional outcomes in addition to the subjective feedback of their patients.

The book's title emphasizes the need for prescribers to act responsibly – to educate themselves about the risks of opioids, to focus on their patients' behaviors and risk factors, and to monitor carefully and document the success or failure of treatment to achieve functional outcomes.

The book was recently revised, with a new title (*Responsible Opioid Prescribing: A Clinician's Guide*) and new information about the risks associated with opioids as well as safety and risk management. The new information and additional sections support the original – and still-central – theme of the book, which continues to be that the use of opioids must be grounded in solid risk-management and caution by prescribers.

The FSMB firmly stands behind the integrity of the book, the development of which was overseen by an advisory board of respected medical and policy experts and which presents an unbiased and impartial view of opioid prescribing. All revenue generated from the sale of the FSMB's *Responsible Opioid* guides was dedicated to support the development and distribution of these materials. Funding contributors had no input or influence on its content.

It is important to note that contributions and support for the book have come from non-industry sources, such as the Lance Armstrong Foundation and the Mayday Fund, and that a wide variety of not-for-profit organizations have supported the book's distribution through their independent purchases of it. Examples include SAMHSA, the American Academy of Family Physicians, Kaiser Permanente, the American Cancer Society, the New Jersey

Academy of Family Physicians, the Pennsylvania Medical Society, Vanderbilt University Center for Professional Health and the U.S. Department of Veterans Affairs.

The Model Guidelines for the Use of Controlled Substances for the Treatment of Pain (1998), the Model Policy Guidelines for Opioid Addiction Treatment in the Medical Office (2002), the Model Policy for the Use of Controlled Substances for the Treatment of Pain (2004), and the two editions of Responsible Opioid Prescribing provide guidance for physicians to ensure that a balance is struck between the dual realities of opioid misuse, abuse and diversion and the legitimate medical needs of millions of Americans who suffer from pain. The FSMB believes the appropriate role for the regulatory community is to ensure that, in seeking this balance, physicians are apprised of their responsibility to manage the inherent risks of opioids and to remain in full compliance with laws and regulations governing their use, should they choose to prescribe them. While there can be divergent views within the medical community on the best way forward in this area of medical practice, as in others, we believe the guidelines, policies, and books we have developed, with consensus from stakeholders, provide a prudent framework for patient safety as our understanding of pain management and opioid use continues to evolve.

Turning to the questions in the May 8, 2012 Senate Finance Committee letter, to the best of our knowledge, after reasonable due diligence and good faith efforts and to comply with the information requested, the following is provided in response to the questions contained in that letter.

Question 1:

Provide a detailed account of all payments/transfers received from all organizations that develop, manufacture, produce, market, or promote the use of opioid-based drugs from 1997 to the present. For each payment identified, provide:

- i. Date of payment
- ii. Payment description (CME, royalty, honorarium, research support, etc.)
- iii. Amount of payment
- iv. Year end or year-to-date payment total and cumulative total payments for each organization or individual.
- v. For each year a payment was received, the percentage of funding from organizations identified above relative to total revenue.

Answer 1:

The requested payments/transfers received by the Federation of State Medical Boards (FSMB) and the Federation of State Medical Boards Research and Education Foundation (FSMB Foundation) from 1997 to the present are:

Payer Organization	Date	FSMB Fiscal Year (5/1 – 4/30)**	Payment Description	Amount of Payment	Percent of Total Revenue (Consolidated)
		Total for FY 1997		\$0.00	0.00%
		Total for FY 1998		\$0.00	0.00%
		Total for FY 1999		\$0.00	0.00%

		Total for FY 2000		\$0.00	0.00%
Purdue Pharma	7/14/2000	2001	Purchase of Copies of FSMB Pain Model Guidelines	\$28,324.56	
Pfizer Corp.	8/4/2000	2001	Support for the FSMB National Clearinghouse on Internet Prescribing	\$50,000.00	
Purdue Pharma	9/27/2000	2001	Support for the FSMB National Clearinghouse on Internet Prescribing	\$10,000.00	
		Total for FY 2001		\$88,324.56	1.09%
Purdue Pharma	1/29/2002	2002	Support for the FSMB National Clearinghouse on Internet Prescribing	\$10,000.00	
Pfizer Corp.	2/6/2002	2002	Support for the FSMB National Clearinghouse on Internet Prescribing	\$10,000.00	
		Total for FY 2002		\$20,000.00	0.23%
Purdue Pharma	1/24/2003	2003	Purchase of Copies of FSMB Pain Model Guidelines	\$25,180.50	
Purdue Pharma	3/26/2003	2003	Grant in Support of 2003 FSMB Annual Meeting Session	\$60,000.00	
		Total for FY 2003		\$85,180.50	0.76%
Purdue Pharma	4/27/2004	Total for FY 2004	Grant for Project to Update <i>FSMB Model Guidelines for the Use of Controlled Substances in the Treatment of Pain</i> ; Educate FSMB Member Boards; and Assess Changes in Knowledge and Attitudes of FSMB Member Boards, as Assessed by Surveys (5 Total Payment Installments)	\$87,895.00	0.53%
Purdue Pharma	11/24/2004	2005	Grant for Continued Support of Aforementioned Project	\$112,000.00	

Purdue Pharma	3/31/2005	2005	Grant for Continued Support of Aforementioned Project	\$132,000.00	
		Total for FY 2005		\$244,000.00	1.50%
Purdue Pharma	7/29/2005	2006	Grant for Continued Support of Aforementioned Project	\$132,000.00	
Purdue Pharma	12/13/2005	2006	Grant for Continued Support of Aforementioned Project	\$75,000.00	
		Total for FY 2006		\$207,000.00	1.05%
Endo Pharmaceuticals	6/22/2006	2007	Grant in Support of <i>FSMB Physician Education Initiative on Safe & Effective Prescribing Practices in Pain Management</i>	\$40,000.00	
Purdue Pharma	7/6/2006	2007	Grant in Support of <i>FSMB Physician Education Initiative on Safe & Effective Prescribing Practices in Pain Management</i>	\$50,000.00	
Abbott Laboratories	8/16/2006	2007	Support of <i>FSMB Physician Education Initiative on Safe & Effective Prescribing Practices in Pain Management</i>	\$30,000.00	
Cephalon	9/5/2006	2007	Donation	\$30,000.00	
		Total for FY 2007		\$150,000.00	0.75%
Alpharma	8/28/2007	2008	Grant to Support the Distribution of <i>Responsible Opioid Prescribing to State Medical Boards (SMBs)</i>	\$100,000.00	
Endo Pharmaceuticals	9/11/2007	2008	Grant to Support the Distribution of <i>Responsible Opioid Prescribing to SMBs</i>	\$100,000.00	
Cephalon	9/11/2007	2008	Grant to Support the Distribution of <i>Responsible Opioid Prescribing to SMBs</i>	\$100,000.00	
Purdue Pharma	11/8/2007	2008	Grant to Support the Distribution of <i>Responsible Opioid Prescribing to SMBs</i>	\$100,000.00	

		Total for FY 2008		\$400,000.00	2.10%
King Pharmaceuticals	6/17/2008	2009	Grant to Support the Distribution of <i>Responsible Opioid Prescribing</i> to SMBs	\$100,000.00	
Endo Pharmaceuticals	12/4/2008	2009	Grant to Support the Distribution of <i>Responsible Opioid Prescribing</i> to SMBs	\$100,000.00	
Alpharma	1/15/2009	2009	Purchase of 20 Copies of <i>Responsible Opioid Prescribing</i>	\$238.23	
		Total for FY 2009		\$200,238.23	1.18%
King Pharmaceuticals	12/15/2009	Total for FY 2010	Support for the Distribution of <i>Responsible Opioid Prescribing</i> to SMBs	\$75,000.00	0.32%
Mallinckrodt* (*a Covidien Company)	8/18/2010	2011	Grant to Support the Distribution of <i>Responsible Opioid Prescribing</i> to SMBs	\$100,000.00	
Cephalon	11/10/2010	2011	Donation to Support the Distribution of <i>Responsible Opioid Prescribing</i> to SMBs	\$50,000.00	
Endo Pharmaceuticals	1/28/2011	2011	Grant for Proposed CME Activity Related to FDA Opioid REMS	\$125,000.00	
Covidien	4/15/2011	2011	Grant for Proposed CME Activity Related to FDA Opioid REMS	\$85,000.00	
		Total for FY 2011		\$360,000.00	1.60%
Endo Pharmaceuticals	7/1/2011	Total for FY 2012	Purchase of 6,000 Copies of <i>Responsible Opioid Prescribing</i>	\$46,620.00	0.24%
		Total for FY 1997 – 2012		\$1,964,258.29	0.81%

**The FSMB's Fiscal Year was changed in 1999 from Dec 1 – Nov 30 to May 1 – April 30.

Question 2:

Identify any grants or financial transfers used to fund the production of the book, “Responsible Opioid Prescribing” by Dr. Scott M. Fishman. Provide the date, amount, and source of each grant.

Answer 2:

Payment Description	Payer Organization	Date	Amount of Payment
Grant to Support the <i>FSMB Physician Education Initiative on Safe & Effective Prescribing Practices in Pain Management</i>	Endo Pharmaceuticals	6/22/2006	\$40,000.00
Grant to Support the <i>FSMB Physician Education Initiative on Safe & Effective Prescribing Practices in Pain Management</i>	Purdue Pharma	7/6/2006	\$50,000.00
Payment to Publisher, Waterford Life Sciences	FSMB Foundation	7/10/2006	\$40,000.00
Payment to Publisher, Waterford Life Sciences	FSMB Foundation	7/18/2006	\$50,000.00
Support for <i>FSMB Physician Education Initiative on Safe & Effective Prescribing Practices in Pain Management</i>	Abbott Laboratories	8/16/2006	\$30,000.00
Payment to Publisher, Waterford Life Sciences	FSMB Foundation	9/20/2006	\$25,000.00

Question 3:

How much revenue was generated by sales of “Responsible Opioid Prescribing?” Provide amounts by year, state, and total.

Answer 3:

Revenue from sales includes a combination of retail, in-house and external bulk orders, online sales, and royalties. The following chart reflects revenue based on retail, in-house sales and bulk orders. It should be noted that the amounts listed below are not necessarily an indication of where the books were distributed. For example, JBS International, based in Maryland, is a contractor for SAMHSA, and purchased thousands of copies of the book to distribute at SAMHSA/CSAT educational workshops around the country. The revenue provided by state is based on the origin of the payment.

State & Year	Revenue
Alabama	
2008	\$38.85
2009	\$42.95
Arizona	
2008	\$217.45
2010	\$16.80
California	
2009	\$1,541.35
2010	\$1,213.80
Colorado	
2011	\$111.00
Connecticut	
2010	\$16.80
Delaware	
2010	\$572.74
Florida	
2008	\$142.45
Georgia	
2008	\$25.90
2009	\$621.15
Illinois	
2008	\$55.00
2010	\$16.80
Indiana	
2009	\$149.00
Iowa	
2009	\$260.44
Kansas	
2008	\$383.47
2009	\$4,678.00
2010	\$137.80
Kentucky	
2008	\$12.95
2009	\$245.80
Maine	
2009	\$270.35
2011	\$137.80
Maryland	
2008	\$35,799.44

2009	\$787.12
2010	\$9,547.51
2011	\$5,379.80
Massachusetts	
2008	\$25.90
Michigan	
2010	\$16.80
Minnesota	
2008	\$51.80
2009	\$3,133.25
2010	\$1,560.91
2011	\$1,932.00
Missouri	
2008	\$38.85
Nebraska	
2008	\$12.95
New Hampshire	
2008	\$51.80
2010	\$264.12
New Jersey	
2009	\$3,368.20
2010	\$17.24
2012	\$16.80
New York	
2008	\$103.60
2010	\$287.47
North Carolina	
2008	\$29.75
2010	\$90.02
Ohio	
2008	\$38.85
2009	\$16.70
Oklahoma	
2008	\$30,000.00
2009	\$6,300.00
2011	\$137.01
Oregon	
2009	\$16.80
Pennsylvania	
2010	\$1,165.87

2011	\$47,595.66
Rhode Island	
2010	\$70.00
South Carolina	
2008	\$12.95
Tennessee	
2008	\$12.95
2009	\$1,054.36
2011	\$306.30
Texas	
2009	\$3,750.00
Utah	
2008	\$25.90
Virginia	
2008	\$729.99
2009	\$332.75
2010	\$15,455.47
Washington	
2008	\$12.95
Wisconsin	
2008	\$77.70
2009	\$97.60
2010	\$33.80
2012	\$16.80
Wyoming	
2010	\$14,825.07
Total (2008-2012):	\$195,509.46

Additional Sales

Year	Revenue
2008	\$262.95
2009	\$7,875.16
2010	\$657.60
2011	\$137.80
Total (2008-2011):	\$8,933.51

The following chart provides online sales of *Responsible Opioid Prescribing* through Midpoint National, an online order fulfillment company, and includes advanced purchases for the 2nd edition of the book. The sales revenue listed below accounts for the charges deducted by Midpoint National for its fees.

Year	Total Revenue
2009	\$11,469.80
2010	\$14,352.50
2011	\$14,715.29
2012	\$12,557.73
Total (2009-2012):	\$53,095.32

The following chart provides royalties received from the *Responsible Opioid Prescribing* publication:

Year	Total Revenue
2008	\$13,437
2009	\$4,779
2011	\$3,629
Total (2008-2011):	\$21,845

Question 4:

List each state that has distributed copies of “Responsible Opioid Prescribing” and the number of copies distributed.

Answer 4:

The following is a chart of state-level distributions of *Responsible Opioid Prescribing*. Books were distributed directly by state medical boards or in conjunction with and support from state/federal health departments and agencies, and non-profit organizations.

State	# Books Distributed
Alabama	450
Arizona	100
Connecticut	1,130
District of Columbia	4,140
Florida	9,100
Georgia	18,121
Illinois	500
Iowa	1,550
Maine	3,840
Michigan	42,366
Minnesota	900
Montana	1,800
New Hampshire	4,100
New Mexico	4,500

North Carolina	2,000
North Dakota	300
Oklahoma	6,000
Pennsylvania	601
Rhode Island	6,006
South Carolina	8,070
Vermont	4,412
Virginia	20,000
Washington	15,395
West Virginia	5,200
Wyoming	2,550
Total:	163,131

Question 5:

Provide the names of any people or organizations, other than Federation of State Medical Boards employees or Dr. Scott M. Fishman, involved in writing or editing the content of “Responsible Opioid Prescribing.”

- i. For each person or organization identified, list any financial transfers between the identified person or organization and the Federation of State Medical Boards.
- ii. For each individual or organization identified, provide a description of the involvement.

Answer 5:

The following individuals participated in advising, writing, and/or editing the content of the first or second edition of *Responsible Opioid Prescribing*. The job title presented below corresponds with the participant’s position held at the time of the production of each edition of *Responsible Opioid Prescribing*.

The following individuals did not receive monetary compensation or an honorarium from the FSMB or its Foundation for their participation in the production of *Responsible Opioid Prescribing*.

Several individuals serving on the Advisory Board, including then FSMB Chair and current U.S. Surgeon General Regina M. Benjamin, MD, MBA, and William L. Harp, MD, Executive Director of the Virginia Board of Medicine, have served the FSMB and its Foundation in various capacities (i.e. Board and Committee leadership, workgroups, educational faculty, etc.), and some may have received travel reimbursements and/or stipends in connection with other FSMB-related activities. Such financial transfers were not related in any way to the production of the book.

Responsible Opioid Prescribing: A Physician’s Guide (2007)

Advisory Board:

Upon the author’s completion of the manuscript of ‘Responsible Opioid Prescribing’, the Advisory Board was charged with reviewing content and making recommendations as deemed necessary.

Regina M. Benjamin, MD, MBA

Bayou Clinic

Bayou La Barre, AL

Chair, FSMB Board of Directors

Anton C. Bizzell, MD

Immediate Past Medical Officer
Center for Substance Abuse Treatment
Division of Pharmacologic Therapies
Substance Abuse & Mental Health Administration

Myra Christopher

President/CEO
Center for Practical Bioethics

Perry G. Fine, MD

Professor of Anesthesiology
University of Utah, School of Medicine

Rollin M. Gallagher, MD, MPH

Director, Center for Pain Medicine, Research & Policy
University of Pennsylvania

Aaron Gilson, PhD

Co-Director for U.S. Policy Research
Pain & Policy Studies Group/WHO Collaborating Center
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Responsible Opioid Prescribing: A Clinician's Guide (2012)

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Answer 6:

The following employees of the Federation of State Medical Boards (FSMB) served in some capacity in the development and/or distribution of the *Responsible Opioid Prescribing* publication.

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			Commission for Foreign Medical Graduates, the American Medical Association, the Association of American Medical Colleges, and the American Osteopathic Association.	
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Conclusion

The FSMB, and the state medical boards it represents, are committed to helping address the nation's dual public health issues of under-treated pain and opioid prescription misuse, abuse and diversion. The FSMB shares the Committee's concern over the problems stemming from addiction to opioid medications. The FSMB has launched a wide range of activities in response, ranging from educational initiatives for physicians to close collaboration with federal health care and law enforcement agencies and strong efforts to expand tools such as prescription drug monitoring programs.

At the center of the FSMB's work is the belief that the prescribing of medications that are FDA-approved for pain management, such as long-acting and extended release opioids, should involve a careful balance by physicians between the benefits of these medications to control pain and suffering, and the rising concerns associated with their misuse, abuse and diversion.

The FSMB supports educating physicians about these concerns and emphasizing responsible and appropriate prescribing when a decision is made to use this class of drugs.

The FSMB and state medical boards' efforts to educate physicians about the responsible prescribing of opioids do not advocate for opioid therapy; but rather, ensure that those who do choose to prescribe FDA-approved pain medications do so in a medically appropriate way that properly manages risk and reduces adverse outcomes.

The FSMB's efforts give physicians the knowledge and understanding of best practices and guidelines so they have the confidence to prescribe in a manner that ensures patient safety and is in compliance with federal regulations. This is in direct alignment with the FSMB's mission and purpose of protecting the public and the integrity of medical practice while ensuring access to medical treatment.

The FSMB joins other medical organizations in acknowledging the need for more robust data on opioid use and effectiveness. Until more data is available, we must ensure that physicians fully understand and adhere to best-practice guidelines for the proper prescribing of these drugs. In a major report on pain in 2011, the IOM concurred, writing: "Health professions education and training programs, professional associations, and other groups that sponsor continuing education for health professionals should develop and provide educational opportunities for primary care practitioners and other providers to improve their knowledge and skills in pain assessment and treatment, including safe and effective opioid prescribing."¹⁷ The FSMB is committed to filling this vital need as a part of its service to the nation.

We urge you to read these documents in their entirety and full medical context. We stand ready to provide any additional information, if needed, and welcome the opportunity to discuss these questions further with you personally. We would also be pleased to engage in a full discussion with you regarding the FSMB Model Policies and our publication, *Responsible Opioid Prescribing*.

Respectfully,

Humayun J. Chaudhry, DO, FACP
President and CEO

Enclosures

- 1) *The Model Guidelines for the Use of Controlled Substances for the Treatment of Pain* (1998)
- 2) *The Model Policy Guidelines for Opioid Addiction Treatment in the Medical Office* (2002)
- 3) *The Model Policy for the Use of Controlled Substances for the Treatment of Pain* (2004)
- 4) *Balance, Uniformity and Fairness: Effective Strategies for Law Enforcement for Investigating and Prosecuting the Diversion of Prescription Pain Medications While Protecting Appropriate Medical Practice.* (2009)
- 5) *Responsible Opioid Prescribing: A Clinician's Guide* (2012)

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EXHIBIT 23

Pain:

Current Understanding of Assessment, Management, and Treatments



NATIONAL
PHARMACEUTICAL
COUNCIL, INC



Joint Commission
on Accreditation of Healthcare Organizations

This monograph was developed by NPC as part of a collaborative project with JCAHO.

December 2001

DISCLAIMER: This monograph was developed by the National Pharmaceutical Council (NPC) for which it is solely responsible. Another monograph related to measuring and improving performance in pain management was developed by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) for which it is solely responsible. The two monographs were produced under a collaborative project between NPC and JCAHO and are jointly distributed. The goal of the collaborative project is to improve the quality of pain management in health care organizations.

This monograph is designed for informational purposes only and is not intended as a substitute for medical or professional advice. Readers are urged to consult a qualified health care professional before making decisions on any specific matter, particularly if it involves clinical practice. The inclusion of any reference in this monograph should not be construed as an endorsement of any of the treatments, programs or other information discussed therein. NPC has worked to ensure that this monograph contains useful information, but this monograph is not intended as a comprehensive source of all relevant information. In addition, because the information contained herein is derived from many sources, NPC cannot guarantee that the information is completely accurate or error free. NPC is not responsible for any claims or losses arising from the use of, or from any errors or omissions in, this monograph.

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Section I:
Background
and Significance

Section I: Background and Significance

A. INTRODUCTION

After years of neglect, issues of pain assessment and management have captured the attention of both health care professionals and the public. Factors that prompted such attention include the high prevalence of pain, continuing evidence that pain is undertreated, and a growing awareness of the adverse consequences of inadequately managed pain.

Pain is common. About 9 in 10 Americans regularly suffer from pain,¹ and pain is the most common reason individuals seek health care.² Each year, an estimated 25 million Americans experience acute pain due to injury or surgery and another 50 million suffer chronic pain.^{3,4} Chronic pain is the most common cause of long-term disability, and almost one third of all Americans will experience severe chronic pain at some point in their lives.⁵ As the population ages, the number of people who will need treatment for pain from back disorders, degenerative joint diseases, rheumatologic conditions, visceral diseases, and cancer is expected to rise.⁵

Pain is often undertreated. Improved understanding of pain mechanisms has advanced treatment for pain. Sufficient knowledge and resources exist to manage pain in an estimated 90% of individuals with acute or cancer pain.⁶ Safe and effective medical treatment for many types of chronic pain also is available.⁷ Yet recent studies, reports, and a position statement^{2,8-9} suggest that many types of pain (e.g., postoperative pain, cancer pain, chronic noncancer pain) and patient populations (e.g., elderly patients, children, minorities, substance abusers)¹⁰⁻¹¹ are undertreated. Data from a 1999 survey suggest that only 1 in 4 individuals with pain receive appropriate therapy.^{4,12}

Inadequate pain management has adverse consequences. The adverse consequences of undertreated pain are considerable. Poorly managed acute pain may cause serious medical complications (e.g., pneumonia, deep venous thrombosis), impair recovery from injury or procedures, and/or progress to chronic pain.¹³ Undertreated chronic pain can impair an individual's ability to carry out daily activities and diminish quality of life.¹⁴ In addition to disability, undertreated pain causes significant suffering. Individuals with poorly controlled pain may experience anxiety, fear, anger, or depression.¹⁵ Pain is also a major cause of work absenteeism, underemployment, and unemployment.² Mounting health care costs and disability compensation reflect, in part, poor care for pain-related conditions.¹⁶ Thus, undertreated pain

has significant physical, psychological, and financial consequences.

The undertreatment of pain is not a new problem. The Agency for Health Care Policy and Research (AHCPR)^a published the first clinical practice guideline (CPG) for pain management in 1992. The authors of this guideline acknowledged the prior efforts of multiple health care disciplines (e.g., surgery, anesthesiology, nursing) and pain management groups (e.g., American Pain Society, International Association for the Study of Pain) to address this situation.¹³ Multiple groups have subsequently produced CPGs that address the management of many types of pain. The recently introduced Joint Commission on Accreditation of Healthcare Organizations (JCAHO) standards for pain assessment and management¹⁷ represent a giant step forward in improving pain management.^b

To facilitate these efforts, this monograph has two primary objectives: 1) to provide practical knowledge that will enhance the reader's understanding and management of pain and 2) to introduce some strategies to improve pain management (e.g., CPGs, standards), as further explored in monograph 2. Due to the breadth and complexity of the subject matter, a comprehensive discussion of all aspects of pain assessment and management is beyond the scope of this monograph. The scope and potential limitations of this monograph are as follows:

- The neurological and psychological mechanisms that underlie pain are complex, and knowledge of mechanisms is limited. The discussion of pathophysiology in this monograph emphasizes practical knowledge that will facilitate diagnosis and/or the selection of appropriate interventions.
- Controversy exists over how both pain and analgesics should be classified. This monograph reviews only a few of the many classification systems.
- Various factors (e.g., insufficient funding for studies, lack of good diagnostic codes) limit the availability of current, reliable epidemiological data related to pain.
- A host of factors, including the setting, characteristics of the pain, and patient factors (e.g., age, medical condition, language and cognitive abilities) influence pain

^a The Agency for Health Care Policy and Research is now the Agency for Healthcare Research and Quality.

^b These JCAHO standards first appeared in the 2000-2001 JCAHO standards manual and apply to ambulatory care, behavioral health, managed behavioral health, health care networks, home care, hospitals, long-term care organizations, and pharmacies.

Section I: Background and Significance

- assessment. This monograph provides an overview of pain assessment, but primarily focuses on the initial assessment.
- Many strategies exist to manage various types of pain. This monograph reviews pharmacologic and nonpharmacologic treatments for pain, with greater emphasis on the former. Specific information about the treatment of certain conditions is limited to some common and treatable types of pain. Coverage of treatment issues relevant to special populations (e.g., children, the elderly) is limited.
- The discussion of pharmacologic treatments emphasizes: 1) the major classes of drugs used for pain management; 2) examples and salient features of these drugs; and 3) some means of ensuring the safe, strategic, and effective use of these agents. However, this information is only an overview. The reader should consult CPGs for specific guidance in managing patients.
- Due to the large volume of associated literature, a review of the mechanisms, assessment, and management of pain associated with some conditions (e.g., cancer) is beyond the scope of this monograph. This monograph focuses on the pathophysiology, epidemiology, assessment, and treatment of acute pain and chronic noncancer pain (CNCP).

B. DEFINITIONS AND MECHANISMS OF PAIN

This section of the monograph explores mechanisms that underlie the perception of pain. It also reviews a pain classification system based on underlying pathophysiology. The goal is to provide practical information that will facilitate pain assessment and management. A question-and-answer format is used to provide information about the following:

- The definition of pain
- The process by which noxious stimuli generate neural signals and the transmission of these signals to higher centers (nociception)
- The role of inflammatory mediators, neurotransmitters, and neuropeptides in these processes (i.e., targets of many pharmacologic therapies)

- Definitions and causes of some clinical pain states
- Underlying mechanisms and characteristics of somatic pain, visceral pain, and neuropathic pain.

1. What Is Pain?

In 1968, McCaffery defined pain as “whatever the experiencing person says it is, existing whenever s/he says it does”.¹⁸ This definition emphasizes that pain is a subjective experience with no objective measures. It also stresses that the patient, not clinician, is the authority on the pain and that his or her self-report is the most reliable indicator of pain.¹³ In 1979, the International Association for the Study of Pain (IASP) introduced the most widely used definition of pain. The IASP defined pain as an “unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”¹⁹ This definition emphasizes that pain is a complex experience that includes multiple dimensions.

2. How Does Injury Lead to Pain?

Nociception refers to the process by which information about tissue damage is conveyed to the central nervous system (CNS). Exactly how this information is ultimately perceived as painful is unclear. In addition, there can be pain without nociception (e.g., phantom limb pain) and nociception without pain. But classic descriptions of pain typically include four processes:²⁰⁻²³

- *Transduction*: the conversion of the energy from a noxious thermal, mechanical, or chemical stimulus into electrical energy (nerve impulses) by sensory receptors called nociceptors
- *Transmission*: the transmission of these neural signals from the site of transduction (periphery) to the spinal cord and brain
- *Perception*: the appreciation of signals arriving in higher structures as pain
- *Modulation*: descending inhibitory and facilitatory input from the brain that influences (modulates) nociceptive transmission at the level of the spinal cord.

Section I: Background and Significance

3. What Happens During Transduction?

a. Nociceptor activation and sensitization

Nociceptors are sensory receptors that are preferentially sensitive to tissue trauma or a stimulus that would damage tissue if prolonged.¹⁹ These receptors are the free endings of (primary afferent) nerve fibers distributed throughout the periphery (Figure 1). Signals from these nociceptors travel primarily along two fiber types: slowly conducting unmyelinated C-fibers and small, myelinated, and more rapidly conducting A-delta fibers^c (Figure 2).

Injury to tissue causes cells to break down and release various tissue byproducts and mediators of inflammation (e.g., prostaglandins, substance P, bradykinin, histamine, serotonin, cytokines).^{24,25} Some of these substances activate nociceptors (i.e., cause them to generate nerve impulses) and

^cIn addition to these nociceptors, A-beta fibers (which normally subserve touch) sometimes act as nociceptors when sensitized. The functioning of nociceptors depends upon the electrophysiological properties of the tissues, co-factors, and cytokines.²⁴

most sensitize nociceptors (i.e., increase their excitability and discharge frequency).^{26,27} Ongoing activation of nociceptors may cause nociceptive pain (see I.B.9). Peripheral (nociceptor) sensitization amplifies signal transmission and thereby contributes to central sensitization and clinical pain states (see I.B.7-8).²⁸

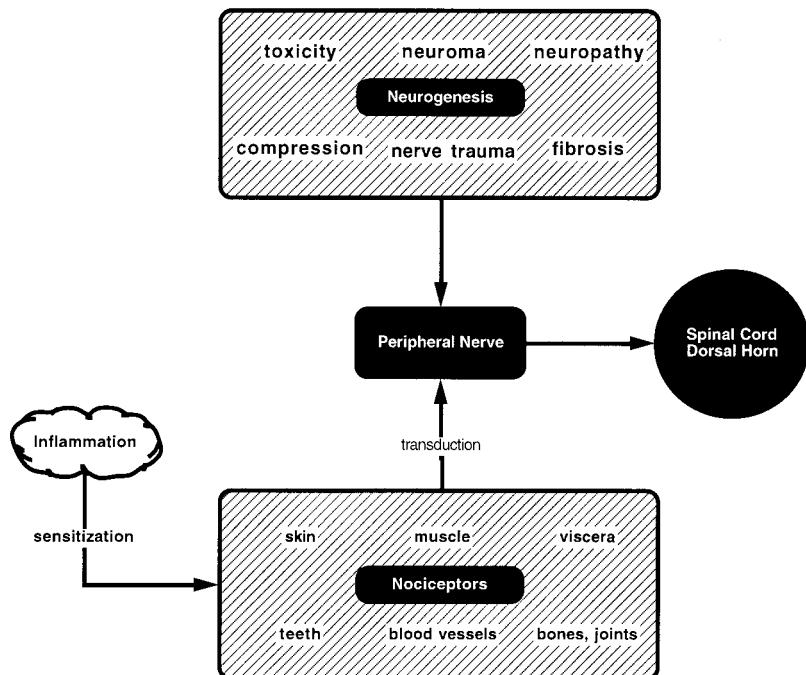
b. Peripheral neuropathic pain

Not all pain that originates in the periphery is nociceptive pain. Some neuropathic pain is caused by injury or dysfunction of the peripheral nervous system (i.e., peripheral nerves, ganglia, and nerve plexi)(see I.B.10)(Figure 1).²²

c. Clinical implications

Some analgesics target the inflammatory process that produces sensitization. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX), thus decreasing the synthesis of prostaglandins.²⁹⁻³⁰ Other analgesics (e.g., antiepileptic drugs, local anesthetics) block or modulate channels, thus inhibiting the generation of nerve impulses.

Figure 1.



Source: Reference 22.

Peripheral origins of pain. Noxious signaling may result from either abnormal firing patterns due to damage or disease in the peripheral nerves or stimulation of nociceptors (free nerve endings due to tissue trauma). Inflammation in injured or diseased tissue sensitizes nociceptors, lowering their firing thresholds. Some clinical pain states have no peripheral origin, arising from disorders of brain function.

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4. What Is Transmission?

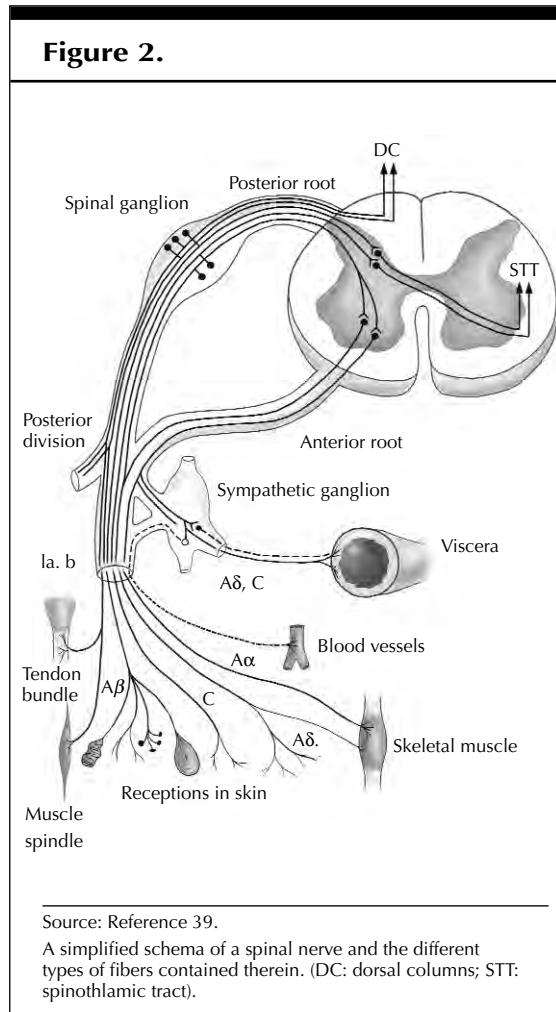
Nerve impulses generated in the periphery are transmitted to the spinal cord and brain in several phases:^{21,31}

a. Periphery to the spinal cord

Most sensory nerve impulses travel via the nerve processes (axons) of primary afferent neurons to the dorsal horn (DH) of the spinal cord (Figure 2).³² There, primary afferent neurons propagate nerve impulses to DH neurons through the release of excitatory amino acids (EAAs) (e.g., glutamate, aspartate) and neuropeptides (e.g., substance P) at synapses (connections) between cells.^{4,39} Activated DH projection neurons forward nociceptive impulses toward the brain.

However, not all events in the DH facilitate

⁴The excitatory amino acids (EAAs) glutamate and aspartate mediate most excitatory transmission in the CNS, including that related to nociception.³³ The neuropeptide substance P activates spinal neurons and enhances their responsiveness to EAA, thus also facilitating nociception.³⁴⁻³⁸



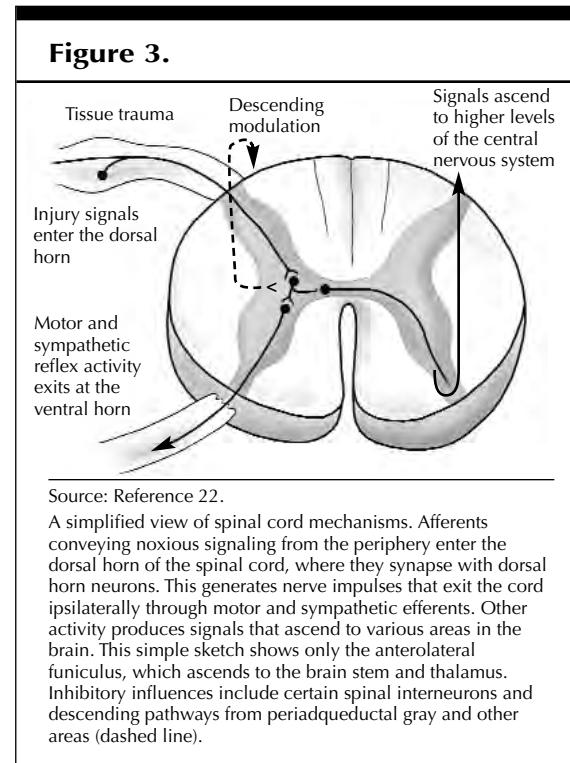
nociception. Spinal interneurons release inhibitory amino acids (e.g., γ -aminobutyric acid [GABA]) and neuropeptides (endogenous opioids) that bind to receptors on primary afferent and DH neurons and inhibit nociceptive transmission by presynaptic and postsynaptic mechanisms.³⁹⁻⁴² Descending inhibitory input from the brain also modulates DH nociceptive transmission (see I.B.6) (Figure 3). Thus, nociceptive traffic in the DH is not merely relayed to higher centers but rather is heavily modulated. These inhibitory events are part of a natural nociceptive-modulating system that counterbalances the activity of the nociceptive-signaling system.

b. Spinal cord to the brain

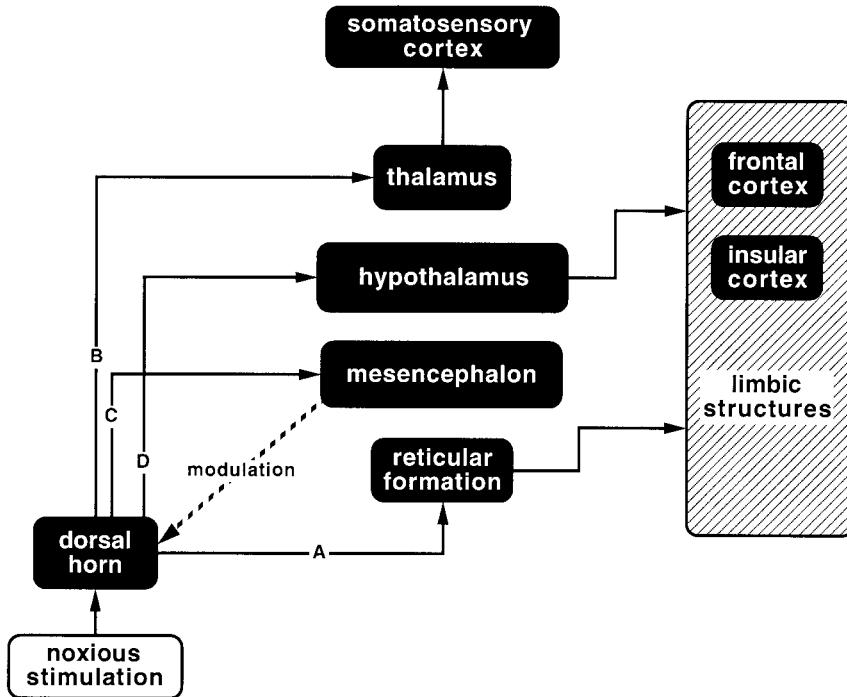
The nerve processes of DH projection neurons project to the brain in bundles called ascending tracts. Projection neurons from some DH regions transmit nociceptive signals to the thalamus via the spinothalamic tract (STT) (Figures 2, 4).^{39,43} Others transmit nociceptive information to the reticular formation, mesencephalon, and hypothalamus via the spinoreticular, spinomesencephalic, and spinohypothalamic tracts (Figure 4).^{22,44}

c. Clinical implications

Some analgesics inhibit nociception in the



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Figure 4.

Source: Reference 22.

Multiple pathways of nociceptive transmission for the spinal cord to central structures. There are four major pathways the A: spinoreticular; B: spinothalamic; C: spinothalamic; and D: spinothalamic tracts.

DH. For example, opioid analgesics bind to opioid receptors on primary afferent and DH neurons and mimic the inhibitory effects of endogenous opioids. They also bind to opioid receptors in the brain and activate descending pathways that further inhibit DH nociceptive transmission.⁴⁵ Baclofen, a GABA agonist, binds to GABA_B receptors and mimics the inhibitory effects of GABA on nociceptive transmission.⁴⁶

other nociceptive input to the limbic system.⁴⁴ This input joins input from the spinoreticular and spinothalamic tracts to mediate affective aspects of pain.²⁰ Immediate social and environmental context influences the perception of pain, as do past experience and culture. Consequently, a standard cause of pain (e.g., surgery) can generate enormous individual differences in pain perception.

5. What Is Perception?

The perception of pain is an uncomfortable awareness of some part of the body, characterized by a distinctly unpleasant sensation and negative emotion best described as threat. Both cortical and limbic system structures are involved.⁴⁷ Nociceptive information from some DH projection neurons travels via the thalamus to the contralateral somatosensory cortex³⁹ (Figure 4), where input is somatotopically mapped to preserve information about the location, intensity, and quality of the pain.^{43,48} The thalamus relays

6. What Is Modulation?

a. Descending pathways

Modulation of nociceptive transmission occurs at multiple (peripheral, spinal, supraspinal) levels. Yet, historically, modulation has been viewed as the attenuation of DH transmission by descending inhibitory input from the brain. Melzack and Wall's Gate Control Theory brought this notion to the forefront in 1965.⁴⁹ Models of descending pain systems now include both inhibitory and facilitatory descending pathways.

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Multiple brain regions contribute to descending inhibitory pathways.³⁹ Nerve fibers from these pathways release inhibitory substances (e.g., endogenous opioids, serotonin, norepinephrine, GABA) at synapses with other neurons in the DH. These substances bind to receptors on primary afferent and/or DH neurons and inhibit nociceptive transmission. Such endogenous modulation may contribute to the wide variations in pain perception observed among patients with similar injuries.^{20,50-51}

b. Clinical implications

Some analgesics enhance the effects of descending inhibitory input. For example, some antidepressants interfere with the reuptake of serotonin and norepinephrine at synapses, increasing their relative interstitial concentration (availability)⁵²⁻⁵³ and the activity of endogenous pain-modulating pathways.^{21,50,53a} Thus, some, but not all, antidepressants are used to treat some types of chronic pain.

temporal summation-refers to a progressive increase in pain experienced over the course of a repeated stimulus.⁶⁶

Repeated or prolonged input from C-nociceptors or damaged nerves causes a longer-lasting increase in DH neuron excitability and responsiveness (i.e., central sensitization^f)^{67,75} which may outlast the stimulus by minutes to hours.³⁸ Central sensitization is associated with a reduction in central inhibition, spontaneous DH neuron activity, the recruitment of responses from neurons that normally only respond to low-intensity stimuli (i.e., altered neural connections), and expansion of DH neuron receptive fields.^{27,60,67,76-78} Clinically, these changes may manifest as: 1) an increased response to a noxious stimulus (hyperalgesia), 2) a painful response to a normally innocuous stimulus (allodynia), 3) prolonged pain after a transient stimulus (persistent pain), and 4) the spread of pain to uninjured tissue (i.e., referred pain).^{60,79} In contrast to hyperalgesia caused by peripheral mechanisms (i.e., primary hyperalgesia), such secondary hyperalgesia extends beyond the region of injury.^{48,80}

b. Clinical implications

Sensitization is likely responsible for most of the continuing pain and hyperalgesia after an injury.⁸¹ This sensitivity may be due to “normal” noxious input from injured and inflamed tissue or “abnormal” input from injured nerves or ganglia. In the former case, sensitization serves an adaptive purpose. That is, the hyperalgesia and allodynia encourage protection of the injury during the healing phase. However, these processes can persist long after healing of the injury in the setting of chronic pain.

Central sensitization plays a key role in some chronic pain, especially pain induced by nerve injury or dysfunction (i.e., neuropathic pain). It explains why neuropathic pain often exceeds the provoking stimulus, both spatially and temporally.^{48,60} Central sensitization also explains the long-standing observation that established pain is more

^fEarly transient changes include removal of the voltage-dependent magnesium blockade of NMDA receptors. This permits glutamate to activate NMDA receptors, with subsequent temporal summation of slow synaptic potentials that manifests as wind-up.^{27,62-63}

^gCentral sensitization reflects a complex series of changes that may begin with the release of excitatory substances (e.g., glutamate, substance P) from cells following noxious stimulation. These substances activate NMDA and non-NMDA (NK) receptors, which increases intracellular calcium levels⁶⁷⁻⁷⁰ and activates calcium-dependent intracellular kinases.^{38,71} These kinases break down arachidonic acid (releasing byproducts)⁷² and phosphorylate ion channels and NMDA receptors. Potential consequences of these changes include altered synaptic transfer and gene expression (e.g., c-fos).^{27,60,73-74} Collectively, these changes may promote long-lasting increases in DH neuron excitability (i.e., central sensitization).

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difficult to suppress than acute pain.^{13,75,82-83}

In contrast to nociceptive pain, neuropathic pain is often unresponsive or poorly responsive to NSAIDs and opioids.⁸⁴⁻⁸⁵ However, it may respond to antiepileptic drugs, antidepressants, or local anesthetics.⁸⁶

9. What Is Nociceptive Pain?

Pain that is classified on the basis of its presumed underlying pathophysiology is broadly categorized as nociceptive or neuropathic pain.⁸⁷ Nociceptive pain is caused by the ongoing activation of A- δ and C-nociceptors in response to a noxious stimulus (e.g., injury, disease, inflammation).⁸⁸ Pain arising from visceral organs is called visceral pain, whereas that arising from tissues such as skin, muscle, joint capsules, and bone is called somatic pain. Somatic pain may be further categorized as superficial (cutaneous) or deep somatic pain (Table 1).

In contrast to neuropathic pain, the nervous system associated with nociceptive pain is functioning properly. Generally, there is a close correspondence between pain perception and stimulus intensity, and the pain is indicative of real or potential tissue damage. Differences in how stim-

uli are processed across tissue types contribute to the pain's varying characteristics (Table 1).²² For example, cutaneous pain is often described as a well-localized sharp, pricking, or burning sensation; deep somatic pain, as a diffuse dull or aching sensation; and visceral pain, as a deep cramping sensation that may be referred to other sites (i.e., referred pain).⁸⁸ Associated clinical pain states (e.g., hyperalgesia, allodynia) reflect sensitization (see I.B.7-8).^{88,90}

10. What Is Neuropathic Pain?

Neuropathic pain is caused by aberrant signal processing in the peripheral or central nervous system.^{g,96} In other words, neuropathic pain reflects nervous system injury or impairment. Common causes of neuropathic pain include trauma, inflammation, metabolic diseases (e.g., diabetes), infections (e.g., herpes zoster), tumors, toxins, and primary neurological diseases.⁸¹ Neuropathic pain can be broadly categorized as peripheral or central

^gData from animal studies suggest that the following changes may contribute to neuropathic pain: 1) generation of spontaneous ectopic activity, 2) loss of normal inhibitory mechanisms in the dorsal horn (i.e., central disinhibition), 3) altered primary afferent neuron phenotypes, and 4) sprouting of nerve fibers (i.e., altered neural connections).^{27,63-91-95} Collectively, these changes cause abnormal nerve impulse firing and/or abnormal signal amplification.⁴⁸

Table 1. Examples and Characteristics of Nociceptive Pain

	Superficial Somatic Pain	Deep Somatic Pain	Visceral Pain
Nociceptor location	Skin, subcutaneous tissue, and mucous membranes	Muscles, tendons, joints, fasciae, and bones	Visceral organs ^a
Potential stimuli	External mechanical, chemical, or thermal events Dermatologic disorders	Overuse strain, mechanical injury, cramping, ischemia, inflammation	Organ distension, muscle spasm, traction, ischemia, inflammation
Localization	Well localized	Localized or diffuse and radiating	Well or poorly localized
Quality	Sharp, pricking, or burning sensation	Usually dull or aching, cramping	Deep aching or sharp stabbing pain, which is often referred to cutaneous sites
Associated symptoms and signs	Cutaneous tenderness, hyperalgesia, hyperesthesia, allodynia	Tenderness, reflex muscle spasm, and sympathetic hyperactivity ^b	Malaise, nausea, vomiting, sweating, tenderness, reflex muscle spasm
Clinical examples	Sunburn, chemical or thermal burns, cuts and contusions of the skin	Arthritis pain, tendonitis, myofascial pain	Colic, appendicitis, pancreatitis, peptic ulcer disease, bladder distension

Sources: References 22-24 and 88-89.

^aVisceral organs include the heart, lungs, gastrointestinal tract, pancreas, liver, gallbladder, kidneys, and bladder.

^bSymptoms and signs of sympathetic (autonomic) nervous system hyperactivity include increased heart rate, blood pressure, and respiratory rate; sweating; pallor; dilated pupils; nausea; vomiting; dry mouth; and increased muscle tension.

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in origin.⁹⁶ Painful peripheral mononeuropathy and polyneuropathy, deafferentation pain, sympathetically maintained pain, and central pain are subdivisions of these categories.

Neuropathic pain is sometimes called “pathologic” pain because it serves no purpose.⁸¹ A chronic pain state may occur when pathophysiological changes become independent of the inciting event.⁴⁶ Sensitization plays an important role in this process (see I.B.7-8). Although central sensitization is relatively short lived in the absence of continuing noxious input, nerve injury triggers changes in the CNS that can persist indefinitely.⁴⁸ Thus, central sensitization explains why neuropathic pain is often disproportionate to the stimulus (e.g., hyperalgesia, allodynia) or occurs when no identifiable stimulus exists (e.g., persistent pain, pain spread). Neuropathic pain may be continuous or episodic and is perceived in many ways (e.g., burning,

tingling, prickling, shooting, electric shock-like, jabbing, squeezing, deep aching, spasm, or cold).⁹⁷ Table 2 summarizes examples and characteristics of neuropathic pain.

C. CLASSIFICATION OF PAIN

Although pain classes are not diagnoses, categorizing pain helps guide treatment. Multiple systems for classifying pain exist. These include multidimensional classification systems, such as the IASP Classification of Chronic Pain,¹⁹ and a variety of systems based on a single dimension of the pain experience. Of the latter systems, those

Table 2. Examples and Characteristics of Neuropathic Pain

	Painful Mononeuropathies and Polyneuropathies	Deafferentation Pain	Sympathetically Maintained Pain ^a	Central Pain
Definition	Pain along the distribution of one or multiple peripheral nerve(s) caused by damage to the affected nerve(s)	Pain that is due to a loss of afferent input	Pain that is maintained by sympathetic nervous system activity	Pain caused by a primary lesion or dysfunction of the CNS
Pain characteristics and associated symptoms	Three main types: <ul style="list-style-type: none"> • Continuous, deep, burning, aching or bruised pain • Paroxysmal lancinating (shock-like) pain • Abnormal skin sensitivity 	<ul style="list-style-type: none"> • Quality: burning, cramping, crushing, aching, stabbing, or shooting • Hyperalgesia • Hyperpathia • Dysesthesia • Other abnormal sensations 	<ul style="list-style-type: none"> • Quality: burning, throbbing, pressing, or shooting • Allodynia • Hyperalgesia • Associated ANS dysregulation and trophic changes^b 	<ul style="list-style-type: none"> • Quality: burning, numbing, tingling, shooting • Spontaneous and steady or evoked • +/- sensory loss • Allodynia • Hyperalgesia
Sources	<ul style="list-style-type: none"> • Metabolic disorders (e.g., diabetes) • Toxins (e.g., alcohol, chemotherapy agents) • Infection (e.g., HIV, herpes zoster) • Trauma • Compressive (nerve entrapment) • Autoimmune and hereditary diseases 	<ul style="list-style-type: none"> • Damage to a peripheral nerve, ganglion, or plexus • CNS disease or injury (occasional) 	<ul style="list-style-type: none"> • Peripheral nerve damage (e.g., CRPS II) • Sympathetic efferent (motor) innervation • Stimulation of nerves by circulating catecholamines 	<ul style="list-style-type: none"> • Ischemia (e.g., stroke) • Tumors • Trauma (e.g., spinal cord injury) • Syrinx • Demyelination
Clinical examples	<ul style="list-style-type: none"> • Diabetic neuropathy • Alcoholic neuropathy • Postherpetic neuralgia • Carpal tunnel syndrome 	<ul style="list-style-type: none"> • Phantom limb pain • Post-mastectomy pain 	<ul style="list-style-type: none"> • CRPS • Phantom limb pain • Postherpetic neuralgia • Some metabolic neuropathies 	<ul style="list-style-type: none"> • Post-stroke pain • Some cancer pain • Pain associated with multiple sclerosis

Sources: References 22-23, 87, and 97a-97d.

^aSympathetically maintained pain is a pain mechanism, not a diagnosis. It is associated with several types of pain, but it also may exist as a single entity.^{97c}

^bFocal autonomic dysregulation can manifest with signs and symptoms such as swelling, pallor, erythema (redness), sweating, and temperature changes. Trophic changes include thinning of the skin, abnormal hair or nail growth, and bone changes.

ANS: autonomic nervous system; CNS: central nervous system; CRPS: complex regional pain syndrome types I and II; CRPS II: complex regional pain syndrome type II; HIV: human immunodeficiency virus.

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based on pain duration (i.e., acute vs. chronic pain) and underlying pathophysiology (i.e., nociceptive vs. neuropathic pain) are used most often (see I.B.9-10).

This section of the monograph explores the distinction between acute and chronic pain. It also reviews elements of a mixed pain classification system in which pain is categorized as acute pain, cancer pain, or chronic noncancer pain (CNCP).

1. Acute Pain

Acute pain was once defined simply in terms of duration. It is now viewed as a “complex, unpleasant experience with emotional and cognitive, as well as sensory, features that occur in response to tissue trauma.”²² In contrast to chronic pain, relatively high levels of pathology usually accompany acute pain and the pain resolves with healing of the underlying injury. Acute pain is usually nociceptive, but may be neuropathic. Common sources of acute pain include trauma, surgery, labor, medical procedures, and acute disease states. Table 3 summarizes its key features.

Acute pain serves an important biological function, as it warns of the potential for or extent of injury. A host of protective reflexes

(e.g., withdrawal of a damaged limb, muscle spasm, autonomic responses) often accompany it. However, the “stress hormone response” prompted by acute injury also can have adverse physiologic and emotional effects (see I.D.3).¹³ Even brief intervals of painful stimulation can induce suffering, neuronal remodeling, and chronic pain;¹⁰ associated behaviors (e.g., bracing, abnormal postures, excessive reclining) may further contribute to the development of chronic pain. Therefore, increasing attention is being focused on the aggressive prevention and treatment of acute pain to reduce complications, including progression to chronic pain states.⁸⁸

2. Chronic Pain

Chronic pain was once defined as pain that extends 3 or 6 months beyond onset or beyond the expected period of healing.⁹⁸ However, new definitions differentiate chronic pain from acute pain based on more than just time (Table 3). Chronic pain is now recognized as pain that extends beyond the period of healing, with levels of identified pathology that often are low and insufficient to explain the presence and/or extent of the pain.⁹⁹ Chronic pain is also defined as a persistent pain that “disrupts sleep and normal living, ceases to serve a protective

Table 3. Key Features of Pain Types and Syndromes

Type of Pain	Features
Acute pain	Pain usually concordant with degree of tissue damage, which remits with resolution of the injury Reflects activation of nociceptors and/or sensitized central neurons Often associated with ANS and other protective reflex responses (e.g., muscle spasm, “splinting”)
Chronic pain	Low levels of identified underlying pathology that do not explain the presence and/or extent of the pain Perpetuated by factors remote from the cause Continuous or intermittent with or without acute exacerbations Symptoms of ANS hyperactivity less common Irritability, social withdrawal, depressed mood and vegetative symptoms (e.g., changes in sleep, appetite, libido), disruption of work, and social relationships
Cancer pain	Strong relationship between tissue pathology and levels of pain Limited time frame that permits aggressive pain management Rarely involves medical-legal or disability issues
CNPC	Weak relationship between tissue pathology and pain levels Prolonged, potentially life-long, pain May involve medical, legal, disability issues/conflicts, work or relationship problems, physical deconditioning, psychological symptoms (see chronic pain above) May progress to CPS
CPS	Preoccupation with somatic functioning Lifestyle centered on seeking immediate pain relief, with excessive, nonproductive, and often harmful use of health care services Repeated attempts to obtain pain-related financial compensation (e.g., Social Security, Veterans’ benefits) Numerous symptoms and signs of psychosocial dysfunction that the patient attributes to the pain (e.g., anger, depression, anxiety, substance abuse, disrupted work or personal relationships)

Sources: References 88 and 98-100.

ANS: autonomic nervous system; CNCP: chronic noncancer pain; CPS: chronic pain syndrome; VA: Veterans Administration.

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function, and instead degrades health and functional capability.”¹⁰¹ Thus, unlike acute pain, chronic pain serves no adaptive purpose.

Chronic pain may be nociceptive, neuropathic, or both and caused by injury (e.g., trauma, surgery), malignant conditions, or a variety of chronic non-life-threatening conditions (e.g., arthritis, fibromyalgia, neuropathy). In some cases, chronic pain exists *de novo* with no apparent cause. Although injury often initiates chronic pain, factors pathogenetically and physically remote from its cause may perpetuate it.⁹⁸ Environmental and affective factors also can exacerbate and perpetuate chronic pain, leading to disability and maladaptive behavior.

3. Cancer Pain

Pain associated with potentially life-threatening conditions such as cancer is often called “malignant pain” or “cancer pain.” However, there is movement toward the use of new terms such as “pain associated with human immunodeficiency virus (HIV) infection” or “pain associated with cancer.” (The term “cancer pain” is used in this monograph for the sake of brevity.) Cancer pain includes pain caused by the disease itself (e.g., tumor invasion of tissue, compression or infiltration of nerves or blood vessels, organ obstruction, infection, inflammation) and/or painful diagnostic procedures or treatments (e.g., biopsy, postoperative pain, toxicities from chemotherapy or radiation treatment).¹⁰²

There are several reasons why some experts feel that cancer pain merits a discrete category. First, its acute and chronic components and multiple etiologies make it difficult to classify based on duration or pathology alone. Second, cancer pain differs from chronic noncancer pain (CNCP) in some significant ways (e.g., time frame, levels of pathology, treatment strategies) (Table 3).⁹⁹ However, there is little evidence to support a distinction between these pain types based on underlying neural processes. Therefore, many pain experts categorize cancer pain as acute or chronic pain.⁹⁸

4. Chronic Noncancer Pain

A subtype of chronic pain is CNCP, which refers to persistent pain not associated with cancer. In contrast to patients with chronic cancer pain, patients with CNCP often report pain lev-

els that only weakly correspond to identifiable levels of tissue pathology and/or respond poorly to standard treatments.⁹⁹⁻¹⁰⁰ As CNCP may last for many years, some consider use of the traditional term for such pain, “chronic nonmalignant pain,” inappropriate. Thus, there is movement toward use of alternate terms such as “chronic noncancer pain” and “chronic non-cancer-related pain.”

Causes of CNCP include acute injury that has proceeded to chronic pain (e.g., whiplash) and various chronic conditions (Table 4). In some cases, there is no discernable cause, and the pain is considered the disease. CNCP can affect virtually any body system or region, and pain severity ranges from mild to excruciating. Some types of CNCP have well-defined characteristics and patterns, whereas others do not. Neuropathic and myofascial CNCP can be particularly hard to diagnose, as they may occur in the absence of a known injury or disease process.¹⁰⁰

Because of its chronicity and impact on daily activities, patients with CNCP may experience vocational, interpersonal, and/or psychological problems (Table 3).¹⁵ If the symptoms of CNCP consume the attention of and incapacitate the patient, he or she may suffer from a psychosocial disorder known as “chronic pain syndrome” (CPS) (Table 3).¹⁰⁰ The pain experienced by these patients is real, and not all patients with CNCP develop this syndrome. Appropriate management of both CNCP and CPS requires an

Table 4. Examples of Chronic Noncancer Pain

- Osteoarthritis
- Low back pain
- Myofascial pain
- Fibromyalgia
- Headaches (e.g., migraine^a, tension-type, cluster)
- “Central pain” (e.g., spinal cord injury, stroke, MS)
- Chronic abdominal pain (e.g., chronic pancreatitis, chronic PUD, IBS)
- Sickle cell disease^a
- CRPS, Types I and II
- Phantom limb pain
- Peripheral neuropathy
- Neuralgia (e.g., post-herpetic, trigeminal)

Sources: References 99 and 100.

^aMigraines and sickle cell disease may be more accurately classified as intermittent pain but are treated as chronic noncancer pain for purposes of this discussion.

CRPS: complex regional pain syndrome; IBS: Irritable bowel syndrome; MS: multiple sclerosis; PUD: peptic ulcer.

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interdisciplinary approach that addresses the complex interaction of physical, psychological, and social factors that contribute to the ongoing pain.

D. PREVALENCE, CONSEQUENCES, AND COSTS OF PAIN

Pain is common, and inadequately managed pain is associated with many adverse consequences. This section of the monograph reviews epidemiological data, evidence that pain is undertreated, and consequences of inadequately managed pain. These consequences affect patients, their families, and society as a whole and can be broadly categorized as physiological, psychosocial (quality of life), and financial.

1. What Is the Size and Scope of Pain As A Health Care Problem?

Acute pain is the most common reason why patients seek medical attention.⁸⁸ Common reasons for visits to health care professionals include acute pain (e.g., musculoskeletal pain, gastrointestinal pain, chest pain, headache) and injuries (e.g., fractures, sprains, lacerations).¹⁰³ Chronic pain is also a problem of epidemic proportions. About 50 million of the estimated 75 million Americans who live with "serious pain" suffer from chronic pain.¹⁰⁴ Many have been living with their pain for more than 5 years and experience pain almost 6 days a week.¹⁴ A survey of self-help organization members suggested that back and neck pain, myofascial pain/fibromyalgia, headache, arthritis pain, and neuropathic pain are the most common types of CNCP.¹⁰⁵ Low back pain, arthritis, and migraine headache alone account for pain in tens of millions of Americans.⁸⁸

2. What Evidence Suggests That Pain Is Undertreated?

In 1992, the AHCPR developed a CPG for acute pain management, in part due to mounting reports of inadequate postoperative pain control.¹³ Clinical surveys indicated that routine

orders for as-needed intramuscular (IM) injections of opioids failed to relieve pain in about half of all postoperative patients (e.g., Marks and Sachar,¹⁰⁶ Donovan et al.,¹⁰⁷ Oden¹⁰⁸). This finding prompted recommendations including the scheduled administration of pain medications via other routes. A national survey of perioperative pain in hospitalized patients recently assessed adherence to these and other (American Society of Anesthesiologists) CPGs.¹⁰⁹ Although overall guideline adherence was excellent, frequent IM administration of opioids and infrequent use of nonpharmacologic pain management methods were important exceptions.

Results of other 1990s studies (e.g., Abbott et al.,¹¹⁰ Gu and Belgrade,¹¹¹ Ward and Gordon,¹¹² Warfield and Kahn,¹¹³ Drayer et al.¹¹⁴) contribute to concerns about the management of acute pain. In one study of pain management in hospitalized patients, 61% of the 217 patients interviewed reported pain ratings of 7 to 10 (on a scale from 0 for no pain and 10 for the worst imaginable pain) within the preceding 24 hours.¹¹² Forty-nine percent reported a current pain level between 4 and 10, and this was after analgesic administration in 20%. A study of the adequacy of analgesia in an urban emergency department produced some disturbing results. Hispanic patients with long-bone fractures were half as likely as non-Hispanic white patients to receive pain medication.¹¹⁵

A 1998 survey of a random cross-section of U.S. households suggests that CNCP also is undertreated.¹⁴ Of 805 adults interviewed, 70% reported sufficient control of moderate pain. However, this percentage decreased to 51% in patients with severe pain and to 39% in those with very severe pain. Results from a 2001 survey suggest that most individuals with severe CNCP still do not have their pain under control.¹⁴ Of those who do, it took almost half of them a year to achieve adequate pain control.¹⁴

Undertreatment of cancer pain also is well documented. A landmark study involved 1308 cancer outpatients at 54 treatment sites.¹¹⁶ Approximately two-thirds (67%) of the patients interviewed reported pain sufficient to require daily analgesics, and 36% reported that the pain limited their ability to function. However, only 42% of those with pain reported receiving sufficient pain relief. Data from more recent studies (e.g., Zhukovsky et al.,¹¹⁷ Cleeland et al.,¹¹⁸ Anderson et al.,¹¹⁹ Wolf et al.,¹²⁰ Weiss et al.¹²¹) suggest that pain associated with terminal illnesses, including cancer, is still undertreated. Elderly, female, minority, and pediatric patients

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are at greatest risk for inadequate management of cancer pain.^{120,122}

3. What Are the Consequences and Costs of Undertreatment of Pain?

a. Physiological consequences

As discussed in Section I.C.1, acute tissue injury triggers physiological “stress” responses intended to protect the body. Yet these responses can have adverse effects if allowed to persist unchecked. Table 5 summarizes some of the adverse physiological consequences of inadequately controlled postinjury and postoperative pain (e.g., pneumonia, blood clots, infection, shock). Very young, very old, and frail patients are at greatest risk for such complications.¹³ In one study of neonates who underwent cardiac surgery, patients who received “light” versus “deep” anesthesia and postoperative analgesia had higher mortality rates.¹²³

Another key adverse effect of poorly controlled acute pain is progression to chronic pain.¹²⁴⁻¹²⁵ Some chronic neuropathic pain (e.g., postmastectomy pain, postthoracotomy pain, phantom limb pain) results, in part, from a

lack of aggressive pain management and/or early rehabilitation following surgery.¹²⁶⁻¹²⁷

Inadequate control of pain associated with acute herpes zoster (shingles) may increase the likelihood of subsequent postherpetic neuralgia.¹²⁸ One study showed that pain levels in patients hospitalized for serious conditions (e.g., chronic obstructive pulmonary disease, liver failure, cancer) determined future pain levels.¹²⁹ Under-treated pain early in life is associated with pain later in life.¹³⁰⁻¹³¹

b. Quality of life

Inadequate control of pain interferes with the pain sufferer’s ability to carry out activities of daily living (e.g., work, relationships, hobbies, sex).¹⁴ It also has adverse psychological consequences. Patients with inadequately managed pain may experience anxiety, fear, anger, depression, or cognitive dysfunction,¹⁵ and family members report varying levels of helplessness, frustration, and “heartbreak.”¹³²

These consequences are especially likely to occur in patients with chronic pain. These individuals report impairments on multiple measures of physical, social, and psychological well-being, and many experience psychological symptoms (e.g., depression, anxiety) that adversely influ-

Table 5. Examples of Physiological Consequences of Unrelieved Pain

Functional Domain	Stress Responses to Pain	Examples of Clinical Manifestations
Endocrine/metabolic	Altered release of multiple hormones (e.g., ACTH, cortisol, catecholamines, insulin) with associated metabolic disturbances	Weight loss Fever Increased respiratory and heart rate Shock
Cardiovascular	Increased heart rate Increased vascular resistance Increased blood pressure Increased myocardial oxygen demand Hypercoagulation	Unstable angina (chest pain) Myocardial infarction (heart attack) Deep vein thrombosis (blood clot)
Respiratory	Decreased air flow due to involuntary (reflex muscle spasm) and voluntary (“splinting”) mechanisms that limit respiratory effort	Atelectasis Pneumonia
Gastrointestinal	Decreased rate of gastric emptying Decreased intestinal motility	Delayed gastric emptying, constipation, anorexia, ileus ^a
Musculoskeletal	Muscle spasm Impaired muscle mobility and function	Immobility Weakness Fatigue
Immune	Impaired immune function	Infection
Genitourinary	Abnormal release of hormones that affect urine output, fluid volume, and electrolyte balance	Decreased urine output Hypertension (fluid retention) Electrolyte disturbances

Sources: References 13 and 23.

^aMechanical, dynamic, or adynamic obstruction of bowel often manifests as colicky pain, distension, vomiting, and absence of the passage of stool.

ACTH: adrenocorticotrophic hormone.

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ence health care.¹⁵ Left unchecked, these symptoms can contribute to more serious consequences. In one study, about half of the patients with CNCP reported that they had considered suicide despite the availability of resources and coping strategies.¹⁰⁵

c. Financial consequences

Pain costs Americans an estimated \$100 billion each year.^{4,133} Patients, families, health care organizations, and society bear this financial burden. Patients with chronic pain are five times as likely as those without chronic pain to use health care services.¹⁵ In addition, medical complications associated with inadequately controlled acute pain can increase length of stay, re-hospitalization rates, and outpatient visits.¹³⁵ Results from some studies (e.g., Burke et al.^{h,135}) suggest that adequate management of acute (postoperative) pain can reduce length of stay and costs.

Pain is also costly in terms of lost productivity and income. It is a leading cause of medically related work absenteeism and results in more than 50 million lost work days per year in the United States.^{2,136} About 25% of the population in industrialized nations suffers from chronic pain of sufficient severity that they miss days of work.¹³⁷ Individuals with chronic pain often face long-term or permanent unemployment or underemployment.

E. BARRIERS TO THE APPROPRIATE ASSESSMENT AND MANAGEMENT OF PAIN

The undertreatment of pain reflects barriers to both assessment and management. These barriers can be broadly categorized as those attributable to the health care system, clinicians, patients and families, laws and regulations, and society.^{134,138-139} Collectively, these barriers contribute to a failure to assess pain, to accept the patient's self-report of pain, and/or to take appropriate action.¹⁴⁰

^hBurke et al. compared resource utilization and costs between groups of patients who did or did not receive ketorolac for management of postoperative pain.¹³⁵

1. Barriers Within the Health Care System

Systems barriers to pain assessment and management include an absence of clearly articulated practice standards and failure of the system to make pain relief a priority.^{134,141-142} For example, some health care organizations fail to adopt a standard pain assessment tool or to provide staff with sufficient time and/or chart space for documenting pain-related information.¹³⁴ Others fail to provide clinicians with practical tools and training to improve pain management such as CPGs, algorithms, protocols, and computer help screens. However, the greatest systems barrier to appropriate pain management is a lack of accountability for pain management practices. Institutions and health care organizations must implement means of holding clinicians accountable for adequate pain assessment and management (e.g., chart audits of pain documentation, pain competencies in staff orientation and performance evaluations, formal reviews for critical incidents) to ensure effective pain management.¹³⁴

Recent changes in the health care system (e.g., growth of managed care, shift from inpatient to outpatient treatment settings, new reimbursement policies) also have introduced barriers to pain management. Patient care is more fragmented; thus, the risk of poor coordination of care across treatment settings is increased.^{141,143} The use of gatekeepers and formularies by managed care organizations may impede access to pain specialists, comprehensive pain management facilities, and certain analgesic therapies.^{141,143} In addition, inconsistent reimbursement policies for pain treatment, or concern that aggressive treatment will increase costs, can lead to inadequate treatment of pain.¹⁴⁴

2. Health Care Professional Barriers

Clinicians' attitudes, beliefs, and behaviors contribute to the undertreatment of pain. For example, some clinicians do not view pain relief as important and/or do not want to "waste time" assessing pain.¹⁴¹ Others refuse to accept that the patient's self-report is the most reliable indicator of pain. Studies have shown that lack of assessment, underassessment, and a disparity between the clinician's and the patient's ratings of pain intensity are major causes of inadequately controlled pain (e.g., Donovan et al.,¹⁰⁷ Drayer et al.,¹¹⁴ Grossman et al.,¹⁴⁵ Gu and Belgrade,¹¹¹ Paice et al.,¹⁴⁶ Von Roenn et al.¹⁴⁷).

Section I: Background and Significance

Inappropriate or exaggerated concerns and inadequate or inaccurate clinical knowledge also limit clinicians' abilities to appropriately manage pain.^{139,141,144} Concerns often relate to aspects of pharmacologic treatment such as regulatory scrutiny, analgesic side effects, and iatrogenic addiction (see I.E.5). Problems with clinical knowledge include inadequate understanding of pharmacology and misconceptions about pain (Table 6).

3. Patient and Family Barriers

Whereas poor clinician-patient communication may reflect deficits in the clinician's skills, certain patient characteristics (e.g., age, language, cognitive abilities, coexisting physical or psychological illness, cultural traditions) may impair a patient's ability to communicate.¹³ Alternatively, patients may be reluctant to report pain to clinicians due to low expectations of obtaining relief, stoicism, fears, or concerns about what the pain means (e.g., worsening disease, death), analgesic side effects, or addiction.¹⁴¹ In a recent survey of terminally ill

patients, whereas half experienced moderate to severe pain, only 30% wanted additional pain treatment.¹²¹ Reasons the patients offered for declining additional therapy included fear of addiction, dislike of mental or physical drug side effects, and not wanting to take more pills or injections.

Other patient and family factors that contribute to the undertreatment of pain include financial barriers (e.g., lack of health insurance, high cost of certain medications) and even poor adherence to treatment regimens.^{14,141} Limited data suggest that patients do not always take analgesics as prescribed.¹⁴⁸⁻¹⁵⁰ In addition, some patients with chronic pain do not seek medical attention. A recent survey of individuals with CNCP suggested that, while most chronic pain sufferers have visited a doctor at some point, almost 40% are not currently under the care of a physician.¹⁴ Difficulty in locating a clinician who could effectively manage their pain was a commonly cited reason.

4. Legal and Societal Barriers

Legal and societal issues also contribute to the undertreatment of pain. The former include restrictive laws or regulations about the prescribing of controlled substances as well as confusion about the appropriate role of opioids in pain treatment.^{141,151} Societal issues that contribute to the undertreatment of pain include drug abuse programs and erroneous beliefs about tolerance, physical dependence, and addiction (see I.E.5). For example, some clinicians incorrectly assume that exposure to an addictive drug usually results in addiction.

5. Tolerance, Physical Dependence, and Addiction

a. Definitions

Many medications, including opioids, play important roles in pain management. However, concerns about their potential misuse and misunderstanding of the nature and risk of addiction limit their appropriate use.¹⁵² Disparate definitions of tolerance, physical dependence, and addiction contribute to this problem. Therefore, the American Society of Addiction Medicine (ASAM), the American Academy of Pain

Table 6. Common Misconceptions About Pain

The incorrect beliefs that:

- Physical or behavioral signs of pain (e.g., abnormal vital signs, grimacing, limping) are more reliable indicators of pain than patient self-report.
- Elderly or cognitively impaired patients cannot use pain intensity rating scales.
- Pain does not exist in the absence of physical or behavioral signs or detectable tissue damage.
- Pain without an obvious physical cause, or that is more severe than expected based on findings, is usually psychogenic.
- Comparable stimuli produce the same level of pain in all individuals (i.e., a uniform pain threshold exists).
- Prior experience with pain teaches a person to be more tolerant of pain.
- Analgesics should be withheld until the cause of the pain is established.
- Noncancer pain is not as severe as cancer pain.
- Patients who are knowledgeable about pain medications, are frequent emergency department patrons, or have been taking opioids for a long time are necessarily addicts or "drug seekers."
- Use of opioids in patients with pain will cause them to become addicted.
- Patients who respond to a placebo drug are malingering.
- Neonates, infants, and young children have decreased pain sensation.

Sources: References 13 and 140.

Section I: Background and Significance

Medicine (AAPM), and the American Pain Society (APS) recently recommended use of the following definitions:¹⁵²

- **Tolerance:** “Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug’s effects over time.”
- **Physical Dependence:** “Physical dependence is a state of adaptation that often includes tolerance and is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.”
- **Addiction:** “Addiction is a primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.”

Although other definitions exist (e.g., DSM-IV), experts consider these terms the most applicable to pain management. A related term, pseudoaddiction, refers to patient behaviors that may occur when pain is undertreated, including increased focus on obtaining medications (“drug seeking”), “clock watching,” and even illicit drug use or deception.¹⁵³ Pseudoaddiction can be distinguished from true addiction because such behaviors resolve with effective pain management.¹⁵²

b. Etiology, issues, and concerns

Many medications produce tolerance and physical dependence, and some (e.g., opioids, sedatives, stimulants, anxiolytics, some muscle relaxants) may cause addiction in vulnerable individuals.¹⁵² Most experts agree that patients who undergo prolonged opioid therapy usually develop physical dependence but do not develop addictive disorders.¹⁵² In general, patients in pain do not become addicted to opioids. Although the actual risk of addiction is unknown,¹⁵² it is thought to be quite low. A recent study of opioid analgesic use revealed “low and stable” abuse of opioids between 1990 and 1996 despite significant increases in opioids prescribed.¹⁵⁴ Drug exposure appears to be only one etiologic factor in the development of addiction,¹⁵² and genetic, social, and psycholog-

ic factors may be more significant determinants.¹⁵⁵⁻¹⁵⁸

Fear of causing addiction (i.e., iatrogenic addiction), particularly with opioid use, is a major barrier to appropriate pain management.^{8,159-162} This fear sometimes reflects a lack of understanding of the risk of addiction with therapeutic drug use. Although studies suggest that the risk of iatrogenic addiction is quite low (e.g., Perry and Heidrich,¹⁶³ Zenz et al.¹⁶⁴), surveys indicate that clinicians often overestimate this risk.¹⁶⁵⁻¹⁶⁷ Alternatively, clinicians may be reluctant to prescribe an opioid because they have witnessed the devastation that addiction can cause in a patient’s life.

Clinicians are also often reluctant to prescribe opioids due to concerns about licensing issues, peer review, state disciplinary action, and even legal prosecution (i.e., for over-prescribing, or under-prescribing, controlled substances).¹⁰⁴ The Federation of State Medical Boards of the United States (FSMB) acknowledges such potential in their 1998 “Model Guidelines for the Use of Controlled Substances for the Treatment of Pain.”¹⁶⁰ These guidelines attribute inadequate pain control to three major factors:

- Physicians’ lack of knowledge about pain management,
- Inadequate understanding of addiction, and
- Fear of investigation or sanction by federal, state, and local regulatory agencies.¹⁶⁰

These guidelines acknowledge that: “controlled substances, including opioid analgesics, may be essential in the treatment of acute pain due to trauma or surgery and chronic pain, whether due to cancer or non-cancer origins.”¹⁶⁰ They assert that physicians should not fear disciplinary action for prescribing, dispensing, or administering controlled substances for a legitimate medical purpose (including pain) in the usual course of professional practice.¹⁶⁰ However, they also state that “all such prescribing must be based on clear documentation of unrelieved pain and in compliance with applicable state or federal law.”¹⁶⁰ These guidelines and other information about regulatory issues are located at www.fsbm.org/policy.htm and <http://www.medsch.wisc.edu/painpolicy>, respectively, on the World Wide Web. The latter URL also contains up-to-date information on specific state laws and regulations.



Section II:
**Assessment
of Pain**

Section II: Assessment of Pain

A. INITIAL ASSESSMENT OF PAIN

Assessment is an essential, but challenging, component of any pain management plan. Pain is subjective, so no satisfactory objective measures of pain exist. Pain is also multidimensional, so the clinician must consider multiple aspects (sensory, affective, cognitive) of the pain experience. Finally, the nature of the assessment varies with multiple factors (e.g., purpose of the assessment, the setting, patient population, clinician), so no single approach is appropriate for all patients or settings.

This section reviews some core principles of pain assessment and management to help guide this process. It then explores approaches that clinicians can use in the initial assessment of pain (i.e., patient history, physical examination, diagnostic studies). Subsequent discussions explore tools that facilitate assessment and address the reassessment of pain.

1. Overcoming Barriers to Assessment

Underassessment of pain is a major cause of inadequate pain management (see I.E.). In fact, the most common reason for the undertreatment of pain in U.S. hospitals is the failure of clinicians to assess pain and pain relief.¹ This situation has prompted recent efforts to raise clinicians' awareness of the importance of pain assessment. In 1996, the American Pain Society (APS) introduced the phrase "pain as the 5th vital sign."^{a,2} This initiative emphasizes that pain assessment is as important as assessment of the standard four vital signs and that clinicians need to take action when patients report pain.¹ The Veterans Health Administration recognized the value of such an approach and included pain as the 5th Vital Sign in their national pain management strategy.³

In addition to these efforts, the Joint Commission on Accreditation of Healthcare Organization (JCAHO) recently introduced standards for pain assessment and management relevant to multiple health care disciplines and settings (see V.B.1). These standards stress patients' rights to appropriate assessment and management of pain (JCAHO Standard RI 1.2.8, 2000) and emphasize that pain should be assessed in all patients (JCAHO Standard PE1.4, 2000).⁴ Multiple additional clinical practice guidelines (CPGs) for pain management have emerged

since the first guideline for pain management in 1992 (see V). Thus, the means for improved pain assessment and management are readily available. Successful pain management depends, in part, on clinician adherence to such standards and guidelines and commitment to some core principles of pain assessment and management (Table 7).

2. Goals and Elements of the Initial Assessment

Important goals of the initial assessment of pain include establishing rapport with the patient and providing an overview of the assessment process.⁸ These processes help to engage the patient, foster appropriate treatment expectations, and promote a coordinated approach to management. The clinician's primary objective is to obtain information that will help identify

Table 7. Core Principles of Pain Assessment and Management

- Patients have the right to appropriate assessment and management of pain (JCAHO Standard RI 1.2.8, 2000). Pain (should be) is assessed in all patients (JCAHO Standard PE1.4, 2000).
- Pain is always subjective.¹ Therefore, the patient's self-report of pain is the single most reliable indicator of pain.⁵ A clinician needs to accept and respect this self-report, absent clear reasons for doubt.
- Physiological and behavioral (objective) signs of pain (e.g., tachycardia, grimacing) are neither sensitive nor specific for pain.⁵ Such observations should not replace patient self-report unless the patient is unable to communicate.⁵
- Assessment approaches, including tools, must be appropriate for the patient population. Special considerations are needed for patients with difficulty communicating. Family members should be included in the assessment process, when possible.
- Pain can exist even when no physical cause can be found. Thus, pain without an identifiable cause should not be routinely attributed to psychological causes.
- Different patients experience different levels of pain in response to comparable stimuli. That is, a uniform pain threshold does not exist.
- Pain tolerance varies among and within individuals depending on factors including heredity, energy level, coping skills, and prior experiences with pain.
- Patients with chronic pain may be more sensitive to pain and other stimuli.
- Unrelieved pain has adverse physical and psychological consequences. Therefore, clinicians should encourage the reporting of pain by patients who are reluctant to discuss pain, deny pain when it is likely present, or fail to follow through on prescribed treatments (JCAHO standard PE1.4, 2000).
- Pain is an unpleasant sensory and emotional experience, so assessment should address physical and psychological aspects of pain.

Sources: References 1 and 4-7.

^aThe Pain as the 5th Vital Sign initiative is a concept, not a guide, for pain assessment. Whereas assessing pain with each assessment of the standard four vital signs is appropriate in some clinical situations, more or less frequent assessment may be appropriate in others.

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the cause of the pain and guide management. A patient history, physical examination, and appropriate diagnostic studies are typically conducted for this purpose.

a. Patient history

The patient's self-report of pain is the most reliable indicator of pain.⁵ Physiological and behavioral (objective) signs of pain (e.g., tachycardia, grimacing) are neither sensitive nor specific for pain and should not replace patient self-report unless the patient is unable to communicate.⁵ Therefore, talking to patients and asking them about their pain (i.e., obtaining a "pain history") is integral to pain assessment.

The pain history usually is obtained as part of the patient history, which includes the patient's past medical history, medications, habits (e.g., smoking, alcohol intake), family history, and psychosocial his-

tory. Obtaining a comprehensive history provides many potential benefits, including improved management, fewer treatment side effects, improved function and quality of life, and better use of health care resources.⁹

The manner in which information is elicited from the patient is important. Ideally, the clinician should afford ample time, let the patient tell the story in his or her own words, and ask open-ended questions. Information to be elicited during the initial assessment of pain includes (see Table 8):

- Characteristics of the pain (e.g., duration, location, intensity, quality, exacerbating/alleviating factors)
- Present and past pain management strategies and their outcomes
- Past and present medical problems that may

Table 8. Information From the Patient History

Parameter	Information To Be Obtained	Sample Questions
Pain characteristics	Onset and duration Location(s) Quality Intensity (severity) Associated symptoms Exacerbating or alleviating factors	When did the pain begin? Where does it hurt? (Use diagram, when possible.) What does the pain feel like? How severe is the pain right now? (Use numeric rating scale to obtain score, when possible.) What increases or decreases the pain?
Management strategies	Past and current: • Medications ("natural," nonprescription, and prescription) • Nonpharmacologic treatments • Coping strategies (e.g., prayer, distraction)	What methods have you used to manage the pain? What methods have worked?
Relevant medical history	Prior illnesses (including psychiatric illnesses and chemical dependence), surgeries, and accidents Coexisting acute or chronic illnesses Prior problems with pain and treatment outcomes	How is your general health?
Relevant family history	Health of family members Family history of chronic pain or illnesses	Have you had any problems with pain in the past? If so, how did you manage the pain?
Psychosocial history	Past or current: • Developmental, marital, or vocational problems • Stressors or depressive symptoms • "Reinforcers" of the pain (e.g., compensation-litigation issues)	How is the health of your family? Do any family members have problems with pain?
Impact of the pain on the patient's daily life	Impact of the pain on the patient's: • Work • Other daily activities (e.g., chores, hobbies) • Personal relationships • Sleep, appetite, emotional state	Are there any recent sources of increased stress? How has the pain affected your mood?
Patient's expectations and goals	Expectations and goals for pain management in regard to pain intensity, daily activities, and quality of life	How has the pain affected your work and relationships with others? How is your sleep? How is your appetite?
Sources: References 5 and 7-8.		What are your goals for treatment?

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- influence the pain and/or its management
- Relevant family history
- Current and past psychosocial issues or factors that may influence the pain and its management
- The impact of the pain on the patient's daily life and functioning
- The patient's and family's knowledge of, expectations about, and goals for pain management.

Careful characterization of the pain facilitates diagnosis and treatment (see Table 9). Assessment tools (e.g., rating scales, questionnaires) play an

important role in this process (see II.B). Both the choice of tool and the general approach to assessment should reflect the needs of the patient.

The assessment of pain in some patients warrants special consideration. Tables 10 and 11 summarize approaches to assessment in patients with impaired ability to communicate. Tables 12 and 13 review recommended pre- and post-operative assessment and management methods for perioperative pain, including pain after the surgery (postoperative pain).

Patient education about these methods is a key element of the initial assessment of a surgical patient. As unrelieved pain has adverse physical and psychological consequences, clinicians should encourage the reporting of pain by patients who are reluctant to discuss pain or who deny pain that is likely to be present (JCAHO standard PE1.4, 2000).

The initial assessment of a patient with chronic pain, especially chronic noncancer pain (CNCP), also warrants special consideration. Associated neural remodeling (central sensitization) means that the pain may exist without an apparent physical cause (see I.B.8). In such cases, the clinician needs to avoid attributing the pain to psychological causes and to accept and respect the patient's self-report of pain.⁵ Other clinicians often have seen and/or treated patients with CNCP. Therefore, past medical records, test results, and treatment histories need to be obtained. Given the link between chronic pain and

Table 9. Characteristics of Pain Types

Characteristic	Pain Types and Examples
Location and distribution	Localized pain: pain confined to site of origin (e.g., cutaneous pain, some visceral pain, arthritis, tendonitis) Referred pain: pain that is referred to a distant structure (e.g., visceral pain such as angina, pancreatitis, appendicitis, acute cholecystitis) Projected (transmitted) pain: pain transferred along the course of a nerve with a segmental distribution (e.g., herpes zoster) or a peripheral distribution (e.g., trigeminal neuralgia) Dermatomal patterns: peripheral neuropathic pain Nondermatomal: central neuropathic pain, fibromyalgia No recognizable pattern: complex regional pain syndrome
Duration and periodicity	Brief flash: quick pain such as a needle stick Rhythmic pulses: pulsating pain such as a migraine or toothache Longer-duration rhythmic phase: intestinal colic Plateau pain: pain that rises gradually or suddenly to a plateau where it remains for a prolonged period until resolution (e.g., angina) Paroxysmal: neuropathic pain Continuously fluctuating pain: musculoskeletal pain
Quality	Superficial somatic (cutaneous) pain: sharp pricking or burning Deep somatic pain: dull or aching Visceral pain: dull aching or cramping Neuropathic pain: burning, shock-like, lancinating, jabbing, squeezing, aching Visceral pain: "sickening feeling," nausea, vomiting, autonomic symptoms Neuropathic pain: hyperalgesia, allodynia
Associated signs and symptoms	Complex regional pain syndrome: hyperalgesia, hyperesthesia, allodynia, autonomic changes, and trophic changes (skin, hair, nail changes)

Sources: References 8 and 10.

Table 10. Assessment of Patients With Barriers to Communication

Patient Populations

- Infants and children
- Individuals of advanced age (e.g., older than 85 years)
- Adults with emotional or cognitive disturbances
- Patients with cultural, educational, or language barriers to communication
- Intubated patients
- Patients who are seriously ill

General Approach

- Allow sufficient time for the assessment.
- Give patient the opportunity to use a rating scale or other tool appropriate for that population.
- Use indicators of pain according to the following hierarchy of importance:

Patient self-report
Pathological conditions or procedures known to be painful
Pain-related behaviors (e.g., grimacing, restlessness, vocalization)
Reports of pain by family members or caretakers
Physiological measures (vital signs).

- Rely on behavioral or objective indicators of pain (e.g., vital signs) only when no suitable alternative exists.

Sources: References 5, 7, and 11.

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Table 11. Assessment Challenges and Approaches in Special Populations

Population	Challenges	Approaches
Elderly	Under-reporting of discomfort due to fear, cultural factors, stoicism Impairments (e.g., hearing, vision, comprehension, verbal skills) may limit ability to communicate Difficulty with visually oriented or complex assessment tools	Avoid time pressure in assessment Evaluate for impairments that limit ability to communicate Use tools that the elderly find easy to use (e.g., FPS ^a) Be aware of changes in various parameters in elderly patients (impaired ADLs, social function, walking) that may be indicative of unrelieved pain
Infants and children	Difficulty communicating (e.g., pre-verbal) Difficulty discriminating between anxiety and pain intensity	Select an approach that is consistent with the patient's developmental stage For infants, rely on indicators such as crying and reflex withdrawal In toddlers, watch for pursed lips, wide opening of eyes, rocking, rubbing, defensive behavior (e.g., biting, hitting, kicking, running away) Use age-appropriate assessment tools for children 3 years or older (e.g., Oucher picture scale, FPS, "thermometer" NRS ^a)
Patients of different cultural or language backgrounds	Different languages Different behavioral responses to pain Different treatment preferences	Use words such as "pain," "hurt," and "ache" Use assessment tools in appropriate language Provide patient education materials in native language, when possible

Sources: References 7 and 11-16.

^aSee Table 17 for information about FPS and NRS.

ADLs: activities of daily living; FPS: Faces Pain Scale; NRS: numeric rating scale.

depression, the impact of the pain on the patient's mood, satisfaction, quality of life, and cognitive functioning also requires thorough exploration. Key elements of this evaluation include a more comprehensive psychosocial assessment, psychiatric evaluation, psychometric testing (as appropriate), and assessment of function and any disability (see Table 14).^{9,18}

b. Physical examination

The initial assessment of a patient with pain includes a physical examination. The clinician uses this examination to help identify the underlying cause(s) of the pain and reassure the patient that his or her complaints of pain are taken seriously.⁸ During this examination, the clinician appraises the patient's general physical condition, with special attention to the musculoskeletal and neurological systems and site(s) of pain (see Table 15). The clinician also may evaluate the effect of various physical factors (e.g., motion, applied heat or cold, deep breathing, changes in position) on the pain and/or performance measures of physical function (e.g., range of motion, ability of patient to carry out activities of daily living).

Patients with some types of pain (e.g., chronic and/or neuropathic pain) require more extensive neurological and musculoskeletal assessment. For exam-

ple, a clinician may need to use a dermatome map to determine the origin of neuropathic pain or perform a formal assessment of disability in a patient who is applying for disability benefits.

c. Diagnostic studies

The need for and type of diagnostic studies are determined by characteristics of the pain and suspected underlying condition. Appropriately selected tests can lead to accurate diagnosis and improve outcomes (e.g., reduce pain and adverse effects of therapy, improve function and quality of life).⁹ However, diagnostic studies are meant to supplement, not replace, a comprehensive patient history and physical examination. Table 16 summarizes examples of diagnostic studies used in patients with pain.

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Table 12. Preoperative Assessment and Patient Education Recommendations

- Establish a positive relationship with patients and/or families.
- Obtain a pain history.
- Educate the patient about pain assessment (e.g., methods, frequency) and pharmacologic and nonpharmacologic management strategies.
- Explore concerns/dispel misconceptions about use of pain medications, side effects, and addiction.
- Develop a strategy for postoperative analgesia in collaboration with the patient based on type of surgery, expected severity of postoperative pain, underlying medical conditions, the risk-benefit ratio and costs of available techniques, and patient's preferences and/or previous experience(s) with pain.
- Involve the patient in selecting an appropriate^a pain measurement tool (e.g., NRS, VAS), and review its features with the patient.
- Educate the patient (and/or families) about their responsibilities in pain management (e.g., providing a factual report of pain, preventing or halting pain before it has become well established). Negotiate a criterion (e.g., a score of 3-4 on a 10-point pain intensity scale) that will result in a dose increment or other intervention.
- Document the patient's preferred pain assessment tool and the goals for pain control (pain score).

Sources: References 5 and 17.

^aFactors that help to determine the appropriate tool include: 1) the patient's age; physical, emotional, or cognitive status; and preference; 2) the assessor's expertise, time, and degree of effort available; and 3) the institution's requirements for monitoring and documentation for quality assurance purposes.

NRS: numeric rating scale; VAS: visual analog scale.

Table 13. Postoperative Assessment and Patient Education Recommendations

- Assess multiple indicators of pain, including 1) patient perceptions (self-report), 2) cognitive attempts to manage pain, 3) behavioral responses (e.g., splinting the operative site, distorted posture, decreased mobility, insomnia, anxiety, depression), and 4) physiological responses (vital signs).
- Accept the patient self-report, and only substitute behavior and/or physiological responses if the patient is unable to communicate.
- Measure pain at rest and during activity (e.g., moving, deep breathing, coughing).
- Assess pain frequently during the immediate postoperative period: 1) at regular intervals, consistent with surgery type and pain severity (e.g., every 2 hours while awake for 1 day after surgery); 2) with each new report of pain; and 3) at a suitable interval after each analgesic intervention (e.g., 30 minutes after parenteral drug therapy, and 1 hour after oral analgesics). Increase the frequency of assessment for changing interventions or inadequate pain control.
- Record pain intensity and response to any interventions (including side effects) in a visible and accessible place (e.g., bedside chart).
- Immediately evaluate instances of unexpected intense pain, particularly if sudden or associated with evidence of potential complications.^a
- Consider all reasons for any discrepancies between a patient's self-report of pain and his or her behavior. Such discrepancies may reflect good coping skills or diversionary activities (e.g., distraction, relaxation techniques). Alternatively, a patient may be denying pain because of stoicism or fear of inadequate pain control.
- Give special consideration to needs of special populations, and be aware of potential barriers to effective communication (e.g., mental, cognitive, or hearing impairments; language barriers; cultural traditions).
- Revise the management plan, as needed, if pain behavior is observed or the patient expresses feelings of inadequate pain control.
- Prior to patient discharge, review with the patient the interventions used and their efficacy; provide specific discharge instructions regarding outpatient pain management.

Sources: References 5 and 17.

^aSigns such as fever, hypertension, tachycardia, or oliguria may be indicative of complications including wound dehiscence, infection, or deep venous thrombosis.

B. MEASUREMENT OF PAIN: COMMON ASSESSMENT TOOLS

Tools for pain assessment include unidimensional scales and multidimensional tools. The former (i.e., rating scales) usually assess a single dimension of pain, patient self-report of pain intensity. Although useful for assessing acute pain of clear etiology (e.g., postoperative pain), rating scales may oversimplify the assessment of some types of pain.¹² Therefore, experts recommend the use of multidimensional tools in the assessment of complex or persistent pain.

1. Unidimensional Scales

Rating scales provide a simple means for patients to rate pain intensity. Typical scales use numeric (e.g., 0-10), verbal (word), or visual (image) descriptors to quantify pain or pain relief. The tool should be appropriate for the patient's developmental, physical, emotional, and cognitive status, as well as reli-

able, valid, and easy to use.⁵ Examples of these scales include the following (see Table 17):

- **Numeric rating scale (NRS):** The NRS is the most commonly used rating scale. Patients rate their pain on a 0-to-10 scale or a 0-to-5 scale, with 0 representing "no pain at all" and 5 or 10 representing "the worst imaginable pain." Pain intensity levels are measured at the initial encounter, following treatment, and periodically, as suggested by guidelines and the clinical situation.
- **Visual analog scale (VAS):** The VAS consists of a 10-cm line, with anchors at either end. One end is marked "no pain" and the other end is marked

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Table 14. Additional Aspects of the Patient History in Patients With Chronic Noncancer Pain

- Pain treatment history: full review of results from past work-ups and treatments as well as patient's utilization of health care resources (e.g., office visits).
- Comprehensive psychosocial evaluation focused on: 1) patient responses to chronic pain (e.g., coping skills, avoidance of stressors, presence of chronic pain syndrome); 2) what the pain means to the patient; 3) evidence of family, legal, or vocational issues; and 4) expectations of family members, employers, attorneys, or social agencies (e.g., Social Security Administration). This evaluation may involve interviewing family members, too.
- Psychiatric interview to: 1) identify any psychological symptoms (e.g., depression, anxiety, anger), coexisting psychiatric disorders, or psychological traits; 2) evaluate suicide risk in patients with clinical signs of depression (e.g., sleep or appetite disturbances, hopelessness); and 3) identify history of events (e.g., severe or extreme trauma) that may lead to somatization or pain.
- Psychometric tests,^a when appropriate, to provide information about the pain, associated problems, and any coexisting psychopathology.
- Assessment of function and any disability to determine the patient's ability to perform daily activities (e.g., household chores, work tasks, leisure interests) and function autonomously, as well as the presence and levels of disability. Questionnaires such as the Pain Disability Index can be used to assess levels of disability, when appropriate. More formal evaluation of disability may be needed in some cases (e.g., application for disability benefits).
- Review of results with patient and family: This is the first step in the treatment of chronic noncancer pain, providing an opportunity to establish the rehabilitative focus of pain management and set realistic treatment goals.

Sources: References 8 and 18.

^aPsychometric tests include pain-related instruments (e.g., McGill Questionnaire, Multidimensional Pain Inventory, Beck Depression Inventory) and personality assessment instruments (e.g., Minnesota Multiphasic Personality Inventory-2, Coping Strategies Questionnaire).

selects the face that is consistent with his or her current level of pain.

2. Multidimensional Tools

Although not used as often as they should be, multidimensional tools provide important information about the pain's characteristics and effects on the patient's daily life.^{12,22} These tools are designed for patient self-report, but a clinician may assist the patient. Examples of multidimensional tools include (see Table 18):

- *Initial Pain Assessment Tool:* This tool, which was developed for use in the initial patient evaluation, elicits information about characteristics of the pain, the patient's manner of expressing pain, and the effects of the pain on the patient's life (e.g., daily activities, sleep, appetite, relationships, emotions).⁷ It includes a diagram for indicating pain location(s), a scale for the patient to rate pain intensity, and a space for documenting additional comments and management plans.
- *Brief Pain Inventory (BPI):* This tool is quick and easy to use and quantifies both pain intensity and associated disability.^{12,34-35} It consists of a series of questions that address aspects of the pain experienced over the preceding 24 hours (e.g., pain location and intensity, impact on the patient's life, type and effectiveness of any treatments). The BPI generally takes about 5 to 15 minutes to complete and is useful for a variety of patient populations.³⁶⁻³⁷
- *McGill Pain Questionnaire (MPQ):* The MPQ is one of the most extensively tested multidimensional scales in use.³² This tool assesses pain in three dimensions (i.e., sensory, affective, and evaluative) based on words that patients select to describe their pain. The MPQ can be combined with other tools to improve diagnostic accuracy.¹² A briefer form of the MPQ, the short-form McGill Pain Questionnaire, is also available.³⁹

A number of other multidimensional tools for pain assessment exist.¹² Some are designed to measure chronic pain in general, while others are specific to particular pain syndromes. In addition, some quality of life instruments (e.g., Medical Outcome Study Short-Form 36 Health Survey Instrument) assess pain.

"pain as bad as it could be" or "the worst imaginable pain." The patient marks the place on the line to indicate his or her pain intensity. The clinician then measures the line with a ruler and assigns a score.²⁸

- *Categorical scales:* Categorical scales provide a simple means for patients to rate pain intensity using verbal or visual descriptors of the pain. Melzack and Torgerson²⁹ introduced a scale with five verbal descriptors (i.e., mild, discomforting, distressing, horrible, and excruciating). The Faces Pain Scale (FPS) for Adults and Children¹⁶ and the Wong-Baker Faces Rating Scale (for children)³⁰⁻³¹ are categorical scales with visual descriptors. The FPS consists of eight images of faces with various expressions (e.g., smiling, frowning, grimacing). The patient

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Table 15. Physical Examination of a Patient With Pain

Region	Rationale, Methods, and Potential findings
General	Observe and/or identify: <ul style="list-style-type: none">• Patient's general appearance and vital signs• Evidence of overt abnormalities (e.g., weight loss, muscle atrophy, deformities, trophic changes)• Any subjective manifestations of pain (e.g., grimacing, splinting)
Site of pain	Inspect the pain site(s) for abnormal appearance or color of overlying skin or visible muscle spasm Palpate the site(s) to assess for tenderness and correlate tenderness with any associated subjective or objective findings Use percussion (or jarring) to elicit, reproduce, or evaluate the pain and any tenderness on palpation Use the brush, pinch, pin prick, and/or scratch tests to assess for allodynia, hyperalgesia, or hyperesthesia Determine the effects of physical factors (e.g., motion, applied heat or cold, deep breathing, changes in position) on pain
Other regions	Examine other regions as directed by the patient history or assessment of pain site
Neurological system	At minimum, perform a screening neurological examination (i.e., assess cranial nerves, spinal nerves, sympathetic nervous system function, coordination, and mental status) to screen for: <ul style="list-style-type: none">• Sensory deficits (e.g., impaired vision or hearing) or abnormal sensations (e.g., paresthesia, dysesthesia, allodynia, hyperesthesia)• Motor abnormalities or deficits (e.g., weakness, exaggerated or diminished reflexes)• Lack of coordination• Evidence of sympathetic nervous system dysfunction (e.g., skin flushing, unusual sweating)• Abnormalities or deficits in orientation, recent or remote memory, parietal sensory function, language function, and mood
Musculoskeletal system	Observe and/or identify: <ul style="list-style-type: none">• Body type, posture, and overall symmetry• Abnormal spine curvature or limb alignment and other deformities• Abnormal movements and/or irregular gait during walking• Range of motion (spine, extremities) For muscles in neck, upper extremities, trunk, and lower extremities: <ul style="list-style-type: none">• Assess multiple parameters (e.g., tone, volume, contour, strength and power, range of motion)• Observe for any abnormalities (e.g., weakness, atrophy, hypertrophy, irritability, tenderness, trigger points)

Source: Reference 8.

Table 16. Examples of Diagnostic Tests

Type	Definition	Potential Uses
Screening laboratory tests	Includes CBC, chemistry profile (e.g., electrolytes, liver enzymes, BUN, creatinine), urinalysis, ESR	Screen for illnesses, organ dysfunction
Disease-specific laboratory tests	Includes autoantibodies, sickle cell test	Autoimmune disorders, SCD
Imaging studies	Includes radiographs (x-rays), CT, MRI, US, myelography	Detection of tumors, other structural abnormalities
Diagnostic procedures	Includes lumbar puncture, thoracentesis, paracentesis, biopsy	Detection of various illnesses
Electrodiagnostic tests	Include EMG (direct examination of skeletal muscle via needle electrodes) and NCS (examination of conduction along peripheral sensory and motor nerves or plexuses)	Detection of myopathies, some neuropathies, MS
Diagnostic nerve block	Nerve block (injection of a local anesthetic to determine the source/mechanism of the pain)	Multiple uses, ^a including: <ul style="list-style-type: none">• Identification of structures responsible for the pain (e.g., sacroiliac or facet joint blocks)• Differentiation between types of pain

Sources: References 19-20a.

^aDiagnostic neural blockade (pain blocks) with a local anesthetic may be useful in determining the anatomic source of the pain, nociceptive pathways, or the contribution of the sympathetic nervous system to the pain.^{20a} They also may allow differentiation between local vs. referred pain, somatic vs. visceral pain, or central vs. peripheral pain.

BUN: blood urea nitrogen; CBC: complete blood count; CT: computed tomography; EMG: electromyography; ESR: erythrocyte sedimentation rate; MRI: magnetic resonance imaging; MS: multiple sclerosis; NCS: nerve conduction studies; SCD: sickle cell disease; US: ultrasound.

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Table 17. Unidimensional Pain Assessment Tools

Scale	Administration	Advantages	Disadvantages	Comments
Numeric rating scale (NRS)	Verbal or visual	Easy to use Simple to describe High rate of adherence Flexible administration (including by telephone) Validated for numerous settings and pain types (acute, cancer, CNCP)	Less reliable for some patients (very young or old; patients with visual, hearing, or cognitive impairment)	Most commonly used rating scale
Visual analog scale (VAS)	Visual	Efficient to administer Valid in patients with chronic pain, older than age 5 years, rheumatic disease	Time-consuming scoring Controversial validity Can cause patient confusion Poor reproducibility with cognitive dysfunction	FPS generally preferred to the VAS for assessment in the elderly
Faces pain scale (FPS)	Visual	Perceived as easier than NRS or VAS No influence of culture, gender, or ethnicity Useful in individuals with difficulty communicating (e.g., children, elderly, individuals with limited language fluency or education)	Potential for distorted assessment (i.e., patients' tendency to point to the center of such scales) Need for instrumentation (i.e., a printed form)	Good alternative for patients with difficulty communicating

Sources: Reference 7, 11-13, 16, and 21-27.

CNC: chronic noncancer pain; FPS: Faces Pain Scale; NRS: numeric rating scale; VAS: visual analog scale.

Table 18. Multidimensional Pain Assessment Tools

Scale	Administration	Advantages	Disadvantages or Comments
Brief Pain Inventory (BPI)	Visual	Reliable and valid for many clinical situations (e.g., cancer pain, arthritis pain, pain associated with HIV infection) and across cultures and languages Available in multiple languages Quick, quantifies pain intensity and disability	Used both clinically and in research Good choice of measure in patients with progressive conditions
Initial Pain Assessment Inventory (IPAI)	Visual	May be completed by patient or clinician Includes diagram for illustrating sites of pain	
McGill Pain Questionnaire (MPQ)	Verbal	Extensively tested Assesses sensory and affective dimensions of pain Short form takes only 2-3 minutes	Long form takes 5-15 minutes to complete Some patients confused by vocabulary Total score, but not individual scale scores, is considered valid measure of pain severity
Memorial Pain Assessment Card	Visual	Rapid to use Correlated with other longer measures of pain and mood Can fold card so that the patient views only one scale at a time	Assesses pain relief and mood on VAS and adds a set of adjectives reflecting pain intensity
Pain drawing	Written	May demonstrate nature of pain at a glance (e.g., radiculopathy, peripheral neuropathy, trigeminal neuralgia, arthritis) Helps to avoid overlooking pain that the patient fails to mention	

Sources: References 7, 12, and 32-38.

BPI: Brief Pain Inventory; HIV: human immunodeficiency virus; IPAI: Initial Pain Assessment Inventory; MPQ: McGill Pain Questionnaire; VAS: Visual analog scale.

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3. Neuropathic Pain Scale

Although the Short Form MPQ³⁹ provides some information about neuropathic pain, it does not quantify it. The recently developed Neuropathic Pain Scale provides information about the type and degree of sensations experienced by patients with neuropathic pain.²⁷ It evaluates eight common qualities of neuropathic pain (i.e., sharp, dull, hot, cold, sensitive, itchy, and deep versus surface pain). The patient rates each item on a scale from 0 to 10, with 0 for none and 10 for the “most imaginable.” Although still in its developmental form, this scale may hold diagnostic and therapeutic promise.⁷ Early data suggest that this scale is easy to use and sensitive to treatment effects.²⁷

signs (i.e., as a fifth vital sign) is useful in some clinical settings. However, the frequency of vital signs checks in others settings suggests the need for more or less frequent reassessment. Clinicians should instruct outpatients to contact them to report changes in the pain’s characteristics, side effects of treatment, and treatment outcomes. Periodic reassessment is recommended in patients with chronic pain to evaluate improvement, deterioration, or treatment-related complications.^{9,40} Residents of long-term health care facilities should be assessed for pain upon admission, at quarterly reviews, with changes in the patient’s medical condition, and whenever pain is suspected.⁴¹

C. REASSESSMENT OF PAIN

Reassessment of pain is integral to effective pain management. Many factors influence its frequency, scope, and methods. This section reviews some approaches to reassessment in common clinical settings and situations.

1. Frequency

The 1992 Agency for Health Care Policy and Research^b CPG states that pain should be reassessed: 1) within 30 minutes of parenteral drug administration, 2) within one hour of oral drug administration, and 3) with each report of new or changed pain.⁵ However, these recommendations pertain to the reassessment of acute pain in an acute care setting. Multiple factors determine the appropriate frequency of pain reassessment, including characteristics of the pain (e.g., duration, severity), patient factors and needs, the clinical setting, and pain management plan (i.e., type of drug or intervention).

Reassessing pain with each evaluation of the vital

2. Scope and Methods

The scope and methods of reassessment vary with factors including the setting, characteristics of the pain, the patient’s needs and medical condition, and responses to treatment. Routine screening for pain with a pain rating scale provides a useful means of detecting unidentified or unrelieved pain. Appropriate tools, as well as terms synonymous with pain (e.g., burning, discomfort, aching, soreness, heaviness, tightness), should be used to screen elderly patients.⁴⁰ The presence of any pain indicates the need for further assessment, consideration of pain-relieving interventions, and post-intervention follow-up.³ For example, reassessment of pain in a stable and comfortable postoperative patient may be relatively simple and brief (i.e., score on NRS alone). However, sudden, unexpected intense pain, especially if associated with altered vital signs, should prompt immediate and thorough assessment for potential complications (e.g., wound dehiscence, infection, or deep venous thrombosis).⁵ Patients who have not responded to treatment and/or have complex types of pain (e.g., chronic pain, neuropathic pain) often require more comprehensive reassessment of pain. A pain diary may facilitate this process.⁹ A pain diary or log is a patient-generated record that is used to track various aspects of the pain and its management (e.g., pain intensity, associated activities, medication use, side effects, and other responses to treatment).

^bThe Agency for Health Care Policy and Research is now the Agency for Health Care Research and Quality.



Section III:
**Types of
Treatments**

Section III: Types of Treatments

A. PHARMACOLOGIC TREATMENT

Treatments for pain can be broadly categorized as pharmacologic and nonpharmacologic. This section of the monograph provides an overview of: 1) a commonly used analgesic classification system, 2) some commonly used analgesic classes and individual drugs, and 3) general principles of pharmacologic treatment.

1. Drug Classifications and Terminology

Pharmacologic treatment is the mainstay of pain therapy. Almost half of individuals who suffer from pain choose a nonprescription analgesic as their initial choice for pain relief.¹ Up to one in five Americans take an over-the-counter or prescription analgesic on a daily basis.² As with types of pain, multiple systems for classifying analgesics exist. In the below system, analgesics are broadly categorized as:

- **Nonopioid analgesics (nonopioids):** acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin and other salicylic acid derivatives
- **Opioid analgesics (opioids):** mu opioid agonists (i.e., morphine-like agonists) and agonist-antagonist opioids
- **Adjuvant analgesics or co-analgesics:** a diverse group of drugs, with primary indications for conditions other than pain, with analgesic properties relevant to some conditions. Commonly used adjuvant analgesics include antiepileptic drugs (AEDs), tricyclic antidepressants (TCAs), and local anesthetics (LAs).

Variations of this classification system exist,^a and terminology in the field is also evolving. The term “opioids” has replaced “narcotics,” and “co-analgesics” is an alternate term for “adjuvant analgesics.”

^a Because acetaminophen has some, albeit extremely limited, anti-inflammatory properties,³ some experts consider acetaminophen an NSAID and use the term “NSAIDs” rather than “nonopioids.” Other experts disagree with this classification due to the different mechanisms of action and side effects of these drugs.

2. Common Analgesic Agents

a. Nonopioids

i. Mechanism of action and effects

The primary mechanism of action of NSAIDs is inhibition of the enzyme cyclooxygenase (COX) which blocks prostaglandin synthesis.^{4,5} Acetaminophen, another nonopioid, appears to act mostly via a central mechanism.^{3,6-7} All nonopioids have anti-inflammatory, antipyretic, and analgesic effects, but the anti-inflammatory effect of acetaminophen is essentially negligible.⁸ The analgesic effect of NSAIDs is prompt (minutes to hours), whereas the anti-inflammatory effect may take longer (1-2 weeks or longer).⁹ This latter effect can indirectly relieve some pain by reducing tissue swelling.

The relatively recent discovery that COX has two isoforms, COX-1 and COX-2, has advanced NSAID pharmacology. COX-1 is constitutively expressed in most normal tissues,¹⁰ but plays an especially important role in the gastrointestinal (GI) tract, kidneys, and platelets; COX-1 primarily produces prostaglandins with beneficial effects (e.g., regulation of blood flow to the gastric mucosa and kidneys).^{8,11} In contrast, COX-2 is normally not present but may be induced in response to inflammatory stimuli; COX-2 primarily produces prostaglandins that activate and sensitize nociceptors (see I.B).^b Nonselective NSAIDs inhibit COX-1 and COX-2, which contributes to both their therapeutic actions and side effects. The recently introduced COX-2 selective inhibitors (or “coxibs”) selectively inhibit COX-2 without affecting COX-1 at therapeutic doses.^{15,16} Thus, coxibs offer the advantage of efficacy comparable to that of nonselective NSAIDs, with a reduced risk of certain side effects.¹⁷⁻¹⁸ The coxibs affect COX-2 both centrally and peripherally.

ii. Indications and uses

Nonopioids relieve a variety of types of acute and chronic pain (e.g., trauma, postoperative, cancer, arthritis pain) and are especially effective for certain types of somatic pain (e.g., muscle and joint pain, bone/dental pain, inflammatory pain, postoperative pain) (Table 19).¹⁹⁻²¹ Acetaminophen and NSAIDs, alone, often relieve mild pain, and some NSAIDs relieve certain types of moderate pain (Table 19).⁵¹ Even

^b The division of function between COX-1 and COX-2 is not perfect. COX-1 produces some prostaglandins that contribute to inflammation.¹² COX-2 is constitutively expressed in some organs (e.g., the kidney) where it produces prostaglandins with protective effects.¹³⁻¹⁴

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Table 19. Examples of Nonopioid Analgesics

Chemical Class	Generic Name	Indications	Usual Oral Dosing Interval or Frequency	Dosage Forms and Routes of Administration	Major Side Effects	Comments
Paraaminophenols	Acetaminophen	Mild to moderate pain due to multiple causes including headache, toothache, muscular aches, backache, menstrual cramps, arthritis, common cold, and flu; fever reduction	q 4-6 h ^a	Multiple oral (e.g., tablets, caplets, powder, elixir, suspensions, liquid); rectal suppositories	Acute overdose: hepatic necrosis (liver damage) ^b Chronic overdose: liver toxicity, nephrotoxicity, thrombocytopenia	Lacks anti-inflammatory effects of NSAIDs, but no adverse effects on gastric mucosa or platelets Analgesic and antipyretic effects comparable to aspirin Useful in patients intolerant of NSAIDs and for fever control in children with flu
Salicylates	Aspirin	Mild to moderate pain due to multiple causes including headache, toothache, sinus pain, muscular aches, bursitis, backache, sprains, arthritis, pain due to fever, cold, flu	ASA: q 4-6 h ^a	Multiple oral (caplet, tablet, gelcap, effervescent tablet, gum, liquid); rectal suppositories	NSAID class effects ^c	Combination formulations available (aspirin and acetaminophen, and/or caffeine)
	Diflunisal		Diflunisal: q 8-12 h		Diflunisal hypersensitivity: life-threatening reaction that may involve multiple organs	Diflunisal causes less GI irritation and antiplatelet effects than aspirin
	CMT		CMT: QD, BID, or TID			
Propionic acid derivatives	Ibuprofen	Mild to moderate pain, including pain associated with the common cold, headache, toothache, muscular aches, backache, menstrual cramps, and arthritis; fever reduction	q 4-6 h	Oral (tablets, caplets, geltabs, suspension); rectal suppositories	NSAID class effects Toxic amblyopia	Commonly used NSAID OTC formulations available Combinations with codeine and hydrocodone available Fewer GI effects than other non-selective NSAIDs
	Naproxen	RA, OA, AS, JA, tendonitis, bursitis, gout, primary dysmenorrhea	q 6-12 h	Tablets, oral suspension, delayed-release tablets	NSAID class effects Other: pseudoporphyria	OTC formulations available Delayed-release tablets are NR for initial treatment of acute pain
	Ketoprofen	Signs and symptoms of OA and RA, pain, and primary dysmenorrhea	q 6-8 h; q 24 h for ER form	Capsules, ER capsules	NSAID class effects	OTC formulations available ER capsules NR for treatment of acute pain
	Flurbiprofen	OA, RA	BID, TID, or QID	Tablets	NSAID class effects	
	Oxaprozin	Acute and long-term management of OA and RA	q 24 h	Caplets	NSAID class effects Other: photosensitivity, rash	Long half-life (55 hours), thus can be given once daily
Indoleacetic acids	Indomethacin	Moderate to severe OA, RA, AS; acute gouty arthritis; acute painful shoulder (bursitis and/or tendonitis)	BID, TID, or QID	Oral (capsules, suspension, slow-release capsules) rectal suppositories	NSAID class effects Ocular effects (corneal deposits, retinal disturbances) Exacerbation of Parkinson's disease, epilepsy, or psychiatric disorders	Limited use due to side effects
Benzothiazine derivatives (oxicams)	Piroxicam	Acute and long-term management of OA and RA	q 24 h	Capsules	NSAID class effects Insomnia	Single daily dose
	Meloxicam	OA	q 24 h	Tablets	NSAID class effects	Single daily dose

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Table 19. Examples of Nonopioid Analgesics (continued)

Chemical Class	Generic Name	Indications	Usual Oral Dosing Interval or Frequency	Dosage Forms and Routes of Administration	Major Side Effects	Comments
Pyrroleacetic acid derivatives	Diclofenac	OA, RA, AS, primary dysmenorrhea	BID, TID, or QID ER form q 24 h	Tablets, ER tablets	NSAID class effects Other: acute hemolytic anemia, aseptic meningitis, rash Avoid use in patients with porphyria Combination with misoprostol contraindicated in pregnant women	Lower risk of GI effects
	Ketorolac	Short term (<5 days) treatment of moderately severe acute pain that requires analgesia at the opioid level (e.g., postoperative pain)	Varies for parenteral therapy q 4-6 h oral form	Oral (tablets), IV (injector, sterile cartridges)	NSAID class effects Warning indicating potential for serious NSAID side effects if used inappropriately NR for minor or chronic pain	Parenteral form useful when PO NSAIDs are undesirable and for opioid-sparing effect Combined oral and parenteral therapy should not exceed 5 days IV administration provides pain relief comparable to 10 mg of IM morphine
Selective COX-2 inhibitors ^d	Rofecoxib	OA, acute pain in adults, primary dysmenorrhea	q 24 h	Tablets, oral suspension	Most common: URI, nausea, HTN NSAID class effects less likely (see Comments) Rare aphyllactoid reactions	PI labeling lists some of the same adverse reactions as non-selective NSAIDs, but sparing of COX-1-mediated prostaglandins reduces the risk of serious GI side effects and renal toxicity Also does not alter platelet aggregation nor alter effects of low-dose aspirin on platelets
	Celecoxib	OA, RA, FAP	q 12 or 24 h	Capsules	Most common: HA, URI, dyspepsia NSAID class effects less likely (see Comments) Rare anaphylactoid reactions	PI labeling lists some of the same adverse reactions as non-selective NSAIDs, but sparing of COX-1 mediated prostaglandins reduces the risk of serious GI side effects and renal toxicity Also, no effects on platelet aggregation

Sources: References 8, 19-22, and 27-50.

^aSome sources (e.g., 2001 Physicians' Desk Reference for Nonprescription Drugs and Dietary Supplements,²² the American Pain Society's Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain,¹⁹ McCaffery and Pasero²³) list the dosing interval for aspirin and acetaminophen as 4 to 6 hours. Other sources (e.g., Agency for Health Care Policy and Research Acute Pain Management: Operative or Medical Procedures and Trauma Clinical Practice Guideline No. 1)²⁴ list the dosing interval for these drugs as 4 hours.

^bUse with caution in certain populations (i.e., patients with chronic alcoholism, liver disease, malnourishment).^{19,25-26}

^cAdverse effects of nonselective NSAIDs as a class include gastrointestinal problems (e.g., dyspepsia, ulcers, perforation, bleeding), liver dysfunction, bleeding due to inhibited platelet aggregation (i.e., "antiplatelet effect"), kidney problems (e.g., renal insufficiency, acute renal failure), hypersensitivity reactions (i.e., aspirin sensitivity), and CNS effects (e.g., attention and memory deficits, headache, dizziness, drowsiness).¹⁹ Recommended monitoring includes standard laboratory tests (e.g., complete blood count, liver and kidney function) and stool guaiac test (for occult blood). NSAIDs are generally contraindicated in patients with a history of asthma, urticaria, or allergic-type reactions after taking NSAIDs, including aspirin.

^dThese agents selectively inhibit COX-2 activity and do not affect COX-1 activity at therapeutic doses.

AS: ankylosing spondylitis; ASA: aspirin; BID: twice daily; CMT: choline magnesium trisalicylate; CNS: central nervous system; COX-cyclooxygenase; ER: extended release; ESRD: end-stage renal disease; FAP: familial adenomatous polyposis; GI: gastrointestinal; HA: headache; HTN: hypertension; IM: intramuscular; IV: intravenous; JA: juvenile arthritis; NR: not recommended; NSAID: nonsteroidal anti-inflammatory drug; OA: osteoarthritis; OTC: over-the-counter; PI: package insert; PO: per os (by mouth); QD: once per day; QID: four times daily; RA: rheumatoid arthritis; TID: three times daily; URI: upper respiratory infection.

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for moderate or severe pain that does require an opioid, nonopioids are often added to the regimen for their opioid-sparing effect (i.e., they lower the dose of opioid required).¹⁹ Since nonopioids and opioids relieve pain via different mechanisms, combination therapy offers the potential for improved relief with fewer side effects. Nonopioids do not produce tolerance, physical dependence, or addiction.¹⁹ Choice of NSAID is influenced by factors including medication tolerance, dosing frequency, and cost.⁵²

iii. Routes of administration, formulations, and dosing

Patients usually take nonopioids orally, but other forms (e.g., rectal, topical, parenteral) of some drugs exist.¹⁹ Numerous formulations of acetaminophen and aspirin, as well as some non-selective NSAIDs, are available without a prescription. In addition, some nonopioids are marketed in combination with other drugs (e.g., other nonopioids, opioids, caffeine, sedatives).

Onset and duration of analgesia and, therefore, dosing frequency reflect drug half-life and special formulations (e.g., sustained-release preparations). Some NSAIDs only need to be taken once a day. In contrast to most opioids, all nonopioids have a dosage ceiling.¹⁹ This means that a dose is reached beyond which additional side effects, but not pain relief, can occur. Patient responsiveness to NSAIDs varies greatly, so a patient who has not responded to the maximum therapeutic dose of one NSAID should try another.¹⁹

iv. Side effects

Inhibition of COX-1 causes some of the side effects of nonselective NSAIDs. Adverse effects of nonselective NSAIDs as a class include GI problems (e.g., dyspepsia, ulcers, perforation, bleeding, liver dysfunction), bleeding (i.e., "antiplatelet effect"), kidney dysfunction, hypersensitivity reactions, and CNS effects.¹⁹ Table 20 summarizes precautions and methods of managing these adverse events.

Despite these shared effects, the side effect profiles of individual drugs do differ (see Table 19). For example, some nonselective NSAIDs (e.g., ibuprofen, naproxen) are less likely than others (e.g., ketoprofen) to cause GI problems. Side effects are generally less likely to occur when drugs are used at low doses or for short periods in appropriately selected patients.¹⁹ In addition, the risk of some side effects can be reduced by protective mechanisms (e.g., co-administration of misoprostol to reduce the risk of gastric ulcer).¹⁹ Therefore, in some clinical

circumstances, treatment with a nonselective NSAID is relatively safe and use of a selective COX-2 inhibitor is not necessarily warranted. Conversely, use of a selective COX-2 inhibitor may be preferable in some situations (e.g., preoperative period, bleeding disorder).

Acetaminophen or a selective COX-2 inhibitor may be an appropriate treatment alternative to nonselective NSAIDs in some patients. Acetaminophen does not damage the gastric mucosa or inhibit platelet aggregation and provides pain relief comparable to that of aspirin.¹⁹ However, acetaminophen has negligible anti-inflammatory activity. In addition, acute or chronic overdose with acetaminophen may cause liver or kidney toxicity, so acetaminophen should be used with caution in patients with certain conditions (e.g., malnutrition, chronic alcoholism, liver disease).²⁵ Accidental overdosage also may occur in patients taking over-the-counter combination pain relievers containing acetaminophen.

Although product labeling for selective COX-2 inhibitors and nonselective NSAIDs is similar, evidence suggest that coxibs are less likely to cause certain side effects. For example, clinical trial data suggest that celecoxib produces comparable relief of rheumatoid arthritis (RA) pain and inflammation to diclofenac⁵⁷ and naproxen,⁵⁸ but a lower incidence of endoscopically diagnosed gastroduodenal ulcers. Celecoxib also appears to provide equal symptomatic relief of osteoarthritis (OA) pain to diclofenac but with fewer GI side effects.⁵⁹ Other data suggest that, due to its COX-1-sparing effect, celecoxib does not affect platelet function.⁶⁰

Rofecoxib, another selective COX-2 inhibitor, is associated with similar advantages. In clinical trials, it provided comparable relief of OA pain to diclofenac and ibuprofen⁶¹⁻⁶² and comparable relief of RA pain to naproxen.¹⁸ In a comparison trial, rofecoxib therapy was associated with a lower 12-month cumulative incidence of GI tract perforations, symptomatic gastroduodenal ulcers, and upper GI tract bleeds (but similar incidence of dyspeptic GI side effects) than non-selective NSAIDs including ibuprofen, diclofenac, and nabumetone.⁶³ In a recent controlled study, rofecoxib did not alter platelet aggregation when administered alone nor alter the (desirable) anti-platelet effects of low-dose aspirin when used in combination therapy.⁶⁴ Thus, selective COX-2 inhibitors appear to have less severe GI side effects and do not affect platelet function.

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Table 20. Class Effects of Nonselective NSAIDs

System	Side Effect	Precautions and Contraindications	Prevention and Management
GI	Dyspepsia, ulcer formation, perforation, bleeding (due to inhibited synthesis of PGs that regulate blood flow to gastric mucosa)	Patients at increased risk: <ul style="list-style-type: none">• Elderly• History of GI disease (e.g., ulcer)• Concomitant steroid or anticoagulant therapy• High-dose NSAID therapy	Initiate treatment at low doses Take NSAID with food Avoid alcohol Co-administer gastroprotective agents (e.g., misoprostol, sucralfate, histamine ₂ -blockers) ^a Use NSAIDs with less risk of GI problems (e.g., ibuprofen, selective COX-2 inhibitors) Monitor patient with stool guaiac test (for occult blood) and complete blood count
GI	Liver dysfunction Rare hepatic necrosis	Patients at increased risk: <ul style="list-style-type: none">• Alcoholics• History of liver disease Relative contraindications: <ul style="list-style-type: none">• Elevated liver enzymes• Preexisting liver disease	Baseline and periodic monitoring of liver function enzymes
Heme	Bleeding due to: <ul style="list-style-type: none">• Inhibited platelet aggregation^b or "anti-platelet effect" (due to inhibition of PG synthetase)• Prolonged prothrombin time (due to drug interaction with oral anticoagulant)	Relative contraindications: <ul style="list-style-type: none">• Anticoagulation• Coagulopathy• Thrombocytopenia Other patients at increased risk: <ul style="list-style-type: none">• Surgical patients• Some patients with cancer	Use NSAIDs with minimal or no bleeding risk in high-risk patients (e.g., choline magnesium trisalicylate, selective COX-2 inhibitors) Consider replacing NSAID with acetaminophen Stop ASA therapy 1 week prior to surgery and most other NSAIDs 2-3 days prior to surgery
Renal	Renal insufficiency (uncommon) or acute renal failure (rare) Multiple causes, including inhibited synthesis of vasodilator PGs that preserve blood flow to kidneys	Patients at highest risk for renal insufficiency or failure: <ul style="list-style-type: none">• Elderly• Volume-depleted• Preexisting renal disease• Coexisting illness (e.g., HTN, CHF, diabetes, cirrhosis, multiple myeloma)• Taking diuretics or medications that limit renal blood flow	Usually resolves with drug discontinuation For high-risk patients: <ul style="list-style-type: none">• Use low doses• Monitor kidney function• Avoid indomethacin
Immune	Hypersensitivity reactions: <ul style="list-style-type: none">• Respiratory reaction• Urticaria-angioedema reaction	Patients who are sensitive to aspirin may be cross-sensitive to other NSAIDs	Monitor patients for asthma, rhinitis, and nasal polyps (respiratory reaction) or wheals, urticaria, hypotension, shock (urticaria-angioedema reaction) Seek appropriate emergency treatment, as needed
CNS	CNS dysfunction including attention or memory deficits, headache, tinnitus	Patients at increased risk: <ul style="list-style-type: none">• Elderly• Concomitant use of medications affecting CNS function	To manage cognitive dysfunction: <ul style="list-style-type: none">• Lower dose• If dysfunction persists, discontinue NSAID• Switch to another NSAID and drug class

Sources: References 9, 19, 21, and 53-56.

^aConsider gastroprotective agents, particularly in elderly patients and patients with a history of peptic ulcer disease, GI bleeding, or cardiovascular disease.⁹^bAspirin causes irreversible inhibition of platelet aggregation, and other nonselective NSAIDs cause reversible inhibition of platelet aggregation.¹⁹

ASA: aspirin; CHF: congestive heart failure; CNS: central nervous system; COX: cyclooxygenase; GI: gastrointestinal; HTN: hypertension; NSAID: nonsteroidal anti-inflammatory drug; Heme: hematologic; PGs: prostaglandins.

b. Opioids**i. Mechanism of action and effects**

Opioids bind to opioid receptors in the central nervous system (CNS) to: 1) inhibit the transmission of nociceptive input from the periphery to the spinal cord, 2) activate descending inhibitory pathways that modulate transmission in the spinal cord, and 3) alter limbic system

activity (see I.B).⁶⁵⁻⁶⁸ Thus, opioids modify sensory and affective aspects of pain. The different actions of opioids (i.e., agonist and antagonist) at various opioid receptors (e.g., mu, kappa, and delta) provide one means of classification. In this system, opioids are broadly classified as mu agonists or agonist-antagonists. Because experts do not recommend use of agonist-antagonists as first-line analgesics,^{19,24} this discussion focuses

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on mu agonists.

ii. Indications and uses

Opioids are used to treat moderate to severe pain that does not respond to nonopioids alone.¹⁹ They are often combined with nonopioids because this permits use of lower doses of the opioid (i.e., dose-sparing effect). Nearly all types of pain respond to opioids; however, nociceptive pain is generally more responsive to opioids than neuropathic pain,⁶⁹ which may require higher doses of opioids.^{66,70} Opioids play a major role in the treatment of acute pain (e.g., trauma, postoperative pain), breakthrough pain, cancer pain, and some types of chronic noncancer pain (CNCP).^{19,71} Because responsiveness to opioids varies greatly among individuals, a patient who has failed to respond to an adequate trial of one opioid should try another (Table 21).¹⁹ Although opioids vary in potency, more potent agents are not necessarily superior. Opioids are also categorized as weak opioids and strong opioids (Table 21).

Routes of administration, formulations, and dosing

Opioids are administered via multiple routes (e.g., oral, sublingual, rectal, parenteral, transdermal, intrathecal, epidural). Oral or transdermal administration is generally preferred for chronic treatment.¹⁹ Intramuscular (IM) administration, especially repeated, should not be used due to its multiple disadvantages (e.g., pain, unreliable absorption, tissue fibrosis).^{19,24}

Short-acting drugs often are used to manage intermittent pain and breakthrough pain (i.e., pain that “breaks through” pain relief provided by ongoing analgesia).²⁰ Long-acting and sustained-release opioids are useful for patients with continuous pain, as they lessen the severity of end-of-dose pain and often allow the patient to sleep through the night.¹⁹ Most opioids may be given around the clock (ATC) for continuous pain or on an as-needed basis (PRN). ATC dosing is recommended after an optimal dose is established by dose titration.¹⁹ Dose titration involves administering a small starting dose and gradually increasing or decreasing the dose based on levels of pain relief and side effects.

In contrast to nonopioids, strong mu agonist opioids do not have a ceiling effect (i.e., a dose beyond which no additional analgesia is achieved).⁶⁹ However, many opioids are marketed in combination with a nonopioid, which may limit the maximum dose.¹⁹ The accumulation of toxic metabolites of some opioids (e.g., meperidine) also limits dose increases as well as treat-

ment duration.^{69,96} If these events preclude adequate pain relief, another opioid should be substituted. Equianalgesic dosing charts help clinicians determine the appropriate starting dose of an opioid when changing routes of administration or when changing from one opioid drug to another (see Table 22). These charts list analgesic doses (oral and parenteral) that are approximately equivalent in ability to provide pain relief.

iv. Side effects

Binding of mu agonist opioids to receptors in various body regions (e.g., CNS, GI tract) results in therapeutic effects and side effects. Side effects of mu agonist opioids as a class include sedation, mental clouding or confusion, respiratory depression, nausea, vomiting, constipation, pruritus (itching), and urinary retention. With the exception of constipation, these side effects tend to subside with time. Tables 23 and 24, respectively, summarize general and specific approaches to side effect prevention and management.

Most opioids should be used with caution in patients with impaired ventilation, bronchial asthma, liver failure, or increased intracranial pressure.¹⁹ Opioid-induced respiratory depression is usually short-lived, antagonized by pain, and most common in the opioid-naïve patient.⁹⁷

c. Antiepileptic drugs

i. Mechanism of action and effects

AEDs are a type of adjuvant analgesic. The increasing use of AEDs for neuropathic pain is based on their ability to reduce membrane excitability and suppress abnormal discharges in pathologically altered neurons.⁹⁸⁻¹⁰⁰ However, the exact basis of their analgesic effects is unclear. It does not appear to be specifically related to their antiepileptic activity. Other drugs that suppress seizures (e.g., barbiturates) do not relieve pain, and AEDs with effective antiepileptic activity do not necessarily have good analgesic activity.¹⁰¹

ii. Indications and uses

AEDs (Table 25) are used to treat neuropathic pain, especially lancinating (i.e., episodic shooting, stabbing, or knife-like) pain from peripheral nerve syndromes.^{19,102-103} Most of this use is “off-label.” Exceptions include two first-generation AEDs, carbamazepine and valproate, which have FDA approval for the management of trigeminal neuralgia and migraine prophylaxis, respectively. Phenytoin was the first AED used to treat pain,

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Table 21. Examples of Opioid Analgesics

Generic Name	Indications	Usual Dosing Interval	Routes of Administration ^a and Dosage Forms	Potential Side Effects ^b	Comments
Morphine	Severe acute pain (e.g., trauma, postoperative pain, MI), cancer pain, chronic pain	Varies with IR and CR	PO (IR and CR), PR, IV, SC, EA, IA, SL	Mu agonist class side effects ^c Class precautions, warnings, and contraindications ^d Metabolite can accumulate in setting of RF or hepatic dysfunction	Used as a standard of comparison for all opioid drugs; can stimulate histamine release IR and CR oral preparations available CR tablets are to be taken whole and must not be broken, chewed, or crushed, to prevent potential toxic dosage
Hydromorphone	Oral: management of pain where opioid therapy is appropriate Parenteral: moderate to severe pain (e.g., trauma, MI, surgery, burns, renal colic, biliary colic, cancer)	4-6 h for oral and parenteral 6-8 h for rectal	PO, PR, IV, SC, EA, IA	Mu agonist class side effects, precautions, warnings, and contraindications	Useful alternative to morphine Available as high-potency injectable that facilitates SC administration
Fentanyl	Severe acute pain, cancer pain, CNCP	Varies with ROA and form	IV, EA, IA, TD, OTFC	Mu agonist class side effects, precautions, warnings, and contraindications	TD and oral transmucosal formulations available, including OTFC (fentanyl in sweetened matrix) IV fentanyl is fast-acting and it is often combined with benzodiazepines for procedural analgesia and sedation
	TD fentanyl is only indicated for treatment of chronic pain that requires continuous administration and cannot be managed by lesser means	72 h for TD fentanyl		TD fentanyl is contraindicated for acute pain, postoperative pain, mild or intermittent pain responsive to PRN or nonopioid therapy, and at doses above 25 mcg/h at the initiation of opioid therapy	TD fentanyl is long-acting and can control pain for up to 72 hours but a small number of patients may require q 48-hour dosing Ensure patients follow the correct patch application procedure for TD fentanyl and avoid direct exposure of application site to heat
Oxycodone	Moderate to moderately severe pain (e.g., trauma, postoperative pain, musculoskeletal disorders, abdominal pain, dental pain, cancer pain) CR formulation for moderate to severe pain where opioid is required for an extended period of time	Varies with IR and CR	PO (IR and CR)	Mu agonist class side effects, precautions, warnings, and contraindications CR tablets are to be taken whole and must not be broken, chewed, or crushed, to prevent potential toxic dosage CR (80 and 160 mg) tablets for use in opioid-tolerant patients only	IR and CR preparations Available as single entity and in combination with a nonopioid Can be used like oral morphine for severe pain Often combined with a nonopioid for moderate pain
Meperidine	Moderate to severe pain (e.g., migraine, trauma, postoperative pain, acute abdominal pain)	3-4 h ^e	PO, IV SC, EA, IA	Mu agonist class side effects, precautions, warnings, and contraindications High doses may cause agitation, muscle jerking, and seizures or hypotension Use with care in patients with renal insufficiency, convulsive disorders, cardiac arrhythmias	Not recommended for management of chronic pain due to accumulation of toxic metabolite (normeperidine) that may cause CNS excitement, convulsions Metabolite limits use to less than 48 hours or 600 mg in 24 hours Oral administration NR for severe pain

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Table 21. Examples of Opioid Analgesics (continued)

Generic Name	Indications	Usual Dosing Frequency	Routes of Administration ^a	Potential side effects ^b	Comments
Hydrocodone	Moderate to severe pain (e.g., trauma, back pain, postoperative pain, abdominal pain, dental pain)	4-6 h	PO	Mu agonist class side effects, precautions, warnings, and contraindications Combination hydrocodone + ibuprofen NR for OA or RA or for patients with NSAID hypersensitivity or other contraindication to NSAIDs	Available in combination with nonopioid Hydrocodone plus acetaminophen for moderate or moderately severe pain Hydrocodone plus ibuprofen combination product indicated for short-term (generally <10 days) management of acute pain (e.g., trauma, musculoskeletal and back pain, postoperative pain, abdominal pain, dental pain)
Codeine	Mild to moderately severe pain	4 h	PO, SC	Mu agonist class side effects, precautions, warnings, and contraindications Most common side effects are lightheadness, dizziness, shortness of breath, sedation, nausea, and vomiting	Used orally for mild-to-moderate pain, with limited use for severe pain Usually used in combination with nonopioid, which has an analgesic ceiling Codeine is a pro-drug and not all patients convert it to an active form to achieve analgesia

Sources: References 19-20, 22, 24, 50, 69, and 72-95. Product information (references 76-95) is from the Physicians' Desk Reference, 55th edition.⁵⁰

^aAlthough many of these opioids can be administered by intramuscular (IM) injection, IM administration is not recommended due to its multiple disadvantages (e.g., painful administration, unpredictable absorption, complications including tissue fibrosis and abscesses).¹⁹

^bMany of these opioids only come in combination with a nonopioid (e.g., acetaminophen, NSAID). Therefore, additional contraindications, warnings, and side effects of that nonopioid drug apply. These combination products also are subject to a ceiling effect.

^cCommon side effects of mu agonists as a class include sedation, nausea, vomiting, constipation, pruritis (itching), and respiratory depression.¹⁹ Less common side effects include euphoria or dysphoria. mu₁ receptors mediate supraspinal analgesia, and mu₂ receptors mediate spinal analgesia, physical dependence, and class side effects.⁶⁸

^dMu agonists are generally contraindicated or need to be used with extreme caution in patients with known hypersensitivity to the drug, head injury or lesion associated with increased intracranial pressure, asthma and other respiratory conditions, or paralytic ileus.

^eThe 2001 Physicians' Desk Reference entry for Demerol® lists the dosing interval for meperidine as 3-4 hours, as necessary.⁵⁰ The 1992 Agency for Health Care Policy and Research Acute Pain Management: Operative or Medical Procedures and Trauma Clinical Practice Guideline No. 1 lists the dosing interval for meperidine as 2-3 hours.²⁴ CNCP: chronic noncancer pain; CNS: central nervous system; CR: controlled-release; EA: epidural anesthesia; IA: intrathecal anesthesia; IM: intramuscular; IR: immediate-release; IV: intravenous; MI: myocardial infarction; NR: not recommended; NSAID: nonsteroidal anti-inflammatory drug; OA: osteoarthritis; OTFC: oral transmucosal fentanyl citrate; PO: per os (oral); PR rectal; PRN: as needed; RA: rheumatoid arthritis; RF: renal failure; ROA: route of administration; SC: subcutaneous; SL: sublingual; TD: transdermal.

Table 22. Equianalgesic Dose Chart

Opioid	Equianalgesic Dose (mg)	
	Oral	Parenteral
Morphine	30	10
Hydromorphone	7.5	1.5
Fentanyl	—	0.1
Oxycodone	20	—
Methadone	20 (acute) 2-4 (chronic)	10 (acute) 2-4 (chronic)
Meperidine	300 (NR)	75

Source: Reference 19.

NR: not recommended.

Table 23. General Management of Mu Agonist Opioid Side Effects

- Use preventive measures, especially in populations at high risk.
- Titrate drug doses slowly.
- If a symptom occurs, verify its cause (i.e., opioid side effect or another problem).
- If opioid-related side effects occur, consider changing the dosing regimen or route of administration to obtain relatively constant blood levels.
- Whenever possible, add (or increase dose of) nonopioid or adjuvant analgesic for opioid-sparing effect.
- Consider switching to another opioid.
- Add another drug that counteracts the effect (Table 24).
- Assume constipation will develop and treat it preemptively.

Sources: References 19, 24, 69, and 74.

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Table 24. Specific Approaches to Management of Mu Agonist Opioid Side Effects

Side Effect	Precautions and Contraindications	Prevention and Management
Sedation	Elderly Concurrent sedating medications	General approach ^a plus: <ul style="list-style-type: none"> • Eliminate other nonessential medications with sedating effects • Consider use of mild stimulants during the day (e.g., caffeine) • Consider use of psychostimulant (e.g., methylphenidate) for persistent sedation, although exercise caution in combining psychoactive drugs in the elderly
Confusion Mental clouding	Elderly Preexisting CNS condition	General approach plus: <ul style="list-style-type: none"> • Eliminate other nonessential medications with CNS effects • Consider use of neuroleptics for persistent delirium
Respiratory depression	Opioid-naïve patients taking large opioid doses Head injury, lung disorder	General approach plus: <ul style="list-style-type: none"> • Monitor sedation level and respiratory status regularly, especially during first 24 hours of treatment in opioid-naïve patients • Stop opioid until respiratory depression resolves and reinstitute opioid at 75% of the previous dosage • Stop opioid and administer naloxone^b for minimally responsive or unresponsive patients • Use spirometry and oxygen, as needed
Pruritus (itching)		General approach plus: <ul style="list-style-type: none"> • Consider administering diphenhydramine or hydroxyzine • Consider naloxone infusion titrated to the desired effect if other treatments fail
Nausea and vomiting	Concomitant conditions or treatments producing nausea and vomiting	General approach plus: <ul style="list-style-type: none"> • If nausea is due to stimulation of chemoreceptor trigger zone (central mechanisms), consider adding ondansetron, prochlorperazine, or hydroxyzine • If nausea is due to slowed gastric motility, consider adding metoclopramide • For chronic nausea, consider metoclopramide and/or other antiemetics
Constipation	Advanced age Immobility Abdominal problems or concurrent constipating medications	General approach plus: <ul style="list-style-type: none"> • Implement appropriate dietary changes • Assess regularly and use stool softeners and mild peristaltic stimulants for all patients on ATC opioids (prevention) • If no BM in a 48-hour period, add one or two additional agents (e.g., lactulose, milk of magnesia, senna) • If no BM in a 72-hour period, assess for (and treat) fecal impaction • If not impacted, try additional method (e.g., enema, mineral oil, magnesium citrate) • If impacted, use glycerine suppository or oil retention enema (as needed) to facilitate manual disimpaction, with appropriate analgesia

Sources: References 19, 24, 69, and 74.

^aThe general approach to managing side effects consists of changing the dosage or route of administration, trying a different drug in the same class, or adding a drug that counteracts the effect.^bFor comatose patients, place endotracheal tube prior to administering naloxone. Also, titrate naloxone carefully to avoid profound withdrawal, seizures, and severe pain.¹⁹

ATC: around-the-clock administration; BM: bowel movement; CNS: central nervous system.

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Table 25. Examples of Antiepileptic Drugs, Antidepressants, and Local Anesthetics^a

Class	Generic Name	Indications	Uses in Pain ^b	Dosage Forms and Routes of Administration	Potential Side Effects	Comments
Antiepileptic drugs	Gabapentin	Epilepsy	Neuropathic pains including PDN, PHN, RSD, deafferentation pain, thalamic pain, HIV-related neuropathy, phantom limb pain, migraine prophylaxis	Oral (capsules, tablets, solution)	Generally well tolerated Most common SE: somnolence, dizziness, fatigue, ataxia	First-line off-label treatment for neuropathic pain Well-established efficacy for PHN, PDN, and migraine headache prophylaxis Comparable efficacy to TCAs for PHN and PDN with superior side effect profile
	Carbamazepine	Epilepsy Trigeminal neuralgia	Neuropathic pains including TN, PHN, PDN, glossopharyngeal neuralgia, tabetic lightening pain, paroxysmal MS pain, PSP, dysesthesia (spinal cord injury), post-laminectomy pain, cancer pain, phantom limb pain	Oral (tablets, ER tablets, suspension)	Most common SE: sedation, mental clouding, dizziness, nausea, unsteadiness Other SE: thrombocytopenia, liver damage, hyponatremia, rash	First FDA-approved anticonvulsant for the treatment of neuropathic pain Well-established efficacy in managing TN, PDN, PHN, but side effects limit use Baseline and regular monitoring of hematologic and liver function Monitor serum drug levels
	Divalproex sodium	Mania Epilepsy Migraine HA prophylaxis	Migraine (prophylaxis), TN, PHN	Oral (tablets)	Most common SE: sedation, nausea, vomiting, dizziness, HA Boxed warning for hepatic toxicity and pancreatitis Other SE: thrombocytopenia, inhibited platelet aggregation, hyperammonemia with or without lethargy, abnormal thyroid function tests, androgenization with hirsutism, amenorrhea, hair loss, polycystic ovaries	FDA approved for migraine HA prophylaxis Side effects limit wider use in chronic pain Monitor serum drug levels

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Table 25. Examples of Antiepileptic Drugs, Antidepressants, and Local Anesthetics^a (continued)

Class	Generic Name	Indications	Uses in Pain ^b	Dosage Forms and Routes of Administration	Potential Side Effects	Comments
	Phenytoin	Epilepsy	PHN, PDN, TN, glossopharyngeal neuralgia, tabetic lightening pain, central pain, cancer pain, PSP, Fabry's disease	Oral (suspension, capsules, ER capsules, tablets) Parenteral (solution)	Most common SE: dose-related CNS effects (e.g., confusion, nystagmus, ataxia, decreased coordination) Other SE: lymphadenopathy, hepatotoxicity, hypersensitivity reaction, exfoliative dermatitis, gingival hyperplasia, toxicity and conduction disturbances at high blood levels	First anticonvulsant used for pain management Less commonly used now due to side effects and contradictory evidence of analgesic efficacy Monitor drug levels and watch for signs of toxicity (e.g., nystagmus, gait impairment, nausea, vomiting, sedation)
Antidepressants	Amitriptyline	Depression	Various types of CNCP (e.g., migraine and other HA, OA, chronic LBP, fibromyalgia), and neuropathic pain (e.g., PHN, PDN, central pain, chronic facial pain, cancer pain)	Oral (tablets, capsules, solution)	Common SE: sedation, anticholinergic effects (dry mouth, blurred vision, constipation, urinary retention), orthostatic hypotension Other SE: arrhythmias, MI, stroke, worsening schizophrenia, hyperpyrexia, paralytic ileus Contraindications: status-post acute MI, hypersensitivity, concomitant MOAI use Use with caution in patients with seizures, urinary retention, angle-closure glaucoma, hyperthyroidism, CV disease, advanced age	Well-established analgesic efficacy Most used TCA for pain but least tolerated Produces the most anticholinergic side effects of all antidepressants Commonly associated with sedation, so administer at night Baseline ECG recommended and avoid use if QTc >440, AV block
	Nortriptyline	Depression	PDN, mixed neuropathic pains	Capsules, suspension	Common SE: insomnia, some sedation, anticholinergic effects Other SE and contraindications: see Amitriptyline	Better tolerated than amitriptyline due to less sedation and anticholinergic SE May cause insomnia, so administer during daytime
Local anesthetics (topical)	Lidocaine Lidoderm	Postherpetic neuralgia	PHN, PDN, stump pain, reflex sympathetic dystrophy, painful HIV-related neuropathy	Patch	Most common SE: localized reaction that usually resolves Less common SE: allergic and systemic reactions Use precautions in patients with severe hepatic damage and avoid eye exposure Contraindicated in patients with known sensitivity to LAs or for use on non-intact skin	Only FDA-approved treatment for PHN Anecdotal data suggest may be effective for other pain Low blood levels due to topical application Convenient and generally well tolerated

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Table 25. Examples of Antiepileptic Drugs, Antidepressants, and Local Anesthetics^a (continued)

Class	Generic Name	Indications	Uses in Pain ^b	Dosage Forms and Routes of Administration	Potential Side Effects	Comments
Local anesthetics (other routes)	EMLA®	Local anesthesia on intact skin for procedures or superficial surgery on skin	Needle insertion, intravenous cannulation, spinal needle insertion, electrosurgery of cutaneous lesions, biopsies, PHN, other neuropathic pain	Cream, disc	Toxicity with repeated dosing, eye irritation, allergic reactions, methemoglobinemia	Placebo-controlled trials support efficacy in relieving acute pain associated with multiple procedures
	Bupivacaine	Local or regional anesthesia or analgesia for surgery; oral surgical and obstetrical procedures; and diagnostic and therapeutic procedures	Acute pain management: local infiltration, nerve blocks, epidural blocks, arthroscopy	Parenteral, epidural	Most common SE: dose-related CNS (e.g., anxiety, dizziness) and CV (e.g., arrhythmias, myocardial depression) effects Use with caution in patients with liver or heart disease due to risk of hepatic toxicity and arrhythmias Other SE: familial malignant hyperthermia	Moderate to fast acting, with long duration of action Better able to selectively block nociceptive nerve fibers Can be combined with opioids for epidural analgesia Only use 0.25% and 0.5% concentrations for obstetrical surgery
Lidocaine	Lidocaine	Local or regional anesthesia by infiltration techniques and IV regional anesthesia	Local infusion: local infiltration, nerve blocks, epidural blocks (e.g., postoperative pain, obstetrical pain), arthroscopy	IV, SC	Dose-related CV and CNS toxicity may progress to cardiac arrest, acidosis, and death with IV administration CNS SE: lightheadedness, dizziness, drowsiness, tinnitus, tremors, convulsions, unconsciousness CV SE: bradycardia, hypotension, CV collapse IV lidocaine contraindicated in patients with hypersensitivity to amide-type LAs, Adams-Stokes syndrome, severe heart block	Considered most widely used LA Can be combined with opioids for epidural analgesia IV use for pain normally reserved for pain refractory to other treatments due to risk of toxicity and unclear efficacy Topical lidocaine (see EMLA®, Lidocaine patch) is not associated with same side effects
			IV infusion: (rarely used) for some nociceptive and neuropathic pain, burn pain			

Sources: References 19, 20, 50, and 104-142.

^aThis is a representative, not comprehensive, list.^bMost uses are off label.

AV: atrioventricular; CNCP: chronic noncancer pain; CNS: central nervous system; CV: cardiovascular; ECG: electrocardiogram; EMLA®: Eutectic Mixture of Local Anesthetics (lidocaine and prilocaine); ER: extended release; FDA: Food and Drug Administration; HA: headache; HIV: human immunodeficiency virus; IN: intranasal; IV: intravenous; LA: local anesthetics; LBP: lower back pain; MI: myocardial infarction; MOAI: monoamine oxidase inhibitor; MS: musculoskeletal; OA: osteoarthritis; PDN: peripheral diabetic neuropathy; PHN: postherpetic neuralgia; PSP: postsympathectomy pain; QTc: QT interval corrected for heart rate on ECG; RSD: reflex sympathetic dystrophy; SC: subcutaneous; SE: side effects; TCAs: tricyclic antidepressants; TN: trigeminal neuralgia.

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but clinical trial evidence of its analgesic efficacy is limited and conflicting.^{c,108-109} Clinical trial data support the use of carbamazepine in the treatment of trigeminal neuralgia, diabetic peripheral neuropathy, and postherpetic neuralgia,¹¹² but serious, albeit rare, side effects limit its use.¹⁰¹ Recent data suggest that newer AEDs such as gabapentin are better alternatives to older AEDs.^{101,110,112}

Placebo-controlled clinical trials have demonstrated that gabapentin provides effective analgesia comparable to TCAs for diabetic peripheral neuropathy¹⁴⁶⁻¹⁴⁷ and postherpetic neuralgia;¹¹⁴ it also has a more favorable side effect profile.^{110,112} Data from a large study and a recent placebo-controlled trial also suggest that gabapentin effectively reduces the likelihood of migraine headaches.¹¹⁵⁻¹¹⁶ Uncontrolled studies suggest that gabapentin also may be useful in the management of trigeminal neuralgia, central pain, phantom limb pain, and neuropathy associated with human immunodeficiency virus (HIV) infection.^{120,148-150} Thus, many pain experts consider gabapentin a first-line treatment for neuropathic pain.^{105,109,112,117-118}

iii. Side effects

Side effects of AEDs vary (Table 25). Common side effects of AEDs as a class include sedation, mental clouding, dizziness, nausea, or unsteadiness.¹⁰⁷ Initiating treatment at low doses and slowly titrating upward to optimal efficacy or toxicity diminishes the risk of these effects. Table 26 summarizes other ways to prevent and manage side effects. Less common but more serious adverse effects of some of the older AEDs include hematologic abnormalities, liver dysfunction, hypersensitivity reactions, and rash (Table 25). Thus, use of some of these agents requires close monitoring of drug levels, hematologic parameters, and liver function.¹⁰⁵ Unlike these older AEDs, gabapentin offers easy monitoring and relatively low toxicity (i.e., minimal drug-drug interactions and side effects).^{101,110,112,119-120}

d. Antidepressants

i. Mechanism of action and effects

Antidepressants exhibit analgesic properties in animal models of nociceptive, inflammatory, and neuropathic pain, and some relieve chronic and

neuropathic pain in humans.¹⁵¹ These analgesic effects may reflect the ability of some antidepressants to block the reuptake of serotonin and norepinephrine in the CNS, thus increasing the activity of endogenous pain-modulating pathways.¹⁵²⁻¹⁵⁴ Their analgesic actions do not depend on antidepressant activity,¹⁵⁵ and antidepressants are equally effective in patients with and without depression.¹⁹ While analgesia may occur at lower doses and sooner than antidepressant activity, maximum efficacy may require high antidepressant doses and trial duration.

ii. Indications and uses

TCAs (e.g., amitriptyline, nortriptyline, imipramine) are adjuvant analgesics used to treat a variety of types of chronic (e.g., migraine, other headaches, low back pain, cancer pain, fibromyalgia) and neuropathic (e.g., painful diabetic neuropathy, postherpetic neuralgia, central pain, cancer-related) pain (Table 25).^{107,122} All of these uses are “off-label.” Although often considered most effective for continuous dysesthesias (i.e., burning pain or hypersensitivity), TCAs also may relieve lancinating neuropathic pain.^{122,156-157}

Currently, TCAs are the only antidepressants with clearly demonstrated analgesic efficacy. Placebo-controlled clinical trial data suggest that TCAs provide effective¹⁵⁸⁻¹⁵⁹ and comparable pain relief to AEDs for postherpetic neuralgia and diabetic neuropathy.^{117,122,160-161} Amitriptyline has the best-documented analgesic effects but also the most side effects.¹⁹ Intolerance of side effects, particularly among elderly patients, often limits TCA use.¹¹⁸⁻¹¹⁹ Whereas newer antidepressants (e.g., serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors [SSRIs]) are generally better tolerated,¹²³⁻¹²⁴ randomized controlled trials have yet to demonstrate analgesic efficacy.^{d,123,149,162} There is preliminary evidence that venlafaxine, a new serotonin-norepinephrine reuptake inhibitor that lacks TCA side effects, may be efficacious in the treatment of neuropathic pain.^{123,124} However, these results await formal evaluation in a randomized placebo-controlled trial.

iii. Side effects

TCA selection is largely based on patient characteristics and the drug side effect profile, because analgesic efficacy among individual

^c Double-blind, placebo-controlled trials have demonstrated analgesic efficacy for diabetic neuropathy¹⁴³ and Fabry's disease,¹⁴⁴ although another small trial failed to demonstrate efficacy for diabetic neuropathy.¹⁴⁵

^d Data regarding the analgesic efficacy of SSRIs are conflicting^{159,162-165} but generally suggest that SSRIs have less consistent analgesic effects than TCAs.^{122,155,160,166}

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Table 26. Approaches to Management of Antiepileptic Drugs, Tricyclic Antidepressants, and Local Anesthetic Side Effects

Side Effect	Populations at Increased Risk and Precautions	Prevention and Management
Sedation	Elderly	Titrate drug slowly and monitor drug levels, if recommended Consider changing dosing regimen or drug Administer drug at bedtime Eliminate other nonessential medications with sedating effects Consider use of mild stimulants during the day (e.g., caffeine) Consider use of psychostimulant (e.g., methylphenidate, dextroamphetamine) for persistent sedation, but exercise caution in elderly patients
Confusion Mental clouding	Elderly	Titrate drug slowly and monitor drug levels, if recommended Eliminate other nonessential medications with CNS effects Consider changing dosing regimen or drug
Dizziness/ orthostatic hypotension	Elderly	Titrate drug slowly and monitor drug levels, if recommended Encourage patient to change positions slowly and remain well hydrated Consider changing dosing regimen or drug if unmanageable
Anticholinergic effects	Elderly Patients with urinary retention or angle-closure glaucoma	Lower dose or change to drug with fewer anticholinergic effects Use sugarless hard candies or chewing gum for dry mouth and ensure regular dental examinations Use laxatives and stool softeners for constipation Consider bethanechol
Nausea and vomiting		Consider prochlorperazine or hydroxyzine
Cardiovascular effects	History of CAD, arrhythmias, or heart block	Obtain baseline ECG in all patients Monitor closely Be prepared to manage emergencies, including cardiac arrest

Source: Reference 19.

CAD: coronary artery disease; CNS: central nervous system; ECG: electrocardiogram.

TCAs is comparable.¹²² Lethal side effects of TCAs are uncommon at dosages typically prescribed for pain, but cardiotoxicity with dangerous conduction abnormalities (arrhythmias) may occur.¹²⁵ Therefore, TCAs are relatively contraindicated in patients with conduction abnormalities (e.g., prolonged QT interval corrected for heart rate on the electrocardiogram), and a baseline electrocardiogram is recommended.¹⁹

Common and sometimes significant class effects of TCAs include sedation, orthostatic hypotension, and anticholinergic effects (i.e., dry mouth, blurred vision, constipation, urinary retention) (Table 25). Amitriptyline has the strongest sedative and anticholinergic side effects, so bedtime administration is recommended.¹⁹ Elderly patients are at greatest risk for some side effects, including sedation and orthostatic hypotension. Nortriptyline is less likely than amitriptyline to produce these effects,¹⁹ so it may be a more appropriate initial choice for an elderly patient. Nortriptyline should be administered during the day if it produces insomnia.¹⁹ Table 26 summarizes some ways to prevent and manage common TCA side effects.

e. Local anesthetics**i. Mechanism of action**

LAs are another type of adjuvant analgesic. These drugs block sodium channels and inhibit the generation of abnormal impulses by damaged nerves to exert their peripheral analgesic effects.¹⁶⁷ When used systemically, they do not produce conduction block (anesthesia) as they do with local injection and topical application but may suppress aberrant electrical activity in structures associated with pain.^{107,168-169}

ii. Indications and uses

LAs are used to manage acute and chronic pain (Table 25) and are administered in several ways for different purposes. Topical application provides localized analgesia for a painful procedure or condition with minimal systemic absorption or side effects.¹⁰⁶ EMLA® (Eutectic Mixture of Local Anesthetics [lidocaine and prilocaine]) is a topically applied LA used to prevent pain associated with various procedures (e.g., needle insertion, intravenous cannulation, superficial skin surgery).¹⁷⁰ Placebo-controlled trial data suggest that EMLA® effectively relieves acute pain associated with procedures, including

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venipuncture,¹⁷¹⁻¹⁷³ spinal needle insertion,¹⁷⁴ and excisional biopsy or curettage of cutaneous lesions.¹⁷⁵⁻¹⁷⁶

Topical LAs are also used to treat neuropathic pain.¹⁰⁶ The lidocaine patch (Lidoderm®) is the first FDA-approved treatment for postherpetic neuralgia.¹⁷⁷ A large, multicenter, placebo-controlled trial showed that it relieved pain in patients with long-standing postherpetic neuralgia and mechanical allodynia.¹⁷⁸ Other controlled studies suggest that both the patch and gel forms of lidocaine significantly reduce postherpetic neuralgia, produce no significant side effects, and are easy to use.^{106,179-180} Anecdotal evidence suggests that the lidocaine patch also may be useful for other neuropathic pain, including diabetic neuropathy, HIV-related neuropathy, complex regional pain syndrome, postmastectomy pain, postthoracotomy pain, and stump pain.^{106,181}

LAs also can be used in more invasive approaches collectively referred to as regional anesthesia. For example, LAs (e.g., lidocaine, bupivacaine, ropivacaine) can be injected into tissue (local infiltration), around nerves (i.e., nerve blocks), or into various spaces surrounding the spine (i.e., epidural and intrathecal analgesia). Epidural blocks with LAs with or without opioids play an important role in managing postoperative and obstetrical pain.¹⁰⁷ Nerve blocks with LAs sometimes are used to manage chronic pain (e.g., occipital headaches, lower back pain), and LAs can be combined with other agents (e.g., corticosteroids, saline) for trigger point injections.¹⁸²

Rarely, intravenous LAs (e.g., lidocaine) are used to manage neuropathic pain, arthritis, post-stroke pain, or headache^{107,126-128} or, somewhat more often, to anesthetize an upper extremity. Oral LA-type antiarrhythmic drugs (e.g., flecainide, mexiletine) have, in some cases, been used to manage neuropathic or cancer pain.¹²⁹⁻¹³⁰ However, use of these drugs is generally not recommended, because they may cause serious side effects and evidence of their analgesic efficacy is limited and conflicting.¹⁰⁷

iii. Side effects

Major dose-dependent toxicities associated with systemic administration of LAs include CNS (e.g., dizziness, tremor, paresthesias, encephalopathy, seizures) and cardiovascular (e.g., conduction disturbances, depression of myocardial function) side effects (Table 25). Thus, treatment in some patient populations is contraindicated, and all patients need to be

closely monitored (e.g., with plasma drug levels, electrocardiography). In contrast, topical LAs are well tolerated with a low incidence of side effects.¹⁰⁶ As serum concentrations of the LA remain low, even with chronic use,¹⁷⁷ topical LAs can even be used in patients with cardiovascular disease.

f. Other

Nonopioids and opioids are used to manage most nociceptive pain, although LAs are also useful for postoperative pain management. AEDs, TCAs, and LAs are the mainstay of treatment for neuropathic pain. However, this does not account for all drugs used in pain management. Table 27 summarizes information about other drugs and drug classes used for specific conditions or clinical circumstances. These include drugs used for arthritis pain (e.g., capsaicin), cancer and inflammatory pain (e.g., corticosteroids), migraine headaches (e.g., "trip-tans," beta-blockers), chronic pain (e.g., tramadol, baclofen) and pain refractory to other treatments (N-methyl-D-aspartate antagonists).

3. General Principles of Analgesic Therapy

Some principles of analgesic therapy are drug specific. However, some general principles guide all pharmacologic treatment of pain:

a. Identify and treat the source of the pain.

Whenever possible, identify and treat the underlying cause of the pain. However, pain management can begin before the source of the pain is determined.

b. Select the simplest approach to pain management.

Although invasive methods are sometimes required, most pain can be relieved via simple methods. Cost of treatment is also a consideration in some cases.

c. Select an appropriate drug.

Individualization of a pain management regimen begins with selection of an appropriate drug. Factors that guide this process include:¹⁹⁻²⁰

- Characteristics of the pain (e.g., duration, intensity, quality)
- Characteristics of the agent (e.g., analgesic ceiling, expected time of onset and duration

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Table 27. Other Drugs Used in Pain Management

Class	Generic Name	Indications	Uses in Pain	Routes of Administration and Dosage Forms	Potential Side Effects	Comments
Topical analgesics	Capsaicin	Arthritis, neuropathic pain	PHN, PDN, OA, RA	Topical	Mild to severe burning on application	RCT have shown efficacy for OA and RA but mixed results for PDN and PHN Available OTC
Corticosteroids	Dex-amethasone	Multiple, including endocrine, rheumatic, collagen-vascular, dermatologic, allergic, ophthalmologic, pain related to respiratory, oncologic, hematologic disorders	Cancer-related pain (e.g., malignant epidural spinal cord compression, raised intracranial pressure, superior vena cava syndrome); symptoms of bowel obstruction; musculoskeletal conditions (e.g., OA, RA, bursitis, tendonitis)	PO (tablets, elixir), injectable form	Contraindicated in patients with systemic fungal infections or hypersensitivity to drug Drug-induced adrenocortical insufficiency, mask signs of infection, eye problems (e.g., glaucoma, cataracts), increased blood pressure, electrolyte/body fluid imbalances, increased risk of infection, psychiatric disturbances, GI problems (e.g., ulceration, bleeding), osteoporosis, pathological fractures, withdrawal syndrome with sudden discontinuation	Generally tolerated for short-term treatment, but toxicities often arise with prolonged high-dose therapy
Mixed mu agonist opioid and NE/5-HT reuptake inhibitor	Methylprednisolone			PO		
	Tramadol	Moderate to moderately severe pain	Types of CNCP (e.g., OA, fibromyalgia, PDN, LBP)	PO	Common SE: dizziness, nausea, constipation, headache, sedation Uncommon SE: increased risk of seizures with high doses (>400 mg/day) or history of seizure disorder; rare anaphylactoid reaction	Contraindicated in patients with hypersensitivity or acute drug intoxication Comparable pain relief to acetaminophen + codeine May have lower potential for abuse than opioids
Selective 5-HT _{1B/1D} receptor agonist	Zolmitriptan	Acute treatment of migraine with or without aura in adults	Acute treatment of migraine with or without aura in adults	PO (tablets)	Dizziness, drowsiness, nausea, atypical or pressure sensations Certain contraindications (see comments)	Effective abortive treatment for migraine

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Table 27. Other Drugs Used in Pain Management (continued)

Class	Generic Name	Indications	Uses in Pain	Routes of Administration and Dosage Forms	Potential Side Effects	Comments
	Rizatriptan	Acute treatment of migraine with or without aura in adults	Acute treatment of migraine with or without aura in adults	PO (tablets, orally disintegrating tablets)	Warm/cold sensations, diarrhea, nausea, flushing Certain contraindications: see Zolmitriptan	
	Sumatriptan	Acute treatment of migraine with or without aura in adults	Acute treatment of cluster headache episodes (SC form only)	PO (tablets), IN, SC	Atypical (e.g., flushing, tingling, warmth) and pressure sensations; nausea Certain contraindications: see Zolmitriptan	Intranasal sumatriptan also contraindicated in patients with severe hepatic impairment
Beta-blockers	Propranolol	HTN, MI, migraine prophylaxis, essential tremor, HSS, pheochromocytoma	Migraine prophylaxis	PO (tablets, LA capsules), injectable	Common SE: bradycardia, hypotension Other SE: lethargy, depression Contraindicated in patients with cardiogenic shock, heart block, bronchial asthma, CHF Use caution in patients with history of CHF or angina, diabetes, hyperthyroidism	Effective migraine prophylaxis
GABA _B receptor agonists	Baclofen	Spasticity	Intraspinal baclofen is used for some chronic neuropathic pain refractory to other treatments	Intraspinal	Abrupt discontinuation can trigger withdrawal symptoms, including delirium and seizures	Useful for pain caused by spasticity
NMDA receptor antagonists	Ketamine	General anesthetic	Neuropathic pain (e.g., phantom limb pain), cancer pain, procedural pain (rarely used)	Parenteral	CNS side effects: sedation, ataxia, delirium, hallucinations, psychosis, nightmares, dysphoria Sedation is most common side effect at low doses	Rarely used due to debilitating CNS side effects New NMDA receptor antagonists are in development

Sources: References 19, 50, 104-106, 183-200.

5-HT: 5-hydroxytryptamine (serotonin); 5-HT_{1B/1D}: 5-hydroxytryptamine receptor subtypes 1_{B/1D}; CHF: congestive heart failure; CNCP: chronic noncancer pain; CNS: central nervous system; GABA_B : γ -aminobutyric acid (GABA) type B receptor; GI: gastrointestinal; HSS: hypertrophic subaortic stenosis; HTN: hypertension; LA: long-acting; LBP: lower back pain; MAOI: monoamine oxidase inhibitor; MI: myocardial infarction; NE: norepinephrine; NMDA: N-methyl-D-aspartate; NR: not recommended; OA: osteoarthritis; OTC: over-the-counter (nonprescription); PDN: peripheral diabetic neuropathy; PHN: postherpetic neuralgia; PO: per os (oral); RA: rheumatoid arthritis; RCT: randomized controlled trials; SC: subcutaneous; SE: side effects.

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- of analgesia, available routes of administration, dosing interval, side effects, potential for accumulation of toxic metabolites, potential for addiction)
- Patient factors (e.g., age, coexisting diseases, other medications, preferences, response to previous treatments).

d. Establish a management plan.

The next step is to establish a management plan, which may include the later addition of other drugs. Use of several analgesics in combination offers several advantages. It may:

- Allow use of lower doses of some agents, thus reducing the risk of side effects
- Inhibit nociceptive processing at multiple (i.e., peripheral and central) levels, thus enhancing analgesia
- Facilitate treatment of pain in patients who do not respond to a single agent.

Common acceptable combination regimens include: 1) a nonopioid plus an opioid or 2) a nonopioid plus an opioid plus an adjuvant analgesic.²⁰

e. Select a route of administration.

No single route of drug administration is appropriate for all clinical situations. Patient factors (e.g., preferences, comfort, convenience, GI function) and drug characteristics (e.g., absorption, half-life) influence the selection of an appropriate route. Table 28 reviews advantages and disadvantages of various routes of administration.

Oral administration of drugs, especially for chronic treatment, is generally preferred because it is convenient, flexible, and associated with stable drug levels.¹⁹ Although often used, IM administration has multiple disadvantages (e.g., pain, erratic absorption, fluctuating drug levels, tissue fibrosis), thus should not be used.^{19,24} Intravenous (IV) administration provides a rapid onset of pain relief and, along with rectal, sublingual, and subcutaneous administration, is useful in patients who cannot take medications by mouth. Continuous infusions produce consistent drug blood levels but are expensive, require frequent professional monitoring, and may limit patient mobility.¹⁹ Transdermal administration is a convenient alternate means of continuous drug delivery that does not involve needles or pumps.²⁰² Some data suggest that some patients prefer transdermal opioid (fentanyl) to sustained-release oral morphine.²⁰³⁻²⁰⁵

Table 29 describes some “high-tech” methods

of providing analgesia, including patient-controlled analgesia (PCA), intraspinal (epidural and intrathecal) drug administration (neuroaxial blockade), and other interventional techniques. PCA permits administration of a small dose of drug upon patient command and is especially useful in patients expected to require opioids over a period that exceeds 12 hours. It has mostly been used for IV administration of opioids for acute pain (e.g., postoperative pain), but newer PCA techniques include subcutaneous and epidural drug administration.²⁰⁸ Interventional methods of analgesia include tissue infiltration (e.g., trigger point injections with local anesthetics), sensory nerve blocks, sympathetic blocks, spinal injections (e.g., epidural injections of corticosteroids, caudal blocks, nerve root injections), and continuous spinal analgesia (e.g., infusion of opioids, clonidine, baclofen) (Table 29). Nerve blocks can be used for diagnostic, prognostic, and therapeutic purposes.

f. Titrate the dose.

It may be necessary to titrate the dose of an analgesic to achieve an optimal balance between pain relief and side effects. The goal is to use the smallest dosage necessary to provide the desired effect with minimal side effects.¹⁹ Nonopioids have a ceiling effect and may cause significant toxicity at high doses. However, most opioids do not have an analgesic ceiling, so the dosage can be titrated upwards until pain relief occurs or limiting side effects develop.

g. Optimize administration.

Medications can be administered around-the-clock (ATC) after an optimal dose over a 24-hour interval is determined.¹⁹ Experts recommend ATC dosing for patients with continuous pain, because it provides superior pain relief with fewer side effects.¹⁹ It also helps to break the undesirable undermedication-overmedication cycle that often develops with use of PRN medications alone. However, a short-acting, rapid-onset PRN medication should be used to manage breakthrough pain (i.e., pain that “breaks through” pain relief provided by ongoing analgesics). PRN dosing is also useful for intermittent pain, but patients need to be taught to request pain medication early, before the pain becomes severe.

h. Watch for and manage side effects.

Patients with new or altered analgesic regimens should be observed and assessed for side

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Table 28. Routes of Administration

Route	Definition and Notes	Drug Types	Comments
Oral	By mouth (per os) Requires functioning GI tract, intact swallowing mechanism, sufficient GI tract for absorption to occur	Nonopioids, opioids, adjuvant analgesics	Advantages: convenient, noninvasive, cost-effective, flexible, less discomfort than injections with comparable efficacy Disadvantages: requires functional GI system; slow onset of action and relatively delayed peak effects; requires patient compliance
Rectal	Insertion of suppository into rectum	Nonopioids, opioids	Useful in patients who cannot take medications by mouth Any opioid may be compounded for rectal administration
Intramuscular	Injection into large muscle (e.g., gluteus or vastus lateralis)	Some nonopioids, opioids	IM administration should not be used, especially for chronic treatment, due to multiple disadvantages: <ul style="list-style-type: none">• Painful injections• Wide fluctuations in drug absorption make it difficult to maintain consistent blood levels• Rapid fall-off of action compared with PO administration• Chronic injections may damage tissue (fibrosis, abscesses) IV and SC injections are appropriate alternatives
Intravenous	Injection into vein; may be single or repetitive bolus or continuous infusion with or without PCA	Some nonopioids, opioids, adjuvant analgesics	IV is most efficient ROA for immediate analgesia and permits rapid titration IV bolus produces rapid onset of effect, but shorter duration of action than IM; not recommended for drugs with long half-lives Continuous IV infusion provides steadier drug blood levels, which maximize pain relief while minimizing side effects
Subcutaneous	Placement of drug just under skin with small needle Continuous SC infusion can be obtained with a small needle	Some opioids	Advantages: produces steady blood levels; time until onset of effect is comparable to IM administration and effects are longer lasting, with less painful administration; cheaper than IV administration; obviates need for GI function Disadvantages: slower onset and offset and lower peak effects than IV administration, time consuming, often disliked by patients
Topical	Applied directly to the skin, where the drug penetrates	NSAIDs, local anesthetics (e.g., lidocaine patch and gel, EMLA®, capsaicin)	Advantages: local effect (i.e., no significant serum levels) limits side effects to local reactions; no drug-drug interactions; easy to use, no titration needed Disadvantages: may cause local skin reactions
Transdermal	Absorbed through skin with gradual release into the systemic circulation	Some opioids, adjuvant analgesics	Advantages: convenient, noninvasive, provides prolonged, relatively stable analgesia Disadvantages: delayed onset of action with first dose, drug absorption influenced by internal or external heat
Oral transmucosal	Delivery of drug to mouth, including sublingual (under tongue) and buccal/gingival administration	Some opioids	Advantages: easy, requires little staff supervision; avoids significant liver metabolism associated with oral opioids Disadvantages: variable absorption, bitter taste, dose is limited
OTFC	Fentanyl incorporated into a sweetened matrix on a stick for consumption	Fentanyl	Some absorption via oral mucosa, but most via GI tract; yields higher drug levels and better bioavailability than oral fentanyl
Intranasal	Small aerosol device placed inside nostril that delivers a calibrated dose of a drug	Butorphanol, sumatriptan	Takes advantage of rich blood supply to nose and also avoids significant liver metabolism associated with some drugs
Intraspinal	Epidural and intrathecal administration (see Table 29)		
Other (sublingual, vaginal)	Placement of drug under the tongue (sublingual) or in the vagina	Opioids	Most opioids can be absorbed sublingually or vaginally in patients who have problems such as impaired swallowing, short gut syndrome, or poor IV access

Sources: References 19, 20, 69, and 201.

EMLA®: Eutectic Mixture of Local Anesthetics (lidocaine and prilocaine); GI: gastrointestinal; IM: intramuscular; IV: intravenous; NSAIDs: nonsteroidal anti-inflammatory drugs; OTFC: oral transmucosal fentanyl citrate; PCA: patient-controlled analgesia; PO: per os (oral); ROA: route of administration; SC: subcutaneous.

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Table 29. PCA and Regional Anesthesia

Route	Definition	Example Drug Types	Comments
PCA	Use of infusion pump that allows patient to self-administer small doses of analgesics via one of several routes (e.g., IV, SC, epidural)	Opioids (e.g., morphine, hydromorphone, fentanyl, meperidine), some NSAIDs	Used for numerous surgeries (e.g., C-section, abdominal, orthopedic) and medical conditions (cancer pain, sickle cell crisis, burn pain, HIV pain, pancreatitis, kidney stones, fractures) Advantages: less delay in onset of analgesia than PRN dosing Compared with IM, improved analgesia with smaller doses of opioids and fewer side effects Disadvantages: Patient must understand technique, so less useful in some clinical populations
Single or repetitive epidural bolus	Injection or infusion of agent into the epidural space via insertion of a needle (single bolus) or catheter (repetitive bolus)	Opioids (e.g., morphine, fentanyl, hydromorphone), local anesthetics (e.g., bupivacaine, ropivacaine), corticosteroids, clonidine, baclofen	Used for diagnostic and therapeutic nerve blocks; the latter include surgeries (e.g., C-section, gynecologic, urological surgeries) Advantages: simple, no need for infusion device, delivery to site close to site of action (spinal cord) permits more intense analgesia (greater analgesia for given drug) Disadvantages: limited number of suitable agents, higher incidence of side effects, requires personnel to reinject catheter, higher risk of catheter contamination, does not permit PCA
Continuous epidural	Continuous infusion of agent(s) into the epidural space via a catheter. A long-term catheter can be tunneled under the skin or surgically implanted for long-term pain management (e.g., cancer pain, CNCP)	Opioids, local anesthetics	Used for acute pain (e.g., postoperative, obstetrical, posttraumatic pain) and chronic pain (e.g., cancer pain, neuropathic pain) Advantages: permits concomitant use of local anesthetic and shorter-acting opioids, eliminates need for catheter reinjection, reduces rostral spread of analgesia, less risk of catheter contamination, greater potency than systemic administration Disadvantages: Potential for catheter migration and side effects (e.g., of skin and subcutaneous tissue around catheter site; rarely, hematoma, abscess, or meningitis)
PCEA	Continuous infusion of drugs into epidural space, controlled by a patient-operated infusion pump	Opioids	Allows patient to manage dynamic changes in pain related to activity
Bolus or continuous intrathecal (spinal)	Injection or infusion of agent into the subarachnoid space via insertion of a needle (single bolus) or catheter (repetitive bolus); an indwelling intrathecal catheter can be placed for long-term analgesia to reduce the risk of infection	Opioids (e.g., morphine, hydromorphone, fentanyl), local anesthetics (e.g., lidocaine, bupivacaine, mepivacaine)	Uses include cancer pain (regionalized pain below T1), neuropathic pain Single bolus more commonly used for acute pain due to difficulty in maintaining indwelling intrathecal catheters. May be cost-effective for patients with cancer or CNCP Advantages: provides intense analgesia at lower doses than systemic administration Disadvantages: can be difficult to titrate drug effect, risk of infection and other side effects Onset and duration of effect reflect lipid solubility of agent; greater effects of drug at given dose than with systemic administration
Local infiltration	Infiltration of various body structures with local anesthetics and/or corticosteroids	Local anesthetics (e.g., bupivacaine), corticosteroids	Used for acute pain (e.g., postoperative pain, postoperative joint pain, acute bursitis, tendonitis, muscle spasm) and chronic pain (e.g., painful scars, neuromata, trigger points for myofascial syndromes, arthritis, facet syndrome)
Spinal nerve block	Blockade of spinal neurons outside the spinal canal in the paravertebral region or anywhere along its course	Local anesthetics	Includes cervical spinal blocks, occipital blocks, thoracic spinal blocks, lumbar and sacral spinal nerve blocks, sympathetic blockade Used for severe acute or chronic pain (e.g., postoperative, posttraumatic, postamputation, PVD, cancer pain, visceral pain, CRPS, neuralgias)
Topical application	Application of local anesthetics to skin (e.g., patch, gel, cream, paste)	Topical local anesthetics (e.g., lidocaine, EMLA®); other local anesthetics (e.g., cocaine, benzocaine)	Oral agents used for pain in mucous membranes of mouth Topical anesthetics used for procedural pain (EMLA®) and some chronic pain (e.g., lidocaine patch or gel for postherpetic neuralgia)

Sources: References 19, 69, 206-207.

C-section: Cesarean section; CNCP: chronic noncancer pain; CRPS: chronic regional pain syndrome; EMLA®: Eutectic Mixture of Local Anesthetics (lidocaine and prilocaine); HIV: human immunodeficiency virus; IM: intramuscular; IV: intravenous; NSAIDs: nonsteroidal anti-inflammatory drugs; PCA: patient-controlled analgesia; PCEA: Patient controlled epidural analgesia; PRN: as needed; PVD: peripheral vascular disease; SC: subcutaneous.

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effects as well as pain relief. Tables 20, 23, 24, and 26 review some specific approaches to managing common side effects of nonopioid, opioid, and adjuvant analgesics. The general strategy to managing side effects consists of:¹⁹

- Changing the dosage or route of administration (to achieve stable drug levels),
- Trying a different drug within the same class, and/or
- Adding a drug that counteracts the effect (e.g., antihistamine for pruritus, laxative for constipation).

Combination therapy can alleviate some side effects. For example, adding a nonopioid or adjuvant analgesic to an opioid regimen may allow use of a lower dose of the opioid. Severe side effects, on occasion, may require administration of an opioid antagonist (e.g., naloxone for opioid-induced respiratory depression).¹⁹ Use of agents with potentially hazardous metabolites (e.g., meperidine) should be restricted to short-term treatment.¹⁹

i. Differentiate among tolerance, physical dependence, and addiction and appropriately modify therapy.

Section I.E.5 reviews the definitions of tolerance, physical dependence, and addiction recently recommended by the American Society of Addiction Medicine (ASAM), the American Academy of Pain Medicine (AAPM), and the American Pain Society (APS).²⁰⁹ Confusion regarding these terms is common and adversely influences pain management.

Tolerance normally occurs with use of certain agents (e.g., opioids). Its earliest sign is a decrease in the duration and/or degree of pain relief, which can be managed by increasing the drug dose and/or frequency of administration.¹⁹ Combining opioids with nonopioids, or switching to a lower dose of another opioid, may delay the development of opioid tolerance.¹⁹ However, the latter approach requires a great deal of care and significant expertise.

Signs of physical dependence include the appearance of an abstinence syndrome with abrupt cessation or diminution of chronic drug administration.¹⁹ The nature and time of onset of this syndrome vary with drug actions and half-life. Slow tapering of the drug (e.g., 10-15% reduction in dosage per day or every other day) usually avoids the appearance of an abstinence syndrome.²¹⁰

Although not usually encountered in patients without a history of preceding drug abuse, the

administration of some drugs (e.g., opioids) may cause addiction. Signs of drug craving and/or drug-seeking behavior (e.g., missed appointments with after-hour calls for prescription renewals; solicitation of prescriptions from multiple physicians; reports of lost, destroyed, or stolen medications; selling and buying drugs off the street)¹⁹ should alert the clinician to such a possibility. However, diagnosing addiction requires extreme caution. Similar behaviors, called “pseudoaddiction,” sometimes occur in patients who are not receiving adequate pain management (e.g., doses of opioids too low or infrequent).²¹¹ It is critical that addiction be diagnosed because it is a treatable but serious condition and failure to treat it will hinder efforts to manage pain.

j. Avoid use of placebos to treat pain.

Placebos are sometimes used to assess whether pain is responsive to sympatholysis or other interventions. However, the deceptive use of placebos to treat pain is considered unethical and inappropriate.¹⁹

B. NONPHARMACOLOGIC TREATMENTS FOR PAIN

Pharmacologic approaches to pain management are the mainstay of treatment for acute pain and cancer pain and are increasingly being used to manage chronic noncancer pain (CNCP). However, optimal pain management also includes psychological, physical rehabilitative, and in some cases, surgical treatment strategies. For example, the 1992 Agency for Health Care Policy and Research clinical practice guideline on acute pain management recommends cognitive-behavioral approaches (e.g., patient education, simple relaxation, imagery, hypnosis, and biofeedback) and physical therapeutic agents and modalities (e.g., superficial heat or cold, massage, exercise, immobility, and electroanalgesia) as part of the management of acute pain.²⁴

Nonpharmacologic strategies should supplement, but not replace, the use of medications.²⁴ In addition to supplementing the pain-relieving effects of analgesics, nonpharmacologic approaches offer other advantages. For example, they can improve mood, reduce anxiety, increase a patient's sense of control, strengthen coping

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abilities, assist with sleep, relax muscles, and improve quality of life.²¹²⁻²¹³ Factors that influence the choice of a nonpharmacologic approach to pain management include the pain type, duration, and severity; the patient's preferences, coping skills, and capabilities; the availability of support (e.g., family members); the availability of care within the community; and cost.

1. Psychological Approaches

Psychological interventions used in pain management include contingency management, cognitive behavioral therapy, biofeedback, relaxation, imagery, and psychotherapy. Table 30 defines these terms and describes potential uses of these methods. Some methods (e.g., relaxation, imagery) are simple and can be taught quickly, whereas others require more time. Patient education materials (e.g., printed instruction sheets, audiotapes) can supplement, but not replace, clinician efforts to instruct patients in these methods.²⁴

Patients in whom psychological interventions may be most appropriate include those who express interest in such approaches, manifest anxiety or fear, have inadequate pain relief after appropriate pharmacologic interventions, or experience chronic or recurrent pain.²⁴ When pain is acute, psychological preparation (such as preparation for surgery or for an invasive procedure) or psychological intervention such as relaxation may help to control the affective dimension of pain.²¹⁸ This, in turn, helps minimize the biological stress response that the patient experiences as well as emotional distress and suffering.²¹⁵ When pain is chronic, learning history and operant conditioning (Table 30) sometimes contribute to the persistence of pain and disability, and counterproductive beliefs may impede a positive response to medical intervention.²¹⁴ Therefore, psychological methods are typically an integral part of the interdisciplinary approach to the management of chronic pain. Because such management usually involves rehabilitation, psychological approaches are typically integrated with rehabilitation efforts built around physical therapy.

Psychologists rarely treat pain directly but rather work with other health care professionals to integrate psychological principles into the interdisciplinary management of pain. For example, a psychologist can improve communication between a health care provider and patient or

work with a clinician to alter the characteristics of a treatment regimen (e.g., complexity, dosing frequency, cost). Such psychological interventions may help assess and enhance patient adherence with treatment (e.g., medications, physical therapy), thus increasing the probability of successful management.^{e,215} Unfortunately, psychological approaches to pain management are not used as often as they should be,²¹⁵ due to a variety of reasons (e.g., lack of awareness of the role of psychological factors in the response and adaptation to pain, time constraints, reimbursement policies).

2. Physical Rehabilitative Approaches

Physical rehabilitative methods of pain management are appropriate for many types of pain and are essential in patients with CNCP. In addition to relieving pain, such methods can reduce fear and anxiety, improve physical function, and alter physiological responses to pain. Treatments used in physical rehabilitation include stretching, exercises/reconditioning (to improve strength, endurance, and flexibility), gait and posture training, and attention to ergonomics and body mechanics.¹⁸² Other non-invasive physical treatments for pain include thermotherapy (application of heat), cryotherapy (application of cold), counter-irritation, and electroanalgesia (e.g., transcutaneous electrical stimulation) (Table 31).¹⁸² In some cases, patients choose to pursue non-allopathic (alternative treatments) such as acupuncture or therapeutic massage.

3. Surgical Approaches

Most pain can be managed by simple noninvasive methods. However, more invasive approaches, including surgery, are sometimes needed. Orthopedic approaches to pain management include both nonsurgical ("conservative") approaches and various surgeries (e.g., total joint replacement, laminectomy, spinal fusion).

^e One reason that medical interventions sometimes fail or minimally succeed is poor patient adherence to treatment regimens. Estimates of the prevalence of medication nonadherence for the population as a whole are relatively high (30% to 60%), and patients tend to underreport poor adherence and overreport good adherence.²¹⁹ Although few studies have addressed the prevalence of nonadherence with pain medication regimens, it appears to be a problem.²²⁰⁻²²²

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Neurosurgical procedures for managing pain include neurolysis (i.e., injection of a chemical or application of heat or cold to destroy neural tissue), neuroaugmentation procedures, and neuroablative surgeries (i.e., disruption of neural signals and/or removal of neural structures associated with pain).²²⁹ For example, microvascular

decompression of the trigeminal nerve is sometimes used to manage trigeminal neuralgia.

Although beyond the scope of this monograph, a variety of other surgical approaches to pain management exist. Other sources (e.g., Bonica's Management of Pain, 3rd ed.) provides complete coverage of these methods.

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Table 30. Examples of Psychological Methods Used to Manage Pain

Intervention	Definition	Purpose/Goals	Uses
Patient education	Provision of detailed information about disease or interventions and methods of assessing and managing pain (e.g., preoperative instruction about importance of deep breathing, coughing, and ambulating postoperatively; teaching patients with chronic pain about what may aggravate and relieve pain)	Can reduce pain, analgesic use, and length of hospital stay	Postoperative pain, chronic pain
Contingency management ^a	CM involves the manipulation of environmental consequences of pain behavior in a way that helps patients to modify their behavior; it involves use of social reinforcers to increase "well behavior" (e.g., exercise, non-medical conversation) and decrease "sick role" behavior	Refers to methods not for treating the pain per se but rather helping patients to change behaviors Studies suggest that CM effectively reduces pain	Chronic pain
CBT	CBT combines cognitive therapy techniques (e.g., attention diversion) with behavioral techniques (e.g., relaxation, assertiveness training); there are two major CBT subtypes: cognitive restructuring and coping skills training	Helps patients alter their perceptions or labeling of pain (i.e., decrease negative thoughts, emotions, and beliefs), increase sense of control, and decrease maladaptive behaviors	Chronic pain especially, but also useful for acute pain
Cognitive restructuring	Type of CBT in which patients are taught to monitor and evaluate negative thoughts	The goal is to generate more accurate and adaptive thoughts	Chronic pain
Coping skills training	Type of CBT that helps patients develop coping skills, which includes relaxation and imagery techniques, adaptive coping self-statements, and group psychotherapy	Directed at helping patients to develop skills to manage pain and stress	Multiple types of pain (see below)
Relaxation with imagery	Includes progressive muscle relaxation, imagery, visualization, and meditation One of most widely used nonpharmacologic treatments for pain that can increase focus on feelings of well-being as well as diminish tension, anxiety, depression, and pain-related inactivity. ^b	Relaxation decreases patient's focus on pain, muscle tension, and autonomic and emotional arousal; imagery provides a competing cognitive focus, which can block the perception of pain	Postoperative pain, chronic headache, chronic LBP, cancer pain, arthritis pain, labor pain, TMD
Hypnosis	Technique in which a patient's susceptibility to suggestion is heightened, facilitating modification of memory and perception; hypnosis can be used alone or as a means of enhancing the effectiveness of another clinical intervention	Hypnosis may provide comfort and reduce anxiety and suffering associated with acute, recurrent, and chronic types of pain; it reduces cortical activation associated with painful stimuli	Postoperative, burn, dental, labor, cancer, procedural, neuropathic, and musculoskeletal pain; headache
Distraction	Includes repeating reaffirming phrases, singing, talking, etc., to distract attention from unpleasant awareness of pain; in patients with CNCP, it also may include social and recreational activities	The goal is for the patient to actively occupy his or her attention with an activity or topic other than pain	Multiple acute and chronic types of pain
Biofeedback	Patient learns to take voluntary control over physiological body activities by receiving input (e.g., visual or auditory cues) about these activities (e.g., heart beat, muscle tension, skin temperature)	Directed at teaching a patient how to take control of body responses via mental activity	Most support for use with vascular HA; also used for chronic LBP and other HA, myofascial pain, rectal pain
Psychotherapy	Treatment for a mental illness or maladaptive behaviors that involves a therapist establishing a relationship with a patient to achieve certain goals; includes individual (supportive and dynamic), group, and family psychotherapy	Goals of psychotherapy include modifying symptoms, changing maladaptive behaviors, and promoting growth and development	Chronic pain, cancer pain, pain associated with HIV infection

Sources: References 24, 72, and 214-218.

^aThe terms "contingency management" and "operant conditioning" are used interchangeably. Overlap exists between CM and CBT, but CM focuses more on modifying behavior and CBT helps more with altering patient perceptions or labeling of sensations.²¹⁴^bThese methods can be taught quickly but patients do best with encouragement from health care professionals and family members. Audiotapes and printed materials also can be helpful.²⁴

CBT: cognitive-behavioral therapy; CM: contingency management; CNCP: chronic noncancer pain; HA: headache; HIV: human immunodeficiency virus; LBP: low back pain; TMD: temporomandibular disorder.

Section III: Types of Treatments

Table 31. Examples of Physical Methods Used to Manage Pain

Intervention	Definition	Purpose/Goals	Examples of Uses
Stretching	Gentle exercise to improve flexibility	Improve ROM, function, comfort	Arthritis, LBP, fibromyalgia, myofascial pain syndrome
Exercise/reconditioning	Reconditioning exercises can improve strength and endurance as well as combat stiffness and weakness associated with pain-related inactivity	Useful in regaining muscle and tendon strength, as well as improving ROM, endurance, comfort, and function Transforms painful activities into more easily tolerated ones Minimizes atrophy, demineralization, and deconditioning	Arthritis, LBP, fibromyalgia, CRPS
Gait and posture training	Appropriate attention to gait and posture, including preventive and therapeutic ergonomics	Relieve pain and restore function; prophylaxis against further pain	LBP, neck pain, tension HA
Applied heat or cold	Application of cold (cryotherapy) to decrease pain and swelling and improve function; later application of heat (thermotherapy) to augment performance and diminish pain	Application of cold produces local analgesia, slows nerve conduction, and promotes tendon flexibility Application of heat produces local analgesia, dilates (widens) blood vessels, and promotes flexibility	Acute trauma (e.g., injury, surgery); repetitive trauma, arthritis, muscle pain or spasm, acute LBP
Immobilization	Reduction of activity and avoidance of strain for certain duration; may involve brace to assist, restrict, or limit function of joint	May be needed to maintain proper alignment during post-injury repair but is generally harmful for patients with CNCP	Some postoperative, injury (e.g., fracture)
TENS	Selective stimulation of cutaneous receptors sensitive to mechanical stimuli (mechanoreceptors) by applying low-intensity current via skin electrodes ^a	TENS can reduce pain and analgesic use and improve physical mobility, presumably by interfering with transmission of nociceptive impulses in nerve fibers	Trauma, postoperative, labor, abdominal pain; neuralgias, other neuropathic pain, PVD, angina, musculoskeletal pain
PNS SCS IC	Electrical stimulation of selected regions of the nervous system via implantable devices ^b	The goal of electrical stimulation is to disrupt nociceptive signaling	Chronic pain of the trunk and limbs (e.g., PVD), neuropathic pain (deafferentation, poststroke pain), cancer pain
Massage	Rubbing of painful or nonpainful adjacent area	Facilitates relaxation and decreases muscle tension and pain	Postoperative pain, arthritis, fibromyalgia
Acupuncture	Old Chinese healing technique involves insertion of fine needles into the skin at varying depths; application of pressure at acupuncture sites is called acupressure	Acupuncture may cause the secretion of endorphins and interfere with transmission of nociceptive information to relieve pain	Postoperative, radiculopathy, chronic LBP, fibromyalgia

Sources: References 24, 72, 182, and 223-228.

^aTENS appears to work best when applied to skin close to the pain's site of origin and when sense of touch and pressure are preserved.^bThe implanted portion of the device consists of a pulse generator and leads connected to electrodes located in fascia in close proximity to a peripheral nerve (PNS), the spinal canal (SCS), or brain (IC). The patient or clinician controls stimulation using non-implanted system components.

CNCP: chronic noncancer pain; CRPS: chronic regional pain syndrome types I and II; HA: headache; IC: intracerebral stimulation; LBP: lower back pain; PNS: peripheral nerve stimulation; PVD: peripheral vascular disease; ROM: range of motion; SCS: spinal cord stimulation; TENS: transcutaneous electrical nerve stimulation.



Section IV:

Management of Acute Pain and Chronic Noncancer Pain

Section IV: Management of Acute Pain and Chronic Noncancer Pain

A. ACUTE PAIN

This section reviews the general approach to the treatment of acute pain, including treatment goals, therapeutic strategies, and elements of pain management. It also provides an overview (i.e., summary tables) of the treatment of some common types of acute pain.

1. Treatment Goals

As addressed in Section I.C.1, acute pain is a complex multidimensional experience that usually occurs in response to tissue trauma. Whereas responses to acute pain may be adaptive, they can have adverse physiologic and psychological consequences (e.g., reduced tidal volume, excessive stress response, progression to chronic pain, inability to comply with rehabilitation, patient suffering and dissatisfaction). Acute pain is more difficult to manage if permitted to become severe,¹ so prompt and adequate treatment of acute pain is imperative. Treatment goals and strategies for acute pain can be summarized as:

- Early intervention, with prompt adjustments in the regimen for inadequately controlled pain
- Reduction of pain to acceptable levels
- Facilitation of recovery from underlying disease or injury.

2. Therapeutic Strategies

a. Multimodal analgesia

Recent research on postoperative pain management supports a treatment approach known as “multimodal analgesia” or “balanced analgesia.” This approach involves the use of more than one method or modality of controlling pain (e.g., drugs from two or more classes, drug plus nondrug treatment) to obtain additive beneficial effects, reduce side effects, or both.² These modalities may operate through different mechanisms or at different sites (i.e., peripheral versus central actions). One example of multimodal analgesia is the use of various combinations of opioids and local anesthetics to manage postoperative pain.³⁻⁵ Table 32 summarizes some specific examples of multimodal therapy.

Table 32. Examples of Multimodal Therapy

Combination of Agents	Example
Systemic NSAID ^a plus systemic opioid	PO Ibuprofen plus PO hydromorphone
Systemic NSAID plus epidural opioid and local anesthetic	IV ketorolac plus epidural fentanyl and bupivacaine
Systemic NSAID plus local infiltration of anesthetic plus systemic opioid	IV ketorolac plus lidocaine infiltration of surgical site plus IV PCA morphine
Regional block plus systemic NSAID plus epidural opioid and local anesthetic	Intraoperative anesthetic plus IV ketorolac plus postoperative fentanyl and bupivacaine epidural

Source: Reference 6.

^aNSAIDs need to be used with care in surgical patients due to the risk of bleeding (“anti-platelet” effect).

IV: intravenous; NSAID: nonsteroidal anti-inflammatory drugs; PCA: patient-controlled analgesia; PO: per os (oral).

Benefits of multimodal analgesia include earlier oral intake, ambulation, and hospital discharge for postoperative patients as well as higher levels of participation in activities necessary for recovery (e.g., physical therapy).⁶⁻⁷ It also may reduce postoperative morbidity, mortality, and costs.⁸ Some pain experts advocate revision of traditional postoperative care programs to include accelerated multimodal postoperative recovery programs.⁹ Additional potential applications of multimodal analgesia include other types of acute, as well as chronic, pain.²

b. Preemptive analgesia

Preemptive analgesia refers to the administration of one or more analgesic(s) prior to a noxious event (e.g., surgery) in an attempt to prevent peripheral and central sensitization, minimizing post-injury pain (see I.B.7,8). Compelling evidence of the efficacy of preemptive analgesia exists in animal models, and human studies have produced some promising results. For example, the preoperative administration of selective cyclooxygenase-2 (COX-2) inhibitors decreased use of morphine after spinal fusion surgery in one recent study.¹⁰ There is also some evidence that preoperative epidural blockade (local anesthetic and opioid with or without clonidine) may reduce the incidence of phantom limb pain in patients undergoing limb amputation.¹¹⁻¹²

However, other studies have failed to confirm that preemptive analgesia prevents phantom

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limb pain.^{a,13-14} Furthermore, a recent review of 40 controlled clinical studies revealed no difference in the intensity and duration of postoperative pain after preemptive analgesia with a variety of drugs.¹⁵ This failure to demonstrate clinical efficacy may reflect failure to identify the optimum method or timing for instituting the analgesia. Some investigators contend that multiple factors (e.g., extent and nature of the damaged tissue, duration of the surgery, choice of drug, route and timing of administration, time course of central sensitization) may influence the ability to demonstrate a preemptive analgesic effect.¹⁶ Thus, clinical research into its potential clinical benefits is continuing.

3. Elements of Treatment

a. Pharmacologic management

Pharmacologic management is the cornerstone of acute pain management. Multiple factors (e.g., pain intensity, quality, and pattern; patient preferences; drug side effect profiles) influence the selection of medications. Most acute pain is nociceptive and responds to nonopioids and opioids. However, some adjuvant analgesics (e.g., local anesthetics) also are used to manage acute pain.

In general, mild somatic pain responds well to oral nonopioids (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs]), topical agents (e.g., local anesthetics), and physical treatments (e.g., rest, ice, compression, elevation).¹ Moderate to moderately severe acute pain is more likely to require opioids.¹⁷⁻¹⁸ Nonopioids often are combined with opioids to improve pain relief and diminish the risk of side effects. Various factors (e.g., preferred route of administration, time of onset, dosing frequency, side effect profile) influence the choice of individual agents in a drug class.

Excessive concern about addiction and regulatory scrutiny heavily contribute to the under-treatment of pain (see I.E.4,5). Analgesics, espe-

cially opioids, are underprescribed and under-dosed for both acute and chronic pain. Moderate to severe acute pain should be treated with sufficient doses of opioids to safely relieve the pain. If drug side effects preclude achieving adequate pain relief, the side effects should be treated and/or another opioid should be tried. The concomitant use of other analgesics (e.g., nonopioids, local anesthetics) and nonpharmacologic methods (e.g., applied heat or cold, electroanalgesia, relaxation) maximizes pain relief and minimizes the risk of treatment-limiting side effects.

b. Nonpharmacologic approaches

Nonpharmacologic approaches to acute pain management should supplement, but not replace, analgesics.¹ However, the medical condition of some patients with acute pain (e.g., severe trauma or burns) may limit the use of nonpharmacologic therapy. Postoperative patients who receive preoperative instruction in simple psychological methods (Table 30) such as relaxation and imagery are especially likely to benefit. Thus, instruction in nonpharmacologic methods of pain management is an important part of the preoperative assessment (Table 12). Physical methods of pain management can be helpful in all phases of care, including immediately after tissue trauma (e.g., rest, application of cold, compression, elevation) and late during the healing period (e.g., exercises to regain strength and range of motion) (Table 31).

4. Management of Some Common Types of Acute Pain

Table 33 defines and presents examples of some common types of acute pain, including pain associated with an acute illness, perioperative pain, posttraumatic pain (major and minor), procedural pain, and obstetrical pain. Tables 34 to 36 summarize some pharmacologic and non-pharmacologic approaches to the management of these types of pain. The former category is divided into medications administered via systemic routes (Table 34) and those administered regionally (i.e., regional anesthesia)(Table 35). The reasons these pain types were selected for discussion include:

- Their relatively high prevalence
- The availability of effective pharmacologic and nonpharmacologic methods of management
- The availability of clinical practice guidelines

^a Nikolajsen and colleagues¹³ found that the rate and intensity of phantom and stump pain, as well as the consumption of opioids, did not differ significantly between 29 patients randomly assigned to receive epidural bupivacaine and morphine before, during, and for 1 week after the lower-limb amputation and 31 control-group patients who received epidural saline before and during the amputation then oral or intramuscular morphine. Lambert et al.¹⁴ reported that a perioperative epidural block started 24 hours prior to amputation was not superior to the intra- and post-operative infusion of a local anesthetic via a perineural catheter in preventing phantom pain. However, the former did provide better relief of stump pain during the immediate postoperative period.

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Table 33. Common Types of Acute Pain

Type or Source	Definition	Source or Examples
Acute illness	Pain associated with an acute illness	Appendicitis, renal colic, myocardial infarction
Perioperative (includes postoperative) ^a	Pain in a surgical patient because of preexisting disease, the surgical procedure (e.g., associated drains, chest or nasogastric tubes, complications), or both	• Head and neck surgery • Chest and chest wall surgery • Abdominal surgery • Orthopedic and vascular surgery (back, extremities)
Posttraumatic (major trauma)	Includes generalized or regionalized pain due to a major acute injury	Motor vehicle accident
Posttraumatic (minor trauma)	Pain due to a minor acute injury	Sprain, laceration
Burns	Pain due to thermal or chemical burns	Fire, chemical exposure
Procedural	Pain associated with a diagnostic or therapeutic medical procedure	Bone marrow biopsy, endoscopy, catheter placement, circumcision, chest tube placement, immunization, suturing
Obstetrical	Pain related to labor and delivery	Childbirth by vaginal delivery or Cesarean section

Sources: References 1 and 19.

^aThe American Society of Anesthesiologists defines acute pain in the perioperative setting as “pain that is present in a surgical patient because of preexisting disease, the surgical procedure (e.g., associated drains, chest or nasogastric tubes, complications), or a combination of disease-related and procedure-related sources.”¹⁹ Thus, perioperative pain includes postoperative pain (i.e., pain that follows surgery).

- (CPGs) outlining appropriate care
- Evidence of undertreatment and/or nonadherence to relevant CPGs.

These tables merely provide an overview of treatments. They do not consider all of the risks associated with treatments or the needs of special populations. The reader should refer to the appropriate CPGs to make specific management decisions.

factors contributes to the persistence of pain. Therefore, treatment should address important social and psychological consequences of the pain as well as any physical pathology. Usually this entails a comprehensive approach that includes medication and functional rehabilitation.²⁸

Functional rehabilitation helps the patient develop skills to manage the pain. It includes patient education, regular assessment, management of contributing illnesses (e.g., depression), and the setting of attainable treatment goals.²⁸ The latter should take into account factors such as the patient’s acceptance of his or her condition, the patient’s motivation to participate in treatment, the patient’s ability to follow through with recommendations, and the available time and resources.²⁹ General treatment goals for CNCP include:^{2,28-30}

- Diminish suffering, including pain and associated emotional distress
- Increase/restore physical, social, vocational, and recreational function
- Optimize health, including psychological well-being
- Improve coping ability (e.g., develop self-help strategies, reduce dependence on health care system) and relationships with others (e.g., family, friends, health care professionals).

B. CHRONIC NONCANCER PAIN

This section reviews general approaches to the treatment of chronic noncancer pain (CNCP), including treatment goals, therapeutic approaches, and elements of treatment. It also provides general information about the treatment of some common types of CNCP (i.e., summary tables) and identifies relevant clinical practice guidelines (CPGs).

1. Treatment Goals

As discussed in Section I.C.4, CNCP is a debilitating condition that often is associated with significant physical, emotional, and social disability. A complex interaction among these

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Table 34. Systemic Medications for Acute Pain Management

Pain Type or Source	Nonopioids	Opioids	Adjuvant Analgesics	Other	Comments
Acute illness	Acetaminophen, NSAIDs	Systemic opioids			
Perioperative pain ^a	Acetaminophen, NSAIDs ^b	Systemic opioids ^c , including PCA ^d	Local anesthetics (e.g., lidocaine, bupivacaine ^e)		Use multimodal therapy when possible Recognize needs of special populations Scheduled ATC dosing generally preferred to PRN
Major trauma (generalized pain)	Acetaminophen, NSAIDs during post-trauma healing phase	Bolus or continuous IV opioids ^f during emergency phase; PO or IV opioids during healing phase	IV ketamine (very rare)	Inhaled NO	Use of ketamine is restricted to pain refractory to other treatments due to severe CNS side effects Inhaled NO is used for incident pain
Major trauma (regionalized pain)	NSAIDs (parenteral, oral) during post-trauma healing phase	Bolus or continuous IV opioids during emergency phase plus regional anesthesia	IV ketamine (very rare)	Inhaled NO	Use of ketamine is restricted to pain refractory to other treatments due to severe CNS side effects Inhaled NO is used for incident pain
Burns	Acetaminophen, NSAIDs during rehabilitative phase (i.e., no early role)	High doses of IV opioids (e.g., morphine, fentanyl) ± PCA for NPO patients; oral opioids (e.g., morphine, hydromorphone) when taking PO	Parenteral ketamine (very rare) IV lidocaine (very rare)	BNZ Inhaled NO	Use of ketamine is restricted to pain refractory to other treatments due to severe CNS side effects Inhaled NO is used for incident pain Infusion of low-dose lidocaine is restricted to burn pain refractory to opioids Lorazepam or midazolam for background and procedural anxiolysis
Minor trauma	Acetaminophen, NSAIDs	Opioids for mild-to-moderate pain			
Procedural pain	NSAIDs for preemptive analgesia and post-procedural pain	IV opioids (e.g., morphine, hydromorphone, fentanyl) unless contraindicated ^g	Local anesthetics (e.g., EMLA [®] , lidocaine, bupivacaine, ropivacaine) IV ketamine	BNZ (e.g., diazepam, lorazepam, midazolam) Inhaled NO Propofol ^h	Local anesthetics may be applied topically (e.g., EMLA [®]), injected into tissue, or used for nerve blocks Use of ketamine limited by severe CNS side effects
Obstetrical pain		Bolus IV opioids (e.g., fentanyl, hydromorphone, morphine)			

Sources: References 1 and 17-24.

^aThe American Society of Anesthesiologists defines acute pain in the perioperative setting as pain that is present in a surgical patient because of preexisting disease, the surgical procedure (e.g., associated drains, chest or nasogastric tubes, complications), or a combination of disease-related and procedure-related sources.¹⁹ Thus, perioperative pain includes postoperative pain (i.e., pain that follows surgery).

^bUnless contraindicated, NSAIDs (and acetaminophen) are recommended for mild-to-moderate postoperative pain, and parenteral ketorolac may be used for moderate-to-severe pain.¹ Continue nonopiods even after adding opioids for opioid-sparing effects.¹

^cModerately severe to severe postoperative pain should initially be treated with an opioid analgesic with or without an NSAID.¹ Morphine is the standard agent for opioid therapy; if contraindicated, hydromorphone may be substituted.¹

^dPreferred route of administration is IV (bolus or continuous PCA). Rectal and subcutaneous are alternative routes of administration. Switch to oral administration when the patient can take medication by mouth.

^eLocal anesthetics may be combined with opioids for intraspinal analgesia or used for regional nerve blocks.

^fTitrate opioids carefully to maintain stable cardiovascular and respiratory status. Monitor neurological and neurovascular status continuously in patients with head injury or limb injury, respectively.¹

^gContraindications to opioid analgesia include altered sensorium, full-term pregnancy, lung disease, or inability to monitor and manage certain side effects (e.g., respiratory depression).¹

^hHypnotic general anesthetic that produces good sedation.

ATC: around-the-clock; BNZ: benzodiazepines; CNS: central nervous system; EMLA[®]: Eutectic Mixture of Local Anesthetics (lidocaine and prilocaine); IV: intravenous; LAs: local anesthetics; NO: nitrous oxide; NPO: nothing per os (by mouth); NSAIDs: nonsteroidal anti-inflammatory drugs, including aspirin; PO: per os (oral); PCA: patient-controlled analgesia; PRN: as needed; TD: transdermal.

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Table 35. Regional Anesthesia for Acute Pain Management

Perioperative pain ^a	<ul style="list-style-type: none"> Epidural anesthesia with opioids or opioid plus local anesthesia mixture injected intermittently or infused continuously^b Intrathecal opioids or opioid plus local anesthetics Local neural blockade^c Other regional anesthesia^d techniques
Trauma	<ul style="list-style-type: none"> Limited to local neural blockade^c during emergency phase Also includes epidural analgesia with opioids and/or local anesthetics during post-trauma healing phase, especially for regionalized pain^e
Burns	<ul style="list-style-type: none"> Epidural analgesia with opioids and/or local anesthetics (only after closure of burn wound)
Procedural	<ul style="list-style-type: none"> Includes local infiltration with local anesthetics
Obstetrical pain ^f	<ul style="list-style-type: none"> Epidural analgesia^g or spinal analgesia with local anesthetics (e.g., bupivacaine, ropivacaine) and/or opioid Combined spinal-epidural techniques (combined spinal-epidural techniques)^h with opioids Epidural analgesia, spinal, or combined spinal-epidural techniques for Cesarean section Tissue infiltration with local anesthetics

Sources: References 1, 19-20, and 22-24.

^aThe American Society of Anesthesiologists defines acute pain in the perioperative setting as “pain that is present in a surgical patient because of preexisting disease, the surgical procedure (e.g., associated drains, chest or nasogastric tubes, complications), or a combination of disease-related and procedure-related sources.”¹⁹ Thus, perioperative pain includes postoperative pain (i.e., pain that follows surgery).^bGood analgesia but risk of delayed-onset respiratory depression; requires careful monitoring for potential complications (e.g., abscess development, anesthesia of a nerve root at the site of catheter tip).¹ Addition of a local anesthetic has opioid-sparing effect and improves analgesia.^cLocal neural blockade is by intermittent (e.g., intercostal nerve blockade with local anesthetics or cryoprobe) or continuous (infusion of local anesthetic through an interpleural catheter) methods.^dOther regional anesthesia techniques include: infiltration of incisions with local anesthetic.^eUseful when not contraindicated by sepsis, coagulopathy, or cardiorespiratory instability.¹ Must clear spine before using central conduction block or intraspinal opioids.²³^fGoal of regional anesthesia in pregnant women is to provide adequate analgesia with as little block as possible.²⁰^gEpidural anesthesia is preferred to spinal analgesia and parenteral opioids due to superior analgesia and decreased risk of maternal and/or fetal complications.²⁰ Epidural analgesia with opioids with a local anesthetic provides better analgesia than epidural anesthesia with local anesthetics alone but is associated with greater risk of complications.²⁰^hCombined spinal-epidural techniques may provide rapid and effective analgesia for labor, but there is a higher risk of side effects.²⁰**Table 36. Nonpharmacologic Interventions for Acute Pain**

Pain Type or Source	Physical Methods ^a	Psychological Methods	Other
Acute illness	<ul style="list-style-type: none"> Vibration or cold for some HA; immobilization 	Patient education, relaxation, imagery, distraction	
Perioperative pain ^b	<ul style="list-style-type: none"> Exercise or immobilization Massage Application of heat or cold Electroanalgesia (e.g., TENS) 	Patient education, relaxation, distraction, Acupuncture imagery, biofeedback, hypnosis	
Trauma	<ul style="list-style-type: none"> Rest, ice, compression, elevation (RICE) Physical therapy (e.g., stretching, strengthening, thermal therapy, TENS, vibration) 	Relaxation, hypnosis, distraction, supportive psychotherapy, coping skills training	
Burns	<ul style="list-style-type: none"> Limb elevation Minimize number of dressing changes 	Patient education, distraction, deep relaxation, imagery, hypnosis, operant conditioning	
Procedural	<ul style="list-style-type: none"> Application of cold (pre- and post-procedure) Counterirritation methods (e.g., simple massage, scratching, pressure) Rest or immobilization (post-procedure) 	Patient education, relaxation, distraction, imagery, music relaxation	
Obstetric		Patient education, relaxation breathing, distraction	

Sources: References 1, 18-19, and 21-27.

^aPhysical agents or modalities provide pain relief, improve physical function, and reduce fears associated with pain-related immobility or activity restriction.¹^bThe American Society of Anesthesiologists defines acute pain in the perioperative setting as “pain that is present in a surgical patient because of preexisting disease, the surgical procedure (e.g., associated drains, chest or nasogastric tubes, complications), or a combination of disease-related and procedure-related sources.”¹⁹ Thus, perioperative pain includes postoperative pain (i.e., pain that follows surgery).

HA: headache; TENS: transcutaneous electrical nerve stimulation.

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2. Therapeutic Strategies

a. Multimodal therapy

As with acute pain, the literature and various CPGs support the use of multimodal therapy for chronic pain. In their 1997 Practice Guidelines for Chronic Pain Management, the American Society of Anesthesiologists (ASA) defines multimodal therapy as the “concomitant use of separate therapeutic interventions under the direction of a single practitioner to obtain additive beneficial effects or reduction of adverse effects.”²

Examples of multimodal therapy include use of:

- Medications from different classes (i.e., combination drug therapy)
- Rehabilitative therapies (e.g., physical therapy, occupational therapy) and medications
- Regional anesthesia (e.g., neural blockade) and medications.

b. Interdisciplinary approach to rehabilitation

The literature³¹⁻³² and various organizations (e.g., the Commission on Accreditation of Rehabilitation Facilities [CARF], the American Academy of Family Physicians [AAFP]) also support the use of an interdisciplinary rehabilitative approach to the management of chronic pain. This refers to a process in which health care professionals with disparate training collaborate to diagnose and treat patients suffering from difficult pain states. The Rehabilitation Accreditation Commission (also known as CARF) defines a chronic pain management program (CPMP) as [one that] “provides coordinated, goal-oriented, interdisciplinary team services to reduce pain, improve functioning, and decrease the dependence on the health care system of persons with chronic pain syndrome.”³³⁻³⁴ Various reviews of program outcomes suggest that potential benefits of participation in a CPMP include reduced pain intensity, improved sense of control over the pain, physical reconditioning, lower use of opioids and health care resources, reduced health care costs, and increased employment.^{2,30-32,35-36}

Essential functions of a CPMP include medical diagnosis, assessment of physical function, psychosocial assessment, pharmacologic therapy, physical rehabilitation, patient education, and appropriate psychological approaches (e.g., relaxation, biofeedback, coping skills training, psychotherapy).^{30,36} In some patients, more

Table 37. Interdisciplinary Management of CNCP: Examples of Interventions

- Patient education: counseling about the pain, aggravating and alleviating factors, management strategies, lifestyle factors that may influence the pain (e.g., use of nicotine, alcohol)
- Physical rehabilitative approaches: physical therapy modalities for reconditioning (e.g., walking, stretching, exercises to improve strength and endurance, oscillatory movements)
- Other physical approaches: application of heat or cold, TENS, massage, acupuncture
- Occupational therapy: attention to proper body mechanics, resumption of normal levels of activities of daily living
- Pharmaceuticals: nonopioids, opioids, antidepressants, antiepileptic drugs, stimulants, antihistamines
- Regional anesthesia: nerve blocks (e.g., diagnostic, somatic, sympathetic, visceral, trigger point) and/or intraspinal analgesia (e.g., opioids, clonidine, baclofen, local anesthetics)
- Psychological approaches: relaxation training, hypnosis, biofeedback, coping skills, behavior modification, psychotherapy
- Surgery: neuroablation, neurolysis, microvascular decompression

Sources: References 2, 28, 30, and 36-37.

CNCP: chronic noncancer pain; TENS: transcutaneous electrical nerve stimulation.

invasive approaches (e.g., nerve blocks, trigger point or steroid injections, epidural or intrathecal analgesia, neurosurgical procedures) and/or intensive chronic pain rehabilitation are warranted. Team members represent a number of health care disciplines and include physicians (e.g., neurologists, psychiatrists, anesthesiologists, rheumatologists, neurosurgeons, physiatrists), nurses, pharmacists, case managers, social workers, physical therapists, occupational therapists, and vocational counselors.³⁷ Interventions are diverse, as summarized in Table 37.

3. Elements of Treatment

a. Pharmacologic management

Although similarities exist, the pharmacologic management of CNCP differs from that for acute pain in some important ways.

Greater use of adjuvant analgesics: The greater use of adjuvant analgesics for chronic pain reflects, in part, the greater frequency of neuropathic pain and reduced responsiveness of such pain to traditional analgesics. The results of multiple placebo-controlled clinical trials and various CPGs^{2,28} support the use of antidepres-

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sants, antiepileptic drugs, and local anesthetics as first-line approaches to the treatment of chronic pain. The 1997 ASA CPGs for Chronic Pain Management state that membrane stabilizing agents, antidepressants, and NSAIDs “provide analgesic and health benefits” in patients with chronic pain.² The 2000 AAFP CPGs for the treatment of CNCP note that secondary benefits of antidepressants include improved sleep and the treatment of any associated depression or anxiety.²⁸ Similarly, the antiepileptic drug gabapentin improves sleep and mood, as well as pain and quality of life, in patients with some types of neuropathic pain.³⁸⁻³⁹

More judicious use of opioids: For many years, use of opioids to treat CNCP was considered ill-advised. This position reflected multiple fears and concerns, including the potential for iatrogenic addition, declining efficacy, toxicities, and potential interference with optimal functioning (e.g., promotion of regression, reinforcement of pain behaviors, diversions, decreased motor and cognitive functioning).⁴⁰ However, a number of pain-related organizations and experts have expressed recent support for the judicious use of opioids in patients with chronic pain. For example, the American Academy of Pain Medicine and the American Pain Society recently issued a statement that supports the use of opioids in select patients with CNCP.⁴¹ As with other medical interventions, such a decision must be based on careful consideration of the ratio of benefits to risks (e.g., toxicity, functional impairment, addiction).^{b,40} Table 38 summarizes some recommendations regarding use of opioids in patients with CNCP.⁴⁸

b. Nonpharmacologic approaches

Nonpharmacologic approaches play a key role in managing CNCP. Patient education is potentially the most critical therapy, as it is often essential for rehabilitation. Invalidism and family enabling may result from uncertainty or inaccurate information.³⁰ Reconditioning reduces pain, promotes physical and psychological rehabilitation, and empowers the patient. In addition to reducing emotional distress, psychological techniques (e.g., relaxation, biofeedback) can relax muscles and reduce autonomic nervous arousal. In its 2000 CPGs, the AAFP recom-

^b Some studies have shown beneficial effects of long-term opioid therapy in carefully selected patients with CNCP, including reduced pain, improved performance, and enhanced quality of life.⁴²⁻⁴⁴ However, clinicians should remain aware of the potential for opioid-induced hyperalgesia and/or analgesia without associated improvement in function in some patients.^{40,43,45-47}

Table 38. Recommendations for Opioid Therapy in Patients with Chronic Noncancer Pain

Before treatment:

- Perform comprehensive assessment, including a pain history and assessment of the impact of the pain, a directed physical examination, a review of prior diagnostic study results or interventions, a drug history (i.e., past abuse), and an assessment of coexisting diseases or conditions.
- Consider obtaining a second opinion from a physician or psychologist with expertise in pain management and use of interdisciplinary team.
- Optimize nonpharmacologic and nonopioid therapies.
- Inform patient of potential risks of use of controlled substances, including addiction (informed consent)
- Agree on issues including how drugs will be provided, acceptable number of rescue doses, pharmacy to be used for prescription refills, and the follow-up interval.

During treatment:

- Administer opioids primarily via oral or transdermal routes, using long-acting medications when possible.
- Use a fixed dosed (“around-the-clock”) regimen.
- Perform careful drug titration, balancing analgesia against side effects.
- Continue efforts to improve analgesia via complementary approaches (e.g., behavioral approaches, formal rehabilitation program, other medications).
- Consider use of hospitalization for pain that is not treated by transient, small dose increments.
- Monitor for evidence of drug hoarding, unauthorized dose increases, and other aberrant behavior. Reconsider therapy in the occurrence of such behaviors.
- Perform frequent follow-up evaluation to monitor analgesia, side effects, functional status, quality of life, and any evidence of medication misuse.
- Consider use of self-report instruments (e.g., pain diary).
- Carefully document the overall pain management treatment plan and include the reason for opioid prescribing, any consultations received, and results of periodic review of the patient’s status.

Sources: References 29, 41, and 48.

mends the use of nonpharmacologic interventions (i.e., patient education, physical therapy [PT], occupational therapy [OT], treatment of coexisting psychological disorders) in the management of all patients with CNCP.²⁸

4. Management of Some Common Types of Chronic Noncancer Pain

There are many types of CNCP. This section provides a brief overview through the summary tables of a few common types. In addition to their relatively high prevalence, these pain types were selected because effective treatments and/or evidence of inadequate management

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exist. Tables 39 to 42 summarize management approaches, including systemic administration of medications (Tables 39 and 40), interventional techniques (Table 41), and nonpharmacologic strategies (Table 42), for the following types of CNCP:

Arthritis pain

Arthritis pain can result from more than 100 rheumatic diseases, which cause pain, stiffness, and swelling of joints as well as damage to sup-

porting structures.⁵⁵ Osteoarthritis (OA) and rheumatoid arthritis (RA) are the most common types of arthritis. OA (often referred to as degenerative joint disease) is characterized by a progressive loss of articular (joint) cartilage, mostly affecting weight-bearing and frequently used joints (e.g., hip, knee).⁵³ It often manifests as deep aching pain, stiffness, and limited range of motion. RA is a common inflammatory arthritis of unknown etiology that affects multiple joints.⁵³ RA manifests clinically as aching,

Table 39. Pharmacologic Management for Chronic Noncancer Pain: Selected Examples

Type of Pain	Nonopioids	Opioids	Adjuvant Analgesics and Disease-Specific Drugs	Comments
Arthritis pain	Acetaminophen NSAIDs Selective COX-2 inhibitors ^a	Short-term, mild opioids for flare-ups	Corticosteroids (oral for RA, injections for OA and RA) Topical capsaicin DMARDs ^b (e.g., MTX, DP, gold salts, AZA, SSZ, HCQ) BRMs ^c (e.g., entanercept, infliximab)	Select NSAID based on dosing, efficacy, tolerance, costs, and patient preference Monitor closely for NSAID side effects Selective COX-2 inhibitors have a lower incidence of certain side effects Opioids are appropriate for long-term treatment in selected patients
Low back pain	Acetaminophen NSAIDs Selective COX-2 inhibitors	Short-term opioids for mild-to-moderate flare-ups	TCAs (e.g., amitriptyline, nortriptyline) AEDs Muscle relaxants (short term)	Opioids are appropriate for long-term treatment in selected patients
Fibromyalgia	Acetaminophen NSAIDs Selective COX-2 inhibitors	Opioids (occasional use for "flares") Tramadol	TCAs (e.g., amitriptyline, nortriptyline, doxepin) Muscle relaxants (short-term) (e.g., cyclobenzaprine)	Tramadol may have less potential for abuse
Sickle cell disease pain	Acetaminophen, NSAIDs	Short-acting ^d or long-acting opioids	Sedatives Anxiolytics	Use short-acting opioids for short-term treatment and longer-acting opioids for longer treatment
Peripheral neuropathy (e.g., PDN, PHN)	Acetaminophen NSAIDs	Opioids (short-term only)	TCAs (e.g., amitriptyline) AEDs (e.g., gabapentin, carbamazepine, valproate) Topical agents (e.g., lidocaine patch, capsaicin) Local anesthetics (e.g., lidocaine, mexiletine) ^e (rarely used) NMDA antagonists (e.g., ketamine) ^f (rarely used)	AEDs, TCAs, and topical local anesthetics are first-line treatments Lidoderm® is first FDA-approved treatment for PHN Placebo-controlled trials found TCAs and gabapentin equally effective for treatment of PDN and PHN NSAIDs are rarely effective Try opioids as last resort

Sources: References 17, 38-39, and 49-70.

^aInitial recommended treatment for OA includes acetaminophen and nonpharmacologic management (e.g., education, exercises, joint protection).⁴⁹⁻⁵¹ Patients who need additional pain relief and symptom control should receive low- or full-dose NSAIDs, topical capsaicin, or corticosteroids, as indicated. The initial drug treatment of RA usually involves NSAIDs.⁵² Patients with inadequate response to NSAIDs may require DMARDs.⁵²

^bDMARDs are associated with multiple toxicities; therefore, they require careful balancing of the risks and benefits and close patient monitoring.⁵²

^cBiological response modifiers are used to reduce symptoms in some patients with RA.⁵³

^dMorphine or hydromorphone is preferred to meperidine due to potential toxicity of the meperidine metabolite.⁵⁴

^eThese medications are contraindicated in patients with cardiac conduction abnormalities, left ventricular dysfunction, or severe liver or renal disease. Topical lidocaine (Lidoderm®) is not associated with the toxicities seen with systemic administration of lidocaine.

^fNMDA antagonists are effective but are used very rarely due to severe central nervous system side effects.

AEDs: antiepileptic drugs; AZA: azathioprine; BRM: biological response modifiers; COX-2 inhibitors: cyclooxygenase-2 inhibitors; DMARDs: disease-modifying anti-rheumatic drugs; DP: D-penicillamine; FDA: Food and Drug Administration; HCQ: hydroxychloroquine; MTX: methotrexate; NMDA: N-methyl-D-aspartate; NSAIDs: nonsteroidal anti-inflammatory drugs; OA: osteoarthritis; PDN: painful diabetic neuropathy; PHN: postherpetic neuralgia; RA: rheumatoid arthritis; SSZ: sulfasalazine; TCAs: tricyclic antidepressants.

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burning joint pain (often with swelling and redness), joint enlargement, joint and muscle stiffness, and various constitutional symptoms (e.g., fatigue, weakness, fever, weight loss). OA affects about 16 million, mostly older, Americans, whereas approximately 2.1 million Americans suffer from RA.⁵⁵ Approaches to management of arthritis pain include medications (e.g., disease-modifying anti-rheumatic drugs, nonsteroidal anti-inflammatory drugs, acetaminophen), physical rehabilitative approaches (e.g., exercises, OT, PT, massage, heat and cold, electroanalgesia), psychological approaches, and in some cases, acupuncture or surgery (Tables 39, 41, and 42).^{49-52,55, 90}

b. Chronic low back pain

Chronic low back pain (LBP) is the commonest cause of disability in industrialized nations. About four out of five Americans will experience back pain at some point in their lives.⁸⁶ Whereas (acute) back pain resolves within 4-6 weeks in 90% of patients,⁵⁹⁻⁶⁰ the pain persists in others. LBP has many causes (e.g., trauma, musculoskeletal spasm, arthritis, herniated disc

with nerve compression, myofascial pain, ankylosing spondylitis, spinal stenosis, arachnoiditis, cancer, kidney disease, obesity) but, in most cases, no specific cause can be identified.⁵⁹⁻⁶⁰ Management options for chronic LBP include medications, psychological approaches (education, "back school," psychotherapy, biofeedback), exercises, other physical approaches (e.g., OT, PT, electroanalgesia, heat and cold) and, in some cases, acupuncture, manipulation, or surgery (Tables 39, 41, and 42).^{28,58,60-61}

c. Fibromyalgia

Fibromyalgia is a chronic syndrome that manifests as widespread musculoskeletal pain and multiple "tender points" localized to areas in the neck, spine, shoulders, and hips.⁶⁴ In addition to chronic pain with acute flares, patients often experience sleep disturbances, morning stiffness, anxiety, and irritability.⁶³⁻⁶⁴ Fibromyalgia is diagnosed based on criteria established by the American College of Rheumatology.⁶⁴ Its cause is unknown, but theories about its etiology include trauma and infection.⁶³ About 3 to 6 million Americans suffer from fibromyalgia,

Table 40. Pharmacologic Management of Migraine and Other Types of Headache

Headache Type	Prophylaxis	Abortive	Comments
Migraine	AEDs (e.g., divalproex sodium ^a , gabapentin) BBs (e.g., propranolol, timolol) ^a CCBs (e.g., verapamil, nimodipine) TCAs (e.g., amitriptyline) NSAIDs (e.g., ASA, flurbiprofen) Estradiol ^b Methysergide ^c	NSAIDs (e.g., ASA, ibuprofen, naproxen, diclofenac, flurbiprofen, piroxicam) Opioids, including butorphanol ^d Combination treatment: • Acetaminophen plus ASA plus caffeine • ASA plus butalbital plus caffeine ^e • Acetaminophen plus codeine Dihydroergotamine ^f : (intranasal, SC, IV) Selective 5HT _{1B/1D} receptor agonists ("tripans") • Rizatriptan (PO) • Zolmitriptan (PO) • Sumatriptan (PO, SC, or intranasal)	Acetaminophen plus ASA plus caffeine considered first-line treatment First-choice NSAIDs are ASA, ibuprofen, and naproxen; others also are effective Triptans are effective and appropriate initial choice for patient with mild to severe HA and no contraindications
Tension	TCAs (e.g., amitriptyline, doxepin)	Acetaminophen NSAIDs	
Cluster	CCBs (e.g., verapamil) Corticosteroids Methysergide AEDs (e.g., divalproex sodium)	Ergotamine Dihydroergotamine Inhalation of oxygen	

Sources: References 71-80.

^aDivalproex sodium, timolol, and propranolol are indicated for migraine prophylaxis.

^bEstradiol administered premenstrually can prevent migraine in women who have migraine related to menses.⁷¹⁻⁷⁴

^cMethysergide is effective but of limited utility due to the risk of complications (e.g., retroperitoneal or retropleural fibrosis).⁷¹⁻⁷⁴

^dIntranasal butorphanol is effective for migraine⁷¹⁻⁷⁴ and is good rescue therapy.⁷⁵ IV opioids also may be appropriate for rescue therapy.⁷¹⁻⁷⁴

^eThis combination requires careful monitoring due to the potential for abuse of butalbital.⁷¹⁻⁷⁴

^fConsider dihydroergotamine for headaches that have not responded to other first-line treatments or patients who cannot take PO.

5-HT: 5-hydroxytryptamine; AEDs: antiepileptic drugs; ASA: aspirin; BBs: beta blockers; CCBs: calcium channel blockers; HA: headache; IV: intravenous; NSAIDs: nonsteroidal anti-inflammatory drugs; PO: per os (oral); SC: subcutaneous; TCAs: tricyclic antidepressants.

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Table 41. Regional Anesthesia for Chronic Noncancer Pain

Pain Type	Method
Arthritis pain	Intra-articular injection ^a of corticosteroids (e.g., methylprednisolone) Intra-articular injections of sodium hyaluronate ^b
Low back pain	Facet joint injections with local anesthetic ^c Sciatic nerve block with local anesthetic for backache due to sciatica Epidural steroid injections (e.g., methylprednisolone), often with local anesthetic (e.g., lidocaine) ^d
Headache and migraine	Occipital nerve block with local anesthetic for occipital headache

Sources: References 51 and 83-84.

^aCorticosteroid injections are used for the knees and hips and are limited to 3-4 per year.⁵¹^bThese injections are approved for the knee, and studies have shown mixed results in regard to efficacy.⁸¹⁻⁸²^cControversy exists over the efficacy of therapeutic facet blocks but they are useful diagnostic blocks.⁸³^dControversy exists over the efficacy of epidural steroids for low back pain. Frequent epidural steroids can suppress hypothalamic-pituitary-adrenal axis function. Also, there is the potential for complications due to the epidural approach (e.g., hematoma, infection), the steroids (e.g., hypertension, hyperglycemia), or local anesthetic (heart arrhythmias).⁸⁴

mostly women of child-bearing age.⁶⁴ Fibromyalgia generally is managed with medications, psychological approaches (education, relaxation therapy, hypnosis, psychotherapy), aerobic exercise, other physical approaches (e.g., OT, PT, electroanalgesia, heat and cold, vibration), and in some cases, acupuncture or manipulation (Tables 39 and 42).^{56,63,91}

d. Sickle cell disease pain

Sickle cell disease (SCD) refers to a group of inherited blood disorders in which an abnormal form of hemoglobin, hemoglobin S, is the predominant form of hemoglobin. Chronic hemolytic anemia and vaso-occlusive events are its major pathologic features, and the primary clinical manifestation of SCD is pain.⁵⁴ Deoxygenated hemoglobin S causes red blood cells to sickle (change shape) at sites of low oxygen availability, stick to the lining of small blood vessels, and occlude (plug) them. Along with inflammation, these vaso-occlusive events cause pain. Other causes of pain in these patients include infection, infarction, and the accumulation of blood in various organs. According to the 1999 American Pain Society Guideline for the Management of

Acute and Chronic Pain in Sickle Cell Disease, SCD pain may be acute, chronic, or of mixed duration and attributable to the disease or its treatment.⁵⁴ Sickle cell pain is managed with medications, physical approaches (e.g., adequate hydration, applied heat, PT, massage, ultrasound, electroanalgesia) and psychological approaches (e.g., deep breathing, relaxation, biofeedback) appropriate for acute and chronic pain management (Tables 39 and 42).^{54,66} SCD is also managed with a various treatments (e.g., transfusions) that reduce sickling.

e. Peripheral neuropathy

Peripheral neuropathy (PN) is a disorder caused by damage to one or more peripheral nerve(s). Its incidence is unknown, but it is a common feature of many systemic diseases.⁸⁹ Diabetes and alcohol are the most common causes of PN in developed countries.⁸⁹ Other causes include other endocrine disorders and nutritional deficiencies, infection (e.g., post herpetic neuralgia, human immunodeficiency virus-related neuropathy), hereditary conditions, trauma, nerve entrapment (e.g., carpal tunnel syndrome), collagen-vascular disorders, toxic agents, and cancer.⁶⁸ Yet, in many cases, the cause of the neuropathy is unknown.^{67,89} Clinically, PN often manifests as weakness, numbness, paresthesias (abnormal sensations, such as pins and needles, burning, tingling, or prickling), and pain in the hands, arms, legs, or feet.⁶⁷ Treatment of the PN depends on the underlying cause and includes medications, physical approaches (e.g., PT, electroanalgesia, cold and heat), psychological approaches (including education about management of the underlying condition), and in some cases, surgery (Tables 39 and 42).⁶⁷⁻⁶⁸

f. Headache

Headache includes migraine with and without aura, tension-type, and cluster headaches. Headache disorders may be acute, chronic, or both, but are classified as chronic for the purpose of this discussion. Symptoms, triggers, and treatment vary with headache type. Migraine without aura (formerly common migraine) is an idiopathic chronic headache disorder characterized by a unilateral, pulsating headache of moderate to severe intensity. The headache ranges in duration from 4 to 72 hours and is accompanied by various symptoms (e.g., photophobia, nausea, vomiting).⁷⁹ Migraine with aura (formerly classic migraine) is similar but is preceded by transient

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Table 42. Nonpharmacologic Interventions for Chronic Noncancer Pain

Type of Pain	Surgical	Other Physical Methods	Psychological Methods	Other
Arthritis pain	Includes arthroscopy and TJR for OA ^a and synovectomy, osteotomy, spinal fusion, and arthroscopy and TJR for RA	TENS, applied heat or cold, low-impact aerobic and ROM exercises, joint protection (splint or brace), massage, PT, OT	PE (rest, exercise, nutrition) and social support	Acupuncture Nutritional supplements ^b
Low back pain	For example, laminectomy, discectomy, lumbar fusion, lumbar stabilization ^c	SCS, cryoanalgesia, radiofrequency coagulation, exercise (for strength and flexibility), PT, OT, TENS, braces, vibration	PE, "back school," biofeedback, psychotherapy	Acupuncture Manipulation therapy
Fibromyalgia		Applied heat, massage, gentle aerobic exercise and stretching, attention to proper posture, PT, TENS, vibration	PE, relaxation, hypnosis, psychotherapy	Acupuncture ^d
Sickle cell disease		Careful hydration, applied heat, massage, ultrasound, PT, TENS	PE, deep breathing and relaxation techniques, distraction, imagery, hypnosis, meditation, biofeedback, psychotherapy	Acupuncture/ acupressure
Peripheral neuropathy (e.g., PDN, PHN)	For example, decompressive surgery for nerve entrapment, vascular surgery for vascular insufficiency	Good skin care and foot care, PT, TENS, possibly SCS, applied heat or cold, massage	PE (e.g., need for tight blood glucose control, good skin and foot care), relaxation, biofeedback, psychotherapy	
Migraine and other types of headache		Application of heat or cold, exercise (prophylaxis), vibration	PE (triggers, medication compliance), relaxation and biofeedback (thermal, EMG training) for headache prophylaxis	

Sources: References 49-52, 54-56, 58, 60, 65, 67-68, 86, and 88-89.

^aSurgery for OA is for patients with moderate to severe pain and functional disability who have not responded to medical therapy.⁵ Total joint arthroplasty usually is associated with a good outcome and improved quality of life.⁸⁵

^bNot currently recommended due to lack of data. Trials for some supplements (glucosamine and chondroitin sulfate) are underway.⁵¹

^cThe Food and Drug Administration has approved medical devices such as the Intervertebral Body Fusion device, Anterior Spinal Implant, and Posterior Spinal Implant to treat degenerative disk disease and stabilize and fuse the spine.⁸⁶

^dUsually reserved for patients with fibromyalgia syndrome/myofascial pain syndrome who do not respond to other measures.^{56,87}

EMG: electromyography; OA: osteoarthritis; OT: occupational therapy; PDN: painful diabetic neuropathy; PE: patient education; PHN: postherpetic neuralgia; PT: physical therapy; RA: rheumatoid arthritis; ROM: range of motion; SCS: spinal cord stimulation; TENS: transcutaneous electrical nerve stimulation; TJR: total joint replacement.

neurologic symptoms (e.g., visual disturbances, aphasia, hemiparesis). Tension-type headache refers to a bilateral pressing or tightening type of headache of mild to moderate severity, which may be episodic or chronic.⁷⁹ Cluster headaches are unilateral headaches usually located around the eye (periorbital). Patients may experience excruciating boring, knife-like, or burning pain,

tearing, and rhinorrhea. The attacks are relatively short but may recur numerous times a day.⁷⁹ Treatment of migraine includes medications (abortive and prophylactic), physical approaches (e.g., cold and heat), psychological approaches (e.g., relaxation, biofeedback), and in some cases, regional anesthesia (Tables 40 to 42).⁷¹⁻⁷⁸



Section V:

Strategies to Improve Pain Management

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A. CLINICAL PRACTICE GUIDELINES

1. Which Practice Guidelines Apply to Pain Management?

The Agency for Health Care Policy and Research (AHCPR)^a introduced the first clinical practice guideline (CPG) for pain management in 1992.¹ Other groups, including the American Pain Society (APS), the American Society of Anesthesiologists (ASA), and the American Academy of Family Physicians (AAFP), have since produced an assortment of CPGs relevant to the management of acute and chronic pain

^a The Agency for Health Care Policy and Research is now the Agency for Healthcare Research and Quality.

Table 43. Examples of Practice Guidelines for Management of Acute or Chronic Pain

Year	Source	Title
1992	AHCPR ^a	Acute Pain Management: Operative or Medical Procedures and Trauma Clinical Practice Guideline No. 1 (Publication No. 92-0032)
1993	AHCPR ^a	Acute Pain Management In Adults: Operative Procedures Quick Reference Guide for Clinicians No. 1a (Publication No. 92-0019)
1995	ASA	Practice guidelines for acute pain management in the perioperative setting
1996	ASA	Practice guidelines for sedation and analgesia by non-anesthesiologists
1997	ASA	Practice guidelines for chronic pain management
1997 (revised 1999)	UIGNIC	Acute pain management
1998	AGS	The management of chronic pain in older persons
1999	APS	Principles of analgesic use in the treatment of acute pain and cancer pain
1999	AMDA	Chronic pain management in the long-term care setting
2000	AAFP	Treatment of nonmalignant chronic pain
2000	ICSI	Assessment and management of acute pain

Sources: Reference 1-11.

^aThe Agency for Health Care Policy and Research is now the Agency for Healthcare Research and Quality.

AAFP: American Academy of Family Physicians; AGS: American Geriatrics Society; AHCPR: Agency for Health Care Policy and Research; AMDA: American Medical Directors Association; APS: American Pain Society; ASA: American Society of Anesthesiologists; ICSI: Institute for Clinical Systems Improvement; UIGNIC: University of Iowa Gerontological Nursing Interventions Center.

(Table 43). In addition, numerous disciplines have developed CPGs relevant to specific types of pain or the management of conditions with a painful component (Table 44).

Table 44. Examples of Practice Guidelines for the Management of Specific Types of Pain or Conditions With Painful Components

Year	Source	Title
1994	AHCPR ^a	Clinical Practice Guideline: Management of Cancer Pain (Publication No. 94-0592)
1994	AHCPR ^a	Acute Low Back Problems in Adults Guideline No. 14 (Publication No. 95-0642)
1995	ACR	Guidelines for the medical management of osteoarthritis Part I. Osteoarthritis of the hip
1995	ACR	Guidelines for the medical management of osteoarthritis Part II. Osteoarthritis of the knee
1996	ACR	Guidelines for the management of rheumatoid arthritis
1996	ASA	Practice guidelines for cancer pain management
1997	NIH	Acupuncture. NIH Consensus Statement
1999	ICSI	Adult low back pain
1999	ASA	Practice guidelines for obstetrical anesthesia
1999	SNM	Procedure guideline for bone pain treatment
1999	AAOS	Clinical guideline on hip pain
1999	AAOS	Clinical guideline on knee pain
1999	AAOS	Clinical guideline on wrist pain
1999	APS	Guideline for the management of acute and chronic pain in sickle cell disease
1999, 2000	AAN	Evidence-based guidelines for migraine headache (series)
2000	AAFP	Guidelines on migraine (series)
2000	AAFP	Osteoarthritis: current concepts in diagnosis and management
2000	AAFP	Management of pain in sickle cell disease
2000	ICSI	Health care guideline. Migraine headache
2000	ICSI	Health care guideline. Diagnosis and treatment of adult degenerative joint disease (DJD) of the knee

Sources: References 12-39.

^aThe Agency for Health Care Policy and Research is now the Agency for Healthcare Research and Quality.

AAN: American Academy of Neurology; AAOS: American Academy of Orthopaedic Surgeons; ACR: American College of Rheumatology; AHCPR: Agency for Health Care Policy and Research; AAFP: American Academy of Family Physicians; ASA: American Society of Anesthesiologists; ICSI: Institute for Clinical Systems Improvement; NIH: National Institutes of Health; SNM: Society of Nuclear Medicine.

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2. Are Clinicians Adopting and Using Clinical Practice Guidelines?

Pain management remains inadequate, despite the availability of CPGs. To clarify the basis of this problem, various studies have explored clinicians' adoption and use of CPGs or the effects of a specific CPG initiative on clinical practice. Table 45 summarizes some of these studies. Overall, these data suggest that, despite some

improvements, inconsistent assessment and inappropriate treatment of pain (e.g., intramuscular injections) persist.^{41,45} Furthermore, administrative mandates rather than education alone appear necessary to change practice patterns.⁴⁸

Table 45. Examples of Studies of Guideline Adherence and Interventions

Source	Purpose	Methods	Findings and Conclusions
Pellegrini et al, 1999	Assess compliance with AHCPR guidelines in prescribing meperidine for obstetrical patients	Review of 300 charts of obstetric patients	Of 157 obstetrical patients receiving meperidine, 124 (79.8%) were not treated in accordance with AHCPR guidelines. The most frequent conflicts with the guidelines were suboptimal dosing and the treatment of chronic pain.
Carr et al, 1998	Assess compliance with AHCPR and ASA guidelines	National survey of pain in perioperative patients	Overall adherence was excellent except for continuing frequent intramuscular administration of opioids and infrequent use of nonpharmacologic pain management methods
Data Strategic Benchmarks, 1999	Assess compliance with AHCPR guidelines for management of postoperative pain	Review of records from multiple Wisconsin hospitals	Data from a multi-hospital study shows low compliance with pain management protocols for postoperative pain.
Cleland et al, 1994	Assess compliance with WHO analgesic guidelines in managing cancer pain	Survey of 1308 outpatients with metastatic cancer treated at 54 sites affiliated with ECOG	42% of patients reported receiving insufficient analgesics; inadequate pain control was higher among some groups (e.g., racial minorities, women, elderly).
Cleland et al, 1997	Assess compliance with guideline-recommended analgesic prescriptions for cancer in clinic setting	Survey of minority cancer patients	65% of minority cancer patients did not receive guideline-recommended analgesic prescriptions compared with 50% of non-minority patients.
Stratis Health, 1997	Assess compliance with AHCPR and American Pain Society guidelines for assessing cancer pain	Review of records for 271 cancer patients treated in Minnesota hospitals	Whereas 93% of the hospitals had documented some form of the patient's initial self-assessment of pain, only 26% used effective means of communicating pain intensity. Pain reassessment was also inconsistent.
Rischer and Childress, 1996	Assess whether the implementation of an AHCPR guideline-based action plan would improve pain and satisfaction among cancer patients	Chart audits at seven acute care hospitals in Utah before and after implementation	Process measures of care showed improved compliance with guidelines for managing cancer pain post-intervention; however, investigators concluded that "more needed to be done to prevent patient suffering."
Du Pen et al, 1999	Assess whether the implementation of an AHCPR guideline-based treatment algorithm for cancer pain would improve pain management in the community setting	Comparison of pain and symptom management in 81 cancer outpatients treated according to algorithm or standard-practice (control)	Cancer patients in the treatment algorithm group experienced a significant reduction in usual pain intensity compared with controls. The investigators concluded that comprehensive pain assessment and evidence-based analgesic decision-making processes enhance usual pain outcomes.
Harwood et al, 1997	Assess whether an AHCPR guideline-based educational program would improve the assessment of new low back pain by physicians	Compliance with the assessment protocol was measured by computer-based surveillance; the educational program included group and individual sessions, with extensive follow-up	An administrative mandate to change, but not the educational program alone, resulted in a significant increase in physician compliance in completing a standardized examination (assessment) for low back pain.

Sources: References 40-48.

AHCPR: Agency for Health Care Policy and Research (now the Agency for Health Care Research and Quality); ASA: American Society of Anesthesiologists; ECOG: Eastern Cooperative Oncology Group; WHO: World Health Organization.

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B. STANDARDS AND OUTCOME MEASURES

1. JCAHO Standards

Various groups (e.g., the Joint Commission on Accreditation of Healthcare Organizations [JCAHO], APS, ASA) have proposed standards, outcome measures, and other initiatives in efforts to improve pain management (Table 46). Outcome measures complement CPGs because they help quantify the effects of a given therapy on the patient's health and well-being. Combined with other data (e.g., measures of guideline adherence), health care organizations can use outcome data to evaluate and optimize provider performance. Standards provide a clear

definition of what appropriate care entails; thus, they also improve quality of care.

Of these strategies, the recently introduced JCAHO standards for pain management have attracted the most attention. The standards clearly outline appropriate pain management practices for ambulatory care facilities, behavioral health care facilities, health care networks, home care, hospitals, long-term care organizations, long-term care pharmacies, and managed behavioral health care organizations seeking accreditation.⁴⁹ These new standards are available on the World Wide Web (<http://www.jcaho.org>), and the second monograph in this series discusses these standards in greater detail. Briefly, the standards call upon organizations and facilities to:

- Recognize the right of patients to appropri-

Table 46. Examples of New Outcome Measures, Standards, and Initiatives Related to Pain Management

Organization	What Is Being Done	Purpose
ASA Committee on Pain Management	Recent development of pain outcome assessment questionnaire called the "ASA Nine"; this questionnaire considers nine items (domains) in assessing the efficacy of pain therapy	To measure outcomes in patients receiving pain therapy from anesthesiologists
APS	Pain as the 5th Vital Sign initiative (i.e., measure pain as a fifth vital sign with each evaluation of the standard four vital signs [i.e., temperature, pulse, respiration, and blood pressure])	Pain management improvement strategy directed at raising clinician awareness of need to assess pain regularly
APS	Alteration of WHO analgesic ladder	To make WHO ladder a more appropriate form of guidance, which recognizes that pain should be assessed for severity and treated with adequate analgesia in a timely manner
VHA National Pain Management Strategy	Initiative calling for a series of assessments to be performed by clinicians, including regular assessment of pain intensity with the NRS	To prevent pain and suffering in individuals receiving care in the VHA system
HCFA	Current evaluation of outcome measures to be used by hospice workers for assessing patient comfort during the dying process	To improve the quality of pain management at end of life for Medicare and Medicaid beneficiaries
HCFA	Recent identification of pain management at the end of life as a PRO program priority	Proposed project will implement an intervention to increase quality of care with respect to pain management and comfort in a population and setting where there is a demonstrated need ^a
JCAHO	Inclusion of new standards for pain assessment and management in JCAHO standards	To provide standards of care to be followed by ambulatory care facilities, behavioral health care facilities, health care networks, home care, hospitals, long-term care organizations, long-term care pharmacies, and managed behavioral health care organizations
NCQA	Involved in developing outcome measures related to pain management	Advance assessment of pain outcomes

^aA population with a "demonstrated need" includes patients with cancer, congestive heart failure, chronic obstructive pulmonary disease, human immunodeficiency virus infection, acquired immunodeficiency syndrome, diabetes, end-stage renal disease, or another progressive illness.

APS: American Pain Society; ASA: American Society of Anesthesiologists; HCFA: Health Care Financing Administration; JCAHO: Joint Commission on Accreditation of Healthcare Organizations; NCQA: National Committee for Quality Assurance; NRS: Numeric Rating Scale; PRO: peer-reviewed organization; VHA: Veteran's Healthcare Administration; WHO: World Health Organization

Section V: Strategies to Improve Pain Management

- ate assessment and management of pain
- Screen for the presence and assess the nature and intensity of pain in all patients
- Record the results of the assessment in a way that facilitates regular reassessment and follow-up
- Determine and ensure staff competency in pain assessment and management (e.g., provide education), and address pain assessment and management in the orientation of all new clinical staff
- Establish policies and procedures that support the appropriate prescribing or ordering of pain medications
- Ensure that pain does not interfere with a patient's participation in rehabilitation
- Educate patients and their families about the importance of effective pain management
- Address patient needs for symptom management in the discharge planning process
- Incorporate pain management into performance review activities (i.e., establish a means of collecting data to monitor the appropriateness and effectiveness of pain management)

2. Institutional Commitment to Pain Management

Whereas the new JCAHO standards tell organizations what needs to occur in the assessment and management of pain, they do not tell organizations how to do it. Because education alone does not change practice patterns, health care organizations and institutions need to support system changes to improve pain management and comply with the new JCAHO standards. That is, in addition to providing staff with practical clinical resources for pain management, health care organizations and institutions need to make pain "visible" and establish mechanisms to ensure accountability for pain control.⁵⁰ The book *Building an Institutional Commitment to Pain Management: Wisconsin Resource Manual* describes key steps to "institutionalizing" effective pain management, as summarized in Table 47.⁵⁰ In addition, the second monograph in this series reviews organizational performance measurement and improvement related to pain management to facilitate organizational initiatives.

Table 47. Building an Institutional Commitment to Pain Management

- Develop an interdisciplinary work group to promote practice change and collaborative practice. At a minimum, this work group should consist of representatives (clinicians, administrators) from medicine, nursing, and pharmacy, with those from other disciplines (e.g., OT, PT, RT, social work, pastoral care) when possible. Levels of experience should range from experts to novice.
- Analyze current pain management issues and practices in the health care setting, with the goal of continuous quality improvement. Plan a needs assessment to collect information about the quality of pain management and to identify causes of inadequate pain management. Sources of data include systematic observation of current practice, patient and staff surveys, medical record audits, and drug utilization reviews.
- Articulate and implement a standard for pain assessment and documentation to ensure the prompt recognition, documentation, and treatment of pain. This standard should define:
 - 1) how, when, and by whom pain should be assessed;
 - 2) where the results should be documented;
 - 3) methods of communicating this information among caregivers; and
 - 4) explicit conditions for interventions directed at relieving pain.
- Establish explicit policies and procedures to guide the use of specialized techniques for administering analgesics (e.g., intraspinal and intravenous analgesia and anesthesia, inhalational therapy, conscious or deep sedation).
- Establish accountability for quality pain management. This should include clearly defining caregiver responsibilities in pain management and embedding accountability for pain management in existing systems (e.g., practice standards, position descriptions, policies and procedures, competency statements, performance reviews).
- Provide readily available information about pharmacologic and nonpharmacologic interventions to clinicians to facilitate planning of care (e.g., order writing, interpretation and implementation of physician orders). This information can be presented in a variety of formats including clinical practice guidelines and pathways, decision or treatment algorithms, protocols, pocket reference guides, and computer help screens.
- Promise patients a prompt response to their reports of pain. According to the APS guidelines for quality improvement of pain management, all patients at risk for pain should be informed that: 1) effective pain relief is important to treatment, 2) their report of pain is essential, and 3) staff will promptly respond to patient requests for pain treatment.⁵¹ Therefore, patients and their families should be provided appropriate educational materials that address important aspects of pain assessment and management (e.g., the importance of controlling pain, the use of pain rating scales to report pain intensity, how to establish realistic pain relief goals, pharmacologic and non-pharmacologic interventions for pain).
- Provide education about pain management to staff. This education may be provided in a variety of formats, including orientation and continuing education programs; rounds, lectures, and case conferences; self-directed learning packages; case studies, and interactive techniques (e.g., brainstorming, role playing, experiential techniques, games).
- Continually evaluate and work to improve the quality of pain management.

Source: References 50-51.

APS: American Pain Society; OT: occupational therapy; PT: physical therapy; RT: recreation.

Glossary

Glossary of Abbreviations and Acronyms

AAFP: American Academy of Family Physicians.

AAPM: American Academy of Pain Medicine.

AEDs: Antiepileptic drugs.

AHCPR: Agency for Health Care Policy and Research; now known as the Agency for Healthcare Research and Quality (AHRQ).

AHRQ: Agency for Healthcare Research and Quality; formerly known as the Agency for Health Care Policy and Research (AHCPR).

APS: American Pain Society.

ASA: American Society of Anesthesiologists.

ASAM: American Society of Addiction Medicine.

ATC: Around-the-clock.

BPI: Brief Pain Inventory.

CARF: Commission on Accreditation of Rehabilitation Facilities.

CBT: Cognitive behavioral therapy.

CNCP: Chronic noncancer pain

CNMP: Chronic nonmalignant pain

CNS: Central nervous system

COX: Cyclooxygenase

CPGs: Clinical practice guidelines.

CPMP: Chronic pain management program.

CPS: Chronic pain syndrome

DH: Dorsal horn

ECG: Electrocardiogram.

EEAs: Excitatory amino acids

EMLA®: Eutectic Mixture of Local Anesthetics (lidocaine and prilocaine).

FPS: Faces Pain Scale.

FSMB: The Federation of State Medical Boards of the United States.

GABA: γ -Aminobutyric acid, which is an inhibitory neurotransmitter.

GI: Gastrointestinal.

HIV: Human immunodeficiency virus.

IASP: International Association for the Study of Pain.

IM: Intramuscular.

IV: Intravenous.

JCAHO: Joint Commission on Accreditation of Healthcare Organizations.

Las: Local anesthetics.

LBP: Low back pain.

MPQ: McGill Pain Questionnaire.

NMDA: N-methyl, D-aspartic acid.

NRS: Numeric rating scale.

NSAIDs: Nonsteroidal anti-inflammatory drugs.

OA: Osteoarthritis.

OT: Occupational therapy.

PCA: Patient-controlled anesthesia

PGs: Prostaglandins.

PN: Peripheral neuropathy.

PO: Per os (oral).

PRN: As needed.

PT: Physical therapy.

RA: Rheumatoid arthritis.

SCD: Sickle cell disease.

TCAs: Tricyclic antidepressants.

TENS: Transcutaneous electrical nerve stimulation.

VAS: Visual analog scale.

VHA: Veterans Health Administration.

Glossary of definitions

A- δ nociceptors: Nociceptors associated with relatively rapidly conducting A-delta fibers.

abstinence syndrome: A syndrome that may occur with abrupt cessation or diminution of chronic drug administration; the nature and time of onset of this syndrome vary with drug actions and half-life.

activation: Excitation of a neuron sufficient to generate a nerve impulse (action potential).

addiction: A primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations; addiction is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

adjuvant analgesic: A medication that is not a primary analgesic but that has independent or additive pain-relieving effects.

agonists: Agents that exert pharmacologic effects by binding to and activating stereospecific receptors.

allodynia: Pain caused by a stimulus that normally does not provoke pain.

analgesia: Absence of pain.

analgesic ceiling: A dose of an analgesic beyond which no additional analgesia is obtained.

ankylosing spondylitis: Ankylosing (fusing together) spondylitis (spinal inflammation) is a type of arthritis that affects the spine.

Glossary

antagonists: Agents that competitively bind with the binding sites of agonists and thereby inhibit the agonist's actions.

arachnoiditis: Inflammation and thickening of the arachnoid membrane (one of three membranes covering the central nervous system) around nerve roots.

atelectasis: The absence of gas in part or all of lung (i.e., partial or complete lung collapse).

autonomic responses: See sympathetic (nervous system) hyperactivity.

biofeedback: The process of training a person (or animal) to regulate physiologic responses by providing feedback (typically sounds or light patterns) about those responses. Clinically, patients are typically taught to control finger temperature, perspiration, muscle tension, and other responses.

breakthrough pain: Pain that "breaks through" pain relief provided by ongoing analgesics.

C-nociceptors: Nociceptors associated with slowly conducting unmyelinated C-fibers.

central nervous system (CNS): Consists of the brain and spinal cord.

central sensitization: Enhanced excitability and responsiveness of spinal neurons.

cerebral cortex: Gray cellular "mantle" of the brain, which includes the sensory cortex, motor cortex, and association cortex.

chronic noncancer pain (CNCP): Persistent pain that is not associated with cancer.

chronic nonmalignant pain (CNMP): Persistent pain that is not attributable to a life-threatening condition; some prefer to use alternate terms (i.e., chronic non-cancer pain, chronic non-cancer-related pain).

chronic pain syndrome (CPS): Psychosocial disorder that occurs in some patients with chronic noncancer pain in which symptoms of the pain consume the attention of and incapacitate the patient.

continuous dysesthesia: A continuous type of neuropathic pain that manifests as burning, electrical, or other abnormal sensations.

cyclooxygenase (COX): Enzyme involved in prostaglandin synthesis; there are two isoforms: COX-1 and COX-2.

deep somatic pain: A type of somatic pain associated with ongoing activation of nociceptors in muscles, tendons, joint capsules, fasciae, or bones.

deep tissues: Tissues including bone, muscle, tendons, joint capsules, and fasciae.

dermatomes: Cutaneous sensory pathways that are defined by sensation; each dermatome corresponds to the area of skin that is supplied by the dorsal roots of a particular sensory nerve.

dorsal horn (DH): The posterior gray matter of the

spinal cord, which contains cell bodies or neurons; the spinal cord consists of 10 laminae (segments), and laminae I-VI comprise the dorsal horn.

dorsal horn neurons: Neurons in the dorsal horn of the spinal cord, including interneurons and second order (projection) neurons.

dysesthesia: An unpleasant abnormal sensation, which may be spontaneous or evoked.

endogenous opioids: Natural opioids produced by the body; also referred to as enkephalins and endorphins.

epidural: Situated on the outside of the dura mater (a tough lining that surrounds the spinal cord).

equianalgesic: Having an equivalent analgesic effect.

equianalgesic dose chart: A chart that is used to convert from one analgesic or route of administration to another. Such charts typically describe the dose of an opioid required to produce the same degree of pain relief provided by a standard oral or parenteral dose of morphine.

excitatory amino acids (EAAs): These include the neurotransmitters glutamate and aspartate, which mediate most excitatory transmission in the central nervous system.

glutamate: An excitatory amino acid neurotransmitter responsible for much of excitatory transmission in the central nervous system.

hyperalgesia: An abnormally painful response to a stimulus.

hyperpathia: An abnormally painful and exaggerated response to a stimulus, especially a repetitive stimulus.

iatrogenic: A response to a medical or surgical treatment induced by the treatment itself.

inflammation: A pathologic process involving complex chemical and cellular reactions that occurs in tissues in response to injury or abnormal stimulation. Its cardinal signs— rubor (redness), calor (heat or warmth), tumor (swelling), and dolor (pain)—reflect processes directed at destroying/removing injurious material and at promoting repair and healing.

inflammatory mediators: Inflammatory mediators include prostaglandins, bradykinin, serotonin, and histamine.

ischemia: A reduction in local blood flow due to obstruction of the blood supply.

lancinating pain: A type of neuropathic pain that manifests as an episodic shooting, stabbing, or knifelike pain.

limbic system: The limbic system includes structures such as the amygdala, hippocampus, septal nuclei, hypothalamus, and transitional cortical regions (e.g., cingulate gyrus). This part of the brain is involved with emotional responses.

mu agonists: Opioids that bind to m₁ and m₂ receptors in the brain, spinal cord, and under certain conditions

Glossary

(i.e., inflammation), the periphery to exert their effects.

multimodal analgesia: Also known as “balanced analgesia,” this approach to pain management involves the use of more than one method or modality of controlling pain (e.g., drugs from two or more classes, drug plus nondrug treatment) to obtain additive beneficial effects, reduce side effects, or both.

neuroablation: Destruction of tissue, typically by surgical, chemical (phenol), or heat (radiofrequency) lesions; the goal of neuroablative surgeries is to interrupt signal flow between peripheral sources of pain and the brain or to remove neural structures that contribute to pain.

neurolysis: A technique for destroying neural tissue that involves injection of a destructive chemical or use of cold (cryotherapy) or heat (radiofrequency coagulation).

NMDA receptors: A type of glutamate receptor involved in mediating excitatory neurotransmission; these receptors are thought to play an important role in central sensitization.

nociceptors: Sensory receptors that are preferentially sensitive to tissue trauma or a stimulus that would damage tissue if prolonged.

parenteral administration: Administration of a drug via a route other than the gastrointestinal system, such as by intravenous, intramuscular, or subcutaneous injection.

paresthesia: An abnormal sensation (e.g., “pins and needles” from a foot “going to sleep”), which may be spontaneous or evoked.

patient-controlled anesthesia (PCA): The self-administration of analgesics by a patient; often involves an intravenous, subcutaneous, or epidural opioid administered via a pump.

perioperative pain: Pain that is present in a surgical patient because of preexisting disease, the surgical procedure (e.g., associated drains, chest or nasogastric tubes, complications), or a combination of disease-related and procedure-related sources.

peripheral sensitization: A lowering of the stimulus (pain) threshold for nociceptor activation and an increase in the frequency of nerve impulse firing.

physical dependence: A state of adaptation that often includes tolerance and is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood levels of the drug, and/or administration of an antagonist.

potency: The dose of a drug required to produce a particular effect (e.g., pain relief).

preemptive analgesia: A pharmacologic intervention performed before a noxious event (e.g., surgery) that is intended to minimize the impact of the stimulus by preventing peripheral and central sensitization.

primary afferent (nerve) fibers: Axons of primary affer-

ent (or “first order”) neurons that transmit impulses from the periphery toward the central nervous system. Each neuron has a cell body that resides in sensory ganglia (e.g., dorsal root ganglia) and a bifurcated axon. One branch extends along a peripheral nerve and ends in a sensory receptor; the other branch projects to the spinal cord, where it synapses with a spinal neuron (e.g., interneuron, projection neuron).

projection neurons: Neurons in the dorsal horn of the spinal cord with nerve fibers that project to the brain in tracts; these neurons are responsible for transmitting nociceptive information from the spinal cord to higher centers.

pseudoaddiction: Patient behaviors that may occur when pain is undertreated (e.g., increased focus on obtaining medications or “drug seeking,” “clock watching,” use of illicit drugs, or deception) and that can be mistaken for true addiction.

responsiveness: The probability of achieving adequate pain relief with an analgesic without encountering unmanageable side effects.

somatic pain: Pain arising from tissues such as skin, muscle, tendon, joint capsules, fasciae, and bone.

somatosensory cortex: A subdivision of the sensory cortex.

spinothalamic tract (STT): Major pathway by which nociceptive information travels from the dorsal horn of the spinal cord to the thalamus.

“stress hormone” response: A series of responses to an acute injury or stress that leads to an increase in the metabolic rate, blood clotting, and water retention; impaired immune function; and a “fight or flight” alarm reaction with autonomic features. These responses minimize further damage and blood loss, promote healing, prevent or fight infection, and reduce blood flow to vital organs, among other functions.

substance P: A neuropeptide that activates spinal neurons and enhances their responsiveness to excitatory amino acids, thus facilitating nociception.

superficial (cutaneous) somatic pain: A type of somatic pain associated with ongoing activation of nociceptors in the skin, subcutaneous tissue, or mucous membranes.

sympathetic (nervous system) hyperactivity: Symptoms and signs of sympathetic (autonomic) nervous system hyperactivity include increased heart rate, blood pressure, and respiratory rate; sweating; pallor; dilated pupils; nausea; vomiting; dry mouth; and increased muscle tension.

tolerance: A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug’s effects over time.

visceral pain: Pain arising from visceral organs (e.g., heart, lungs, gastrointestinal tract, liver, gallbladder, kidneys, bladder).

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EXHIBIT 24

GAO

Report to Congressional Requesters

December 2003

PRESCRIPTION DRUGS

OxyContin Abuse and Diversion and Efforts to Address the Problem



December 2003



Highlights of GAO-04-110, a report to congressional requesters

Why GAO Did This Study

Amid heightened awareness that many patients with cancer and other chronic diseases suffer from undertreated pain, the Food and Drug Administration (FDA) approved Purdue Pharma's controlled-release pain reliever OxyContin in 1995. Sales grew rapidly, and by 2001 OxyContin had become the most prescribed brand-name narcotic medication for treating moderate-to-severe pain. In early 2000, reports began to surface about abuse and diversion for illicit use of OxyContin, which contains the opioid oxycodone. GAO was asked to examine concerns about these issues. Specifically, GAO reviewed (1) how OxyContin was marketed and promoted, (2) what factors contributed to the abuse and diversion of OxyContin, and (3) what actions have been taken to address OxyContin abuse and diversion.

What GAO Recommends

To improve efforts to prevent or identify abuse and diversion of controlled substances such as OxyContin, FDA's risk management plan guidance should encourage pharmaceutical manufacturers with new drug applications to submit plans that contain a strategy for identifying potential problems with abuse and diversion. FDA concurred with GAO's recommendation. DEA agreed that such risk management plans are important, and Purdue stated that the report appeared to be fair and balanced.

www.gao.gov/cgi-bin/getrpt?GAO-04-110.

To view the full product, including the scope and methodology, click on the link above. For more information, contact Marcia Crosse at (202) 512-7119.

PRESCRIPTION DRUGS

OxyContin Abuse and Diversion and Efforts to Address the Problem

What GAO Found

Purdue conducted an extensive campaign to market and promote OxyContin using an expanded sales force to encourage physicians, including primary care specialists, to prescribe OxyContin not only for cancer pain but also as an initial opioid treatment for moderate-to-severe noncancer pain. OxyContin prescriptions, particularly those for noncancer pain, grew rapidly, and by 2003 nearly half of all OxyContin prescribers were primary care physicians. The Drug Enforcement Administration (DEA) has expressed concern that Purdue's aggressive marketing of OxyContin focused on promoting the drug to treat a wide range of conditions to physicians who may not have been adequately trained in pain management. FDA has taken two actions against Purdue for OxyContin advertising violations. Further, Purdue did not submit an OxyContin promotional video for FDA review upon its initial use in 1998, as required by FDA regulations.

Several factors may have contributed to the abuse and diversion of OxyContin. The active ingredient in OxyContin is twice as potent as morphine, which may have made it an attractive target for misuse. Further, the original label's safety warning advising patients not to crush the tablets because of the possible rapid release of a potentially toxic amount of oxycodone may have inadvertently alerted abusers to methods for abuse. Moreover, the significant increase in OxyContin's availability in the marketplace may have increased opportunities to obtain the drug illicitly in some states. Finally, the history of abuse and diversion of prescription drugs, including opioids, in some states may have predisposed certain areas to problems with OxyContin. However, GAO could not assess the relationship between the increased availability of OxyContin and locations of abuse and diversion because the data on abuse and diversion are not reliable, comprehensive, or timely.

Federal and state agencies and Purdue have taken actions to address the abuse and diversion of OxyContin. FDA approved a stronger safety warning on OxyContin's label. In addition, FDA and Purdue collaborated on a risk management plan to help detect and prevent OxyContin abuse and diversion, an approach that was not used at the time OxyContin was approved. FDA plans to provide guidance to the pharmaceutical industry by September 2004 on risk management plans, which are an optional feature of new drug applications. DEA has established a national action plan to prevent abuse and diversion of OxyContin. State agencies have investigated reports of abuse and diversion. In addition to developing a risk management plan, Purdue has initiated several OxyContin-related educational programs, taken disciplinary action against sales representatives who improperly promoted OxyContin, and referred physicians suspected of improper prescribing practices to the authorities.

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Abbreviations

DAWN	Drug Abuse Warning Network
DEA	Drug Enforcement Administration
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug and Cosmetic Act
HHS	Department of Health and Human Services
HIDTA	High Intensity Drug Trafficking Area
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
NFLIS	National Forensic Laboratory Information System
ONDCP	Office of National Drug Control Policy
PDUFA	Prescription Drug User Fee Act of 1992
PhRMA	Pharmaceutical Research and Manufacturers of America
RADARS	Researched Abuse, Diversion, and Addiction-Related Surveillance
SAMHSA	Substance Abuse and Mental Health Services Administration
STRIDE	System to Retrieve Information from Drug Evidence
WHO	World Health Organization

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United States General Accounting Office
Washington, DC 20548

December 23, 2003

The Honorable Frank R. Wolf
Chairman
Subcommittee on Commerce, Justice, State, and the Judiciary,
and Related Agencies
Committee on Appropriations
House of Representatives

The Honorable James C. Greenwood
Chairman
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
House of Representatives

The Honorable Harold Rogers
House of Representatives

Patients with cancer may suffer from fairly constant pain for months or years. Patients with other diseases or conditions, such as rheumatoid arthritis, osteoarthritis, chronic back pain, or sickle cell anemia, may also suffer from pain that lasts for extended periods of time. Since 1986, the World Health Organization (WHO) and others have reported that the inadequate treatment of cancer and noncancer pain is a serious public health concern. To address this concern, efforts have been made to better educate health care professionals on the need to improve the treatment of both cancer and noncancer pain, including the appropriate role of prescription drugs.

Amid the heightened awareness that many people were suffering from undertreated pain, in 1995 the Food and Drug Administration (FDA) approved the new drug OxyContin, a controlled-release semisynthetic opioid analgesic manufactured by Purdue Pharma L.P.,¹ for the treatment of moderate-to-severe pain lasting more than a few days.² According to

¹OxyContin is an opioid analgesic—a narcotic substance that relieves a person's pain without causing the loss of consciousness. Hereafter, we refer to the company as Purdue.

²As discussed later in this report, FDA approved the revised OxyContin label in July 2001 to describe the time frame as "when a continuous around-the-clock analgesic is needed for an extended period of time."

Purdue, OxyContin provides patients with continuous relief from pain over a 12-hour period, reduces pain fluctuations, requires fewer daily doses to help patients adhere to their prescribed regimen more easily, allows them to sleep through the night, and allows a physician to increase the OxyContin dose for a patient as needed to relieve pain.³ Sales of the drug increased rapidly following its introduction to the marketplace in 1996. By 2001, sales had exceeded \$1 billion annually, and OxyContin had become the most frequently prescribed brand-name narcotic medication for treating moderate-to-severe pain in the United States.

In early 2000, media reports began to surface in several states that OxyContin was being abused—that is, used for nontherapeutic purposes or for purposes other than those for which it was prescribed—and illegally diverted.⁴ According to FDA and the Drug Enforcement Administration (DEA), the abuse of OxyContin is associated with serious consequences, including addiction, overdose, and death.⁵ When OxyContin was approved, the federal government classified it as a schedule II controlled substance under the Controlled Substances Act because it has a high potential for abuse and may lead to severe psychological or physical dependence.⁶ DEA has characterized the pharmacological effects of OxyContin, and its active ingredient oxycodone, as similar to those of heroin. Media reports indicated that abusers were crushing OxyContin tablets and snorting the powder or dissolving it in water and injecting it to defeat the intended controlled-release effect of the drug and attain a “rush” or “high” through

³According to FDA, there is no known limit to the amount of oxycodone, the active ingredient in OxyContin, that can be used to treat pain.

⁴Prescription drug diversion can involve such activities as “doctor shopping” by individuals who visit numerous physicians to obtain multiple prescriptions, prescription forgery, and pharmacy theft. Diversion can also involve illegal sales of prescription drugs by physicians, patients, or pharmacists, as well as obtaining controlled substances from Internet pharmacies without a valid prescription.

⁵According to the National Institute on Drug Abuse, addiction is a chronic, relapsing disease, characterized by compulsive drug seeking and use and by neurochemical and molecular changes in the brain, whereas physical dependence is an adaptive physiological state that can occur with regular drug use and results in withdrawal symptoms when drug use is discontinued.

⁶Under the Controlled Substances Act, which was enacted in 1970, drugs are classified as controlled substances and placed into one of five schedules based on their medicinal value, potential for abuse, and safety or dependence liability. Schedule I drugs have no medicinal value; have not been approved by FDA; and along with schedule II drugs, have the highest potential for abuse. Schedule II drugs have the highest potential for abuse of any approved drugs.

the body's rapid absorption of oxycodone. During a December 2001 congressional hearing, witnesses from DEA and other law enforcement officials from Kentucky, Virginia, and West Virginia described the growing problem of abuse and diversion of OxyContin.⁷ Questions were raised about what factors may have caused the abuse and diversion, including whether Purdue's efforts to market the drug may have contributed to the problem. In February 2002, another congressional hearing was conducted on federal, state, and local efforts to decrease the abuse and diversion of OxyContin.⁸

Because of your concerns about these issues, you asked us to examine the marketing and promotion of OxyContin and its abuse and diversion. Specifically, we addressed the following questions:

1. How has Purdue marketed and promoted OxyContin?
2. What factors contributed to the abuse and diversion of OxyContin?
3. What actions have been taken to address OxyContin abuse and diversion?

To identify how Purdue marketed and promoted OxyContin, we interviewed Purdue officials and analyzed company documents and data. We also interviewed selected Purdue sales representatives who were high and midrange sales performers during 2001 and physicians who were among the highest prescribers of OxyContin. To determine how Purdue's marketing and promotion of OxyContin compared to that of other drugs, we examined the promotional materials and information related to FDA actions and interviewed officials from companies that manufacture and market three other opioid drugs, Avinza, Kadian, and Oramorph SR, that like OxyContin are classified as schedule II controlled substances.⁹ Because of their concern about the proprietary nature of the information,

⁷OxyContin, Hearings of the Subcommittee on the Departments of Commerce, Justice, and State, the Judiciary, and Related Agencies, House Committee on Appropriations, 107th Cong. Part 10 (Dec. 11, 2001).

⁸OxyContin: Balancing Risks and Benefits, Hearing of the Senate Committee on Health, Education, Labor, and Pensions, 107th Cong. 287 (Feb. 12, 2002).

⁹Avinza was approved by FDA in 2002 and is marketed by Ligand Pharmaceuticals; Kadian was approved in 1996 and is marketed by Alpharma-US Human Pharmaceuticals; and Oramorph SR was approved in 1991 and is now owned by Élan Corporation, which told us it is not currently marketing the drug.

the three companies that market these drugs did not provide us with the same level of detail about the marketing and promotion of their drugs as did Purdue. We also examined data from DEA on promotional expenditures for OxyContin and two other schedule II controlled substances. To examine what factors may have contributed to the abuse and diversion of OxyContin, we interviewed officials from DEA, FDA, and Purdue and physicians who prescribe OxyContin. We also analyzed IMS Health data on sales of OxyContin nationwide and Purdue's distribution of sales representatives, as part of an effort to compare the areas with large sales growth and more sales representatives per capita with the areas where abuse and diversion problems were identified. However, limitations on the abuse and diversion data prevented an assessment of the relationship between the availability of OxyContin and areas where the drug was abused or diverted. To determine what actions have been taken to address OxyContin abuse and diversion, we interviewed FDA officials and examined FDA information regarding the drug's approval and marketing and promotion. We also interviewed DEA officials and examined how DEA determined the prevalence of OxyContin abuse and diversion nationally. In addition, we examined state efforts to identify those involved in the abuse and diversion of OxyContin. We also reviewed actions taken by Purdue to address this problem. (See app. I for a detailed discussion of our methodology.)

We performed our work from August 2002 through October 2003, in accordance with generally accepted government auditing standards.

Results in Brief

Purdue conducted an extensive campaign to market and promote OxyContin using an expanded sales force and multiple promotional approaches to encourage physicians, including primary care specialists, to prescribe OxyContin as an initial opioid treatment for noncancer pain. OxyContin sales and prescriptions grew rapidly following its market introduction in 1996, with the growth in prescriptions for noncancer pain outpacing the growth in prescriptions for cancer pain from 1997 through 2002. By 2003, nearly half of all OxyContin prescribers were primary care physicians. DEA has expressed concern that Purdue's aggressive marketing of OxyContin focused on promoting the drug to treat a wide range of conditions to physicians who may not have been adequately trained in pain management. Purdue has been cited twice by FDA for using potentially false or misleading medical journal advertisements for OxyContin that violated the Federal Food, Drug and Cosmetic Act (FD&C Act), including one advertisement that failed to include warnings about the potentially fatal risks associated with OxyContin use. Further, Purdue did

not submit an OxyContin promotional video for FDA review at the time of its initial distribution in 1998, as required by FDA regulations. Therefore, FDA did not have the opportunity to review the video at the time of its distribution to ensure that the information it contained was truthful, balanced, and accurately communicated. FDA reviewed a similar video in 2002 and told us that the video appeared to have made unsubstantiated claims about OxyContin and minimized its risks.

Several factors may have contributed to OxyContin's abuse and diversion. OxyContin's controlled-release formulation, which made the drug beneficial for the relief of moderate-to-severe pain over an extended period of time, enabled the drug to contain more of the active ingredient oxycodone than other, non-controlled-release oxycodone-containing drugs. This feature may have made OxyContin an attractive target for abuse and diversion, according to DEA. OxyContin's controlled-release formulation, which delayed the drug's absorption, also led FDA to include language in the original label stating that OxyContin had a lower potential for abuse than other oxycodone products. FDA officials thought that the controlled-release feature would make the drug less attractive to abusers. However, FDA did not recognize that the drug could be dissolved in water and injected, which disrupted the controlled-release characteristics and created an immediate rush or high, thereby increasing the potential for abuse. In addition, the safety warning on the label that advised patients not to crush the tablets because a rapid release of a potentially toxic amount of the drug could result—a customary precaution for controlled-release medications—may have inadvertently alerted abusers to a possible method for misusing the drug. The rapid growth in OxyContin sales, which increased the drug's availability in the marketplace, may have made it easier for abusers to obtain the drug for illicit purposes. Further, some geographic areas have been shown to have a history of prescription drug abuse and diversion that may have predisposed some states to the abuse and diversion of OxyContin. However, we could not assess the relationship between the increased availability of OxyContin and locations where it is being abused and diverted because the data on abuse and diversion are not reliable, comprehensive, or timely.

Since 2000, federal and state agencies and Purdue have taken several actions to try to address abuse and diversion of OxyContin. In July 2001, FDA approved a revised OxyContin label adding the highest level of safety warning that FDA can place on an approved drug product. The agency also collaborated with Purdue to develop and implement a risk management plan to help detect and prevent abuse and diversion of OxyContin. Risk management plans were not used at the time OxyContin was approved.

The plans are an optional feature of new drug applications that are intended to decrease product risks by using one or more interventions or tools beyond the approved product labeling. FDA plans to provide guidance on risk management plans to the pharmaceutical industry by September 2004. Also at the federal level, DEA initiated 257 OxyContin-related abuse and diversion cases in fiscal years 2001 and 2002, which resulted in 302 arrests and about \$1 million in fines. At the state level, Medicaid fraud control units have investigated OxyContin abuse and diversion; however, they do not maintain precise data on the number of investigations and enforcement actions completed. Similarly, state medical licensure boards have investigated complaints about physicians who were suspected of abuse and diversion of controlled substances, but they could not provide data on the number of investigations involving OxyContin. Purdue has initiated education programs and other activities for physicians, pharmacists, and the public to address OxyContin abuse and diversion. Purdue has also taken disciplinary action against its sales representatives who improperly promoted OxyContin and has referred physicians who were suspected of misprescribing OxyContin to the appropriate authorities. Although Purdue has used very specific information on physician prescribing practices to market and promote OxyContin since its approval, it was not until October 2002 that Purdue began to use this information and other indicators to identify patterns of prescribing that could point to possible improper sales representative promotion or physician abuse and diversion of OxyContin.

To improve efforts to prevent or identify the abuse and diversion of schedule II controlled substances such as oxycodone, we recommend that FDA's risk management plan guidance encourage the pharmaceutical manufacturers that submit new drug applications for these substances to include plans that contain a strategy for monitoring the use of these drugs and identifying potential abuse and diversion problems.

We received comments on a draft of this report from FDA, DEA, and Purdue. FDA agreed with our recommendation that risk management plans for schedule II controlled substances contain a strategy for monitoring and identifying potential abuse and diversion problems. DEA reiterated its statement that Purdue's aggressive marketing of OxyContin exacerbated the abuse and diversion problems and noted that it is essential that risk management plans be put in place prior to the introduction of controlled substances into the marketplace. Purdue said the report appeared to be fair and balanced, but that we should add the media as one of the factors contributing to abuse and diversion problems

with OxyContin. We incorporated their technical comments where appropriate.

Background

Ensuring that pharmaceuticals are available for those with legitimate medical need while combating the abuse and diversion of prescription drugs involves the efforts of both federal and state government agencies. Under the FD&C Act, FDA is responsible for ensuring that drugs are safe and effective before they are available in the marketplace. The Controlled Substances Act,¹⁰ which is administered by DEA, provides the legal framework for the federal government's oversight of the manufacture and wholesale distribution of controlled substances, that is, drugs and other chemicals that have a potential for abuse. The states address certain issues involving controlled substances through their own controlled substances acts and their regulation of the practice of medicine and pharmacy. In response to concerns about the influence of pharmaceutical marketing and promotional activities on physician prescribing practices, both the pharmaceutical industry and the Department of Health and Human Services's (HHS) Office of Inspector General have issued voluntary guidelines on appropriate marketing and promotion of prescription drugs.

Medical Treatment of Pain

As the incidence and prevalence of painful diseases have grown along with the aging of the population, there has been a growing acknowledgment of the importance of providing effective pain relief. Pain can be characterized in terms of intensity—mild to severe—and duration—acute (sudden onset) or chronic (long term). The appropriate medical treatment varies according to these two dimensions.

In 1986, WHO determined that cancer pain could be relieved in most if not all patients, and it encouraged physicians to prescribe opioid analgesics. WHO developed a three-step analgesic ladder as a practice guideline to provide a sequential use of different drugs for cancer pain management. For the first pain step, treatment with nonopioid analgesics, such as aspirin or ibuprofen, is recommended. If pain is not relieved, then an opioid such as codeine should be used for mild-to-moderate pain as the second step. For the third step—moderate-to-severe pain—opioids such as morphine should be used.

¹⁰Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (Pub. L. No. 91-513, §§100 et seq., 84 Stat. 1236, 1242 et seq.).

Beginning in the mid-1990s, various national pain-related organizations issued pain treatment and management guidelines, which included the use of opioid analgesics in treating both cancer and noncancer pain. In 1995, the American Pain Society recommended that pain should be treated as the fifth vital sign¹¹ to ensure that it would become common practice for health care providers to ask about pain when conducting patient evaluations. The practice guidelines issued by the Agency for Health Care Policy and Research provided physicians and other health care professionals with information on the management of acute pain in 1992 and cancer pain in 1994, respectively.¹² Health care providers and hospitals were further required to ensure that their patients received appropriate pain treatment when the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), a national health care facility standards-setting and accrediting body, implemented its pain standards for hospital accreditation in 2001.

OxyContin

OxyContin, a schedule II drug manufactured by Purdue Pharma L.P., was approved by FDA in 1995 for the treatment of moderate-to-severe pain lasting more than a few days, as indicated in the original label.¹³ OxyContin followed Purdue's older product, MS Contin, a morphine-based product that was approved in 1984 for a similar intensity and duration of pain and during its early years of marketing was promoted for the treatment of cancer pain. The active ingredient in OxyContin tablets is oxycodone, a compound that is similar to morphine and is also found in oxycodone-combination pain relief drugs such as Percocet, Percodan, and Tylox. Because of its controlled-release property, OxyContin contains more active ingredient and needs to be taken less often (twice a day) than these

¹¹The other four vital signs physicians use to assess patients are pulse, blood pressure, core temperature, and respiration.

¹²In 1999, the name of the Agency for Health Care Policy and Research was changed to the Agency for Healthcare Research and Quality. The agency, which is part of HHS, is responsible for supporting research designed to improve the quality of health care, reduce its costs, and broaden access to essential services.

¹³When we refer to OxyContin's label we are also referring to the drug's package insert that contains the same information about the product.

other oxycodone-containing drugs.¹⁴ The OxyContin label originally approved by FDA indicated that the controlled-release characteristics of OxyContin were believed to reduce its potential for abuse. The label also contained a warning that OxyContin tablets were to be swallowed whole, and were not to be broken, chewed, or crushed because this could lead to the rapid release and absorption of a potentially toxic dose of oxycodone. Such a safety warning is customary for schedule II controlled-release medications. FDA first approved the marketing and use of OxyContin in 10-, 20-, and 40-milligram controlled-release tablets. FDA later approved 80- and 160-milligram controlled-release tablets for use by patients who were already taking opioids.¹⁵ In July 2001, FDA approved the revised label to state that the drug is approved for the treatment of moderate-to-severe pain in patients who require “a continuous around-the-clock analgesic for an extended period of time.” (See app. II for a summary of the changes that were made by FDA to the original OxyContin label.)

OxyContin sales and prescriptions grew rapidly following its market introduction in 1996. Fortuitous timing may have contributed to this growth, as the launching of the drug occurred during the national focus on the inadequacy of patient pain treatment and management. In 1997, OxyContin’s sales and prescriptions began increasing significantly, and they continued to increase through 2002. In both 2001 and 2002, OxyContin’s sales exceeded \$1 billion, and prescriptions were over 7 million. The drug became Purdue’s main product, accounting for 90 percent of the company’s total prescription sales by 2001.

Media reports of OxyContin abuse and diversion began to surface in 2000. These reports first appeared in rural areas of some states, generally in the Appalachian region, and continued to spread to other rural areas and larger cities in several states. Rural communities in Maine, Kentucky, Ohio, Pennsylvania, Virginia, and West Virginia were reportedly being devastated by the abuse and diversion of OxyContin. For example, media reports told of persons and communities that had been adversely affected by the rise of addiction and deaths related to OxyContin. One report noted that drug

¹⁴For example, according to Purdue’s comparable dose guide a patient taking one Percodan 4.5-milligram tablet or one Tylox 5-milligram tablet every 6 hours can be converted to either a 10- or a 20-milligram OxyContin tablet to be taken every 12 hours. For a 12-hour dosing period, one OxyContin tablet replaces two Percodan or Tylox tablets, and one OxyContin tablet contains twice as much oxycodone as one of the other tablets.

¹⁵In April 2001, Purdue discontinued distribution of the 160-milligram tablets because of OxyContin abuse and diversion concerns.

treatment centers and emergency rooms in a particular area were receiving new patients who were addicted to OxyContin as early as 1999. Pain patients, teens, and recreational drug users who had abused OxyContin reportedly entered drug treatment centers sweating and vomiting from withdrawal. In West Virginia, as many as one-half of the approximately 300 patients admitted to a drug treatment clinic in 2000 were treated for OxyContin addiction. The media also reported on deaths due to OxyContin. For example, a newspaper's investigation of autopsy reports involving oxycodone-related deaths found that OxyContin had been involved in over 200 overdose deaths in Florida since 2000.¹⁶ In another case, a forensic toxicologist commented that he had reviewed a number of fatal overdose cases in which individuals took a large dose of OxyContin, in combination with alcohol or other drugs.

After learning about the initial reports of abuse and diversion of OxyContin in Maine in 2000, Purdue formed a response team made up of its top executives and physicians to initiate meetings with federal and state officials in Maine to gain an understanding of the scope of the problem and to devise strategies for preventing abuse and diversion. After these meetings, Purdue distributed brochures to health care professionals that described several steps that could be taken to prevent prescription drug abuse and diversion. In response to the abuse and diversion reports, DEA analyzed data collected from medical examiner autopsy reports and crime scene investigation reports. The most recent data available from DEA show that as of February 2002, the agency had verified 146 deaths nationally involving OxyContin in 2000 and 2001.

According to Purdue, as of early October 2003, over 300 lawsuits concerning OxyContin were pending against Purdue, and 50 additional lawsuits had been dismissed. The cases involve many allegations, including, for example, that Purdue used improper sales tactics and overpromoted OxyContin causing the drug to be inappropriately prescribed by physicians, and that Purdue took inadequate actions to prevent addiction, abuse, and diversion of the drug. The lawsuits have been brought in 25 states and the District of Columbia in both federal and state courts.

¹⁶Doris Bloodsworth, "Pain Pill Leaves Death Trail: A Nine-Month Investigation Raises Many Questions about Purdue Pharma's Powerful Drug OxyContin," *Orlando Sentinel*, Oct. 19, 2003.

Controlled Substances Act	<p>The Controlled Substances Act established a classification structure for drugs and chemicals used in the manufacture of drugs that are designated as controlled substances.¹⁷ Controlled substances are classified by DEA into five schedules on the basis of their medicinal value, potential for abuse, and safety or dependence liability. Schedule I drugs—including heroin, marijuana, and LSD—have a high potential for abuse and no currently accepted medical use. Schedule II drugs—which include opioids such as morphine and oxycodone, the primary ingredient in OxyContin—have a high potential for abuse among drugs with an accepted medical use and may lead to severe psychological or physical dependence. Drugs on schedules III through V have medical uses and successively lower potentials for abuse and dependence. Schedule III drugs include anabolic steroids, codeine, hydrocodone in combination with aspirin or acetaminophen, and some barbiturates. Schedule IV contains such drugs as the antianxiety drugs diazepam (Valium) and alprazolam (Xanax). Schedule V includes preparations such as cough syrups with codeine. All scheduled drugs except those in schedule I are legally available to the public with a prescription.¹⁸</p>
FDA's Regulation of Prescription Drugs	<p>Under the FD&C Act and implementing regulations, FDA is responsible for ensuring that all new drugs are safe and effective. FDA reviews scientific and clinical data to decide whether to approve drugs based on their intended use, effectiveness, and the risks and benefits for the intended population, and also monitors drugs for continued safety after they are in use.</p> <p>FDA also regulates the advertising and promotion of prescription drugs under the FD&C Act. FDA carries out this responsibility by ensuring that prescription drug advertising and promotion is truthful, balanced, and accurately communicated.¹⁹ The FD&C Act makes no distinction between</p>

¹⁷Section 201, classified to 21 U.S.C. § 811.

¹⁸Some schedule V drugs that contain limited quantities of certain narcotic and stimulant drugs are available over the counter, without a prescription.

¹⁹FDA regulations require that promotional labeling and advertisements be submitted to FDA at the time of initial dissemination (for labeling) and initial publication (for advertisements). The FD&C Act defines labeling to include all labels and other written, printed, or graphic matter accompanying an article. For example, promotional materials commonly shown or given to physicians, such as sales aids and branded promotional items, are regulated as promotional labeling. FDA may also regulate promotion by sales representatives on computer programs, through fax machines, or on electronic bulletin boards.

controlled substances and other prescription drugs in the oversight of promotional activities. FDA told us that the agency takes a risk-based approach to enforcement, whereby drugs with more serious risks, such as opioids, are given closer scrutiny in monitoring promotional messages and activities, but the agency has no specific guidance or policy on this approach. The FD&C Act and its implementing regulations require that all promotional materials for prescription drugs be submitted to FDA at the time the materials are first disseminated or used, but it generally is not required that these materials be approved by FDA before their use. As a result, FDA's actions to address violations occur after the materials have already appeared in public. In fiscal year 2002, FDA had 39 staff positions dedicated to oversight of drug advertising and promotion of all pharmaceuticals distributed in the United States. According to FDA, most of the staff focuses on the oversight of promotional communications to physicians. FDA officials told us that in 2001 it received approximately 34,000 pieces of promotional material, including consumer advertisements and promotions to physicians, and received and reviewed 230 complaints about allegedly misleading advertisements, including materials directed at health professionals.²⁰

FDA issues two types of letters to address violations of the FD&C Act: untitled letters and warning letters. Untitled letters are issued for violations such as overstating the effectiveness of the drug, suggesting a broader range of indicated uses than the drug has been approved for, and making misleading claims because of inadequate context or lack of balanced information. Warning letters are issued for more serious violations, such as those involving safety or health risks, or for continued violations of the act. Warning letters generally advise a pharmaceutical manufacturer that FDA may take further enforcement actions, such as seeking judicial remediation, without notifying the company and may ask the manufacturer to conduct a new advertising campaign to correct inaccurate impressions left by the advertisements.

Under the Controlled Substances Act, FDA notifies DEA if FDA is reviewing a new drug application for a drug that has a stimulant, depressant, or hallucinogenic effect on the central nervous system and has abuse potential. FDA performs a medical and scientific assessment as

²⁰For details on FDA's oversight of drug advertising see U.S. General Accounting Office, *Prescription Drugs: FDA Oversight of Direct-to-Consumer Advertising Has Limitations*, GAO-03-177 (Washington, D.C.: Oct. 28, 2002).

required by the Controlled Substances Act, and recommends to DEA an initial schedule level to be assigned to a new controlled substance.

FDA plans to provide guidance to the pharmaceutical industry on the development, implementation, and evaluation of risk management plans as a result of the reauthorization of the Prescription Drug User Fee Act of 1992 (PDUFA).²¹ FDA expects to issue this guidance by September 30, 2004. FDA defines a risk management program as a strategic safety program that is designed to decrease product risks by using one or more interventions or tools beyond the approved product labeling. Interventions used in risk management plans may include postmarketing surveillance, education and outreach programs to health professionals or consumers, informed consent agreements for patients, limitations on the supply or refills of products, and restrictions on individuals who may prescribe and dispense drug products. All drug manufacturers have the option to develop and submit risk management plans to FDA as part of their new drug applications.

DEA's Regulation of Controlled Substances

DEA is the primary federal agency responsible for enforcing the Controlled Substances Act. DEA has the authority to regulate transactions involving the sale and distribution of controlled substances at the manufacturer and wholesale distributor levels. DEA registers legitimate handlers of controlled substances—including manufacturers, distributors, hospitals, pharmacies, practitioners, and researchers—who must comply with regulations relating to drug security and accountability through the maintenance of inventories and records. All registrants, including pharmacies, are required to maintain records of controlled substances that have been manufactured, purchased, and sold. Manufacturers and distributors are also required to report their annual inventories of controlled substances to DEA. The data provided to DEA are available for use in monitoring the distribution of controlled substances throughout the United States and identifying retail-level registrants that received unusual quantities of controlled substances. DEA regulations for schedule II prescription drugs, unlike those for other prescription drugs, require that each prescription must be written and signed by the physician and may not be telephoned in to the pharmacy except in an emergency. Also, a

²¹The Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571, title I, 106 Stat. 4491, was reauthorized by the Food and Drug Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296, and, most recently, by the Prescription Drug User Fee Amendments of 2002, Pub. L. No. 107-188, title V, subtitle A, 116 Stat. 594, 687.

prescription for a schedule II drug may not be refilled. A physician is required to provide a new prescription each time a patient obtains more of the drug. DEA also sets limits on the quantity of schedule II controlled substances that may be produced in the United States in any given year. Specifically, DEA sets aggregate production quotas that limit the production of bulk raw materials used in the manufacture of controlled substances. DEA determines these quotas based on a variety of data including sales, production, inventories, and exports. Individual companies must apply to DEA for manufacturing or procurement quotas for specific pharmaceutical products. For example, Purdue has a procurement quota for oxycodone, the principle ingredient in OxyContin, that allows the company to purchase specified quantities of oxycodone from bulk manufacturers.

States' Regulation of the Practice of Medicine and Pharmacy and Role in Monitoring Illegal Use and Diversion of Prescription Drugs

State laws govern the prescribing and dispensing of prescription drugs by licensed health care professionals. Each state requires that physicians practicing in the state be licensed, and state medical practice laws generally outline standards for the practice of medicine and delegate the responsibility of regulating physicians to state medical boards. States also require pharmacists and pharmacies to be licensed. The regulation of the practice of pharmacy is based on state pharmacy practice acts and regulations enforced by the state boards of pharmacy. According to the National Association of Boards of Pharmacy, all state pharmacy laws require that records of prescription drugs dispensed to patients be maintained and that state pharmacy boards have access to the prescription records. State regulatory boards face new challenges with the advent of Internet pharmacies, because they enable pharmacies and physicians to anonymously reach across state borders to prescribe, sell, and dispense prescription drugs without complying with state requirements.²² In some cases, consumers can purchase prescription drugs, including controlled substances, such as OxyContin, from Internet pharmacies without a valid prescription.

²²For more details on Internet pharmacies, see U.S. General Accounting Office, *Internet Pharmacies: Adding Disclosure Requirements Would Aid State and Federal Oversight*, GAO-01-69 (Washington, D.C.: Oct. 19, 2000).

In addition to these regulatory boards, 15 states operate prescription drug monitoring programs as a means to control the illegal diversion of prescription drugs that are controlled substances. Prescription drug monitoring programs are designed to facilitate the collection, analysis, and reporting of information on the prescribing, dispensing, and use of controlled substances within a state. They provide data and analysis to state law enforcement and regulatory agencies to assist in identifying and investigating activities potentially related to the illegal prescribing, dispensing, and procuring of controlled substances. For example, physicians in Kentucky can use the program to check a patient's prescription drug history to determine if the individual may be "doctor shopping" to seek multiple controlled substance prescriptions. An overriding goal of prescription drug monitoring programs is to support both the state laws ensuring access to appropriate pharmaceutical care by citizens and the state laws deterring diversion. As we have reported, state prescription drug monitoring programs offer state regulators an efficient means of detecting and deterring illegal diversion. However, few states proactively analyze prescription data to identify individuals, physicians, or pharmacies that have unusual use, prescribing, or dispensing patterns that may suggest potential drug diversion or abuse. Although three states can respond to requests for information within 3 to 4 hours, providing information on suspected illegal prescribing, dispensing, or doctor shopping at the time a prescription is written or sold would require states to improve computer capabilities. In addition, state prescription drug monitoring programs may require additional legal authority to analyze data proactively.²³

Guidelines for Marketing Drugs to Health Care Professionals

At the time that OxyContin was first marketed, there were no industry or federal guidelines for the promotion of prescription drugs. Voluntary guidelines regarding how drug companies should market and promote their drugs to health care professionals were issued in July 2002 by the Pharmaceutical Research and Manufacturers of America (PhRMA). In April 2003, HHS's Office of Inspector General issued voluntary guidelines for how drug companies should market and promote their products to federal health care programs. Neither set of guidelines distinguishes between controlled and noncontrolled substances.

²³For more details on these programs, see U.S. General Accounting Office, *Prescription Drugs: State Monitoring Programs Provide Useful Tool to Reduce Diversion*, GAO-02-634 (Washington, D.C.: May 17, 2002).

PhRMA's voluntary code of conduct for sales representatives states that interactions with health care professionals should be to inform these professionals about products, to provide scientific and educational information, and to support medical research and education.²⁴ The question-and-answer section of the code addresses companies' use of branded promotional items, stating, for example, that golf balls and sports bags should not be distributed because they are not primarily for the benefit of patients, but that speaker training programs held at golf resorts may be acceptable if participants are receiving extensive training. Purdue adopted the code.

In April 2003, HHS's Office of Inspector General issued final voluntary guidance for drug companies' interactions with health care professionals in connection with federal health care programs, including Medicare and Medicaid. Among the guidelines were cautions for companies against offering inappropriate travel, meals, and gifts to influence the prescribing of drugs; making excessive payments to physicians for consulting and research services; and paying physicians to switch their patients from competitors' drugs.

Purdue Conducted an Extensive Campaign to Market and Promote OxyContin

Purdue conducted an extensive campaign to market and promote OxyContin that focused on encouraging physicians, including those in primary care specialties, to prescribe the drug for noncancer as well as cancer pain. To implement its OxyContin campaign, Purdue significantly increased its sales force and used multiple promotional approaches. OxyContin sales and prescriptions grew rapidly following its market introduction, with the growth in prescriptions for noncancer pain outpacing the growth in prescriptions for cancer pain. DEA has expressed concern that Purdue marketed OxyContin for a wide variety of conditions to physicians who may not have been adequately trained in pain management. Purdue has been cited twice by FDA for OxyContin advertisements in medical journals that violated the FD&C Act. FDA has also taken similar actions against manufacturers of two of the three comparable schedule II controlled substances we examined, to ensure that

²⁴In addition, the American Medical Association, a professional association for physicians, issued guidelines in 1990 regarding gifts given to physicians by drug industry representatives. For example, physicians may accept individual gifts of nominal value that are related to their work, such as notepads and pens, and may attend conferences sponsored by drug companies that are educational and for which appropriate disclosure of financial support or conflicts of interest is made.

their marketing and promotion were truthful, balanced, and accurately communicated. In addition, Purdue provided two promotional videos to physicians that, according to FDA appear to have made unsubstantiated claims and minimized the risks of OxyContin. The first video was available for about 3 years without being submitted to FDA for review.

Purdue Focused on Promoting OxyContin for Treatment of Noncancer Pain

From the outset of the OxyContin marketing campaign, Purdue promoted the drug to physicians for noncancer pain conditions that can be caused by arthritis, injuries, and chronic diseases, in addition to cancer pain. Purdue directed its sales representatives to focus on the physicians in their sales territories who were high opioid prescribers. This group included cancer and pain specialists, primary care physicians, and physicians who were high prescribers of Purdue's older product, MS Contin. One of Purdue's goals was to identify primary care physicians who would expand the company's OxyContin prescribing base. Sales representatives were also directed to call on oncology nurses, consultant pharmacists, hospices, hospitals, and nursing homes.

From OxyContin's launch until its July 2001 label change, Purdue used two key promotional messages for primary care physicians and other high prescribers. The first was that physicians should prescribe OxyContin for their pain patients both as the drug "to start with and to stay with." The second contrasted dosing with other opioid pain relievers with OxyContin dosing as "the hard way versus the easy way" to dose because OxyContin's twice-a-day dosing was more convenient for patients.²⁵ Purdue's sales representatives promoted OxyContin to physicians as an initial opioid treatment for moderate-to-severe pain lasting more than a few days, to be prescribed instead of other single-entity opioid analgesics or short-acting combination opioid pain relievers. Purdue has stated that by 2003 primary care physicians had grown to constitute nearly half of all OxyContin prescribers, based on data from IMS Health, an information service providing pharmaceutical market research. DEA's analysis of physicians prescribing OxyContin found that the scope of medical specialties was wider for OxyContin than five other controlled-release, schedule II narcotic analgesics. DEA expressed concern that this resulted in

²⁵Following OxyContin's July 2001 label change, Purdue modified its promotional messages but continued to focus on encouraging physicians to prescribe OxyContin for patients taking pain relievers every 4 to 6 hours. In 2003, Purdue began using the promotional claim "there can be life with relief" in OxyContin promotion.

OxyContin's being promoted to physicians who were not adequately trained in pain management.

Purdue's promotion of OxyContin for the treatment of noncancer pain contributed to a greater increase in prescriptions for noncancer pain than for cancer pain from 1997 through 2002.²⁶ According to IMS Health data, the annual number of OxyContin prescriptions for noncancer pain increased nearly tenfold, from about 670,000 in 1997 to about 6.2 million in 2002.²⁷ In contrast, during the same 6 years, the annual number of OxyContin prescriptions for cancer pain increased about fourfold, from about 250,000 in 1997 to just over 1 million in 2002. The noncancer prescriptions therefore increased from about 73 percent of total OxyContin prescriptions to about 85 percent during that period, while the cancer prescriptions decreased from about 27 percent of the total to about 15 percent. IMS Health data indicated that prescriptions for other schedule II opioid drugs, such as Duragesic²⁸ and morphine products, for noncancer pain also increased during this period. Duragesic prescriptions for noncancer pain were about 46 percent of its total prescriptions in 1997, and increased to about 72 percent of its total in 2002. Morphine products, including, for example, Purdue's MS Contin, also experienced an increase in their noncancer prescriptions during the same period. Their noncancer prescriptions were about 42 percent of total prescriptions in 1997, and increased to about 65 percent in 2002. DEA has cited Purdue's focus on promoting OxyContin for treating a wide range of conditions as one of the reasons the agency considered Purdue's marketing of OxyContin to be overly aggressive.

²⁶IMS Health reported noncancer prescriptions written for the following types of pain conditions: surgical aftercare; musculoskeletal disorders including back and neck disorders, arthritis conditions, and injuries and trauma including bone fractures; central nervous system disorders including headache conditions such as migraines; genitourinary disorders including kidney stones; and other types of general pain.

²⁷The IMS Health data included information from the National Disease and Therapeutics Index and the National Prescription Audit. The National Disease and Therapeutics Index does not capture data from anesthesiologists and dental specialties. The National Prescription Audit data include retail pharmacy, long-term-care, and mail-order prescriptions.

²⁸Duragesic is a skin patch used to deliver the opioid pain reliever fentanyl over a 72-hour period.

Purdue Significantly Increased Its Sales Force to Market and Promote OxyContin

Purdue significantly increased its sales force to market and promote OxyContin to physicians and other health care practitioners. In 1996, Purdue began promoting OxyContin with a sales force of approximately 300 representatives in its Prescription Sales Division.²⁹ Through a 1996 copromotion agreement, Abbott Laboratories provided at least another 300 representatives, doubling the total OxyContin sales force.³⁰ By 2000, Purdue had more than doubled its own internal sales force to 671. The expanded sales force included sales representatives from the Hospital Specialty Division, which was created in 2000 to increase promotional visits on physicians located in hospitals. (See table 1.)

Table 1: Sales Representative Positions Available for OxyContin Promotion, 1996 through 2002

Positions available^a	1996	1997	1998	1999	2000	2001	2002
Purdue Prescription Sales Division	318	319	377	471	562	641	641
Purdue Hospital Specialty Division	0	0	0	0	109	125	126
Subtotal—All Purdue sales representatives	318	319	377	471	671	766	767
Abbott Laboratories sales representatives ^b	300	300	300	300	300	300	300
Total	618	619	677	771	971	1,066	1,067

Source: GAO analysis of Purdue data.

^aAll positions were not necessarily filled in a given year.

^bUnder the OxyContin copromotion agreement, Abbott Laboratories provided at least 300 sales representatives each year.

The manufacturers of two of the three comparable schedule II drugs have smaller sales forces than Purdue. Currently, the manufacturer of Kadian has about 100 sales representatives and is considering entering into a copromotion agreement. Elan, the current owner of Oramorph SR, has approximately 300 representatives, but told us that it is not currently marketing Oramorph SR. The manufacturer of Avinza had approximately 50 representatives at its product launch. In early 2003, Avinza's manufacturer announced that more than 700 additional sales

²⁹These sales representatives were also responsible for promoting other Purdue products.

³⁰Abbott Laboratories sales representatives' promotion of OxyContin is limited to hospital-based anesthesiologists and surgeons and major hospitals, medical centers, and freestanding pain clinics.

representatives would be promoting the drug under its copromotion agreement with the pharmaceutical manufacturer Organon—for a total of more than 800 representatives.

By more than doubling its total sales representatives, Purdue significantly increased the number of physicians to whom it was promoting OxyContin. Each Purdue sales representative has a specific sales territory and is responsible for developing a list of about 105 to 140 physicians to call on who already prescribe opioids or who are candidates for prescribing opioids. In 1996, the 300-plus Purdue sales representatives had a total physician call list of approximately 33,400 to 44,500. By 2000, the nearly 700 representatives had a total call list of approximately 70,500 to 94,000 physicians. Each Purdue sales representative is expected to make about 35 physician calls per week and typically calls on each physician every 3 to 4 weeks. Each hospital sales representative is expected to make about 50 calls per week and typically calls on each facility every 4 weeks.

Purdue stated it offered a “better than industry average” salary and sales bonuses to attract top sales representatives and provide incentives to boost OxyContin sales as it had done for MS Contin. Although the sales representatives were primarily focused on OxyContin promotion, the amount of the bonus depended on whether a representative met the sales quotas in his or her sales territory for all company products. As OxyContin’s sales increased, Purdue’s growth-based portion of the bonus formula increased the OxyContin sales quotas necessary to earn the same base sales bonus amounts. The amount of total bonuses that Purdue estimated were tied to OxyContin sales increased significantly from about \$1 million in 1996, when OxyContin was first marketed, to about \$40 million in 2001. Beginning in 2000, when the newly created hospital specialty representatives began promoting OxyContin, their estimated total bonuses were approximately \$6 million annually. In 2001, the average annual salary for a Purdue sales representative was \$55,000, and the average annual bonus was \$71,500. During the same year, the highest annual sales bonus was nearly \$240,000, and the lowest was nearly \$15,000. In 2001, Purdue decided to limit the sales bonus a representative could earn based on the growth in prescribing of a single physician after a meeting with the U.S. Attorney for the Western District of Virginia at which the company was informed of the possibility that a bonus could be based on the prescribing of one physician.

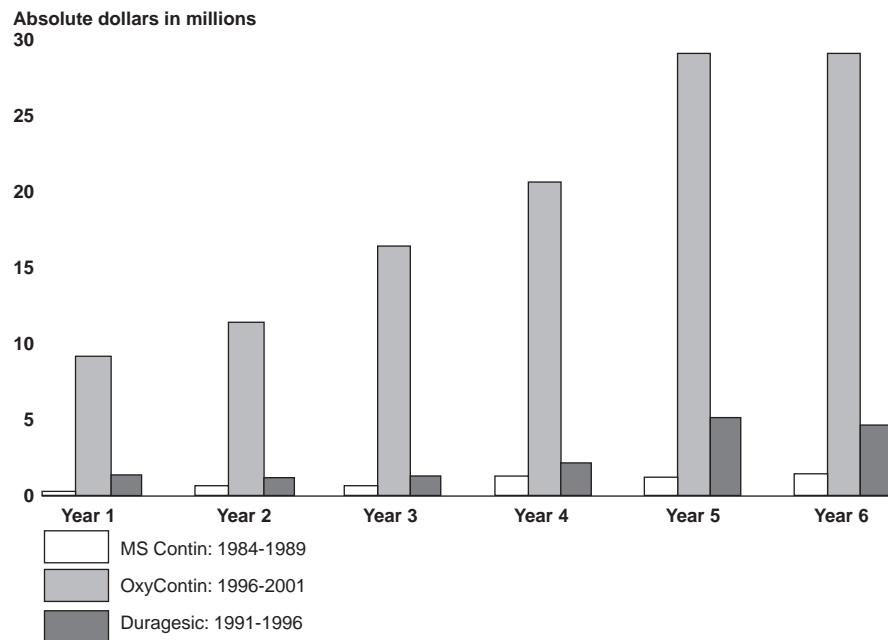
Purdue Employed Multiple Approaches to Market and Promote OxyContin

In addition to expanding its sales force, Purdue used multiple approaches to market and promote OxyContin. These approaches included expanding its physician speaker bureau and conducting speaker training conferences, sponsoring pain-related educational programs, issuing OxyContin starter coupons for patients' initial prescriptions, sponsoring pain-related Web sites, advertising OxyContin in medical journals, and distributing OxyContin marketing items to health care professionals.

In our report on direct-to-consumer advertising, we found that most promotional spending is targeted to physicians.³¹ For example, in 2001, 29 percent of spending on pharmaceutical promotional activities was related to activities of pharmaceutical sales representatives directed to physicians, and 2 percent was for journal advertising—both activities Purdue uses for its OxyContin promotion. The remaining 69 percent of pharmaceutical promotional spending involved sampling (55 percent), which is the practice of providing drug samples during sales visits to physician offices, and direct-to-consumer advertising (14 percent)—both activities that Purdue has stated it does not use for OxyContin.

According to DEA's analysis of IMS Health data, Purdue spent approximately 6 to 12 times more on promotional efforts during OxyContin's first 6 years on the market than it had spent on its older product, MS Contin, during its first 6 years, or than had been spent by Janssen Pharmaceutical Products, L.P., for one of OxyContin's drug competitors, Duragesic. (See fig. 1.)

³¹U.S. General Accounting Office, *Prescription Drugs: FDA Oversight of Direct-to-Consumer Advertising Has Limitations*, GAO-03-177 (Washington, D.C.: Oct. 28, 2002).

Figure 1: Promotional Spending for Three Opioid Analgesics in First 6 Years of Sales

Source: DEA and IMS Health, Integrated Promotional Service Audit.

Note: Dollars are 2002 adjusted.

During the first 5 years that OxyContin was marketed, Purdue conducted over 40 national pain management and speaker training conferences, usually in resort locations such as Boca Raton, Florida, and Scottsdale, Arizona, to recruit and train health care practitioners for its national speaker bureau. The trained speakers were then made available to speak about the appropriate use of opioids, including oxycodone, the active ingredient in OxyContin, to their colleagues in various settings, such as local medical conferences and grand round presentations in hospitals involving physicians, residents, and interns. Over the 5 years, these conferences were attended by more than 5,000 physicians, pharmacists, and nurses, whose travel, lodging, and meal costs were paid by the company. Purdue told us that less than 1 percent annually of the physicians called on by Purdue sales representatives attended these conferences. Purdue told us it discontinued conducting these conferences in fall 2000. Purdue's speaker bureau list from 1996 through mid-2002 included nearly 2,500 physicians, of whom over 1,000 were active participants. Purdue has paid participants a fee for speaking based on the physician's qualifications; the type of program and time commitment

involved; and expenses such as airfare, hotel, and food. The company currently marketing the comparable drug Avinza has a physician speaker bureau, but does not sponsor speaker training and conferences at resort locations. Kadian's current company does not have a physician speaker bureau and has not held any conferences.

From 1996, when OxyContin was introduced to the market, to July 2002, Purdue has funded over 20,000 pain-related educational programs through direct sponsorship or financial grants. These grants included support for programs to provide physicians with opportunities to earn required continuing medical education credits, such as grand round presentations at hospitals and medical education seminars at state and local medical conferences. During 2001 and 2002, Purdue funded a series of nine programs throughout the country to educate hospital physicians and staff on how to comply with JCAHO's pain standards for hospitals and to discuss postoperative pain treatment. Purdue was one of only two drug companies that provided funding for JCAHO's pain management educational programs.³² Under an agreement with JCAHO, Purdue was the only drug company allowed to distribute certain educational videos and a book about pain management; these materials were also available for purchase from JCAHO's Web site. Purdue's participation in these activities with JCAHO may have facilitated its access to hospitals to promote OxyContin.

For the first time in marketing any of its products, Purdue used a patient starter coupon program for OxyContin to provide patients with a free limited-time prescription. Unlike patient assistance programs, which provide free prescriptions to patients in financial need, a coupon program is intended to enable a patient to try a new drug through a one-time free prescription. A sales representative distributes coupons to a physician, who decides whether to offer one to a patient, and then the patient redeems it for a free prescription through a participating pharmacy. The program began in 1998 and ran intermittently for 4 years. In 1998 and 1999, each sales representative had 25 coupons that were redeemable for a free 30-day supply. In 2000 each representative had 90 coupons for a 7-day supply, and in 2001 each had 10 coupons for a 7-day supply. Approximately 34,000 coupons had been redeemed nationally when the

³²During 2000 through 2002, JCAHO sponsored a series of educational programs on pain management standards with various cosponsors, including pain-related groups such as the American Pain Society and the American Academy of Pain Medicine.

program was terminated following the July 2001 OxyContin label change. The manufacturers of two of the comparable drugs we examined—Avinza and Kadian—used coupon programs to introduce patients to their products. Avinza's coupon program requires patients to make a copayment to cover part of the drug's cost.

Purdue has also used Web sites to provide pain-related information to consumers and others. In addition to its corporate Web site, which provides product information, Purdue established the "Partners Against Pain" Web site in 1997 to provide consumers with information about pain management and pain treatment options. According to FDA, the Web site also contained information about OxyContin. Separate sections provide information for patients and caregivers, medical professionals, and institutions. The Web site includes a "Find a Doctor" feature to enable consumers to find physicians who treat pain in their geographic area.³³ As of July 2002, over 33,000 physicians were included. Ligand, which markets Avinza, one of the comparable drugs, has also used a corporate Web site to provide product information. Purdue has also funded Web sites, such as FamilyPractice.com, that provide physicians with free continuing medical educational programs on pain management.³⁴ Purdue has also provided funding for Web site development and support for health care groups such as the American Chronic Pain Association and the American Academy of Pain Medicine. In addition, Purdue is one of 28 corporate donors—which include all three comparable drug companies—listed on the Web site of the American Pain Society, the mission of which is to improve pain-related education, treatment, and professional practice. Purdue also sponsors painfullyobvious.com, which it describes as a youth-focused "message campaign designed to provide information—and stimulate open discussions—on the dangers of abusing prescription drugs."

Purdue also provided its sales representatives with 14,000 copies of a promotional video in 1999 to distribute to physicians. Entitled *From One Pain Patient to Another: Advice from Patients Who Have Found Relief*, the video was to encourage patients to report their pain and to alleviate patients' concerns about taking opioids. Purdue stated that the video was to be used "in physician waiting rooms, as a 'check out' item for an office's

³³The "Find a Doctor" feature is a physician listing service provided by the National Physicians DataSource, LLC.

³⁴Purdue has also helped to fund the Dannemiller Memorial Education Foundation and the American Academy of Physician Assistants Web sites.

patient education library, or as an educational tool for office or hospital staff to utilize with patients and their families.” Copies of the video were also available for ordering on the “Partners Against Pain” Web site from June 2000 through July 2001. The video did not need to be submitted to FDA for its review because it did not contain any information about OxyContin. However, the video included a statement that opioid analgesics have been shown to cause addiction in less than 1 percent of patients. According to FDA, this statement has not been substantiated.

As part of its marketing campaign, Purdue distributed several types of branded promotional items to health care practitioners. Among these items were OxyContin fishing hats, stuffed plush toys, coffee mugs with heat-activated messages, music compact discs, luggage tags, and pens containing a pullout conversion chart showing physicians how to calculate the dosage to convert a patient to OxyContin from other opioid pain relievers.³⁵ In May 2002, in anticipation of PhRMA’s voluntary guidance for sales representatives’ interactions with health care professionals, Purdue instructed its sales force to destroy any remaining inventory of non-health-related promotional items, such as stuffed toys or golf balls. In early 2003, Purdue began distributing an OxyContin branded goniometer—a range and motion measurement guide. According to DEA, Purdue’s use of branded promotional items to market OxyContin was unprecedented among schedule II opioids, and was an indicator of Purdue’s aggressive and inappropriate marketing of OxyContin.

Another approach Purdue used to promote OxyContin was to place advertisements in medical journals. Purdue’s annual spending for OxyContin advertisements increased from about \$700,000 in 1996 to about \$4.6 million in 2001. All three companies that marketed the comparable drugs have also used medical journal advertisements to promote their products.

OxyContin Advertisements Violated the FD&C Act

Purdue has been cited twice by FDA for using advertisements in professional medical journals that violated the FD&C Act. In May 2000, FDA issued an untitled letter to Purdue regarding a professional medical

³⁵It is common drug industry practice for companies to provide conversion tables for sales representatives to distribute to health care practitioners. Purdue used a similar pen for its older product, MS Contin.

journal advertisement for OxyContin.³⁶ FDA noted that among other problems, the advertisement implied that OxyContin had been studied for all types of arthritis pain when it had been studied only in patients with moderate-to-severe osteoarthritis pain, the advertisement suggested OxyContin could be used as an initial therapy for the treatment of osteoarthritis pain without substantial evidence to support this claim, and the advertisement promoted OxyContin in a selected class of patients—the elderly—without presenting risk information applicable to that class of patients.³⁷ Purdue agreed to stop dissemination of the advertisement. The second action taken by FDA was more serious. In January 2003, FDA issued a warning letter to Purdue regarding two professional medical journal advertisements for OxyContin that minimized its risks and overstated its efficacy, by failing to prominently present information from the boxed warning on the potentially fatal risks associated with OxyContin and its abuse liability, along with omitting important information about the limitations on the indicated use of OxyContin.³⁸ The FDA requested that Purdue cease disseminating these advertisements and any similar violative materials and provide a plan of corrective action. In response, Purdue issued a corrected advertisement, which called attention to the warning letter and the cited violations and directed the reader to the prominently featured boxed warning and indication information for OxyContin.³⁹ The FDA letter was one of only four warning letters issued to drug manufacturers during the first 8 months of 2003.⁴⁰

In addition, in follow-up discussions with Purdue officials on the January 2003 warning letter, FDA expressed concerns about some of the information on Purdue's "Partners Against Pain" Web site. The Web site appeared to suggest unapproved uses of OxyContin for postoperative pain that may have been inconsistent with OxyContin's labeling and lacked risk

³⁶FDA indicated that in 2000, it issued 75 untitled letters to 46 drug manufacturers, as well as 4 warning letters to 4 drug manufacturers, for using promotional activities that violated the FD&C Act.

³⁷The advertisement appeared in the *New England Journal of Medicine* in May 2000.

³⁸The advertisements appeared in the *Journal of the American Medical Association* in October and November 2002.

³⁹According to FDA, the corrective advertisement ran for 3 months and appeared in approximately 30 medical journals.

⁴⁰FDA indicated that from January through August 2003, it issued 4 warning letters to four manufacturers and 12 untitled letters to seven drug manufacturers for using promotional activities that violated the FD&C Act.

information about the drug. For example, one section of the Web site did not disclose that OxyContin is not indicated for pain in the immediate postoperative period—the first 12 to 24 hours following surgery—for patients not previously taking the drug, because its safety in this setting has not been established. The Web site also did not disclose that OxyContin is indicated for postoperative pain in patients already taking the drug or for use after the first 24 hours following surgery only if the pain is moderate to severe and expected to persist for an extended period of time. Purdue voluntarily removed all sections of the Web site that were of concern to FDA.

FDA has also sent enforcement letters to other manufacturers of controlled substances for marketing and promotion violations of the FD&C Act. For example, in 1996, FDA issued an untitled letter to Zeneca Pharmaceuticals, at the time the promoter of Kadian,⁴¹ for providing information about the drug to a health professional prior to its approval in the United States. Roxane Laboratories, the manufacturer of Oramorph SR, was issued four untitled letters between 1993 and 1995 for making misleading and possibly false statements. Roxane used children in an advertisement even though Oramorph SR had not been evaluated in children, and a Roxane sales representative issued a promotional letter to a pharmacist that claimed, among other things, that Oramorph SR was superior to MS Contin in providing pain relief. FDA has sent no enforcement letters to Ligand Pharmaceuticals concerning Avinza.

Purdue Distributed an OxyContin Video without FDA's Review That Appears to Have Made Unsubstantiated Claims and Minimized Risks

Beginning in 1998, Purdue, as part of its marketing and promotion of OxyContin, distributed 15,000 copies of an OxyContin video to physicians without submitting it to FDA for review. This video, entitled *I Got My Life Back: Patients in Pain Tell Their Story*, presented the pain relief experiences of various patients and the pain medications, including OxyContin, they had been prescribed. FDA regulations require pharmaceutical manufacturers to submit all promotional materials for approved prescription drug products to the agency at the time of their initial use. Because Purdue did not comply with this regulation, FDA did not have an opportunity to review the video to ensure that the information it contained was truthful, balanced, and accurately communicated. Purdue has acknowledged the oversight of not submitting the video to FDA for

⁴¹Zeneca Pharmaceuticals promoted Kadian for Faulding Laboratories, the drug's manufacturer at that time.

review. In February 2001, Purdue submitted a second version of the video to FDA, which included information about the 160-milligram OxyContin tablet. FDA did not review this second version until October 2002, after we inquired about its content. FDA told us it found that the second version of the video appeared to make unsubstantiated claims regarding OxyContin's effect on patients' quality of life and ability to perform daily activities and minimized the risks associated with the drug.

The 1998 video used a physician spokesperson to describe patients with different pain syndromes and the limitations that each patient faced in his or her daily activities. Each patient's pain treatment was discussed, along with the dose amounts and brand names of the prescription drugs, including OxyContin, that either had been prescribed in the past or were being prescribed at that time. The physician in the videos also stated that opioid analgesics have been shown to cause addiction in less than 1 percent of patients—a fact that FDA has stated has not been substantiated. At the end of the video, the OxyContin label was scrolled for the viewer.

In 2000, Purdue submitted another promotional video to FDA entitled *I Got My Life Back: A Two Year Follow up of Patients in Pain*, and it submitted a second version of this video in 2001, which also included information on the 160-milligram OxyContin tablet. Purdue distributed 12,000 copies of these videos to physicians. Both versions scrolled the OxyContin label at the end of the videos. FDA stated that it did not review either of these videos for enforcement purposes because of limited resources. Distribution of all four Purdue videos was discontinued by July 2001, in response to OxyContin's labeling changes, which required the company to modify all of its promotional materials, but copies of the videos that had already been distributed were not retrieved and destroyed.

FDA said that it receives numerous marketing and promotional materials for promoted prescription drugs and that while every effort is made to review the materials, it cannot guarantee that all materials are reviewed because of limited resources and competing priorities. FDA officials also stated that pharmaceutical companies do not always submit promotional materials as required by regulations and that in such instances FDA would not have a record of the promotional pieces.

Several Factors May Have Contributed to OxyContin Abuse and Diversion, but Relationship to Availability Cannot Be Assessed

There are several factors that may have contributed to the abuse and diversion of OxyContin. OxyContin's formulation as a controlled-release opioid that is twice as potent as morphine may have made it an attractive target for abuse and diversion. In addition, the original label's safety warning advising patients not to crush the tablets because of the possible rapid release of a potentially toxic amount of oxycodone may have inadvertently alerted abusers to possible methods for misuse. Further, the rapid growth in OxyContin sales increased the drug's availability in the marketplace and may have contributed to opportunities to obtain the drug illicitly. The history of abuse and diversion of prescription drugs in some geographic areas, such as those within the Appalachian region, may have predisposed some states to problems with OxyContin. However, we could not assess the relationship between the growth in OxyContin prescriptions or increased availability with the drug's abuse and diversion because the data on abuse and diversion are not reliable, comprehensive, or timely.

OxyContin's Formulation May Have Made It an Inviting Drug for Abuse and Diversion

While OxyContin's potency and controlled-release feature may have made the drug beneficial for the relief of moderate-to-severe pain over an extended period of time, DEA has stated that those attributes of its formulation have also made it an attractive target for abuse and diversion. According to recent studies, oxycodone, the active ingredient in OxyContin, is twice as potent as morphine.⁴² In addition, OxyContin's controlled-release feature allows a tablet to contain more active ingredient than other, non-controlled-release oxycodone-containing drugs.

One factor that may have contributed to the abuse and diversion of OxyContin was FDA's original decision to label the drug as having less abuse potential than other oxycodone products because of its controlled-release formulation. FDA officials said when OxyContin was approved the agency believed that the controlled-release formulation would result in less abuse potential because, when taken properly, the drug would be absorbed slowly, without an immediate rush or high. FDA officials acknowledged that the initial wording of OxyContin's label was "unfortunate" but was based on what was known about the product at that time.

⁴²See, for example, G.B. Curtis, et al. "Relative Potency of Controlled-Release Oxycodone and Morphine in a Postoperative Pain Model," *European Journal of Clinical Pharmacology*, vol. 55, no. 6 (1999): 55:425-429.

FDA officials told us that abusers typically seek a drug that is intense and fast-acting. When OxyContin was approved, FDA did not recognize that if the drug is dissolved in water and injected its controlled-release characteristics could be disrupted, creating an immediate rush or high and thereby increasing the potential for misuse and abuse. DEA officials told us that OxyContin became a target for abusers and diverters because the tablet contained larger amounts of active ingredient and the controlled-release formulation was easy for abusers to compromise.

The safety warning on the OxyContin label may also have contributed to the drug's potential for abuse and diversion, by inadvertently providing abusers with information on how the drug could be misused. The label included the warning that the tablets should not be broken, chewed, or crushed because such action could result in the rapid release and absorption of a potentially toxic dose of oxycodone. FDA places similar safety warnings on other drugs to ensure that they are used properly. FDA officials stated that neither they nor other experts anticipated that crushing the controlled-release tablet and intravenously injecting or snorting the drug would become widespread and lead to a high level of abuse.

OxyContin's Wide Availability May Have Increased Opportunities for Illicit Use

The large amount of OxyContin available in the marketplace may have increased opportunities for abuse and diversion. Both DEA and Purdue have stated that an increase in a drug's availability in the marketplace may be a factor that attracts interest by those who abuse and divert drugs. Following its market introduction in 1996, OxyContin sales and prescriptions grew rapidly through 2002. In 2001 and 2002 combined, sales of OxyContin approached \$3 billion, and over 14 million prescriptions for the drug were dispensed. (See table 2.) OxyContin also became the top-selling brand-name narcotic pain reliever in 2001 and was ranked 15th on a list of the nation's top 50 prescription drugs by retail sales.⁴³

⁴³This information is from the National Institute for Health Care Management's Prescription Drug Expenditures reports for 2000 and 2001, prepared using American Institutes for Research analysis of Scott-Levin Prescription Audit Data. OxyContin was ranked 18th in 2000.

Table 2: Total OxyContin Sales and Prescriptions for 1996 through 2002 with Percentage Increases from Year to Year

Year	Sales	Percentage increase	Number of prescriptions	Percentage increase
1996	\$44,790,000	N/A	316,786	N/A
1997	125,464,000	180	924,375	192
1998	286,486,000	128	1,910,944	107
1999	555,239,000	94	3,504,827	83
2000	981,643,000	77	5,932,981	69
2001	1,354,717,000	38	7,183,327	21
2002	1,536,816,000	13	7,234,204	7

Sources: Purdue and IMS Health.

Legend: N/A = not applicable.

Note: GAO analysis of OxyContin sales and prescription data from Purdue and IMS Health, which includes data from all 50 states and the District of Columbia. Sales include combined retail and nonretail sales in drugstores, hospitals, and long-term-care facilities from the IMS Health U.S. National Sales database. Prescriptions include retail pharmacy, long-term-care, and mail-order prescriptions from IMS Health's National Prescriptions Audit.

History of Prescription Drug Abuse in Some States May Have Predisposed Them to Problems with OxyContin

According to DEA, the abuse and diversion of OxyContin in some states may have reflected the geographic area's history of prescription drug abuse. The White House Office of National Drug Control Policy (ONDCP) designates geographic areas with illegal drug trade activities for allocation of federal resources to link local, state, and federal drug investigation and enforcement efforts. These areas, known as High-Intensity Drug Trafficking Areas (HIDTA), are designated by ONDCP in consultation with the Attorney General, the Secretary of the Treasury, heads of drug control agencies, and governors in the states involved.⁴⁴

According to a 2001 HIDTA report,⁴⁵ the Appalachian region, which encompasses parts of Kentucky, Tennessee, Virginia, and West Virginia,

⁴⁴In making a designation, ONDCP considers whether the geographic area is a center of drug production, manufacturing, importation, or distribution; whether state and local law enforcement agencies have committed resources to respond aggressively to the drug trafficking problem; whether drug activities in the area are having a harmful impact on other areas of the country; and whether a significant increase in federal resources is necessary to respond to the area's drug-related activities.

⁴⁵Appalachia High Intensity Drug Trafficking Area Task Force, *The OxyContin Threat in Appalachia* (London, Ky.: August 2001).

has been severely affected by prescription drug abuse, particularly pain relievers, including oxycodone, for many years. Three of the four states—Kentucky, Virginia, and West Virginia—were among the initial states to report OxyContin abuse and diversion. Historically, oxycodone, manufactured under brand names such as Percocet, Percodan, and Tylox, was among the most diverted prescription drugs in Appalachia. According to the report, OxyContin has become the drug of choice of abusers in several areas within the region. The report indicates that many areas of the Appalachian region are rural and poverty-stricken, and the profit potential resulting from the illicit sale of OxyContin may have contributed to its diversion and abuse. In some parts of Kentucky, a 20-milligram OxyContin tablet, which can be purchased by legitimate patients for about \$2, can be sold illicitly for as much as \$25. The potential to supplement their incomes can lure legitimate patients into selling some of their OxyContin to street dealers, according to the HIDTA report.

Limitations on Abuse and Diversion Data Prevent Assessment of the Relationship with OxyContin's Availability

The databases DEA uses to track the abuse and diversion of controlled substances all have limitations that prevent an assessment of the relationship between the availability of OxyContin and areas where the drug is being abused or diverted. Specifically, these databases, which generally do not provide information on specific brand-name drugs such as OxyContin, are based on data gathered from limited sources in specific geographic areas and have a significant time lag. As a result, they do not provide reliable, complete, or timely information that could be used to identify abuse and diversion of a specific drug.

DEA officials told us that it is difficult to obtain reliable data on what controlled substances are being abused by individuals and diverted from pharmacies because available drug abuse and diversion tracking systems do not capture data on a specific brand-name product or indicate where a drug product is being abused and diverted on a state and local level. Because of the time lags in reporting information, the data reflect a delayed response to any emerging drug abuse and diversion problem. For example, the Drug Abuse Warning Network (DAWN) estimates national drug-related emergency department visits or deaths involving abused drugs using data collected by the Substance Abuse and Mental Health Services Administration (SAMHSA). The data are collected from hospital emergency departments in 21 metropolitan areas that have agreed to voluntarily report drug-abuse-related information from a sample of patient

medical records, and from medical examiners in 42 metropolitan areas.⁴⁶ However, DAWN cannot make estimates for rural areas, where initial OxyContin abuse and diversion problems were reported to be most prevalent, nor does it usually provide drug-product-specific information, and its data have a lag time of about 1 year. DEA stated that development of enhanced data collection systems is needed to provide “credible, legally defensible evidence concerning drug abuse trends in America.”⁴⁷

DEA relies primarily on reports from its field offices to determine where abuse and diversion are occurring. DEA officials stated that the initial areas that experienced OxyContin abuse and diversion problems included rural areas within 8 states—Alaska, Kentucky, Maine, Maryland, Ohio, Pennsylvania, Virginia, and West Virginia. In July 2002, DEA told us that it learned that OxyContin abuse and diversion problems had spread into larger areas of the initial 8 states, as well as parts of 15 other states, to involve almost half of the 50 states.⁴⁸ According to DEA officials, while DEA field offices continue to report OxyContin as a drug of choice among abusers, OxyContin has not been and is not now considered the most highly abused and diverted prescription drug nationally.⁴⁹ OxyContin is the most abused single-entity prescription product according to those DEA state and divisional offices that report OxyContin abuse.

⁴⁶The reliability of the data collected depends on whether the emergency room patient visit was reported as drug related, whether the patient reported taking a particular drug, and whether the emergency room physician indicated a drug's brand name in the patient's medical record.

⁴⁷See app. III for more details on the abuse and diversion databases DEA uses.

⁴⁸The 15 states are Alabama, Arizona, Colorado, Connecticut, Florida, Louisiana, Massachusetts, Mississippi, Missouri, New Jersey, North Carolina, South Carolina, Texas, Washington, and Wisconsin.

⁴⁹Hydrocodone products, such as Anexsia, Hycodan, Lorcet, Lortab, and Vicodin, remain among the most abused and diverted scheduled prescription drugs nationally.

Federal and State Agencies and Purdue Have Taken Actions to Prevent Abuse and Diversion of OxyContin

Since becoming aware of reports of abuse and diversion of OxyContin, federal and state agencies and Purdue have taken actions intended to address these problems. To protect the public health, FDA has strengthened OxyContin label warnings and requested that Purdue develop and implement an OxyContin risk management plan. In addition, DEA has stepped up law enforcement actions to prevent abuse and diversion of OxyContin. State Medicaid fraud control units have also attempted to identify those involved in the abuse and diversion of OxyContin. Purdue has initiated drug abuse and diversion education programs, taken disciplinary actions against sales representatives who improperly promote OxyContin, and referred physicians who were suspected of improperly prescribing OxyContin to the appropriate authorities. However, until fall 2002 Purdue did not analyze its comprehensive physician prescribing reports, which it routinely uses in marketing and promoting OxyContin, and other indicators to identify possible physician abuse and diversion.

Reports of Abuse and Diversion Led to Label Changes and Other Actions by FDA

Reports of abuse and diversion of OxyContin that were associated with an increasing incidence of addiction, overdose, and death prompted FDA to revise the drug's label and take other actions to protect the public health. In July 2001, FDA reevaluated OxyContin's label and made several changes in an effort to strengthen the "Warnings" section of the label. FDA added a subsection—"Misuse, Abuse, and Diversion of Opioids"—to stress that physicians and pharmacists should be alert to the risk of misuse, abuse, and diversion when prescribing or dispensing OxyContin. FDA also added a black box warning—the highest level of warning FDA can place on an approved drug product. FDA highlighted the language from the original 1995 label—stating that OxyContin is a schedule II controlled substance with an abuse liability similar to morphine—by moving it into the black box. Also, while the original label suggested that taking broken, chewed, or crushed OxyContin tablets "could lead to the rapid release and absorption of a potentially toxic dose of oxycodone," a more strongly worded warning in the black box stated that taking the drug in this manner "*leads to* rapid release and absorption of a potentially *fatal* dose of oxycodone" (emphasis added). (See table 3.) In addition to the black box warning, FDA also changed the language in the original label that described the incidence of addiction inadvertently induced by physician prescribing as rare if opioids are legitimately used in the management of pain. The revised label stated that data are not available to "establish the true incidence of addiction in chronic patients."

Table 3: Selected Language Approved by FDA in Warning Sections of OxyContin Labels, 1995 and 2001

Warning label in 1995	Black box warning in 2001
<p>“Warning:</p> <p>OxyContin Tablets are to be swallowed whole, and are not to be broken, chewed, or crushed. Taking broken, chewed, or crushed OxyContin Tablets could lead to the rapid release and absorption of a potentially toxic dose of oxycodone.”</p>	<p>“Warning: OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.”</p> <p>“OxyContin Tablets are to be swallowed whole and are not to be broken, chewed, or crushed. Taking broken, chewed, or crushed OxyContin Tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone.” (emphasis added)</p>

Source: FDA-approved label for Purdue's OxyContin.

As mentioned earlier, the indication described in the original label was also revised to clarify the appropriate time period for which OxyContin should be prescribed for patients experiencing moderate-to-severe pain. The language in the 1995 label was changed from “where use of an opioid analgesic is appropriate for more than a few days” to “when a continuous, around-the-clock analgesic is needed for an extended period of time.” (See table 4.) A summary of changes made by FDA to the original OxyContin label is given in appendix II.

Table 4: Selected Language Approved by FDA in the Indication Sections of OxyContin Labels, 1995 and 2001

Indication in 1995	Black box indication change in 2001
<p>“OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate-to-severe pain where use of an opioid analgesic is appropriate for more than a few days.”</p>	<p>“OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate-to-severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.” (emphasis added)</p>

Source: FDA-approved label for Purdue's OxyContin.

Beginning in early 2001, FDA collaborated with Purdue to develop and implement a risk management plan to help identify and prevent abuse and diversion of OxyContin. As a part of the risk management plan in connection with the labeling changes, Purdue was asked by FDA to revise all of its promotional materials for OxyContin to reflect the labeling

changes. In August 2001, FDA sent a letter to Purdue stating that all future promotional materials for OxyContin should prominently disclose the information contained in the boxed warning; the new warnings that address misuse, abuse, diversion, and addiction; and the new precautions and revised indication for OxyContin. Purdue agreed to comply with this request.

FDA officials told us that it is standard procedure to contact a drug manufacturer when the agency becomes aware of reports of abuse and diversion of a drug product so that FDA and the drug manufacturer can tailor a specific response to the problem. While FDA's experience with risk management plans is relatively new, agency officials told us that OxyContin provided the opportunity to explore the use of the plans to help identify abuse and diversion problems. FDA is currently making decisions about whether risk management plans will be requested for selected opioid products. Also, in September 2003, FDA's Anesthetic and Life Support Drugs Advisory Committee held a public hearing to discuss its current review of proposed risk management plans for opioid analgesic drug products to develop strategies for providing patients with access to pain treatment while limiting the abuse and diversion of these products.

FDA has also taken other actions to address the abuse and diversion of OxyContin. It put information on its Web site for patients regarding the appropriate use of OxyContin.⁵⁰ FDA worked with Purdue to develop "Dear Health Care Professional" letters, which the company distributed widely to health care professionals to alert them that the package insert had been revised to clarify the indication and strengthen the warnings related to misuse, abuse, and diversion. FDA also has worked with DEA, SAMHSA, the National Institute on Drug Abuse, ONDCP, and the Centers for Disease Control and Prevention to share information and insights on the problem of abuse and diversion of OxyContin.

DEA Developed an Action Plan to Deter OxyContin Abuse and Diversion

In April 2001, DEA developed a national action plan to deter abuse and diversion of OxyContin. According to DEA officials, this marked the first time the agency had targeted a specific brand-name product for monitoring because of the level and frequency of abuse and diversion associated with the drug. Key components of the action plan include coordinating enforcement and intelligence operations with other law

⁵⁰See www.fda.gov/cder/drug/infopage/oxycontin/default.htm.

enforcement agencies to target people and organizations involved in abuse and diversion of OxyContin, pursuing regulatory and administrative action to limit abusers' access to OxyContin, and building national outreach efforts to educate the public on the dangers related to the abuse and diversion of OxyContin. DEA has also set Purdue's procurement quota for oxycodone at levels lower than the levels requested by Purdue.

DEA has increased enforcement efforts to prevent abuse and diversion of OxyContin. From fiscal year 1996 through fiscal year 2002, DEA initiated 313 investigations involving OxyContin, resulting in 401 arrests. Most of the investigations and arrests occurred after the initiation of the action plan. Since the plan was enacted, DEA initiated 257 investigations and made 302 arrests in fiscal years 2001 and 2002. Among those arrested were several physicians and pharmacists. Fifteen health care professionals either voluntarily surrendered their controlled substance registrations or were immediately suspended from registration by DEA. In addition, DEA reported that \$1,077,500 in fines was assessed and \$742,678 in cash was seized by law enforcement agencies in OxyContin-related cases in 2001 and 2002.

Among several regulatory and administrative actions taken to limit abusers' access to OxyContin and controlled substances, DEA's Office of Diversion Control, in collaboration with the Department of Justice's Office of Justice Programs, Bureau of Justice Assistance, provides grants to states for the establishment of prescription drug monitoring programs. The conference committee report for the fiscal year 2002 appropriation to the Department of Justice directed the Office of Justice Programs to make a \$2 million grant in support of the Harold Rogers Prescription Drug Monitoring Program, which enhances the capacity of regulatory and law enforcement agencies to collect and analyze controlled substance prescription data. The program provided grants to establish new monitoring programs in Ohio, Pennsylvania, Virginia, and West Virginia. California, Kentucky, Massachusetts, Nevada, and Utah also received grants to enhance existing monitoring programs.

DEA has also attempted to raise national awareness of the dangers associated with abuse and diversion of OxyContin. In October 2001 DEA joined 21 national pain and health organizations in issuing a consensus statement calling for a balanced policy on prescription medication use. According to the statement, such a policy would acknowledge that health care professionals and DEA share responsibility for ensuring that prescription medications, such as OxyContin, are available to patients who need them and for preventing these drugs from becoming a source of

abuse and diversion. DEA and the health organizations also called for a renewed focus on educating health professionals, law enforcement, and the public about the appropriate use of opioid pain medications in order to promote responsible prescribing and limit instances of abuse and diversion. DEA is also working with FDA to encourage state medical boards to require, as a condition of their state licensing, that physicians obtain continuing medical education on pain management.

When OxyContin was first introduced to the market in 1996, DEA granted Purdue's initial procurement quota request for oxycodone. According to DEA, increases in the quota were granted for the first several years. Subsequently, concern over the dramatic increases in sales caused DEA to request additional information to support Purdue's requests to increase the quota. In the last several years, DEA has taken the additional step of lowering the procurement quota requested by Purdue for the manufacture of OxyContin as a means for addressing abuse and diversion. However, DEA has cited the difficulty of determining an appropriate level while ensuring that adequate quantities were available for legitimate medical use, as there are no direct measures available to establish legitimate medical need.

State Agencies Have Responded to Reports of OxyContin Abuse and Diversion

State Medicaid fraud control units and medical licensure boards have taken action in response to reports of abuse and diversion of OxyContin. State Medicaid fraud control units have conducted investigations of abuse and diversion of OxyContin, but generally do not maintain precise data on the number of investigations and enforcement actions completed.

Although complete information was not available from directors of state Medicaid fraud control units in Kentucky, Maryland, Pennsylvania, Virginia, and West Virginia with whom we spoke, each of those directors told us that abuse and diversion of OxyContin is a problem in his or her state. The directors told us that they had investigated cases that involved physicians or individuals who had either been indicted or prosecuted for writing medically unnecessary OxyContin prescriptions in exchange for cash or sexual relationships.

State medical licensure boards have also responded to complaints about physicians who were suspected of abuse and diversion of controlled substances, but like the Medicaid fraud control units, the boards generally do not maintain data on the number of investigations that involved OxyContin. Representatives of state boards of medicine in Kentucky, Pennsylvania, Virginia, and West Virginia told us that they have received complaints from various sources, such as government agencies, health

care professionals, and anonymous tipsters, about physicians suspected of abuse and diversion of controlled substances. However, each of the four representatives stated that his or her board does not track the complaints by specific drug type and consequently cannot determine whether the complaints received allege physicians' misuse of OxyContin. Each of the four representatives also told us that his or her medical licensure board has adopted or strengthened guidelines or regulations for physicians on prescribing, administering, and dispensing controlled substances in the treatment of chronic pain. For example, in March 2001, the Kentucky Board of Medical Licensure adopted guidelines to clarify the board's position on the use of controlled substances for nonterminal/nonmalignant chronic pain.⁵¹ The boards of medicine in Pennsylvania, Virginia, and West Virginia each have guidelines for the appropriate use of controlled substances that are similar to those adopted by Kentucky.

Purdue Is Implementing a Risk Management Plan for OxyContin

In response to concerns about abuse and diversion of OxyContin, in April 2001 FDA and Purdue began to discuss the development of a risk management plan to help detect and prevent abuse and diversion of OxyContin. Purdue submitted its risk management plan to FDA for review in August 2001.⁵² The plan includes some actions that Purdue proposed to take, as well as others that it has already taken. Purdue's risk management plan includes actions such as strengthening the safety warnings on OxyContin's label for professionals and patients, training Purdue's sales force on the revised label, conducting comprehensive education programs for health care professionals, and developing a database for identifying and monitoring abuse and diversion of OxyContin.

Under the risk management plan, OxyContin's label was strengthened, effective in July 2001, by revising the physician prescribing information and adding a black box warning to call attention to OxyContin's potential

⁵¹The Kentucky guidelines for the use of controlled substances in pain treatment provide that (1) a complete medical history and examination be conducted and documented in patient medical records, (2) a written treatment plan state objectives for determining treatment success, (3) the risks and benefits of the use of controlled substances be discussed by physician and patient, (4) periodic review of the course of treatment be conducted, (5) consultation or referral to an expert in pain management be considered for patients who are at risk for substance abuse, (6) patient's medical record be kept accurate and complete, and (7) physicians be in compliance with applicable federal and state controlled substance laws and regulations.

⁵²Amended versions of Purdue's risk management plan for OxyContin were submitted to FDA for review in April 2002 and in March 2003.

for misuse, abuse, and diversion. (See app. II.) Purdue trained its sales force on the specifics of the revised label and provided sales representatives with updated information on the appropriate use of opioid analgesics, legal guidelines associated with promotion of its products, and their responsibility and role in reporting adverse events. Purdue also reiterated to its sales representatives that failure to promote products according to the approved label, promotional materials, and applicable FDA standards would result in disciplinary action by the company. According to Purdue, from April 2001 through May 2003 at least 10 Purdue employees were disciplined for using unapproved materials in promoting OxyContin. Disciplinary actions included warning letters, suspension without pay, and termination.

Purdue also has provided education programs for health care professionals and the public under its risk management plan. For example, in 2001 Purdue supported seminars that examined ways health care professionals can help prevent abuse and diversion of opioids. Purdue worked with DEA and other law enforcement agencies to develop and implement antidi diversion educational programs. In 2002, Purdue also launched the Web site painfullyobvious.com to educate teenagers, parents, law enforcement officers, and discussion leaders about the dangers of prescription drug abuse.

Because reliable data on the abuse and diversion of controlled substance drugs are not available, Purdue developed the Research Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System, as part of its risk management plan, to study the nature and extent of abuse of OxyContin and other schedule II and III prescription medications and to implement interventions to reduce abuse and diversion.⁵³ According to Purdue, RADARS collects and computes abuse, diversion, and addiction rates for certain drugs based on population and determines national and local trends.

Since the launch of OxyContin, Purdue has provided its sales force with considerable information to help target physicians and prioritize sales contacts within a sales territory. Sales representatives routinely receive daily, weekly, monthly, and quarterly physician prescribing reports based

⁵³RADARS will collect information on brand-name and generic versions of buprenorphine, fentanyl, hydrocodone, hydromorphone, oxycodone, morphine, and methadone. Benzodiazepine is scheduled to be added to RADARS in late 2003.

on IMS Health data that specify the physicians who have written prescriptions for OxyContin and other opioid analgesics, and the number of prescriptions written. Although this information has always been available for use by Purdue and its sales representatives, it was not until fall 2002 that Purdue directed its sales representatives to begin using 11 indicators to identify possible abuse and diversion and to report the incidents to Purdue's General Counsel's Office for investigation. Among the possible indicators are a sudden unexplained change in a physician's prescribing patterns that is not accounted for by changes in patient numbers, information from credible sources such as a pharmacist that a physician or his or her patients are diverting medications, or a physician who writes a large number of prescriptions for patients who pay with cash. As of September 2003, Purdue—through its own investigations—had identified 39 physicians and other health care professionals who were referred to legal, medical, or regulatory authorities for further action. Most of the 39 referrals stemmed from reports by Purdue's sales force.

Other actions included in the plan that were taken by Purdue prior to submission of its risk management plan include discontinuance of the 160-milligram tablet of OxyContin to reduce the risk of overdose from this dosage strength, the development of unique markings for OxyContin tablets intended for distribution in Mexico and Canada to assist law enforcement in identifying OxyContin illegally smuggled into the United States, and the distribution of free tamper-resistant prescription pads designed to prevent altering or copying of the prescription. Purdue also implemented a program in 2001 to attempt to predict "hot spots" where OxyContin abuse and diversion were likely to occur, but discontinued the program in 2002 when Purdue concluded that nearly two-thirds of the counties identified had no abuse and diversion.

Conclusions

At present, both federal agencies and the states have responsibilities involving prescription drugs and their abuse and diversion. FDA is responsible for approving new drugs and ensuring that the materials drug companies use to market and promote these drugs are truthful, balanced, and accurate. However, FDA examines these promotional materials only after they have been used in the marketplace because the FD&C Act generally does not give FDA authority to review these materials before the drug companies use them. Moreover, the FD&C Act provisions governing drug approval and promotional materials make no distinction between controlled substances, such as OxyContin, and other prescription drugs. DEA is responsible for registering handlers of controlled substances, approving production quotas and monitoring distribution of controlled

substances to the retail level. It is the states, however, that are responsible for overseeing the practice of medicine and pharmacy where drugs are prescribed and dispensed. Some states have established prescription drug monitoring programs to help them detect and deter abuse and diversion. However, these programs exist in only 15 states and most do not proactively analyze prescription data to identify individuals, physicians, or pharmacies that have unusual use, prescribing, or dispensing patterns that may suggest potential drug diversion or abuse.

The significant growth in the use of OxyContin to treat patients suffering from chronic pain has been accompanied by widespread reports of abuse and diversion that have in some cases led to deaths. The problem of abuse and diversion has highlighted shortcomings at the time of approval in the labeling of schedule II controlled substances, such as OxyContin, and in the plans in place to detect misuse, as well as in the infrastructure for detecting and preventing the abuse and diversion of schedule II controlled substances already on the market.

Addressing abuse and diversion problems requires the collaborative efforts of pharmaceutical manufacturers; the federal and state agencies that oversee the approval and use of prescription drugs, particularly controlled substances; the health care providers who prescribe and dispense them; and law enforcement. After the problems with OxyContin began to surface, FDA and Purdue collaborated on a risk management plan to help detect and prevent abuse and diversion. Although risk management plans were not in use when OxyContin was approved, they are now an optional feature of new drug applications. FDA plans to complete its guidance to the pharmaceutical industry on risk management plans by September 30, 2004. The development of this guidance, coupled with FDA's current review of proposed risk management plans for modified-release opioid analgesics, provides an opportunity to help ensure that manufacturers include a strategy to monitor the use of these drugs and to identify potential problems with abuse and diversion.

Recommendation for Executive Action

To improve efforts to prevent or identify the abuse and diversion of schedule II controlled substances, we recommend that the Commissioner of Food and Drugs ensure that FDA's risk management plan guidance encourages pharmaceutical manufacturers that submit new drug applications for these substances to include plans that contain a strategy for monitoring the use of these drugs and identifying potential abuse and diversion problems.

Agency and Purdue Comments and Our Evaluation

We provided a draft of this report to FDA, DEA, and Purdue, the manufacturer of OxyContin, for their review. FDA and DEA provided written comments. (See apps. IV and V.) Purdue's representatives provided oral comments.

FDA said that it agreed with our recommendation that its risk management plan guidance should encourage all pharmaceutical manufacturers submitting new drug applications for schedule II controlled substances to include strategies to address abuse and diversion concerns. FDA stated that the agency is working on the risk management plan guidance. FDA also noted that the FD&C Act makes no distinction between controlled substances and other prescription drugs in its provisions regulating promotion, but that as a matter of general policy, the agency more closely scrutinizes promotion of drugs with more serious risk profiles. However, FDA does not have written guidance that specifies that promotional materials for controlled substances receive priority or special attention over similar materials for other prescription drugs. Furthermore, our finding that FDA did not review any of the OxyContin promotional videos provided by Purdue until we brought them to the agency's attention raises questions about whether FDA provides extra attention to promotional materials for controlled substances that by definition have a high potential for abuse and may lead to severe psychological or physical dependence. FDA recommended that we clarify our description of the content of the warning letter issued to Purdue and provide additional information describing the extent of the corrective action taken by Purdue. FDA also recommended noting in the report that part of the risk management plan in connection with the 2001 labeling changes was a requirement that all OxyContin promotional materials be revised to reflect the labeling changes and all future materials prominently disclose this information. Finally, FDA noted that the promotional videos discussed in the report were submitted by Purdue prior to the labeling change and discontinued as a result of the labeling change. As we note in the report, Purdue acknowledged that all the promotional videos were not submitted to FDA at the time they were distributed. Moreover, although Purdue told us that these videos were no longer distributed after the label change, those videos that had been distributed were not collected and destroyed. We revised the report to reflect FDA's general comments. FDA also provided technical comments that we incorporated where appropriate.

In its written comments, DEA agreed that the data on abuse and diversion are not reliable, comprehensive, or timely, as we reported. DEA reiterated its previous statement that Purdue's aggressive marketing of OxyContin fueled demand for the drug and exacerbated the drug's abuse and

diversion. DEA also stated that Purdue minimized the abuse risk associated with OxyContin. We agree with DEA that Purdue conducted an extensive campaign to market and promote OxyContin using an expanded sales force and multiple promotional approaches to encourage physicians, including primary care specialists, to prescribe OxyContin as an initial opioid treatment for noncancer pain, and that these efforts may have contributed to the problems with abuse and diversion by increasing the availability of the drug in the marketplace. However, we also noted that other factors may have contributed to these problems. We also agree that Purdue marketed OxyContin as having a low abuse liability, but we noted that this was based on information in the original label approved by FDA. DEA also acknowledged that the lack of a real measure of legitimate medical need for a specific product (OxyContin), substance (oxycodone), or even a class of substances (controlled release opioid analgesics) makes it difficult to limit manufacturing as a means of deterring abuse and diversion. DEA also noted that it is essential that risk management plans be put in place prior to the introduction of controlled substances into the marketplace, consistent with our recommendation. We revised the report to provide some additional detail on problems associated with OxyContin and Purdue's marketing efforts. DEA provided some technical comments on the draft report that we incorporated where appropriate.

Purdue representatives provided oral comments on a draft of this report. In general, they thought the report was fair and balanced; however, they offered both general and technical comments. Specifically, Purdue stated that the report should add the media as a factor contributing to the abuse and diversion of OxyContin because media stories provided the public with information on how to "get high" from using OxyContin incorrectly. Our report notes that the safety warning on the original label may have inadvertently alerted abusers to a possible method for misusing the drug. However, we note that the original label was publicly available from FDA once OxyContin was approved for marketing. Purdue also suggested that we include Duragesic, also a schedule II opioid analgesic, as a fourth comparable drug to OxyContin. The three comparable drugs we used in the report were chosen in consultation with FDA as comparable opioid analgesics to OxyContin, because they were time-released, morphine-based schedule II drugs formulated as tablets like OxyContin. In contrast, Duragesic, which contains the opioid analgesic fentanyl and provides pain relief over a 72-hour period, is formulated as a skin patch to be worn rather than as a tablet. Purdue representatives also provided technical comments that were incorporated where appropriate.

We also provided sections of this draft report to the manufacturers of three comparative drugs we examined. Two of the three companies with a drug product used as a comparable drug to OxyContin reviewed the portions of the draft report concerning their own product, and provided technical comments, which were incorporated where appropriate. The third company did not respond to our request for comments.

As agreed with your offices, unless you publicly announce this report's contents earlier, we plan no further distribution until 30 days after its issue date. At that time, we will send copies of this report to the Commissioner of Food and Drugs, the Administrator of the Drug Enforcement Administration, Purdue, and the other pharmaceutical companies whose drugs we examined. We will also make copies available to others upon request. In addition, the report will be available at no charge on the GAO Web site at <http://www.gao.gov>.

If you or your staffs have any questions about this report, please call me at (202) 512-7119 or John Hansen at (202) 512-7105. Major contributors to this report were George Bogart, Darryl Joyce, Roseanne Price, and Opal Winebrenner.



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Appendix I: Scope and Methodology

To identify the strategies and approaches used by Purdue Pharma L.P. (Purdue) to market and promote OxyContin, we interviewed Purdue officials and analyzed company documents and data. Specifically, we interviewed Purdue officials concerning its marketing and promotional strategies for OxyContin, including its targeting of physicians with specific specialties and its sales compensation plan to provide sales representatives with incentives for the drug's sales. We also interviewed selected Purdue sales representatives who had high and midrange sales during 2001 from Kentucky, Pennsylvania, Virginia, and West Virginia—four states that were initially identified by the Drug Enforcement Agency (DEA) as having a high incidence of OxyContin drug abuse and diversion—and from California, Massachusetts, and New Jersey—three states that DEA did not initially identify as having problems with OxyContin. We asked the sales representatives about their training, promotional strategies and activities, and targeting of physicians. We also interviewed physicians who were among the highest prescribers of OxyContin regarding their experiences with Purdue sales representatives, including the strategies used to promote OxyContin, as well as their experiences with sales representatives of manufacturers of other opioid analgesics. We reviewed Purdue's quarterly action plans for marketing and promoting OxyContin for 1996 through 2003, Purdue's sales representative training materials, and materials from ongoing OxyContin-related litigation. To obtain information on how Purdue's marketing and promotion of OxyContin compared to that of other companies, we identified, in consultation with the Food and Drug Administration (FDA), three opioid analgesics that were similar to OxyContin. The three drugs—Avinza, Kadian, and Oramorph SR—are all time-released, morphine-based analgesics that are classified as schedule II controlled substances. We examined the promotional materials each drug's manufacturer submitted to FDA and any actions FDA had taken against the manufacturers related to how the drugs were marketed or promoted. We also interviewed company officials about how they marketed and promoted their respective drugs. Because of their concerns about proprietary information, the three companies did not provide us with the same level of detail about their drugs' marketing and promotion as did Purdue.

To examine factors that contributed to the abuse and diversion of OxyContin, we reviewed DEA abuse and diversion data as part of an effort to compare them with DEA's OxyContin state distribution data and with IMS Health data on the rates of OxyContin sales and prescription dispensing to determine if they occurred in similar geographic areas. We also analyzed the distribution of Purdue sales representatives by state and compared them with the availability of OxyContin and abuse and diversion

Appendix I: Scope and Methodology

data to determine whether states with high rates of OxyContin sales and prescription dispensing and abuse and diversion problems had more sales representatives per capita than other states. However, limitations in the abuse and diversion data prevent an assessment of the relationship between the availability of OxyContin and areas where the drug was abused and diverted. We also reviewed the High Intensity Drug Trafficking Area (HIDTA) reports on states with histories of illegal drug activities. We interviewed DEA and FDA officials, physicians who prescribed OxyContin, officials from physician licensing boards in selected states, officials from national health practitioner groups, and company officials and sales representatives about why OxyContin abuse and diversion have occurred.

To determine the efforts federal and state agencies and Purdue have made to identify and prevent abuse and diversion of controlled substances such as OxyContin, we interviewed FDA officials and analyzed information from FDA regarding the marketing and promotion of controlled substances, specifically OxyContin; FDA's decision to approve the original label for OxyContin; and FDA's subsequent decision to revise OxyContin's labeling, as well as FDA's role in monitoring OxyContin's marketing and advertising activities. We also interviewed DEA officials about the agency's efforts to identify and prevent abuse and diversion, including its national action plan for OxyContin, and how it determines the prevalence of OxyContin abuse and diversion nationally. We also interviewed officials from national practitioner associations, Medicaid fraud control units, and physician licensing boards in states with initial reports of abuse and diversion—Kentucky, Maryland, Pennsylvania, Virginia, and West Virginia—regarding concerns they had about the abuse and diversion of OxyContin. We reviewed Purdue's OxyContin risk management plan submissions to FDA from 2001 through 2003 to identify actions taken by Purdue to address abuse and diversion of OxyContin.

Appendix II: Summary of FDA Changes to the Original Approved OxyContin Label

Table 5 provides a description of the changes made by FDA to sections of the original OxyContin approved label from June 1996 through July 2001. These changes included a black box warning, the strongest warning an FDA-approved drug can carry, and specifically addressed areas of concern related to the opioid characteristics of oxycodone and its risk of abuse and diversion.

Table 5: FDA Changes to the Original OxyContin Label Made from June 1996 through July 2001

Summary of FDA changes to original OxyContin label in 2001	Language in OxyContin label approved in 2001
Black box warning was added to stress the opioid nature of oxycodone and risks for abuse and diversion of the drug.	<p>"WARNING:</p> <p>OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.</p> <p>Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.</p> <p>OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.</p> <p>OxyContin Tablets are NOT intended for use as a prn analgesic. OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.</p> <p>OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE."</p>
Clinical pharmacology	"CLINICAL PHARMACOLOGY
<ul style="list-style-type: none"> —Provides a pharmacological description of oxycodone as a pure opioid agonist whose principal action is analgesia. —Identifies other members of the opioid agonist class, such as morphine, hydromorphone, fentanyl, and hydrocodone. —Describes the pharmacological properties of opioids in general (anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, cough suppression, and analgesia). —Describes respiratory depression as one of the most serious side effects of opioids that could lead to overdose or death. 	<p>Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, hydromorphone, fentanyl, codeine, and hydrocodone. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, as well as analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression."</p>

**Appendix II: Summary of FDA Changes to the
Original Approved OxyContin Label**

Summary of FDA changes to original OxyContin label in 2001	Language in OxyContin label approved in 2001
Misuse, abuse, and diversion of opioids <p>A subsection on misuse, abuse and diversion was added to the WARNINGS section of the label.</p> <p>—Characterizes oxycodone as an opioid agonist of the morphine-type and stresses that opioid agonists are sought by drug abusers and people with addiction disorders and are subject to diversion.</p> <p>—Makes clear that oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit, and that physicians and pharmacists should be aware of and alert to risk of misuse, abuse, and diversion when prescribing or dispensing oxycodone.</p> <p>—Modifies original label statement that iatrogenic addiction (addiction induced inadvertently by a physician or a physician's treatment) is rare if opioids were legitimately used in the management of pain to state that data are not available to establish the true incidence of addiction in chronic patients.</p>	"Misuse, Abuse and Diversion of Opioids <p>Oxycodone is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.</p> <p>Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.</p> <p>OxyContin has been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see WARNINGS and DRUG ABUSE AND ADDICTION).</p> <p>Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.</p> <p>Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse of this product."</p>

**Appendix II: Summary of FDA Changes to the
Original Approved OxyContin Label**

Summary of FDA changes to original OxyContin label in 2001	Language in OxyContin label approved in 2001
Drug abuse and addiction <ul style="list-style-type: none"> —Emphasizes that the abuse potential of oxycodone is equivalent to that of morphine. —Describes the controlled status of OxyContin and emphasizes that, like morphine and other opioids used in analgesia, oxycodone can be abused and is subject to criminal diversion. —Stresses proper prescribing practices, dispensing, and storage. —Deletes statement that delayed absorption of OxyContin was believed to reduce the abuse liability of the drug. —Stresses the risks associated with parenteral injection of OxyContin and reiterates the original label's description of drug addiction and "drug-seeking" behaviors commonly in addicts and abusers. 	<p>"DRUG ABUSE AND ADDICTION</p> <p>OxyContin is a mu-agonist with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.</p> <p>Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.</p> <p>"Drug-seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.</p> <p>Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. OxyContin, like other opioids, has been diverted for non-medical use. Careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.</p> <p>Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.</p> <p>OxyContin consists of a dual-polymer matrix, intended for oral use only. Abuse of the crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients, especially talc, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious disease such as hepatitis and HIV."</p>
Safety and handling <ul style="list-style-type: none"> —Emphasizes the controlled status of OxyContin. —Alerts health care professionals that OxyContin could be a target for theft and diversion and instructs that they should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of the product. 	<p>"SAFETY AND HANDLING</p> <p>OxyContin Tablets are solid dosage forms that contain oxycodone which is a controlled substance. Like morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act.</p> <p>OxyContin has been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product."</p>

Source: FDA-approved label for Purdue's OxyContin.

Appendix III: Databases Used to Monitor Abuse and Diversion of OxyContin and Its Active Ingredient Oxycodone

DEA uses several databases to monitor abuse and diversion of controlled substances, including OxyContin and its active ingredient oxycodone. Specifically, the agency monitors three major databases—the Drug Abuse Warning Network (DAWN), the National Forensic Laboratory Information System (NFLIS), and the System to Retrieve Information from Drug Evidence (STRIDE).¹ DEA also monitors other data sources to identify trends in OxyContin abuse and diversion, such as the Substance Abuse and Mental Health Services Administration's (SAMHSA) National Survey on Drug Use and Health, formerly the National Household Survey on Drug Abuse, and the Monitoring the Future Study funded by the National Institute on Drug Abuse.²

DAWN Data

SAMHSA operates the DAWN system, which estimates national drug-related emergency department visits and provides death counts involving abused drugs. DAWN collects data semiannually on drug abuse from hospital emergency department admission and medical examiner data from 21 metropolitan areas and a limited number of metropolitan medical examiners who agree to voluntarily report medical record samples. The emergency department and medical examiner data generally do not differentiate oxycodone from OxyContin, unless the individual provides the information to the hospital or identifiable tablets are found with the person. Although samples from hospitals outside the 21 metropolitan areas are also available, DAWN is not able to make drug-related emergency department visit or death estimates for rural or suburban areas.

NFLIS Data

NFLIS, a DEA-sponsored project initiated in 1997, collects the results of state and local forensic laboratories' analyses of drugs seized as evidence by law enforcement agencies. NFLIS is used to track drug abuse and trafficking involving both controlled and noncontrolled substances and reports results by a drug's substance, such as oxycodone, and not by its brand name. DEA stated that because new laboratories are being added,

¹Other databases used by DEA to assess changes in drug abuse and diversion include the Drug Early Warning System, the Drug and Alcohol Services Information System, the Treatment Episode Data Set, the National Survey of Substance Abuse Treatment Services, the Uniform Facility Data Set, the Poison Control Center Data or Toxic Exposure Surveillance System, the Automation of Reports and Consolidated Ordering System, the DEA Theft System, and the DEA Field Reports and Investigative Teletypes.

²The National Institute on Drug Abuse is part of the National Institutes of Health within the Department of Health and Human Services.

**Appendix III: Databases Used to Monitor
Abuse and Diversion of OxyContin and Its
Active Ingredient Oxycodone**

its data should not yet be used for trending purposes. As of March 2003, 35 state laboratories and 52 local or municipal laboratories participated in the project.

STRIDE Data

STRIDE, another DEA database, reports the results of chemical evidence analysis done by DEA laboratories in drug diversion and trafficking cases. Oxycodone data are reported by combining single and combination oxycodone drugs and do not provide specific enough information to distinguish OxyContin cases and exhibits. The database's lag time, which varies by laboratory, depends on how quickly the findings are entered after the seizure of the drug substance and its analysis.

National Survey on Drug Use and Health Data

The National Survey on Drug Use and Health, another SAMHSA database, is used to develop national and state estimates of trends in drug consumption.³ Prior to 2001, the self-reported survey asked participants if they had illicitly used any drug containing oxycodone. In 2001, the survey included a separate section for pain relievers, and asked participants if they had used OxyContin, identifying it by its brand name, that had not been prescribed for them. State samples from the survey are combined to make national- and state-level estimates of drug use, and because the estimated numbers derived for OxyContin are so small, it is not possible to project illicit OxyContin use on a regional, state, or county basis.

Monitoring the Future Survey Data

The Monitoring the Future Survey, funded by the National Institute on Drug Abuse and conducted by the University of Michigan, annually monitors the illicit use of drugs by adolescent students in the 8th, 10th, and 12th grades. The 2002 survey included new questions using the brand names of four drugs, including OxyContin, in its survey on the annual and 30-day prevalence of drug use.

³Self-reporting individuals are interviewed regarding their illicit drug use over three periods—within the last 30 days, during the past year, and during their lifetime. The survey data are limited, as it is not possible to determine specifically which year respondents may have used a drug illicitly, because they are asked both whether they have ever used the drug illicitly in their lifetime and whether they have used it during the past year.

Appendix IV: Comments from the Food and Drug Administration



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

November 6, 2003

Marcia Crosse
Director, Health Care-Public Health
and Military Health Care Issues
United States General Accounting Office
441 G Street, NW
Washington, DC 20548

Dear Ms. Crosse:

Please find the enclosed comments from the Food and Drug Administration on the GAO draft report entitled, PRESCRIPTION DRUGS: Factors That May Have Contributed to OxyContin Abuse and Diversion and Efforts to Address the Problem. (GAO-04-110). The Agency provided technical comments directly to your staff.

We appreciate the opportunity to review and comment on this draft report before its publication as well as the opportunity to work with your staff in developing this report.

Sincerely,

A handwritten signature in black ink, appearing to read "Mark B. McClellan".

Mark B. McClellan, M.D., Ph.D.
Commissioner of Food and Drugs

Enclosure

Appendix IV: Comments from the Food and Drug Administration

General Comments by the Department of Health and Human Service's Food and Drug Administration (FDA) on General Accounting Office's (GAO) Draft Report, PRESCRIPTION DRUGS: Factors That May Have Contributed to OxyContin Abuse and Diversion Efforts to Address the Problem (GAO-04-110)

FDA appreciates the opportunity to comment on GAO's draft report which focuses additional attention on the abuse and diversion of prescription drugs.

We have a few general comments regarding the overall report, as follows:

FDA's Regulation of Prescription Drugs

As currently written, GAO's draft report suggests that FDA decided as a matter of policy not to distinguish between types of drugs in regulating promotion. FDA believes it is important to clarify that the FD&C Act makes no distinction between controlled substances and other prescription drugs in its provisions regulating promotion, but that as a matter of general policy, the Agency more closely scrutinizes promotion of drugs with more serious risk profiles.

OxyContin Advertisements Violated the FD&C Act

FDA believes it is important to clarify the content of the warning letter issued to Purdue Pharma. In January 2003, FDA issued a warning letter to Purdue regarding two journal advertisements for OxyContin that minimized its risks and overstated its efficacy, by failing to present any information from the boxed warning on the potentially fatal risks associated with OxyContin and its abuse liability, along with omitting important information about the limitations on the indicated use of OxyContin. The FDA requested that Purdue cease disseminating these advertisements and any similar violative materials and provide a plan of corrective action.

We recommend that GAO include additional information describing the widespread dissemination of the corrective advertisement and the nature of its content, because we believe it gives important information on the extent to which complete and accurate information on OxyContin's risks and its limited indication was disseminated to healthcare providers this year resulting from the warning letter. This corrective advertisement ran for three months and appeared in approximately 30 medical journals. The three-paged advertisement, entitled "Important Correction of Drug Information," contained a two-paged spread, with a "Dear Healthcare Practitioner" letter on one side, which called attention to the warning letter and the cited violations, and directed the reader to the boxed warning and indication information for OxyContin prominently featured on the opposite side of the spread.

Reports of Abuse and Diversion Led to Label Changes and Other Actions by FDA

FDA recommends noting in the report that an important part of the risk management plan in connection with the 2001 labeling changes was that all OxyContin promotional materials be revised to reflect the labeling changes and all future promotional materials prominently disclose this information. As part of the risk management plan in connection with the labeling changes, Purdue was asked to revise all of its promotional materials for OxyContin to reflect the labeling changes. The FDA sent a letter to Purdue, dated August 3, 2001, stating that all future promotional materials for OxyContin should prominently disclose the information contained in the boxed warning, the new warnings that address misuse, abuse, diversion, and addiction, and the new precautions and revised indication for OxyContin. Purdue agreed to comply with this request in a letter dated August 7, 2001.

**Appendix IV: Comments from the Food and
Drug Administration**

- 2 -

We also believe it is important to clarify that all three of the patient videos discussed in the report were submitted prior to the labeling change and discontinued as a result of the labeling change and these communications. As the discussion of these patient videos is currently written in the report, it could be misinterpreted that two of the patient videos were submitted after the labeling change as part of Purdue's modification of its promotional materials.

Recommendation for Executive Action

"To improve efforts to prevent or identify the abuse and diversion of schedule II controlled substances, the Commissioner of Food and drugs should ensure that FDA's risk management plan guidance encourages pharmaceutical manufacturers that submit new drug applications for these substances to include plans that contain a strategy for monitoring the use of these drugs and identifying potential abuse and diversion problems."

FDA agrees with GAO's recommendation and is currently working on the guidance.

Appendix V: Comments from the Drug Enforcement Administration



U. S. Department of Justice
Drug Enforcement Administration

www.dea.gov

NOV 05 2003

Ms. Marcia Crosse, Director
Health Care-Public Health and
Military Health Care Issues
General Accounting Office
441 G Street, N.W.
Washington, D.C. 20548

Dear Ms. Crosse:

The Drug Enforcement Administration (DEA) submits the following comments on the facts and findings of the draft report, PRESCRIPTION DRUGS: *Factors that May Have Contributed to OxyContin Abuse and Diversion and Efforts to Address the Problem (GAO-04-110)*.

In general, the report is not as forthright as warranted on the causes/factors relating to the diversion of OxyContin. The root of the problem that this GAO report addresses appears to be the unfortunate convergence of Purdue's marketing techniques and the public/policy focus on pain undertreatment. The DEA has previously stated that the company's aggressive methods, calculated fueling of demand and the grasp for major market share very much exacerbated OxyContin's widespread abuse and diversion. While Purdue highlights its funding of pain-related educational programs and websites and its partnership with various organizations, the fact remains that Purdue's efforts—which may be viewed as self-serving public relations damage control—would not have been necessary had Purdue not initially marketed its product aggressively and excessively. Contributing to the abuse and diversion problem (and the product's excessive availability) is the fact that in promoting this drug to practitioners, Purdue deliberately minimized the abuse risk associated with OxyContin, as the report states on pages 21 and 35. The claim in Purdue's 'educational' video for physicians that opioid analgesics cause addiction in less than one percent of patients is not only unsubstantiated but also dangerous because it misleads prescribers.

In a further example of Purdue's pattern of aggressive pursuit of market share, the report states on page 31: "As part of its marketing campaign, Purdue distributed the usual types of branded promotional items to health care practitioners. Among these items were OxyContin fishing hats, stuffed plush animal toys, coffee mugs, compact discs..." In fact, the use of such branded promotional items for a Schedule II opioid is unprecedented. Distribution of promotional items such as hats, plush toys and coffee mugs is an indicator of Purdue's aggressive, excessive, and inappropriate marketing of their product, OxyContin. The DEA suggests the Department of Health and Human Services restrict promotional materials for Schedule II substances to items related to the practice of medicine or pharmacy.

**Appendix V: Comments from the Drug
Enforcement Administration**

Ms. Marcia Crosse, Director

Page 2

Increased availability of controlled substances leads to increased opportunities for diversion. Therefore, it is essential that stringent risk management plans are put in place prior to the introduction of these products into the marketplace.

Unfortunately, there are limitations to DEA's ability to document the extent of diversion of specific products and DEA agrees with GAO's observation, on the bottom of page 36 of the draft report, that "data on abuse and diversion are not reliable, comprehensive, or timely." DEA also advocates the development of a system to provide "credible, legally defensible evidence concerning drug abuse trends in America," as stated on page 42 of the draft report. DEA included an additional \$750,000 in its 2003 budget request for an enhanced scientific data collection system that would include a National Medical Examiner Information System; however, this request has not been funded. This agency welcomes a recommendation by GAO that more reliable, comprehensive and timely databases be developed.

In addition, there are minor inaccuracies in this report, detailed below:

- First remark, ref page 3, 2nd full sentence of GAO draft report: DEA suggests the following edit to the draft report language (new/replacement language is in bold italics): "*Unlike nonopioid pain relievers, OxyContin oxycodone, the active ingredient in OxyContin, has no known analgesic has no ceiling effect, that is, the dose amount a patient can take can be increased by the physician as needed to relieve pain. However, as the dose escalates, there is always a danger of serious side effects, including respiratory depression and death.*"
- Page 5, line 9: refers to "...three other opioid drugs, Avinza, Kadian, and Oramorph SR, that like OxyContin are classified as schedule II controlled substances." These drugs should be further identified as *high dose extended release opioid drugs*, not simply "opioid drugs," here and throughout this document.
- Page 18, first paragraph: states "...a prescription for a schedule II drug may not be refilled, and the patient must see the practitioner again in order to obtain more drugs." While it is correct that schedule II drug prescriptions may not be refilled, a patient is not required to see the practitioner again but must obtain a new prescription.

Please correct the document language noted above to ensure the report's accuracy. The DEA appreciates the opportunity to provide comment to the GAO in these important matters.

Sincerely,



Rogelio Guevara
Chief Inspector

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EXHIBIT 25

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News

Local (/News/Topic/Local/)

American Pain Foundation Shuts Down As Senators Launch Investigation Of Prescription Narcotics

by **Charles Ornstein, Tracy Weber**, ProPublica | May 8, 2012 12:24 p.m. | Updated: July 17, 2012 1:01 a.m.



(<http://www.propublica.org>)

A version of this story

(http://www.washingtonpost.com/national/health-science/senate-panel-investigates-drug-companies-ties-to-pain-groups/2012/05/08/gIQA2X4qBU_story.html?hpid=z4) was published in *The Washington Post*.

As the U.S. Senate Finance Committee launched an investigation Tuesday into makers of narcotic painkillers and groups that champion them, a leading pain advocacy organization said it was dissolving “due to irreparable economic circumstances.”

The American Pain Foundation, which described itself as the nation’s largest organization for pain patients, was the focus of a December investigation (<http://www.propublica.org/article/the-champion-of-painkillers>) by ProPublica in the Washington Post that detailed its close ties to drugmakers.

The group received 90 percent of its \$5 million (<http://www.propublica.org/documents/item/277604-apf-2010-annual-report>) in funding in 2010 from the drug and medical-device industry, ProPublica found, and its guides for patients, journalists and policymakers had played down the risks associated with opioid painkillers while exaggerating the benefits from the drugs.

It is unclear whether the group’s announcement Tuesday evening — that it would “cease to exist, effective immediately” — was related to letters sent earlier in the day from Sens. Max Baucus, D-Mont., the finance panel chairman, and Charles Grassley, R-Iowa, to the foundation, drug companies and others.

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In the letters, the senators cited an “an epidemic of accidental deaths and addiction resulting from the increased sale and use of powerful narcotic painkillers,” including popular brand names like Oxycontin, Vicodin and Opana.

Growing evidence, they wrote, suggests that drug companies “may be responsible, at least in part, for this epidemic by promoting misleading information about the drugs’ safety and effectiveness.”

The American Pain Foundation’s website carried a statement Tuesday night saying its board had voted May 3 to dissolve the organization because it couldn’t stay “operational.” The foundation did not respond to requests for comment Tuesday.

The senators are targeting a who’s who of the pain industry, seeking extensive records and correspondence documenting the links, financial and otherwise, between them and the makers of the top-prescribed narcotic painkillers.

Letters went to three pharmaceutical companies, Purdue Pharma, Endo Pharmaceuticals and Johnson & Johnson, as well as five groups that support pain patients, physicians or research: the American Pain Foundation, American Academy of Pain Medicine, American Pain Society, Wisconsin Pain & Policy Studies Group, and the Center for Practical Bioethics.

The Federation of State Medical Boards (<http://www.fsmb.org/>), the trade group for agencies that license doctors, received a letter, as did The Joint Commission (http://www.jointcommission.org/about_us/about_the_joint_commission_main.aspx), an independent nonprofit that accredits hospitals nationwide and made pain management a national priority in 2001.

A report by the U.S. Government Accountability Office in 2003 noted that the commission (<http://www.gao.gov/new.items/do4110.pdf>) partnered with Purdue Pharma, the maker of Oxycontin, to distribute pain educational materials nationwide. The committee’s letter to Purdue noted that the company pleaded guilty in 2007 to federal criminal charges (<http://www.propublica.org/documents/item/279028-purdue-guilty-plea>) that it misled regulators, physicians and consumers about Oxycontin’s risk of addiction.

The senators requested payment information since 1997 to 10 groups and eight people, including two doctors featured in ProPublica’s December report (<http://www.propublica.org/article/two-leaders-in-pain-treatment-have-long-ties-to-drug-industry>). They asked about any influence the companies had on a 2004 pain guide for physicians that



was distributed by the Federation of State Medical Boards; on the American Pain Society's guidelines; and on the American Pain Foundation's Military/Veterans Pain Initiative.

In addition, to citing ProPublica's work, the letters also mention the reporting of the Milwaukee Journal Sentinel/MedPage Today.

Patients in serious pain need access to opioids, the senators wrote, but drugmakers and health-care groups "must distribute accurate information about these drugs in order to prevent improper use and diversion to drug abusers."

"The problem of opioid abuse is bad and getting worse," Sen. Grassley said in a statement. "Something has to change."

"When it comes to these highly addictive painkillers, improper relationships between pharmaceutical companies and the organizations that promote their drugs can put lives at risk," Baucus said in a prepared statement.

Dr. Andrew Kolodny, chairman of psychiatry at Maimonides Medical Center in Brooklyn, N.Y., and president of Physicians for Responsible Opioid Prescribing, applauded the investigation.

"These groups, these pain organizations ... helped usher in an epidemic that's killed 100,000 people by promoting aggressive use of opioids," Kolodny said. "What makes this especially disturbing is that despite overwhelming evidence that their effort created a public health crisis, they're continuing to minimize the risk of addiction."

Concerns about the overuse and abuse of painkillers have intensified in recent years. As sales of the powerful drugs have boomed — rising 300 percent since 1999 — so, too, have overdose deaths. Opioids were involved in 14,800 overdose deaths in 2008, more than cocaine and heroin combined, according to the U.S. Centers for Disease Control and Prevention (<http://www.cdc.gov/homeandrecreationsafety/rxbrief/>).

In 2009, the use and misuse of the drugs were cited in more than 475,000 emergency department visits, nearly doubling the 2004 number, the CDC said.

Pain doctors and patient groups say that while drug overdoses are a legitimate concern, only a small percentage of deaths involves patients who receive them from their doctors. Most deaths involve illicitly obtained drugs, statistics show.

The groups also say that patients' risk is low if they do not have addictive personalities, and that any restrictions should not punish patients who suffer from serious pain.

In recent weeks, two articles in medical journals have documented different aspects of abuse.

According to a paper published online this week by the Archives of Pediatrics & Adolescent Medicine (<http://archpedi.ama-assn.org/cgi/content/abstract/archpediatrics.2012.85>), one in eight high school seniors surveyed said they had used prescription opioids for nonmedical reasons.

A paper released last month by the Journal of the American Medical Association (<http://jama.ama-assn.org/content/early/2012/04/25/jama.2012.3951.full>) found that the rate of newborns diagnosed with drug withdrawal jumped threefold from 2000 to 2009. And the rate of mothers using opioids at the time of delivery was five times higher in 2009. (Not all babies born to mothers using the drugs exhibit signs of withdrawal.)

Janssen Pharmaceuticals, a Johnson & Johnson subsidiary that makes the painkiller Nucynta, said in a statement that it “is committed to the responsible prescribing and appropriate use of opioid pain medications” and has supported educational websites about safe use.

The company is reviewing the senators’ letter and “will work with them to fulfill their request for information,” spokesman Mark Wolfe said via e-mail.

Purdue Pharma acknowledged in a statement that it had received the letter, was reviewing it, and looked forward to “cooperating with the committee on this matter.”

Endo did not return a request for comment. A spokeswoman for The Joint Commission said the group had just received the senators’ letter and had no comment yet. The Federation of State Medical Boards responded but did not offer immediate comment.

More News

EXHIBIT 26



American Pain Foundation

Dedicated to eliminating the undertreatment of pain in America.



Treatment Options:
A Guide for People
Living with Pain



American Pain Foundation

Dedicated to eliminating the undertreatment of pain in America.

WHO WE ARE

Founded in 1997, the American Pain Foundation is an independent nonprofit 501(c)3 organization serving people with pain through information, advocacy and support. Our mission is to improve the quality of life of people with pain by raising public awareness, providing practical information, promoting research, and advocating to remove barriers and increase access to effective pain management.

WHAT WE DO

Serve as an information clearinghouse and resource center for people with pain, their families and their caregivers, the general public, healthcare professionals, policymakers and the media.

Promote recognition of pain as a critical health issue; correcting damaging myths about pain and pain management, and seeking to remove the stigma often experienced by those with pain.

Advocate for changes in professional training, regulatory policies, and health delivery systems to ensure that people with pain have access to high quality care.

Encourage healthcare professionals to assess pain routinely and provide immediate, ongoing, effective care.

Mobilize organizations and individuals who care about better pain management.

HOW YOU CAN HELP

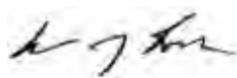
If you would like to further our mission, please visit our web site, www.painfoundation.org, and join the growing number of APF members. Membership is free and open to all. APF members receive online support and resources and useful publications like the *Pain Community News*, which features the latest news about pain and the *Pain Monitor*, which provides updates on pain news and policy issues.

Dear Friend:

As you pick up this publication, you may be asking yourself lots of questions: Can my pain be better controlled? Are there options available that I don't know about? How do various treatments differ? What non-drug therapies are used to manage pain? What questions should I ask my doctor, nurse, pharmacist or social worker about pain?

Treatment Options was written to help answer these and other questions related to pain care. Whether you've just started experiencing pain, have lived with it for several years, or are a caregiver to someone in pain, this guide was written to serve as a useful resource. Each subsection provides easy-to-understand information about a variety of treatment options from medications to psychosocial interventions, rehabilitation therapies, surgical interventions and much more. Words boldfaced in **green** are some common pain terms and are defined at the end of the book.

We trust this will inspire hope and help you in your quest for better pain care. You should not have to suffer with your pain. As always, it is important to talk to your healthcare provider to decide what approach is right for you. Please feel free to share your thoughts and comments by sending an e-mail to info@painfoundation.org. We will update the online version of this book periodically, so check for new tips and information at www.painfoundation.org.



Will Rowe
Executive Director
American Pain Foundation

Whether you are a newcomer searching for information to improve your pain care or a seasoned explorer looking for what's new and different, this guide is for you.

The American Pain Foundation (APF) would like to recognize the significant contributions of others in the creation of this publication.

This book was produced through the generous support of unrestricted education grants from the following companies:

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**The following organizations are represented by those who helped
create this publication:**

American Academy of Pain Management

American Academy of Pain Medicine

American Alliance of Cancer Pain Initiatives

American Board of Hospice and Palliative Medicine

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American Pain Society

American Society for Pain Management Nursing

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Association of Oncology Social Work

Healing Touch International

Intercultural Cancer Council

International Association for the Study of Pain

Midwest Nursing Research Society

National Association of Social Workers

Oncology Nursing Society



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READ THIS BOOK TO FIND OUT:

- Why pain management is important
- How to talk with your healthcare provider about pain
- Information about a variety of drug and non-drug treatment options
- Important goals of therapy
- Benefits and drawbacks of various treatments
- Promising new treatments

As you are reading, remember some approaches span various treatment settings and specialists. For example, some psychosocial interventions, such as hypnosis and guided imagery, may also be advocated for and used by specialists in complementary medicine. This is also true for some rehabilitative techniques (e.g., Rolfing, myofascial therapy).

WHY IS MANAGING PAIN IMPORTANT?

Persistent pain can interfere with your enjoyment of life. It can make it hard to sleep, work, socialize with friends and family and accomplish everyday tasks. When your ability to function is limited, you may become less productive. You may also find yourself avoiding hobbies and other activities that normally bring you happiness in order to prevent further injury or pain. Ongoing pain can cause you to lose your appetite, feel weak and depressed.

Try not to allow your physical illness or pain to take over your life. Pain is a part of you, but it is *not* YOU. It is *not* who you are. Managing your pain is an important step to reclaim your life and ensure it does not control you.

ESTABLISHING A DIAGNOSIS AND ASSESSING YOUR PAIN

To correctly diagnose your pain, your healthcare provider may:

- Perform a complete physical exam
- Complete a pain assessment
- Ask detailed questions about your medical history and lifestyle
- Order blood work, X-rays and other tests

Note: Because of the current state of medical science and limited pain research, there are some causes of pain which might not be able to be confirmed with current medical technology and diagnostic tests.

It is important to give your healthcare provider a complete picture of your pain history. This information will help him or her to determine the right treatment plan for you. To complete a pain assessment, your healthcare provider may ask the following questions about your pain:

- Location
- Intensity
- Description of the sensation(s)
- Nature: Onset, duration, fluctuations
- What makes it better?
- What makes it worse?
- How does it affect your sleep, mood, appetite, activity?

Pain can affect your emotional outlook, your ability to concentrate, your energy level and your sense of self.

If you keep a pain journal, be sure to share it with your healthcare provider. If you don't, consider starting one today. The American Pain Foundation's Pain Notebook is an easy-to-use tool to help you keep a record of your pain (when it occurs, for how long, the level or type of pain, etc.), response to various treatments over time, improvements in daily function and side effects. The *Pain Notebook* can help guide your communication with your healthcare provider and is available by calling 1-888-615-PAIN (7246).

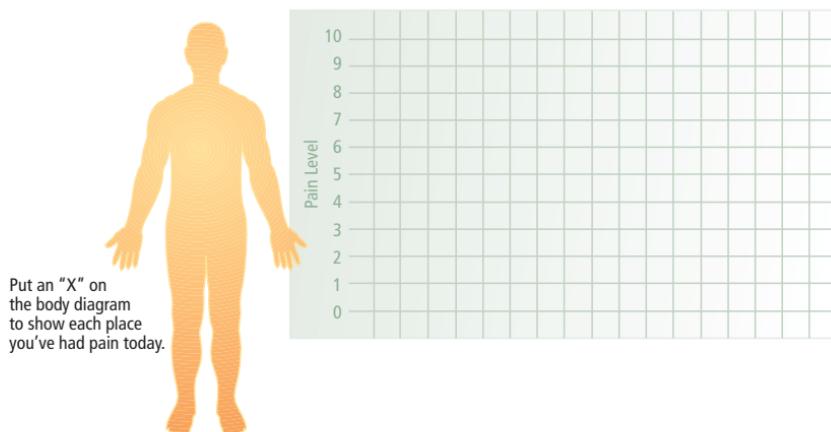
Finding good pain care and taking control of pain can be hard work. As a person with pain, you should become your own best advocate. Learn all you can about pain and possible treatments, and insist on the care you need and deserve.

Use descriptive language when explaining your pain. Describe your pain with words like: sharp, crushing, throbbing, shooting, deep, pinching, tender, aching, among others. Your healthcare provider may also use a pain scale to help assess your pain. Pain scales are tools that can help you describe the intensity of your pain and help your doctor or other healthcare providers diagnose or measure your level of pain. Three types of scales are commonly used: numeric, verbal and visual.

With **numerical scales**, you use numbers from 0 -10 (0 being no pain and 10 being the worst pain ever) to rate the intensity of your pain.

Verbal scales contain commonly used words such as "mild," "moderate" and "severe" to help you describe the severity of your pain.

Visual scales use aids like pictures of facial expressions, colors or gaming objects such as poker chips to help explain the severity of your pain. One type, the Wong Baker Faces Pain Rating Scale, features facial expressions to help you show your healthcare provider how much pain you feel. Body diagrams may be used to help pinpoint where your pain is located.



Mapping Treatment Plan

Pain is complex and unique to each individual. For this reason, your healthcare team will consider many aspects of your pain and daily life before recommending a treatment program, including:

- Type of pain (whether it is **acute** or **chronic**)
- Category of pain (**nociceptive** or **neuropathic**)
- Intensity of your pain
- Your physical condition, coping ability and challenges
- Your lifestyle and preferences for treatment

YOUR PAIN MANAGEMENT TEAM

Common pain problems can often be managed by your primary care provider or treating healthcare professional. This individual could be a physician, nurse practitioner or physician's assistant. When pain is more difficult to treat, help from additional healthcare professionals and others with specialized training in pain may be required. Some of these disciplines may include, but are not limited to:

- Specialty physicians from the fields of neurology, neurosurgery, physical medicine, anesthesia, orthopedics, psychiatry, rheumatology, for example.
- Nurses
- Pharmacists
- Social Workers
- Psychologists
- Case Managers
- Chiropractors
- Physical Therapists, Occupational Therapists, Physiatrists
- Complementary/Alternative Medicine Practitioners

Remember, a therapeutic relationship is a two-way street. It develops over time and trust and open communication are essential. Be sure to find a healthcare professional who is not only trained to treat your pain disorder, but is also willing to work with you to manage your pain. At each follow-up visit, a re-assessment of your pain and pain management plan is very important in order to evaluate the effectiveness of your treatment.

GOALS OF PAIN THERAPY

Your pain management team will work with you to map out a treatment plan tailored to your specific needs. Successful pain management aims to:

1. Lessen the pain
2. Improve functioning
3. Enhance your quality of life

These are considered the hallmarks of pain management and "best practices."

In some cases, pain is best managed using a combination of treatments. This is referred to as a "multi-modality" approach. For example, your healthcare provider may prescribe a medication along with activities to reduce stress (e.g., yoga, deep-breathing exercises). To improve daily functioning, specific therapies may be suggested to increase muscle strength and flexibility, enhance sleep and reduce fatigue, and assist you in performing usual activities and work-related tasks.

While there are a variety of treatment options available for those living with pain, different therapies might not work for everyone. Finding the right combination may take time, but often makes the critical difference in your care. As always, it is important to weigh the risks and benefits of different pain treatments and consult your healthcare provider before starting or changing any treatment.

Pain management is an ongoing process, not just a one-time concern. Finding the right combination of therapies may take time, but often makes the critical difference in your care.

There are factors that can interfere with therapies, including:

- How different drugs interact with each other when taken together
- How different foods might affect how a drug works when taken together
- How different treatments can either complement each other or cause harm
- How your general health and personal habits can play a role in pain treatment (for example, smoking tobacco can interfere with pain treatment and increase pain levels)

TREATING THE WHOLE PERSON

The impact of pain requires an understanding that the whole person experiences pain; that is, the mind, body and spirit. Integrative medicine supports the use of "conventional" treatments, for example, drugs, counseling, exercise or surgery, along with "complementary" pain-relieving techniques like acupuncture, bio-feedback, massage or chiropractic manipulations. This allows healthcare providers to offer more **holistic care**.

TREATING THE CAUSE OF YOUR PAIN

Whenever possible, your healthcare provider should make every effort to treat the cause of your pain. For example:

- If you are a diabetic, it is important to control your blood sugar, because that may prevent nerve and blood vessel damage that can result in a variety of painful problems commonly seen with this disease.
- If you have rheumatoid arthritis, you may be prescribed drugs to treat the arthritis itself because pain medicines will not prevent the disease from damaging your joints.
- If you have migraine headaches, there are medicines that can prevent or reduce the frequency and severity of headaches, reducing the need to use pain medications.
- If you have osteoporosis, your provider may recommend that you take medications to strengthen your bones to help prevent fractures that could result in pain and disability.
- Surgery also plays a critical role in pain control. Replacement of a knee or hip may provide relief of pain and reduce or eliminate the need for analgesics.

Pain is complex and involves every aspect of your being. Because it is not just a physical experience, there is no magic pill to take away the pain.



HELPFUL HINTS ON YOUR ROAD TO PAIN RELIEF

Keep the following tips in mind as you seek treatment for your pain:

- **Chronic pain** can result in physical and psychological challenges. It is important to accept support from loved ones — you need and deserve all the help you can get.
- Be sure to seek treatment as early as possible to avoid further problems.
- Do not allow your physical illness or pain to take over your life. Pain is a part of you, but it should not define who you are.
- Try not to let past frustrations of failed treatments stand in your way; there are a wide range of treatments available as detailed in this guide. While your pain might not go away completely, there are ways to reduce it so that it is bearable and you can reclaim parts of your life.
- Keep a pain journal.
- Only you know the extent of your pain and how it's impacting your life. Don't be afraid to speak up.
- Before going to your appointments, write down any questions you might have and take them with you; it's easy to forget things and you may not have much time with your provider.
- Bring a relative or friend to your appointments to provide any support you might need. They can also take notes and help you to remember things that were said.
- Be certain there is someone on the healthcare team that you can call if you have any questions or concerns after you have been taking your medicine for awhile. Make sure you know how to get in touch with them.
- Know your treatment options. Your healthcare provider should share information about your condition, pain and possible treatment options, but you should also inform yourself.

AVAILABLE TREATMENT OPTIONS

The following areas of pain treatment should be considered:

- Pharmacotherapy (drug options)
- Psychosocial Interventions (coping, counseling, etc.)
- Rehabilitation Techniques (re-conditioning, re-training and lifestyle changes)
- Complementary and Alternative Medicine (CAM)
- Injection and Infusion Therapies
- Implantable Devices and Surgical Interventions

Healthcare professionals who treat pain may not have experience in using or performing every treatment option available. Some pain treatment options require special areas of expertise or training. Referrals to those specialists may be required. Insurance coverage of pain treatment options vary widely, if covered at all.

The information in this guide is provided to help readers find answers and support. Readers are encouraged to share and discuss this information with their doctor.

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Pharmacotherapy

{Drug Options}



USING MEDICINES TO CONTROL PAIN

An overview of pharmacotherapy

Medications play an important role in the treatment of pain. Many different medicines can be used to help relieve pain. A few, such as aspirin, ibuprofen and acetaminophen, can be purchased in a pharmacy or supermarket without a prescription, but most pain relievers are only available with a prescription from your healthcare provider. Some medications used to treat pain are not usually thought of as pain medicines, but they have been shown to relieve specific types of pain. For example:

- Some drugs used to manage depression or seizures can be used to treat neuropathic or nerve pain.
- Some steroid medications, such as prednisone and dexamethasone, may be used to treat pain caused by inflammation or bone disease.
- Some medications used to relax muscles or treat insomnia or anxiety may be used in the overall management of pain.

Don't be afraid to ask your healthcare provider questions about prescribed medications.

Be certain to address the following:

- Why a particular medicine was chosen to manage your pain problem.
- The associated risks and benefits of the drug; common side effects, as well as recommended steps should these side effects appear.
- Exactly how you should take your pain medicine, including the dosage (how much) and how often.
- Whether there are other drugs, foods, drinks, vitamins or herbal supplements that you should not take at the same time. For example, grapefruit juice has been shown to interfere with the action of many medications.

Some pharmacies do not carry every type of pain medication. You can always call your pharmacy to find out if the drug or drugs you are prescribed are available and whether they are covered by your health insurance plan. Tell your provider if you cannot afford to pay for your medicine. Sometimes he/she may be able to prescribe a less expensive medication that works in the same way or help you access the medication at a reduced cost or, sometimes, at no cost. Several pharmaceutical companies have special programs that will assist people with financial need.

CLASSES OF ANALGESICS FOR PAIN CONTROL

There are three major classes of medications for pain control:

Non-opioids: non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen

Opioids (may also be called **narcotics**): codeine and morphine are examples

Adjuvant analgesics: a loose term referring to the many medications originally used to treat conditions other than pain, but now also used to help relieve specific pain problems; examples include some antidepressants and anticonvulsants. Some of these drugs have been shown to work well for specific types of pain.

Drugs that have no direct pain-relieving properties may also be prescribed as part of a pain management plan. These include medications to treat insomnia, anxiety, depression and muscle spasms. They can help a great deal in the overall management of pain in some persons.

THE NON-OPIOIDS

NSAIDs

There are many different drugs in this family of pain relievers. They all relieve mild to moderate pain and reduce fever and inflammation. They decrease the formation of natural substances in the body called prostaglandins. Prostaglandins serve to protect a number of areas in the body such as the stomach and kidneys. They are also produced at sites of injury or inflammation and allow pain receptors in the surrounding area to become more sensitive to pain. *By decreasing prostaglandins, NSAIDs lessen the sensation of pain and reduce inflammation.*

Classes of NSAIDs

Aspirin (acetylsalicylic acid) is the oldest NSAID and was introduced into medicine in 1899. A large number of aspirin-like drugs have been developed since that time. Aspirin, ibuprofen, naproxen and ketoprofen are the only NSAIDs available over-the-counter (OTC) without a prescription. A different class of NSAIDs, the selective COX-2 inhibitors (or coxibs), were not marketed until quite recently and were developed to reduce the risk of ulcers caused by NSAIDs. Only one selective COX-2 inhibitor, celecoxib, is still available at this time.

Clinical uses

NSAIDs are effective against mild to moderate pain, and are important for the management of both acute and chronic pain. For example, an NSAID may be the only analgesic needed to control pain after a minor injury or surgical procedure. They are often used in combination with other drugs such as opioids for treating pain after surgery because, when combined in this way, the pain can often be well controlled with a smaller dose of the opioid. This may help to avoid some of the common side effects of opioids. NSAIDs are especially effective for relieving pain due to inflammation or pain in persons whose cancer has spread to the bone. There is no research evidence that they relieve **neuropathic pain** or are of particular benefit for treating the pain of fibromyalgia.

There is no evidence that one NSAID is a better pain reliever than another; however, each individual may get better pain relief from one than from another. Finding the right NSAID to treat persistent pain is a matter of trial and error. It may take awhile for the drug to work, so you and your provider will need to allow an adequate trial of the drug before judging its benefit. NSAIDs have an important limitation, called a dose ceiling. Taking doses above the ceiling dose will significantly increase the risk of serious side effects, such as kidney failure, which can be life threatening.

How to take these medicines

All NSAIDs are effective when taken by mouth. Different NSAIDs last for different lengths of time, so one must be careful to follow dosing instructions. There is one NSAID, ketorolac (Toradol®), available for injection into a muscle or a vein, which makes it useful to treat pain after surgery or trauma especially when persons may not be able to take medicines by mouth. Others that can be given by injection may be available in the near future.

In an attempt to avoid some of the serious side effects of NSAIDs, topical preparations have also been developed. Topical NSAIDs work at

Common side effects of NSAIDs

- GI distress
- Stomach ulcers
- GI bleeding
- Delayed blood clotting
- Decreased kidney function
- Possible increased risk of stroke or heart attack with selective COX-2 inhibitors

the site of pain and inflammation and do not get into the blood stream like medications taken by mouth. One topical NSAID is a solution that is rubbed on the skin, another is in the form of a patch. Topical NSAIDs have been shown to decrease pain and increase function in persons with osteoarthritis and to relieve **acute pain** associated with soft tissue injuries such as sprains and strains. Be very cautious about buying topical NSAIDs from the Internet as the consistency of their delivery systems and the actual dose delivered are unproven and may result in unsafe or unsatisfactory results.

Side effects

The most common side effects of NSAIDs involve the gastrointestinal (GI) tract. They can produce anything from heartburn to ulcers to bleeding. Serious problems, like ulcers or bleeding, can occur without warning. While taking these medicines with food or milk may reduce stomach upset, this will not protect you against the development of ulcers or bleeding from the GI tract. The risk of a GI bleed is increased in older adults, in those who are also taking aspirin or a steroid such as prednisone, and in those who have had ulcers or any kind of NSAID-induced GI problem in the past. The risk of bleeding from an ulcer is also greater if you are taking a blood thinner such as warfarin (Coumadin). Your healthcare provider may tell you to check your stools for hidden blood. If you ever notice that your stool contains blood or appears darker than usual, contact your healthcare provider immediately.

Your doctor can prescribe medications to protect your stomach from NSAIDs, but some of these can be expensive and also have their own side effects. The most effective are the proton pump inhibitors, including omeprazole, which are available over-the-counter. The selective COX-2 inhibitors were designed to be easier on the stomach and avoid GI problems common to the older NSAID drugs. Unfortunately, recent studies show that if you take COX-2 inhibitors with aspirin, you are likely to have as many stomach problems as if you were taking one of the older drugs.

NSAIDs may also decrease kidney function, which is a significant problem in elders. As a result, the body may retain water, which would be dangerous in persons who have high blood pressure or heart failure. The older NSAIDs interfere with blood clotting and have to be discontinued hours to days before surgery. An advantage of the COX-2 inhibitors is that they do not affect blood clotting. NSAIDs can cause "hypersensitivity reactions" with symptoms similar to an allergic reaction. Some cause headaches or slow thinking.

Recently, concern has been raised about the possibility that NSAIDs, including the COX-2 selective inhibitors, may increase the risk of heart attack and stroke. Although the research is still limited, there is evidence that a small increased risk of these complications occurs whenever an NSAID is taken for a period of time. Two COX-2 inhibitors (Vioxx® and Bextra®) were taken off the market in response to this concern.

Should I take these pain medicines?

It's been known for a long time that NSAIDs can cause life-threatening side effects in some persons. There are 10,000 to 20,000 deaths each year because of the side effects of this class of medicines. In spite of that, these drugs are widely used. A third of Americans over the age of 65 take NSAIDs daily. If you are taking NSAIDs for musculoskeletal pain, keep in mind that there are a variety of non-drug and drug therapies available that are helpful as well. The risks from NSAIDs are greater if higher doses are used or if these drugs are taken for more than a period of months. Discuss these risks with your healthcare provider, particularly if you may be at risk because of a

history of heart disease, stroke, peripheral vascular disease, hypertension, kidney disease or ulcers. Whenever an NSAID is taken for pain, it is prudent to use the lowest effective dose and to stop the therapy unless it is clearly needed over time. Though NSAIDs are commonly used medications, they do have dangers and must be used appropriately.

Acetaminophen

Acetaminophen can be used to relieve mild to moderate pain and treat fever, but it is not an NSAID and does not reduce inflammation. It produces few, if any, side effects at the doses that can relieve pain, but it can damage the liver when used in large doses. Acetaminophen overdose is a medical emergency. The labeling specifies an upper limit of 4 grams in 24 hours (which is equivalent to just eight Extra Strength Tylenol®). Persons with liver disease or a history of alcohol abuse should limit their use to much less than this and should consult their healthcare provider about the safest and most appropriate dose to use.

There are many combination pain medicines that contain an opioid with acetaminophen. Be careful with these drugs as they contain different amounts of acetaminophen. Be sure to check the amount with your pharmacist. Don't decide to take extra acetaminophen on your own if a combination pain medicine is not controlling your pain because you may end up using too much acetaminophen and that could cause liver damage. Be aware that many OTC cough, cold and sinus remedies and combination pain relievers also contain acetaminophen, meaning you could be taking more of the drug than you realize. You should also be aware there is a risk of kidney damage if you take acetaminophen for months or years, especially if you take it together with an NSAID.



OPIOID ANALGESICS (NARCOTICS)

Opioid analgesics are another important class of medications that are very effective pain relievers. As mentioned before, they may also be called "narcotics." Unfortunately, this term is used by law enforcement to refer to drugs that are abused. Cocaine and heroin are called narcotics even though they are very different kinds of drugs. Calling opioid analgesics "narcotics" reinforces myths and misunderstandings as it places emphasis on their potential abuse rather than on the importance of their use as pain medicines. In the pain treatment world, the word opioid is used when speaking about this class of medications.

Clinical uses

Opioids are an essential option for treating moderate to severe pain associated with surgery or trauma, and for pain related to cancer. They may also be an important part of the management of persistent pain unrelated to cancer. These medicines block pain messages in the body, but they also affect the way we feel about our pain and help us better tolerate it. Our body produces natural opioids (endorphins) as part of its survival response to danger and injury. Because the medications of this class work in the same way as endorphins, they work very well in blocking pain.

Despite the great benefits of opioids, they are often under-used. For a number of reasons, providers may be afraid to give them and the public may be afraid to take them. Some feel opioids should not be used to treat persistent pain except in persons

who are dying. Others are concerned that the average person will become addicted to these drugs. These concerns lead to confusion and hesitation on the part of some providers to prescribe these for pain control. Adding to the problem is the increase in abuse of prescription drugs in the U.S. Persons with addictive disease (in the past, the term "addicts" was used) have obtained and misused these drugs. Others have taken them illegally through pharmacy thefts or under false pretenses in order to sell them "on the street" for profit.

Obviously, it is very important to get the facts about these effective and powerful pain medicines because their under-use has been responsible for much unnecessary suffering. Those affected by pain, providers, patients and family alike, need to be well-informed to be sure that myths and misunderstandings do not get in the way of effective pain control.

Classes of opioid analgesics

Familiar medicines in this family of drugs are codeine and morphine. But there are several others that your provider might use for different pain problems. These include hydrocodone, oxycodone, hydromorphone, meperidine, methadone, propoxyphene and fentanyl. Generic and brand name drugs are available, so you may have heard hydrocodone referred to as Vicodin® and oxycodone as Percocet®. Both of these products contain acetaminophen. Opioid pain medicines are not all alike. They differ in how well they control pain, how much you have to take, how long they last and in the routes by which they can be given.

Some opioids such as codeine, hydrocodone and propoxyphene usually are not preferred for the management of severe pain. Tramadol, although not classified as an opioid, is another drug that has some opioid effects and can be beneficial for mild to moderate pain. Persons taking an antidepressant or an antipsychotic drug along with Tramadol may be at increased risk of seizures.

The side effects of codeine become unacceptable if given at high doses. Some people do not make the natural enzyme that breaks codeine down into a pain relieving chemical in the body. In those people, taking codeine for pain is like taking a sugar tablet.

The dose of hydrocodone is limited because it only comes in combination with acetaminophen and, as was mentioned before, acetaminophen can be toxic to the liver in large doses. In the doses usually prescribed for pain, propoxyphene is only as effective as aspirin or acetaminophen. High doses may not be tolerated and toxic doses are associated with serious risk of heart problems.

Meperidine is another opioid for which dose and length of use must be limited because it is metabolized (breaks down) to a chemical that can cause tremors, twitches or even seizures. Although it can provide relief of severe pain, it should only be used in small doses and for short periods (less than 3 days) in healthy adults. More and more hospitals are either restricting or avoiding its use.

The other opioids can relieve severe pain. Their doses can be gradually increased over time. There is no ceiling dose as there is with the NSAIDs. As pain worsens, these medications continue to be useful unless side effects occur. It is a myth that opioids, like morphine should only be used at the final stages of a seriously painful disease. When pain is severe, opioids should be considered.

Ways to take these medicines

One of the advantages of opioid drugs is that they can be given in so many different ways. For example, they can be given by mouth, rectal suppository, intravenous injection (IV), subcutaneously (under the skin), transdermally (in the form of a patch) or into a region around the spinal cord. Patches, IV injections and infusions are very important for patients who cannot swallow or whose GI tracts are not working normally.

Many people benefit from having some form of control in taking their pain medications, whether they are at home or in the hospital. Your healthcare provider may give you the option of taking doses of the opioid on an “as needed” basis at home. You may wish to discuss this option with your healthcare provider.

Another way of allowing you to control the dosing of an opioid is called “patient-controlled analgesia” or PCA. You may have heard of intravenous or subcutaneous patient-controlled analgesia (IV-PCA; SQ-PCA) that is used after surgery or sometimes for severe pain in persons with cancer (see *Infusion Therapy section*). On the horizon is a new patch delivery system that gives an extra dose of medication across the skin; this is called a patient-controlled transdermal system (PCTS).

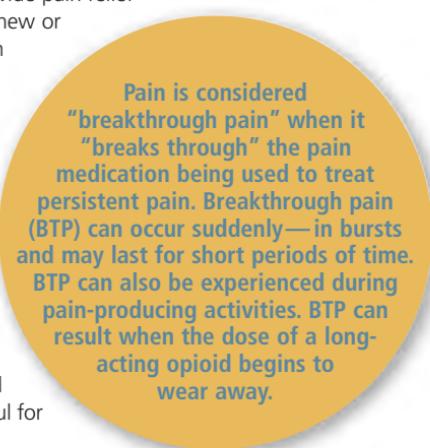
Pain medicine can also be delivered into your back through a very small tube called an epidural or intrathecal catheter. This may be an excellent way to give an opioid if you are having major surgery of the chest, stomach, pelvis or limbs. Opioids may be given through an intrathecal catheter for chronic pain if a person has not responded to more conservative approaches to treatment.

The duration of opioid pain relief

In the absence of a special “extended-release” formulation, most opioids provide just several hours of pain relief after a dose. The extended-release formulations (also called “modified-release,” “controlled-release,” “sustained-release” and sometimes “long-acting”) can be pills or patches and can provide pain relief from eight to as long as 24 hours. NEVER crush, chew or take these long-acting medications differently than prescribed. These changes can destroy the time-release feature and cause an overdose.

Fentanyl is available in a patch worn on the skin for the treatment of persistent pain. The drug is absorbed slowly under the skin and then is absorbed into the blood stream. The patch can give pain relief for as long as 72 hours. DO NOT put heat on the patch after you have placed it on the skin because the drug could get into your blood very quickly and cause side effects, and even a possible overdose. Fentanyl is also available in a lozenge. In this formulation, it has a quick onset and short duration of effect that makes it especially useful for the treatment of “breakthrough” pain.

Opioids can be given as the only treatment for pain, but as mentioned earlier, they are often prescribed in combination with non-opioids or with one of the adjuvant analgesics. A long-acting drug may be used to treat persistent pain. It may be the only medication required to keep pain under control. When moments of increased pain occur two or three times a day or more, a short-acting (SA) medication may be added.



Pain is considered “breakthrough pain” when it “breaks through” the pain medication being used to treat persistent pain. Breakthrough pain (BTP) can occur suddenly—in bursts and may last for short periods of time. BTP can also be experienced during pain-producing activities. BTP can result when the dose of a long-acting opioid begins to wear away.

Side effects

The most common side effects of opioids include constipation, nausea and vomiting, sedation (sleepiness), mental clouding and itching. Some people may also experience dizziness or difficulty urinating. Respiratory depression, a decreased rate and depth of breathing, is a serious side effect associated with overdose.

The good news is that most side effects go away after a few days. However, side effects may continue in some people. Constipation is most likely to persist. Some pain experts believe all patients started on an opioid also should be taking a stool softener or a laxative. Others believe that this treatment is appropriate only if a patient is prone to developing significant constipation because of advanced age, poor diet, other diseases, or the use of other constipating drugs. Your healthcare provider can give advice on what to eat and what medicines to use to treat constipation. Always make certain to drink plenty of fluids and be as active as possible.

If any of the other side effects don't go away, they can also be treated. Be certain to tell your provider if you are having any problems. Serious side effects such as delirium or respiratory depression can occur if the dose is increased too quickly, especially in someone who is just starting to take opioids. Tell your provider if you are unable to concentrate or think clearly after you have been taking an opioid for a few days. Report other medications you may be taking that make you sleepy. Do not drive when you first start taking these drugs or immediately after the dose has been increased. Most persons will adapt to these medicines over time and can drive safely while taking them for pain control. If side effects remain troublesome, your provider may switch you to a different opioid. The amount of pain relief can be maintained after such a switch and often the side effects can be reduced.

Common drugs that can cause physical dependence

- Opioids
- Stimulants
- Sedatives
- Steroids
- Certain Antidepressants
- Certain Heart Medications
- Caffeine

Tolerance, physical dependence and addiction

You and your healthcare provider may worry about tolerance, physical dependence and addiction. It's sometimes easy to confuse the meaning of these words. Tolerance refers to the situation in which a drug becomes less effective over time. However, many persons with persistent pain don't develop tolerance and stay on the same dose of opioid for a long time. Many times when a person needs a larger dose of a drug, it's because their pain is worse or the problem causing their pain has changed.

Physical dependence means that a person will develop symptoms and signs of withdrawal (e.g., sweating, rapid heart rate, nausea, diarrhea, goosebumps, anxiety) if the drug is suddenly stopped or the dose is lowered too quickly. *Physical dependence is normal;* any patient who is taking an opioid on a regular basis for a few days should be assumed to be physically dependent. This does **NOT** mean you are addicted. In fact, many non-addictive drugs can produce physical dependence. To prevent withdrawal from occurring, the dose of the medication must be decreased slowly.

If you believe that you no longer need to take the opioid medication or want to reduce the dose, it is essential to speak to your provider. They will guide you on how to decrease your dose over time to prevent the experience of withdrawal.

Persons who have an addiction have lost control over use of the drug and continue to use it even when the drug is doing them or others harm. The term addiction now refers to a medical diagnosis and is defined as a primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and expression. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving (From the American Pain Society, American Academy of Pain Medicine and American Society of Addiction Medicine <http://www.asam.org/pain/definitions2.pdf>).

People with the disease of addiction may abuse their medications, engaging in unacceptable behaviors like increasing the dose without permission or obtaining the opioid from multiple sources, among other things. Opioids get into the hands of drug dealers and persons with an addictive disease as a result of pharmacy theft, forged prescriptions, Internet sales, and even from other people with pain. It is a problem in our society that needs to be addressed through many different approaches.

Some people who are not substance abusers also engage in these types of behavior. Even if this results in part from a desperate desire to obtain pain relief, it is unacceptable and your healthcare provider must intervene to stop the behavior.

Restricting access to the most effective medications for treating pain is not the solution to drug abuse or addiction. However, your provider may establish very clear guidelines to ensure that you take the opioid as prescribed. Some physicians will require you to sign an agreement (see *Table 1*) before opioids are prescribed.

Table 1: COMMON FEATURES OF AN OPIOID AGREEMENT

- Sign an opioid agreement to be kept in your medical file (ask for your own copy)
- Obtain prescriptions from only **one** doctor
- Have your prescriptions filled at **one** pharmacy
- Come in for regular office visits (every 2-4 weeks or so)
- Agree to have periodic urine drug screening
- Bring your pills in to be counted during visits
- Follow any additional rules not listed above

Once your prescription is filled, it is of the utmost importance that these medications are kept in a secured location to prevent access to children or others. According to law enforcement reports, theft of personal supplies of pain medications stored in the home does occur. If this happens to you, report it immediately to your local police department. Ask for a copy of this report, so you may share it with your healthcare provider. It is very important to remember that drugs of all kinds have a potential to hurt us, but when used properly and with supervision they can be life-savers and give all of us a quality of life we deserve.

ADJUVANT ANALGESICS

Adjuvant analgesics are drugs that are used to treat other illnesses, but have been found to provide relief for certain kinds of pain. These include certain antidepressants, anticonvulsants, corticosteroids and some other drugs used by pain specialists. Adjuvant analgesics are particularly important for the treatment of neuropathic pain. This kind of

pain may be difficult to treat. Drugs recommended for the treatment of neuropathic pain are listed in *Table 2*. You will notice opioid analgesics and tramadol are listed. Finding the drug that works best for you is a matter of trial and error. Your provider will consider your age, your general health and the cost of the medications. Combining different drugs may give the best results. For example, a recent study confirmed that combining gabapentin and morphine gives better relief for neuropathic pain than using either one alone.

Table 2: MEDICATIONS FOR NEUROPATHIC PAIN

Medication	Uses and Impact on Pain
Opioid analgesics and tramadol	These medications were discussed earlier.
Lidocaine patch	Put the patch where it hurts and follow your healthcare provider's instructions about changing it on a daily basis. Do not place it on areas of broken skin.
Antidepressants* Tricyclics such as amitriptyline, nortriptyline, desipramine, doxepin	Dose is increased gradually. These have many possible side effects such as sleepiness, dry mouth, blurred vision, weight gain, decrease in sexual desire or performance.
Venlafaxine and duloxetine	Generally, these have fewer side effects than tricyclics; your doctor will gradually increase the dose of these as well.
Certain anticonvulsants† Gabapentin	Usually needs to be increased gradually over a period of time.
Pregabalin	Increasing the dose to the effective range can be done more quickly and requires fewer steps than gabapentin.

*There are many other antidepressants, but they don't work as well for pain.

†Older anticonvulsants such as carbamazepine, phenytoin and valproic acid may have benefit; newer drugs are also being used in some patients.

Corticosteroids may be useful for treatment of severe inflammatory pain. They can be taken by mouth or injected where there is inflammation. These can cause serious side effects so your provider will use the lowest effective dose for the shortest possible time period. Typical examples include prednisone and dexamethasone. Ask about the potential side effects of corticosteroids. Be sure to notify your healthcare provider if you experience new or worsening joint pain after using prescribed corticosteroids.

Muscle relaxants may decrease muscle pain, but often causes sleepiness. They are usually used for a short period time, such as following a muscle injury or with some diseases that may cause muscle spasms.

Topical Analgesics

There are other drugs that are effective when used topically. One of these topical analgesics is capsaicin, which comes from chili peppers. It must be applied several times a day for about six weeks to get benefit. It can cause burning where it is applied, so you have to be very careful that you don't get it in your eyes. There are many other ointments that you can buy in the pharmacy; some contain menthol and may be helpful for musculoskeletal pain.

Local Anesthetics

Local anesthetics are very important for providing pain control and can be used in many different ways. Many persons have had an injection of lidocaine before having dental work or before having stitches. Longer term administration of a local anesthetic can be done alone or in combination with opioids to block pain in specific regions of the body; this is usually administered in the spine through a catheter. Chronic pain can be treated with a lidocaine patch, as mentioned above. There are also local anesthetic preparations that can be applied to skin and open wounds in the form of a cream or ointment to prevent pain from a needle stick. Disposable devices can be used as another way to deliver anesthetics around an incision or site of injury.

Drugs for Anxiety, Depression and Sleep

Persons with persistent pain may become anxious or depressed or they may have trouble sleeping. Treatment of anxiety and depression may decrease the need for pain medicines. On the other hand, relief of pain may significantly reduce anxiety and depression. There are many effective drugs for depression; as mentioned previously, some are helpful with pain, others are not. Selective serotonin reuptake inhibitors (SSRIs) are often used for depression; they are also beneficial to persons who are anxious. The dose of these drugs needs to be increased slowly over time so they can take a while to begin to work. If persons are extremely anxious, they can get quick benefit from the use of a benzodiazepine. The drug diazepam (Valium®) is a member of that class. There are several medications to treat sleep problems. Several that are available without a prescription contain antihistamines. Others that are more likely to help are available only with a prescription.

Table 3: IMPORTANT CONSIDERATIONS THAT HELP GUIDE THE USE OF PAIN MEDICINES

1. A thorough understanding of your pain (a pain assessment) is essential to any decision about what pain medicines you should take.
2. The severity and type of pain will guide the choice of medications. You may have more than one type of pain.
3. The dose of a medication and the time between doses is based on the specific properties of the medication and how a person responds to the drug. These things can vary from one drug to another and from one person to another. With some drugs, the dose needs to be slowly increased over time before it is known if it will help to control pain.
4. Your provider may combine two or more pain medicines that work in different ways in order to provide the best pain relief with the fewest side effects.
5. Some medications take time to begin to work; this is especially true for some drugs used to treat persistent pain: it can take days, weeks or even sometimes months to know what drug will work best for you.
6. If your pain is chronic and usually present, your healthcare provider will probably offer you medication on a regular schedule. Preventing pain from returning or getting worse is the best way to control it. Your provider may refer to this as "staying on top of the pain" or "staying ahead of the pain."
7. The addition of non-drug therapies, both physical and behavioral (see *additional sections in this publication*), may result in better pain relief and fewer side effects.
8. The purpose of pharmacotherapy is to relieve pain and improve function. Improved function after surgery means, for example, being able to cough, breathe deeply and move about. Improved function in persons living with persistent pain may mean being comfortable while engaging in work or the activities of daily living.

Pain management is complex and often requires several attempts with different combinations of medications to find the best treatment plan for an individual. Medications are often one part of a person's pain management plan and can be quite effective when used properly. *Table 3* discusses helpful tips that guide the use of pain medicines. Remember, using medication to relieve pain is only one treatment option. They work well when combined with other approaches as discussed throughout this book.

Psychosocial Interventions



PSYCHOSOCIAL INTERVENTIONS

Pain is complex and unique to each individual. As with other aspects of life, each of us brings pre-existing thoughts, feelings, beliefs, expectations and behavior patterns to any health experience. Understanding the impact of pain requires that we expand our view to consider the whole person — the mind, body and spirit.

Research shows that pain can affect your emotions and behavior and interfere with your ability to concentrate, manage everyday tasks and cope with stress. Likewise, stress and emotional pressures can make pain worse, provoking “flare ups” and contributing to alterations in the immune system response. These relationships are not always easily recognized or readily fixed by medical procedures or medications alone.

As the science of pain moves forward, there is growing evidence that interventions (drug and non-drug) used to influence emotions, thinking and behavior can aid in the reduction of pain and associated distress. For example, studies are uncovering a biological link between the brain systems involved in depression and pain regulation. Some antidepressant medications may have analgesic properties, which may be because these systems have shared properties. Some people experience depression due to chronic pain. Others may begin to realize that depression was present before their pain began. Depression can make the experience of living with persistent pain more difficult and should be diagnosed and treated.

Others may falsely believe that referral for psychological pain treatment means that their pain is not physical, or feel they are being labeled as having a mental illness rather than a physical problem. You may feel hesitant to try psychosocial therapies due to the associated stigma, or the fear that your provider will no longer treat the physical symptoms of your pain or try new treatment options. Don’t let these fears interfere with your willingness to try a broad class of potentially safe and effective treatments. Consider these a gift to yourself — an investment in your peace of mind and quality of life.

PSYCHOLOGICAL CONSULTATION, COUNSELING & STRESS MANAGEMENT

Consultation

Many people believe knowledge is power. In fact, you may be reading this book to increase your pain knowledge and put it to good use. While reading, ask yourself:

- 1. How does your pain affect the way you think and act?**
- 2. How does your pain affect your loved ones and co-workers?**
- 3. How do they react to you?**
- 4. Does this help or hinder your recovery and healing?**
- 5. Are there ongoing stressors in your life?**

For example, you may find that previous relationship patterns are no longer working for you. Stress and emotions, such as fear and anger, increase pain, which can then heighten stress levels. These kinds of cycles are important to recognize and modify. This action may decrease your pain and, at the same time, boost your sense of control over your life. Change is difficult. Working with a skilled therapist who understands chronic pain may help you recognize the “unhealthy” stressors in your life and guide you through making necessary life changes.

Your healthcare providers may recommend that you consult a behavioral health professional. This could be a social worker, psychologist or psychiatrist, or a therapist with special training in chronic pain. No, they do not think that "you are crazy" or that your pain is "only in your head." This evaluation may include testing and interviews to help assess how you cope with pain. It is important to:

- Identify how your pain interferes with your daily life and relationships
- Understand the stressors that worsen your pain and distress
- Determine which coping skills are helpful and which are harmful

When people have had pain for a long time, they develop ways to deal with pain, which are called coping strategies. Some of these strategies may help, while other may not. As a result, you may need to learn new ways to cope. There are a range of strategies that can help in this process. The following therapies may be recommended:

- Relaxation Therapy (relaxation, mindfulness, imagery)
- Biofeedback Training
- Behavioral Modification
- Stress Management Training
- Hypnotherapy
- Counseling (individual, family or group)

COGNITIVE TECHNIQUES

Some techniques used in stress management include relaxation training, meditation, hypnosis, biofeedback and behavior modification. Common to these approaches is the belief that people have the ability to self-manage some aspects of pain, such as changing attitudes, thoughts feelings or behaviors.

Relaxation therapies teach people how to relax tense muscles, reduce anxiety and alter their mental state. Both physical and mental tension can make pain worse. Headaches or back pain, muscle tension or spasms can be part of the problem. Meditation, which aims to produce a state of conscious relaxation, is sometimes combined with therapies that assist you in thinking of pain as a distant part of you. This skill of detachment helps to regain a sense of control. This approach may be particularly helpful when fear or anxiety accompanies pain.

- **Mindfulness Meditation** is a concentration practice during which people focus their attention on a specific object, most commonly on breathing patterns. For example, the focus might be on the experience of the breath entering the nostrils when inhaling and again when exhaling. When our minds wander off the breath (which is natural to do), we acknowledge that it has wandered and bring it back to the breath. Conscious awareness can bring about a sense of calm, patience, reduced muscle tension and pain and a clear sense of reality. When beginning this practice, you may experience anxiety or increased pain. This is because you may not have spent time being quiet with yourself. It is best to start a meditation practice with the help of a meditation teacher who can give you suggestions on how to proceed when these feelings arise.

Once mastered, meditation can be used in many situations, such as reducing the intensity of pain during flare ups, decreasing anxiety while sitting in the dentist chair and reducing the urge to scream during a traffic jam.

- **Guided Imagery** is a conscious meditation technique. Advocates of imagery believe our imagination is a potent healer, which has been overlooked by practitioners of Western medicine. Imagery may help relieve pain, promote healing from injury or illness, and/or ease depression, anxiety and sleeplessness. Thoughts have a direct influence on feelings and behavior. Negative thoughts may promote sadness and hopelessness, while positive thoughts breed pleasure and drive.

Imagery has been found to be very effective for the treatment of stress. Imagery relaxes the body by aiding the release of brain chemicals that serve as the body's natural tranquilizers. These chemicals lower blood pressure, heart rate and anxiety levels. Practitioners who specialize in imagery may recommend it for a variety of different conditions such as headaches, chronic pain in the neck and back, high blood pressure, spastic colon and cramping due to premenstrual syndrome. Several studies suggest that imagery can also boost the immune system and, therefore, promote healing.

Most guided imagery techniques begin with relaxation followed by the visualization of a mental image. For example, imagine a color for pain and then gradually replace that color with one that is more pleasing. Another is visualizing a peaceful scene, such as the ocean surf, wooded forest, fishing at a quiet pond or watching the sunset. Practicing guided imagery with music or aromatherapy may enhance the overall experience. This eventually may stimulate the ability to relax and create a mental image when those favorite sounds or scents are present.

- **Biofeedback training** teaches people how to recognize their physical reaction to stress and tension by using a variety of monitoring procedures and equipment. Physical responses that might be monitored include brain activity, blood pressure, muscle tension and heart rate. These involuntary responses generally increase with stress (known as the "stress response"), which can accompany pain. By measuring these physical reactions, you can learn relaxation and breathing techniques to help return these responses to normal levels of activity. Often when the stress response is lowered, so is the intensity of pain.



- **Behavioral modification** (sometimes called operant conditioning) is aimed at changing habits, behaviors and attitudes that can develop from living with chronic pain. Some people are overwhelmed by pain and may become dependent, anxious, homebound or perhaps even bedridden. Living with pain is influenced and sometimes complicated by social, family, legal, insurance and political factors. For example, some people are told they will lose financial benefits or other types of critical support if they improve. Those involved in lengthy lawsuits may hesitate to get better or gain function due to the fear that they will lose any chance of financial compensation,

which they believe they deserve. In some instances, pain has spurred an unhappy employee to leave a job in which they never felt valued. At times, having pain becomes a way of saying "no" to situations or people we have never been able to refuse. In some families, pain becomes a way to express anger, get care or be excused from responsibilities. These situations are damaging far beyond what is happening in your body. It is very important to understand how pain fits into the larger context of your life so you can identify ways to diminish harmful influences.

When appropriate, vocational counseling and rehabilitation can help to create a gradual path to more productive, fulfilling employment so that worries about the loss of compensation are replaced with possibilities. Behavioral modification can help people separate the multitude of issues surrounding pain and devise a step-by-step approach to confronting challenges through behavior change and shifting attitudes.

STRESS MANAGEMENT

Stress and anxiety can influence pain in ways you may not realize. Additionally, depression and feeling disheartened influences the ability to cope with pain and any other challenging life experience. When pain levels increase and the usual relief methods do not work as well as before, anxiety and catastrophic thoughts can cause more distress. This can result in a vicious cycle, which can often be avoided or managed. A first step in gaining control over this cycle is to create a process to observe your thoughts and understand your unique, individual pattern. This can be a beginning step in changing how much pain is allowed to rule your quality of life.

Simple Stress Management Suggestions

- **Structure and Predictability:** Try to set and keep a routine schedule of activities, rest and medications. Some people find that controlling the pace and abruptness of change reduces stress. While it is sometimes difficult to predict change, you may find aspects of your daily routine that you can control.
- **Activity:** Find an activity or exercise program that you like and make it part of your daily routine. It might be Tai Chi, yoga, walking or water aerobics. Talk with your pain practitioner for guidance about how to introduce any of these into your pain management regimen. It has been said that once you repeat something at least 25 times, it becomes a new habit.
- **Positive Outlook ("Self-talk"):** Many people living with persistent pain may wonder how to have a positive attitude about their situation when they haven't done so before. Some may find the pain experience too devastating and overwhelming. Others believe they can move beyond their pain to use positive language or think thoughts that give a sense of power rather than those that seem discouraging. You may have to practice this skill over and over and experiment with the results but ... *First you need to hear yourself...*and perhaps you may need to ask those who know you well about how they hear you. You may want to consider the following suggestions as you think about your personal "self-talk."

- Practice POSITIVE self-talk: You are a whole person with a past and a future, with special talents and accomplishments. Do not allow pain to take that away from you.
 - Celebrate your successes, no matter how small they may appear!!!
 - Concentrate on being around people and places that make you feel valued and *GOOD about yourself*.
 - Think about those friends, family members, social settings, projects and/or work situations that bring meaning, joy and satisfaction to your life; surround yourself with these influencers.
 - Think about the situations and/or people who cause you to feel badly and either limit your exposure to them or learn to interact with them so they do not affect your body, your pain and your feelings about yourself.
- **Balance:** Learn how to live in the moment. Experience the now, by shutting off the constant chatter in your mind: your thoughts, plans and perceptions; quiet the pressures caused by expectations from yourself as well as from others.
- Coping techniques that help you relax may already be part of your life and it will be easy to build them into your pain management plan. You may want to learn from others. These techniques might include meditation, prayer, walking, nature, soothing music or scents (lavender, cinnamon, ylang-ylang, vanilla).
 - Practice deep breathing whenever you feel stressed:
 - * Inhale slowly and deeply through your nose, hold for a count of five.
 - * Exhale slowly (through your nose helps slow you down) for a count of ten.
 - * Repeat three to four times until you feel relaxed.
 - Remember what is really important to you in life and make this a priority.

HYPNOTHERAPY/HYPNOSIS

Therapeutic or medical hypnosis is a method of directing one's focused attention inward to achieve benefits like relaxation and the lessening of pain and/or anxiety. With a skilled hypnotherapist, you can explore your own potentials for greater control over your experience of pain. Once you have practiced with the hypnotherapist, self-hypnosis can be taught.

Although hypnosis has been shown to reduce **pain perception**, it is not clear how the technique works. Some studies have shown that a proportion of those with moderate to severe pain were able to achieve total relief while under hypnosis. Other studies report that hypnosis reduces anxiety and depression.

COUNSELING

Living with pain can evoke a range of feelings from fear and anger to hopelessness, confusion and isolation. Family and other significant people in your life may have similar feelings. Counseling for you and, in some cases, with your family can help. Working either in private sessions or within support groups may be suggested. Most of us are familiar with acute pain and react to our loved ones and friends with the expectation that over time the pain will go away. When that doesn't happen, we may continue to act as if it will eventually go away if we ignore it long enough or seek additional medical input to search for the cause and cure. It is very difficult to imagine that persistent pain may be a lifelong condition. Many find tremendous benefit from individual or group counseling specifically focused on pain and related worries. Trained professionals can teach useful skills, and provide needed emotional support and guidance. When choosing a therapist, working with a counselor with experience in pain management is preferable.

Physical Rehabilitation *for* Pain Management



PHYSICAL REHABILITATION FOR PAIN MANAGEMENT

Physical methods have been used for pain relief for centuries. Reportedly, Hippocrates (420 BC) — considered the father of medicine — used a warm water bag to treat pain from sciatica. Today, there are a variety of skilled healthcare professionals with specialized training in the use of physical techniques that help reduce pain. Many work in the field of rehabilitative medicine, and include physiatrists (physicians who specialize in physical medicine), physical therapists, occupational therapists and exercise physiologists.

● **Physiatry**

Physiatry — also called Physical Medicine and Rehabilitation — is a branch of medicine focusing on the diagnosis, treatment and management of disease primarily using "physical" methods of care, such as physical therapy and other methods. Physiatrists provide a wide variety of treatments for the musculoskeletal system (the muscles and bones) and do not perform surgery. Because the back is the core of the musculoskeletal system, many physiatrists are considered specialists in treating back pain. A number of physiatrists have additional training in special areas, like sports medicine, brain (e.g., stroke) or spinal cord injury, pain management or pediatric medicine.

Some physicians of rehabilitative medicine have had different training than others. They may be Doctors of Medicine (MDs) or Doctors of Osteopathy (DOs). A DO has attended an independent medical school and received identical training in basic science and clinical medicine as MDs; however, they are trained to use a holistic approach to healthcare that includes an additional 300-500 hours of training in osteopathic manipulative medicine (OMT). Most DOs practice no differently than MDs, and not all continue to use OMT. To find a DO who uses OMT in their practice, you must ask if they specialize or have additional interest in osteopathic manipulative medicine.

DOs are different than chiropractors (see *CAM section*). Chiropractors are independent practitioners with limited licenses to practice spinal manipulation and may incorporate nutrition into their practices. Unlike DOs or MDs, they cannot prescribe prescription medications, admit patients to hospitals or perform surgery.

● **Physical Therapy**

Physical Therapists (PTs) provide services that help restore function, improve mobility, relieve pain and prevent or limit permanent physical disabilities of those suffering from injuries or disease. They restore, maintain and promote overall fitness and health. They work with accident victims, as well as individuals with disabling conditions such as low-back pain, arthritis, heart disease, fractures, head injuries and cerebral palsy.

Therapists first examine medical histories and then test and measure the individual's strength, range of motion, balance and coordination, posture, muscle performance, respiration and motor function. They help determine one's ability to be independent and assist with the return to the community/workplace after an injury or illness. The overall goal is to improve and maximize how an individual performs in their work setting and at home.

Physical therapists use a variety of treatment methods to relieve pain and reduce swelling including electrical stimulation, hot packs, cold compresses, traction, deep-tissue massage and ultrasound. They also teach patients to use assistive or adaptive devices, such as crutches, prostheses and wheelchairs. Exercise training is often

provided, which can be performed at home to help advance recovery by reducing immobility and improving flexibility, strength and/or endurance. As treatment continues, physical therapists document the individual's progress, conduct periodic examinations and modify therapies when necessary. Besides tracking progress, they help identify areas that may require more or less attention.

PTs consult and practice with a variety of other professionals, such as physicians, dentists, nurses, educators, social workers, occupational therapists, speech-language pathologists and audiologists. Some treat a wide range of conditions; others specialize in areas such as pediatrics, geriatrics, orthopedics, sports medicine, neurology, pain management and cardiopulmonary physical therapy.



● Occupational Therapy

Occupational therapists (OTs) help people perform tasks required for daily living and in the work setting. They work with those who have mentally, physically, developmentally or emotionally disabling conditions. OTs help to improve their basic movement and thinking skills, as well as adaptive behaviors when there is a permanent loss of function. Their overall goal is to help individuals have independent, productive and satisfying lives.

Occupational therapists assist in performing activities of all types, ranging from using a computer to mastering everyday needs such as dressing, cooking and eating. Physical exercises may be used to increase strength and skillfulness. Therapists instruct those with disabilities in the use of adaptive equipment, including wheelchairs, splints and aids for eating and dressing. They can design or make special equipment needed at home or at work.

Some occupational therapists treat individuals whose ability to perform in a work environment has been impaired. OTs can help arrange for work re-training and/or new employment, and may team up with the individual and the employer to evaluate the work environment, plan work activities, and provide a progress report on work performance. If needed, they help modify the work environment so that work can be successfully completed.

● Exercise Physiology

Exercise physiologists (EP) are commonly seen working in wellness or fitness centers. Their duties include developing exercise routines and educating people about the benefits of exercise. EPs may also work in clinical settings prescribing exercise for individuals with special risks, such as cardiac and pulmonary disease. Services they may provide include:

- Assessment of functional abilities, including monitoring cardiovascular and metabolic state
- Risk profile for various exercise modes and intensities
- Health-behavior change counseling and management
- Specific physical activity prescription (to accommodate current health status)
- Exercise supervision or delivery for individual or group settings

They provide the pain management team regular reports on individual progress.

REHABILITATIVE TECHNIQUES

The most common physical methods for pain management offered by rehab services are:

● Exercise

Exercise and physical activity are beneficial not only for the body, but also the mind, spirit and soul. Making a commitment to carve out a little time for exercise everyday is challenging for those who do not live with pain. It is much more difficult when simple movements like walking and changing positions causes pain.

Exercise not only keeps you healthy, it also helps reduce pain over time. Weight-bearing and cardiovascular exercise strengthens your heart, lungs, bones and muscles. This becomes even more important as we age. Physical activity protects against falls and bone fractures in older adults. Research also suggests that exercise may help control joint swelling and pain caused by arthritis. If we don't "use it, we lose it." Exercise helps preserve strength, agility and independence as we age.



The benefits of exercise are not only physically tangible; exercise has a profound effect on your mental state as well. Regular physical activity helps you cope with stress, improve your self-image, and ease anxiety and depression by releasing pleasure chemicals in our brains called endorphins. Research even suggests that physical fitness can make you more mentally alert. By incorporating group exercise with friends or family into your routine, you can also use exercise to strengthen your bonds with others. Connecting with friends and family is a key aspect of good emotional health. Too often, living with pain, leads to isolation.

Here are a few tips:

- Find something that you enjoy.
- Remember your routine need not start out at a vigorous pace. Try walking. Look into yoga classes to help you stretch and become more flexible. Tai Chi offers a low impact workout that promotes physical and mental well-being.
- Ask your instructors if they have experience working with those who live with chronic pain.
- Consult your healthcare professional before beginning any exercise program.

● Hydrotherapy, Heat and Cold

Hydrotherapy is the use of water to maintain health or promote healing. Water has been part of healthcare since the beginning of civilization. Today, aspects of hydrotherapy are taught as part of healthcare training. Also known as Aquatic or Pool Therapy, the use of therapeutically warm water and exercise may help ease painful muscles and joints. Gentle movement may help build strength, relax stiff joints and sore muscles. Water buoyancy greatly reduces the pressure on joints, making it easier to perform range of motion exercises.

The use of ice packs, hot water bottles, heating pads and counter-irritant preparations, like Tiger Balm, Icy Hot or Ben Gay, are familiar in popular culture. For example, many use the application of ice to a sprained ankle or soaking in a hot

tub to soothe sore muscles. Steam can open clogged sinuses; ice packs can relieve swelling. Cold-based hydrotherapies, such as ice packs and cold compresses, decreases swelling and pain by constricting blood vessels and numbing nerve endings. On the other hand, heat-based hydrotherapies, such as whirlpools and hot compresses, have the opposite effect. As the body attempts to throw off the excess heat and keep body temperature from rising, dilation of blood vessels occurs, providing increased circulation to the area being treated. This helps relax muscle spasms and relieve pain.

Today hydrotherapy is a part of the physical therapy department of virtually every hospital and medical center. Various techniques using water are considered standard strategies for rehabilitation and pain relief. Many forms of hydrotherapy are also available at health spas and resorts. Be sure to check with your healthcare provider and verify the credentials of the spa before going.



● Myofascial Therapy

A gentle blend of stretching and massage, myofascial release therapy uses hands-on manipulation of muscle and skin to relieve pain and promote healing. According to practitioners of myofascial release, scarring or injury to this network of connective tissue and muscle is a major cause of pain and restricted motion. The easy stretch is aimed to alleviate these problems by breaking up, or releasing, constrictions or snags in the fascia. People with longstanding back pain, fibromyalgia, recurring headaches, sports injuries and other chronic pain disorders may benefit from this technique.

Myofascial release is part of a larger philosophy of healing that emphasizes the importance of mind-body interactions and preventive care. It is based on the idea that poor posture, physical injury, illness and emotional stress can throw the body out of alignment, which causes the fascia and muscle to become tight and constricted. Scarring or adhesions form. The gentle and sustained stretching of myofascial release is believed to free adhesions and soften and lengthen the fascia. The stretch may be held for one to two minutes, and sometimes for up to five minutes, before a softening, or "release," is felt. The release indicates that the muscle is relaxing, fascial adhesions are slowly breaking down, or the fascia has realigned to its normal position. The process is then repeated until the tissues are fully elongated.

Sessions typically last 30 minutes to an hour and may be given one to three times a week depending on your condition. Some people immediately feel better - even free of pain - and are able to move their joints more freely as soon as the session is over. Others feel some discomfort that night or the next day. Any soreness should subside within a day or two, and you should feel less pain and be able to move more easily than you did before.

Exercises are tailored to your individual needs, and you should be given exercises to do at home. Unlike stretching routines for specific sports, these exercises will be designed to lengthen the muscles and connective tissues in various directions. To relieve tightness in the pelvic region, for instance, you may lie with your hip resting on a small foam ball for several minutes.

● Osteopathic Manipulation Treatment (OMT)

Osteopathic medicine is a form of conventional medicine that highlights diseases arising in the musculoskeletal system. This practice follows an underlying belief that all of the body's systems work together, and disturbances in one system may affect function elsewhere in the body. The use of a hands-on technique called osteopathic manipulation treatment (OMT) may be considered to help reduce pain, restore function and promote health and well-being.

OMT covers a wide range of services including spinal manipulation, connective tissue release, soft-tissue techniques, muscle energy and cranial osteopathy. It is considered more comprehensive than a chiropractic spinal adjustment. OMT works to release blockages in a person's body to promote health. By removing restrictions in the muscles, nerves, blood vessels, ligaments, etc., the patient's body is able to move more freely allowing it to heal itself more effectively. As previously stated, some DOs practice osteopathic manipulation, particularly those who specialize in physical medicine.

● Splints

Casts, splints and braces are more commonly known as tools to support and protect injured bones and tissue following an injury. By shielding the injury, they allow for more rapid healing and help prevent further injury. They can also help reduce pain, swelling and muscles spasms.

At times, pain from inflammation, like in arthritis, causes swelling, which, in turn, increases pain. Your provider may suggest a splint to help you rest the affected area. Periodic rest with support and elevation may help to reduce the swelling and pain that has already occurred.

Wearing splints or braces during certain activities may also be recommended to help prevent pain, particularly when repetitive motion is a primary cause. Whether you are advised to wear a splint all day or only at night, this technique may help decrease additional irritation and lessen the degree of swelling and pain that might occur without one.

Protective devices such as light compression gloves/socks or splints, may be recommended if you have neuropathic pain that affects your hands and/or feet. These may help reduce swelling and decrease pain from light touch or light pressure.



● **Transcutaneous Electrical Nerve Stimulation (TENS)**

TENS is a method commonly managed by physical therapy as a means to decrease pain without needles or surgery. The TENS unit is designed to block or prevent pain by providing opposing stimulation to compete with the unpleasant signals that cause pain. The TENS sensation(s) interrupt pain signals in the body. The mechanisms by which TENS can relieve pain are not understood.

TENS can be used in the treatment of acute and chronic pain, including pain of the lower back, neck, pelvis, nerves (CRPS/RSD, **neuritis**) and muscles (fibromyalgia, myofascial).

Used properly, TENS units are very safe, and do not hurt to apply or wear. The best time to wear TENS is during activities or times of the day when your pain is generally the most severe. The sensation should feel comfortable or pleasurable when the unit is turned on. They are battery-operated (9-volt). A TENS unit will NOT electrocute you. To prevent an unintentional shock, they should NOT be worn in the shower or bath tub or be turned up too high. It is not recommended to be used with a demand-type cardiac pacemaker. Also, there are specific areas of the body that should be avoided, like over the larger blood vessels (arteries) in the neck.

ADDITIONAL PHYSICAL METHODS

There are other physical methods that may be offered to aid in pain reduction and improvement of movement. Depending on the practice size, location and experience of the providers may determine the scope of services. These methods may be performed by a physical therapist with special training or a complementary practitioner (see *CAM section*).

● **Chiropractic** (See *CAM section*)

● **Craniosacral Therapy**

A gentle form of manipulation, **craniosacral therapy**, is a hands-on healing technique typically practiced by physical therapists, massage therapists and chiropractors. Craniosacral therapists believe the movement of spinal fluid within and around the central nervous system creates a vital body rhythm, no less important to health and well-being than the heartbeat or breath. Health problems develop, they contend, when blockages occur. Practitioners assert that craniosacral therapy reestablishes the normal flow of fluids and thus restores health.

By law, craniosacral therapists are not allowed to make a medical diagnosis. For this reason, the technique should not be confused with cranial osteopathy, a diagnostic and therapeutic method of treatment that is practiced by highly trained osteopathic physicians. A session usually lasts from 20 minutes to an hour.

● **Feldenkrais (Functional Integration)**

The **Feldenkrais Method** is a form of somatic education that uses gentle movement and directed attention to improve movement and enhance human functioning. Through this method, you learn to improve your ease of motion, increase your range of motion, expand your flexibility and coordination, and rediscover your ability to move gracefully and effectively. These improvements may enhance functioning in other aspects of your life such as pain reduction.

The **Feldenkrais Method** is based on principles of physics, biomechanics and an understanding of learning and human development. By expanding the self-image through movement sequences that bring attention to the parts of the self that **are out** of awareness, the method enables you to include more of yourself in your everyday activities.

● **Rolfing (Structural Integration)**

Rolfing emerged from the concept that humans function most efficiently and comfortably when key parts of the body, such as the head, torso, pelvis and legs, are properly aligned. There are different versions of Rolfing. Rolfing is a form of myofascial massage guided by the contours of the body. Rolfers use their fingers, hands, elbows and knees to place deep pressure and shift bones into proper alignment. Their goal is to increase range of motion and make movement easier by correcting posture misalignments. Rolfing can sometimes be painful.

● **Trager Approach**

The **Trager Approach** is a form of movement consisting of a series of gentle, passive movements, along with rotation and traction of arms and legs to relieve muscular tightness without pain. This technique was developed in the early 1900s to help polio victims. Some with chronic pain due to muscle spasm have reported noticeable pain relief beginning with the first session.

The practitioner moves select parts of the body in a light rhythmical fashion so that you can experience the feeling of this light, effortless movement. The goal of each session is to help reduce stress and to find more effective ways to deal with stressful situations. Added benefits are enhanced conscious awareness, greater flexibility, improved self image, greater energy and reduced constriction and rigidity.

The following are commonly recommended techniques, which can be done at home as part of a self-care program:

Icing. Ideal for pain related to recent injury, re-injury or inflammation like with strains, sprains and bruises. It can easily be done anywhere. Cold has a numbing effect. However, placing ice directly on your skin can cause nerve damage. Be sure to place a thin towel or pillow case between your skin and the cold source, whether using ice cubes in a plastic bag, a frozen pack of peas (or corn) or a gel pack. Ice for 20 minutes, and then remove it until the surrounding skin returns to normal temperature before re-applying. This can be repeated on a regular basis every two hours throughout the day.

Compresses. To make a wet compress soak a cloth in hot or cold water and squeeze out the excess until the desired amount of moisture remains. Single or double compresses may be used. Grain pillows, gel-packing and certain heating pads (follow the manufacturer directions) can be used. A single compress involves the use of the wet cloth over the affected area. A double compress includes placing a dry material such as wool or flannel over the wet compress.

A cold compress can be used to decrease swelling, reduce blood flow to an area or inhibit inflammation. Cold should not be used in the presence of circulation disorders, like peripheral vascular disease, certain heart conditions and diabetes, unless pre-approved by your healthcare professional.

A hot compress can have an analgesic effect, thereby decreasing pain. When using hot water, the double compress serves to retain the heat. Hot compresses can also be used to lessen the discomfort from muscle cramping or spasm and improve blood flow to a particular part of the body. Separate, alternating or simultaneous use of hot or cold compresses can be applied for pain relief depending on the individual preference. When using a microwave to heat a gel pack or grain pillow, please follow the directions to avoid extreme heat that could cause skin burn.

Baths. Either immersing the entire body or simply the affected part of the body can be

helpful. Hot full-immersion baths can help with arthritic discomfort and conditions where muscles are in painful spasm, such as fibromyalgia. For a neutral (or tepid) bath the temperature should be neither too hot nor too cold. These are mainly used for relaxation purposes and to treat stress-related ailments such as insomnia, anxiety and nervous exhaustion. Cool baths can relieve swelling or inflammation.

Sitz baths. Taking sitz baths involves partially immersing the pelvic region. A hot sitz bath can help reduce pain from hemorrhoids, abdominal cramping or sciatica. A special sitz bath seat can be purchased at most pharmacies.

Cold friction rubs. A friction rub involves massaging a particular area of the body with a rough washcloth, terry towel or loofah that has first been placed in ice water. Friction rubs have a toning effect that helps to increase circulation and tighten muscles.

Counter-irritants. Better known as heating or cooling creams, lotions or salves applied to the skin over the painful area. They are either gently rubbed around the skin surface or used with massage or myofascial release treatments. They can be used as a single agent for either the preferred heat or cooling effects, alternating between the two sensations or in combination with a therapy that provides the opposite effect.

Alternating. Use one preparation that heats, wait for effect to wear off and skin returns to normal temperature, wash off remaining product before applying opposite preparation that cools.

Combination. Apply product that heats. Be sure to protect the skin by placing plastic wrap over area, then place ice pack on top. Remove ice pack within 15-20 minutes and wait 30 minutes before reapplication of ice pack.

Whenever these preparations are used, it is important to avoid using two therapies that enhance the same temperature effect to avoid heat or cold burns to the skin. For example, if you plan to take a hot shower or apply a heating pad to an area previously treated, wait for the product effect to wear away and wash off any remaining product.

Complementary & Alternative Medicine {CAM}



COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM)

Many Americans are using complementary and alternative medicine (CAM) therapies, and many conventional (allopathic) doctors are incorporating these therapies into their practices. Medical schools across the country — including Yale and Harvard — now offer courses in complementary and alternative medicine (CAM). In 1999, the National Institutes of Health opened the National Center for Complementary and Alternative Medicine (NCCAM) to evaluate these methods. NCCAM was created to advance the scientific study of CAM to help answer questions about safety and the effect on health promotion, disease prevention and/or management of medical disorders.

CAM Therapies and Practices On the Rise

More and more Americans are turning to CAM to help manage and treat various health problems, including pain and stress.

Consider these facts:

- According to surveys, seven out of ten Americans use some form of CAM.
- Americans spend at least \$34-47 billion on CAM therapies, exceeding out of pocket expenses for all U.S. hospitalizations. CAM is expected to grow by 15 percent each year.
- People report using CAM because these methods mirror their personal beliefs, values and philosophical orientations toward life.
- Many people use CAM to help relieve back pain, joint pain, severe headache and pain associated with migraines, dental and jaw pain and for a variety of other reasons.
- Being able to deliver integrated medicine, which incorporates proven CAM therapies into “mainstream” care, is increasingly important to consumers and healthcare providers.

CAM: What Is It?

NCCAM defines CAM as “a group of diverse medical and healthcare systems, practices, and products that are not presently considered to be part of conventional medicine.” Most CAM therapies take a *holistic* approach to care — treating the mind, body and spirit. Some of these approaches, such as acupuncture, mind-body therapies (e.g., biofeedback), yoga and massage are widely used and accepted. For this reason, they have been *integrated* into medical care. Integrative approaches may be the most effective for people living with pain. For example, acupuncture, mind-body techniques, energy therapies and chiropractic care can be used along with analgesics (pain

Much of the information presented in this chapter is adapted from the National Center for Complementary and Alternative Medicine (NCCAM) Web site and educational materials on CAM. For more information, visit nccam.nih.gov.

medication) to reduce pain. Other CAM therapies are not widely accepted by the medical community and some carry risks, so make sure to speak with your healthcare provider about CAM.

CAM is expected to grow as therapies are proven safe and effective, adopted into routine healthcare and new approaches become known.

What is the difference between complementary medicine, alternative medicine and integrative medicine?

Complementary medicine is used **together with** conventional medicine. An example of a complementary therapy is using massage therapy to help lessen a patient's discomfort for the relief of musculoskeletal pain/discomfort.

Alternative medicine is used in place of conventional medicine. An example of an alternative therapy is using a special diet to treat cancer instead of undergoing surgery, radiation or chemotherapy that has been recommended by a conventional doctor.

Integrative medicine combines conventional medical therapies and CAM therapies for which there is some high-quality scientific evidence of safety and effectiveness.

NCCAM classifies CAM therapies into five categories:

1. Alternative Medical Systems

Alternative medical systems are built upon complete systems of theory and practice. Often, these systems have evolved apart from and earlier than the conventional medical approach used in the United States. Examples of alternative medical systems that have developed in Western cultures include homeopathic medicine and naturopathic medicine. Examples of systems that have developed in non-Western cultures include traditional Chinese medicine and Ayurveda.

2. Mind-Body Interventions

Mind-body medicine uses a variety of techniques designed to enhance the mind's capacity to affect bodily function and symptoms. Some techniques once considered CAM have been part of conventional medicine for decades, like patient support groups and cognitive-behavioral therapy. Other mind-body techniques are still considered CAM, including meditation, prayer, mental healing and methods that encourage creative expression such as journaling, art or music.

3. Biologically Based Therapies

Biologically based therapies involve substances found in nature, such as herbs, foods and vitamins. Some examples include dietary supplements and herbal remedies. This may include the use of other substances that have unsubstantiated scientific value, such as shark cartilage used in cancer treatment.

4. Manipulative and Body-Based Methods

Manipulative and body-based methods are based on manipulation and/or movement of one or more parts of the body such as chiropractic techniques, osteopathic manipulation and therapeutic massage.

5. Energy Therapies

Energy therapies involve the use of energy fields. They are of two types:

Biofield therapies are intended to affect energy fields that surround and penetrate the human body. The existence of such fields has not yet been scientifically proven. Some forms of energy therapy manipulate biofields by applying pressure and/or manipulating the body by placing the hands in, or through, these fields. Examples include Qigong, Reiki and Therapeutic Touch.

Bioelectromagnetic-based therapies involve the unconventional use of electromagnetic fields, such as pulsed fields, magnetic fields, or alternating current or direct-current fields.

OVERVIEW OF CAM THERAPIES

Alternative Medical Systems

- **Homeopathic medicine** is an alternative medical system. In homeopathic medicine, there is a belief that "like cures like." Highly diluted quantities of medicinal substances are given to cure symptoms, when the same substances given at higher or more concentrated doses would actually cause those symptoms. To date, there is no scientific evidence supporting the use of homeopathic medicine for pain.
- **Naturopathic medicine**, or naturopathy, is an alternative medical system. Naturopathic medicine proposes that there is a healing power in the body that establishes, maintains and restores health. Practitioners work with the patient with a goal of supporting this power through treatments such as nutrition and lifestyle counseling, dietary supplements, medicinal plants, exercise, homeopathy and treatments from traditional Chinese medicine.
- **Traditional Chinese Medicine (TCM)** is the current name for an ancient system of healthcare from China. TCM is based on a concept of balanced qi (pronounced "chee"), or vital energy, that is believed to flow throughout the body. Qi is thought to regulate a person's spiritual, emotional, mental and physical balance and to be influenced by the opposing forces of yin (negative energy) and yang (positive energy). Disease is believed to result from the flow of qi being disrupted and yin and yang becoming imbalanced. Among the components of TCM are herbal and nutritional therapy, restorative physical exercises, meditation, acupuncture and therapeutic massage.

Acupuncture is a method of healing developed in China at least 2,000 years ago. Acupuncture has a growing acceptance in the field of conventional medicine. Today, acupuncture describes a family of procedures involving stimulation of anatomical points on the body by a variety of techniques. American practices of acupuncture incorporate medical traditions from China, Japan, Korea and other countries. The acupuncture technique that has been most studied scientifically involves penetrating the skin with thin, solid, metallic needles that are manipulated by the hands or by electrical stimulation.



Acupressure is an ancient Chinese healing method that involves applying pressure to certain meridian points on the body to relieve pain. These meridians start at the fingertips, connect to the brain, and then connect to the organ associated with the specific meridian. Acupressure relaxes muscular tension and balances what are thought to be the vital life forces of the body. The patient lies fully clothed on a soft massage table while the practitioner presses gently on points situated on various parts of the body. The session is non-invasive and gentle. An average session lasts for about one hour. However, most people require a number of sessions to complete a treatment.

- **Reflexology** is a healing art based on the principle that specific points on the feet and hands correspond to specific parts of the body. By applying pressure to the feet or hands, an increase in circulation and energy is stimulated to specific bodily and muscular functions. People often experience deep relaxation and sense of well-being.
- **Ayurveda** is an ancient Eastern Indian approach to healthcare that has been practiced primarily in the Indian subcontinent for 5,000 years. Ayurveda includes diet and herbal remedies and emphasizes the use of body, mind and spirit in disease prevention and treatment.

Mind-Body Interventions

The mind is the most powerful healing tool.

Mind-body techniques focus on influencing changes at the higher brain centers where information is processed for the perception of pain, where thought can interrupt the pain message, as well as your feelings and fears. Simple changes in our thoughts can change our behavior. For example, when we learn to turn off our negative "self-talk" and change our internal conversation to a dialogue with positive messages, our mood lifts and we feel better physically, emotionally and spiritually.

Mind-body techniques are powerful options to incorporate into daily living. Examples include distraction, meditation, prayer, guided imagery, hypnosis, relaxation/breathing exercises (commonly used in prepared childbirth classes) and biofeedback.

- **Mindfulness Meditation** (*See Psychosocial section*)
- **Prayer** is often considered a spiritually-focused meditation. Prayer has been shown to have dramatic effects. Prayer is used to promote healing, relieve pain, enhance comfort and relaxation and ease the transition during life changes.
- **Guided Imagery** (*See Psychosocial section*)
- **Hypnosis/Hypnotherapy, Relaxation and Breathing Exercises and Biofeedback** (*See Psychosocial section*)
- **Mind-Body Disciplines** are techniques and practices aimed at integrating mind, body and spirit by achieving physical conditioning, as well as a state of peace, being centered or feeling grounded. Yoga and Tai Chi are centuries old, whereas Pilates was developed in the early 1900s.
- **Pilates** is a method of body conditioning that focuses on the core postural muscles essential to spinal alignment, muscular flexibility and strength. By using spring-based equipment, the person uses their own body's resistance to improve strength,

circulation, posture and breathing, critical to decreasing pain and improving body awareness and muscular tone. A teacher should have experience in working with individuals with chronic pain, be certified through a 400-600 hour certification program and have a fully equipped studio.

- **Tai Chi** is an ancient Chinese discipline. In addition to its physical benefits, there are certain psychological effects as well. Tai Chi also provides a form of meditation. This form of meditation is rooted in self-control, which can come from learning how to create a natural balance (harmony) within yourself. The effect of this harmony is to capture both physical and spiritual well-being.

Tai Chi, as it is practiced in the West today, can best be thought of as a yoga and meditation combined. There are a number of *forms* (also called 'sets') which consist of a sequence of movements. Many of these movements are originally derived from the martial arts and from the natural movements of animals and birds. Tai Chi is performed slowly, softly and gracefully with smooth and even transitions between forms.

The concentration used to execute Tai Chi fosters a calm and tranquil mind.
Learning Tai Chi forms correctly provides a practical ground for learning balance, alignment, fine-motor control, rhythm of movement and the peace of silence. Tai Chi can help you to better stand, walk, move and/or run. Many practitioners notice benefits in terms of correcting poor postural, alignment or movement patterns which can contribute to tension or injury. The meditative nature of the exercises is calming and relaxing.

- **Yoga** is an ancient Indian discipline that teaches balance, flexibility and meditation. In its most authentic expression, yoga is not exercise or religion, but an ancient method of stilling the mind, cultivating kindness and compassion towards ourselves, and resisting the urge to over-identify with the physical body. There are different forms of yoga. For example, Hatha yoga is considered the oldest comprehensive form of self care — physical, mental, emotional and spiritual — to bring balance and enhanced wellbeing. Hatha yoga includes body positions or poses, breathing techniques, relaxation and sustained concentration or meditation.

The poses (*asanas*) improve posture through stretching, toning and strengthening the muscles, joints and the spine. They also stimulate and balance the internal organs, glands, nervous system, and circulatory and respiratory systems. Through proper breathing, the mind is calmed and the whole body is cleansed and revitalized. By learning relaxation techniques before and after yoga poses, the body and mind can experience a new form of rest. A goal of the practice of yoga is to learn how to find the calm, quiet place inside yourself, which can console you during times of stress, pain or the need for restoration.



Biologically Based Therapies

- **Aromatherapy** involves the use of essential oils (extracts or essences) from flowers, herbs and trees to promote health and well-being. Essential oils have been used for thousands of years all over the world, and may be used in a bath, vaporizer, spritzer bottle or in other ways. Most essential oils are diluted for use in water, cream or non-scented oils. Some essential oils may be used topically. When using essential oils, you should be told about the expected benefits and risks and the proper way to use them.
- **Dietary supplements** are products (other than tobacco) taken by mouth that contain a "dietary ingredient" intended to supplement the diet. Congress defined the term "dietary supplement" in the Dietary Supplement Health and Education Act (DSHEA) of 1994. Dietary ingredients may include vitamins, minerals, herbs or other botanicals, amino acids and substances such as enzymes, organ tissues, and metabolites. Dietary supplements come in many forms including extracts, concentrates, tablets, capsules, gel caps, liquids and powders. They have special requirements for labeling. Under DSHEA, dietary supplements are considered foods not drugs.

Herbal remedies and supplements are increasingly being used and studied for pain treatment and pain-related symptoms. Ideally, they should be recommended and monitored by a healthcare professional. If you are using them without supervision, please report this to your healthcare provider. Examples are:

Feverfew: Migraine headache; arthritis
Glucosamine & Chondroitin: joint pain, like with arthritis or degenerative disease
Ginger: Anti-inflammatory as with arthritis; reduces nausea
Ginkgo Biloba: Migraine headache; lower leg pain due to poor circulation
Ginseng: Fibromyalgia; Chronic fatigue
Kava Kava: Tension headache, insomnia, neuropathic pain
Melatonin: Insomnia
Pycnogenol: Arthritis
St. John's Wort: Sciatica, arthritis, and neuropathic pain, depression
Tiger Balm (Menthol; Camphor): Muscular pain and spasm (used with massage; myofascial release)
Valerian Root: Insomnia, anxiety, nervousness, spasms, muscle cramps

- **Nutrition.** Maintaining an ideal body weight supports health and well-being and reduces excess burden on painful conditions, including back and knee pain, arthritis and diabetes. If this is a problem for you, a dietician can help you pursue a weight loss program. This can help relieve pain associated with low back pain or joint pain disorders.

Eliminating nicotine and minimizing alcohol use is also beneficial. There is increasing evidence that smoking tobacco has a strong influence on the prevalence of low back pain. Limiting alcohol lowers the risk of alcohol related neuropathies and pancreatitis. Most medications used for pain treatment should not be taken while drinking alcohol. Excessive alcohol intake changes the liver where the filtering of most pain medications takes place upon entering the bloodstream. As the liver becomes damaged, medication therapy is less effective.

Manipulative and Body-Based Methods

- **Chiropractic Care** is a therapeutic approach that focuses on the relationship between bodily structure (primarily that of the spine) and function, and how this relationship affects the protection and restoration of health. Chiropractors use spinal manipulative therapy as a basic treatment tool.

The roots of chiropractic care can be traced to the beginning of recorded time. Ancient writings mention spinal manipulation and the adjustment of the lower extremities to ease low back pain. The primary belief of the chiropractic profession supports a natural method of healthcare that includes a deep respect for the human body's ability to heal itself without the use of surgery or medication. Chiropractors give careful attention to the biomechanics, structure and function of the spine, its effects on the musculoskeletal and neurological systems, and the role played by the proper function of these systems in the preservation and restoration of health.

Chiropractors frequently treat individuals with a variety of pain disorders, such as headaches, joint pain, neck pain, low back pain and sciatica. They also treat patients with osteoarthritis, spinal disk conditions, carpal tunnel syndrome, tendonitis, sprains and strains.

- **Osteopathic Medicine** (*See Rehabilitative section*)

- **Massage** therapists manipulate muscle and connective tissue to enhance function of those tissues and promote relaxation and well-being.

Massage is an old healing art with many techniques and approaches. Massage acts directly on the nervous system, activating the opposite of the "fight or flight syndrome" and promoting relaxation. It eases painful and tight muscles using stretch that gently separates individual muscle fibers that may have become bound and knotted together. This reduces spasm.

Massage can help:

- Increase range of motion in your joints by releasing muscle tension around them;
- Enhance circulation, cleansing your body of waste products (toxins) that can cause fatigue and soreness;
- Stimulate the healthy production of the joint's natural lubrication; and,
- Relieve secondary pain that builds up around a primary pain or injured site.

Secondary pain has been known to last longer than the primary cause. For example, headaches can be caused from tense shoulder and neck muscles, shooting leg pain can originate from tight low back muscles and stiff hip joints. Massage aids in the release of endorphins (your body's natural morphine) that reduces pain and gives the sensation of feeling good.

It is most important to drink plenty of water following massage to help rid the body of toxins that are released. Massage also promotes a restful sleep by helping the body and mind relax. At the same time, people experience an overall increase in vitality, energy and alertness.



● **Therapeutic Massage** is the biomechanical manipulation of soft tissue for the purpose of restoring or maintaining balance within and among the various systems of the body-mind complex while the body is at rest and the mind is letting go. Aromatherapy, music therapy and special massage lotions are frequently used. Therapeutic massage should be administered by an individual with special training and certification in this form of body-mind work.

● **Simple Massage** is either self-massage or a focused-area massage performed by a family member, friend or healthcare provider without special certification in therapeutic massage. This type of massage may be used with counter-irritant products, like Tiger Balm, Icy Hot or warmed lotion/creams.

Energy Therapies

- **Biofield (also known as Touch) Therapies** originate from an ancient technique called "laying-on of hands" or the "sharing of energy." The recipient of the therapy may either accept or reject that "healing" energy.
- **Qigong** is a component of traditional Chinese medicine that combines movement, meditation, and regulation of breathing to enhance the flow of energy in the body, blood circulation and immune function.
The word Qigong is a combination of two ideas: "Qi" means air, breath of life, or vital energy of the body, and "gong" means the skill of working with, or cultivating self-discipline and achievement. The art of Qigong consists primarily of meditation, relaxation, physical movement, mind-body integration and breathing exercises. It is believed that regular practice of Qigong helps to cleanse the body of toxins, restore energy, reduce stress and anxiety, and help individuals maintain a healthy and active lifestyle.
- **Healing Touch** is an energy balancing therapy provided by practitioners to promote healing, relieve pain, increase relaxation, reduce anxiety, prevent illness, manage symptoms of illness and ease dying. Treatments involve light touch on and above the body in the individual's energy field (biofield). Certification of practitioners is provided by Healing Touch International.
- **Reiki** is a Japanese word representing Universal Life Energy. Reiki is a technique used for stress reduction and relaxation that allows one to tap into an unlimited supply of "life force energy" to improve health and enhance the quality of life. Reiki is based on the belief that when spiritual energy is channeled through a Reiki practitioner to another, the spirit can be healed, which in turn heals the physical body. Special training and credentialing is required.

- **Therapeutic Touch** is based on the premise that it is the healing force of the therapist that affects the patient's recovery; healing is promoted when the body's energies are in balance. By passing of the therapist's hands over the patient, they can identify energy imbalances and share energy for healing. Therapeutic Touch involves special training through Nurse Healers Professional Associates International, as well as extensive practice and experience.



Bioelectromagnetic-based therapies

- **Magnet Therapy** uses magnets, which produce a type of energy called magnetic fields, to treat or ease the symptoms of various diseases and conditions, including pain. Most magnets that are used are called “static” magnets because the magnetic field is not changed. Electromagnetic therapy, the use of magnets with electrical currents, is used only under supervision of a healthcare provider.

Including CAM in Your Pain Management Plan: Some Things to Consider

Surprisingly, nearly half of those using complementary and alternative therapies do not tell their primary care doctors about it — either out of embarrassment, fear of being reprimanded and/or not recognizing the importance of informing their providers. But it’s important to tell your healthcare providers the whole truth. If you are thinking about incorporating CAM approaches into your pain management plan, here are some things you should do:

- **Consult with your healthcare provider.** Discuss all conventional and CAM treatments you are using. Ask about CAM therapies, and how they can be included in your pain management plan.
- **Assess the safety and effectiveness of the therapy.** A safe therapy does no harm when used as intended. An effective therapy is one that has measurable benefits. Ask your provider about the safety and effectiveness of the therapy you are interested in. He or she may not be familiar with the type of therapy you are using or plan to use, so bring as much information as you can.
- **Seek out the evidence.** Research studies evaluating CAM therapies are ongoing. Scientific evidence for the benefits of some CAM therapies is extensive, while for others it may be lacking and/or in progress.
- **Talk to the practitioner.** Ask about his or her education, additional training, licenses, and certifications — both conventional and CAM. Will he or she provide you with information about the therapy (e.g., how it is administered, its purpose, any possible side effects)?
- **Investigate the practitioner’s expertise, background, qualifications and competence.** Contact your state or local regulatory agency with authority over the type of treatment you are seeking. Check to see if the practitioner is licensed to deliver services he or she claims to provide. Talk to your provider and other patients about the practitioner.
- **Consider the quality of service delivery.** Learn about how and where the therapy is given, and whether it meets regulated standards for medical safety and care. Visit the practitioner’s setting. Ask about how many patients he or she sees, and how much time is spent with patients. It is important to know that some therapies take longer to provide a significant effect; however, more lasting results may occur. Give yourself a timeframe in which you think you should see results based on information you have gathered.
- **Think about the costs.** Learn about which treatments will be reimbursed by your medical insurer. Many CAM treatments are not covered yet. Contact several practitioners and see what they’re charging for similar therapies.

- **Look at YOURSELF.** Consider what you can do on your own first. Eliminate or significantly decrease potentially harmful habits commonly used to relieve stress: drinking too many caffeinated beverages (coffee, tea, sodas), using alcohol, smoking cigarettes and eating comfort foods. These may be rewarding in the short-term, but when used repeatedly, they significantly contribute to the pain problem. Begin to change those habits by pursuing activities that are rewarding, satisfying and relaxing: walking in the park, listening to music, gardening, playing with your children or pets. Group social support is also extremely beneficial. Group therapy can be as simple as talking with close friends and loved ones, who will listen. Remember to do the same for them.
- **For safety, know the source of your products.** Explore the company that is making the products you chose to use. Ask questions about their standards for manufacturing of the product, quality control and standardization of active ingredients in the product.

Injection and Infusion Therapies



INJECTION AND INFUSION THERAPIES

Injection and infusion therapies may be used for the management of both acute and chronic pain. Acute pain, which you might experience after surgery or a major trauma, may be controlled optimally with pain medications delivered directly into your vein (intravenous) or your spine (intraspinal, which includes epidural or intrathecal), or with local anesthetics injected prior to your procedure (regional anesthesia). Persistent or chronic pain, which is defined as pain lasting longer than three months, may require injection (nerve block) or infusion therapies if other therapies (oral medications, physical therapy, etc.) do not provide adequate pain relief. In this section, we will discuss injection therapies, neuroablative therapies, minimally invasive surgical procedures, infusion therapies and implantables.

Injection Therapies

Injection therapies may be used to treat painful conditions in many areas of the body. The term nerve block was originally used for an injection that targeted specific nerves. It is now associated with any procedure involving placing a needle into a muscle, joint, spine, or around a specific group of nerves, followed by the injection of medication(s) or delivery of some other treatment such as electricity, heat or cold.

Nerve blocks can be used to:

- *Diagnose pain (diagnostic nerve blocks)* – This can help determine if your pain is coming from a nerve, muscle or joint. It may also help identify nerve pathways causing your pain.
- *Predict the effects of permanent nerve blocks (prognostic nerve blocks)* – Certain nerve blocks are first done with a numbing (local anesthetic medication). If you have relief from this type of block, a more permanent type of block, which will provide longer lasting pain relief may be recommended. The local anesthetic block may “predict” what kind of result you will have with the permanent block.
- *Prevent development of chronic pain syndromes (prophylactic nerve blocks)* – Development and spread of certain types of sympathetic nerve pain conditions may be slowed or stopped by using prophylactic nerve blocks.
- *Provide pain relief (therapeutic nerve blocks)* – When the cause of your pain is known, a therapeutic nerve block may provide a reduction in pain that serves as a complement to other pain treatment options.

Prior to any procedure, your pain specialist may perform a complete pain assessment in order to select the most appropriate injection therapy. This usually includes a complete physical exam and a review of your full medical history, including any testing you may have had (X-rays, CT scans, MRIs, etc.), as well as your personal preferences. This will allow your provider to develop a treatment plan tailored to your specific condition and needs. Your pain specialist should go over the type of block, benefits and risks, and potential side effects in detail before getting your consent to perform the procedure.

The most common medications injected include local anesthetics, corticosteroids and neurolytic drugs. (*For additional information, see Pharmacotherapy section.*)

- *Local anesthetics* can numb a painful area by “blocking” sensory and pain pathways. Commonly used local anesthetics are lidocaine and bupivacaine.
- *Corticosteroids* reduce inflammation around the nerves to decrease pain. Commonly used corticosteroids are methylprednisolone acetate and triamcinolone.

- *Neurolytic drugs* destroy nerve pathways to produce a more permanent effect. These drugs include absolute alcohol and phenol, which are otherwise not commonly used in chronic pain management.

In all cases, the area to be injected will be cleaned with an antiseptic solution before any medication or solution is injected into the affected area, which will be numbed with a local anesthetic. Fluoroscopy (a special X-ray) is used for some nerve blocks in order to guide the placement of the needle.

What to Expect Prior to the Procedure (Preparation)

What you may need to do to prepare for each injection therapy will depend on the type of injection and the setting in which the pain specialist will perform the procedure (private office, ambulatory surgery center, hospital center, etc.). Particularly for nerve blocks or minimally invasive surgery, you might need to consider:

- Food and liquids – you **may** be asked to refrain from eating or drinking for a certain period of time prior to your procedure.
- Transportation – you **may** be asked to have someone drive you home after the procedure.
- Medications – you **may** be asked to stop certain medications (blood thinners) prior to your procedure.
- Intravenous (IV) – you **may** have an IV placed prior to your procedure with or without IV fluids running.
- Conscious sedation – you **may** be given medications either before or during your procedure to calm you, make you sleepy while remaining aware and able to follow directions, or to relieve your pain. You should be given specific instructions prior to receiving any type of sedation. These medications may interfere with your memory and functioning, which is why you need to bring a friend or family member with you to listen to your discharge instructions and drive you home.
- Positioning – you **may** be asked to get onto an exam or X-ray table and lie still for a period of time. Be sure to let the pain specialist know if you will require any special assistance.
- Allergies – it is very important that you report if you are allergic to any medications, especially any reactions you may have had to local anesthetics, corticosteroids, iodine, IV dye or shellfish.
- Risk of exposure to radiation (if X-ray/fluoroscopy is used); this is a particular concern in pregnancy.

General Risks

As with any procedure, there are risks of serious complications. While these are uncommon, your pain specialist will be prepared to treat them immediately. Admission to the hospital for at least an overnight observation could be recommended for any of the following:

- Uncontrolled bleeding
- Unplanned perforation of a vital organ located close to the treatment area
- Unplanned nerve damage causing weakness or numbness to the surrounding area of treatment
- Allergic reaction from the local anesthetic causing difficulty breathing



Types of Injection-Based Therapies (e.g., Nerve Blocks) and How They are Used

Diagnostic Injection

- **Discogram**

A discogram is a procedure used to determine which disc(s) in your lower back is causing your back or leg pain. Fluoroscopy is used and X-ray pictures of the discs are taken. This procedure may be performed by a pain specialist or a specialty trained radiologist. You may be asked to take copies of your X-rays back to the physician who ordered the discogram for their review if that is preferred over a written report of findings by the performing physician.

Conscious sedation is commonly used for this procedure. You will be placed in the prone (face down) position on an X-ray table. A thin needle will be placed into each disc being tested and solution will be injected to increase pressure in the disc in an attempt to recreate your pain. You will be asked if the injection of the solution "reproduces" your pain or not. If it does, then this may be the disc that is causing your pain and further treatment options may be available.

Injections

- **Botulinum Toxin Injection**

An injection of botulinum toxin into the muscle/muscle group causing you pain. This toxin causes temporary paralysis of these muscles. This injection may be done if you have dystonia, a disorder characterized by cramping muscles, certain headaches or other conditions where muscles are in chronic spasm causing pain.

The dosage of botulinum toxin is very small. The relief effect takes time to notice. It may take 2-3 days before muscle relaxation is achieved. This effect generally lasts months, but requires follow-up before a repeat injection is recommended. If a poor response or no response occurs with a previous injection, the value of proceeding with further injections should be reviewed first.

- **Sacroiliac (SI) Joint Injections**

An SI joint injection is the injection of medication into the sacroiliac joint in your buttock region. This may be done if you have a certain type of low back/buttock pain.

Fluoroscopy may be used to guide placement of a needle into the SI joint, and inject a local anesthetic or local anesthetic/steroid solution.

- **Trigger Point Injections (TPI)**

TPIs are the injection of medications into your muscles. These muscle "trigger points" are usually painful when you press directly on them.

TPIs may be done to treat trigger point pain from chronic spasm, Myofascial Syndrome or Fibromyalgia. A needle will be inserted into the painful trigger points and a local anesthetic with or without steroid will be injected.

Nerve Blocks

The nerve blocks described below are a representation of the most common nerve blocks done for pain conditions. Ask your healthcare provider about these and nerve blocks not discussed in this section.

● Axillary Block

An axillary block is an injection of a local anesthetic around a group of nerves located in your underarm area. This type of block may be done if you have Complex Regional Pain Syndrome (CRPS), nerve pain in your arm, or for diagnostic purposes.

You will lie flat with the affected arm stretched out with your palm up. A needle will be inserted into your underarm and a local anesthetic is injected. You may feel a sharp tingling sensation at the time of injection. Don't worry, this is normal. This confirms that the needle is in the proper place.

● Celiac Plexus/Hypogastric Plexus Block

These blocks involve the injection of a local anesthetic into the area of a group of nerves which supply the abdominal organs, called celiac plexus nerves. These blocks are performed most commonly for the treatment of upper abdominal pain due to chronic pancreatitis, cancer and pelvic pain. Fluoroscopy is used to guide the placement of needle to the area. After the needle is in the proper area, local anesthetic will be injected in the area of the celiac plexus nerves.

● Epidural Steroid Injection (ESI)

An ESI is the injection of a small amount of steroid into the epidural space that surrounds the spinal cord and spinal nerves. This can be done in the neck (cervical), mid back (thoracic) or low back (lumbar or caudal).

An ESI may be performed if you have back and/or leg pain, neck and/or arm pain. The pain may be due to a herniated spinal disc, spinal stenosis (narrowing of the spinal canal space), or degeneration of your spinal bones (vertebrae) or compression fractures. All of these conditions may cause irritation and inflammation, which may be the root cause your pain.

Fluoroscopy is commonly used as a guide for needle placement, so typically, you will be lying face down on an X-ray table. If X-ray is not used, you may be sitting or lying on your side during the procedure. Conscious sedation may be optional and would require IV placement prior to the procedure. Sometimes, IV placement is required for the first procedure, or if you have a history of fainting or sudden drops in your blood pressure during medical procedures (better known as a vagal response).

The needle may not be placed in exactly the same site as your pain; the medication injected will "float" to coat the nearby nerves. You may feel some pressure in the area of the injection or some re-creation of your pain symptoms as the medication (steroid or steroid/local anesthetic) is injected. This feeling is normal and will go away in a short period of time.

● Facet Nerve Blocks

A facet nerve block is performed if it is suspected that your back or neck pain may be caused by irritation or inflammation of the small nerves near the facet joints of the spine. Pain from facet nerves can occur from injuries that involve twisting and straining while lifting heavy objects or falling. Facet joints are on the back of your spine, one on each side, near the boney spine, but not near the spinal cord.

Fluoroscopy is used to guide the placement of needles to the area. After correct needle placement is confirmed, a small amount of local anesthetic will be injected near the facet nerve.

● Intercostal Nerve Blocks

An intercostal nerve block is the injection of a local anesthetic or a neurolytic agent in the area between two ribs. This may be performed for pain due to nerve injury around the rib area. A needle will be inserted into the intercostal space and a local anesthetic, local anesthetic/steroid, or neurolytic solution is injected.

Because the pain specialist is working close to your lung, you should be made aware that a pneumothorax (collapsed lung) is a possible complication. A highly skilled practitioner, a calm, quiet environment, along with very small and short needles are used to avoid this complication. It is very important that you do not move during the injection phase of this procedure.

● Lumbar Sympathetic Block

A lumbar sympathetic block is the injection of local anesthetic around a group of nerves (lumbar sympathetic "nerve chain" or plexus) in your low back (lumbar) region. This is typically recommended if you have Complex Regional Pain Syndrome/RSD, severe peripheral vascular disease, or neuropathic pain (pain coming from the nerves). Fluoroscopy is used to guide the placement of the needle to the area. After the needle is in the proper area, local anesthetic will be injected in the area of the lumbar plexus nerves.

● Stellate Ganglion Block

A stellate ganglion block is the injection of local anesthetic around a group of nerves (cervical sympathetic "nerve chain" or plexus) in the base of the front of your neck. This type of block may be done if you have Complex Regional Pain Syndrome/RSD or severe peripheral vascular disease.

You may experience a temporary drooping of your eyelid, blurred vision on the side that was injected or minor swallowing difficulties. You should be monitored closely by skilled healthcare professionals until these go away and you are able to swallow liquids without difficulty.

● Occipital Nerve Block

An occipital nerve block is the injection of local anesthetic around the occipital nerves, which are located in the back of your neck near the base of the skull. This may be useful in the diagnosis and treatment of headache and jaw pain. A needle is inserted around your occipital nerve and a local anesthetic or local anesthetic/steroid solution is injected.

● Selective Nerve Root Block

A nerve root block is the injection of a local anesthetic/steroid solution around a nerve root after it leaves the spine, also called the paraspinal region. This may be performed to diagnose a particular pain problem (to determine if your pain is coming from a nerve, muscle or joint) or as an alternative treatment approach to an epidural steroid injection (for a herniated spinal disc or spinal stenosis, which is the narrowing of the spinal space).

Fluoroscopy is used to guide the placement of a needle to the area of the involved nerve root. You may experience a small electric shock-like sensation (similar to when you hit your "funny bone"). This will confirm if the needle is in the right place. A small amount of local anesthetic/steroid or steroid solution will be injected.

OTHER

● Epidural Blood Patch

An epidural blood patch is done when a person has a spinal headache, usually from a myelogram or lumbar puncture. This type of headache can occur when there is a hole or tear in the dura (the covering of the spinal fluid/spinal cord), which causes spinal fluid to leak through. A severe headache results. This headache is usually different from a typical headache; it usually is not present when you lie down and painful when you stand up. Nausea and vomiting commonly occur when the pain is severe.

The blood patch is the injection of your own blood, which is first taken from your arm, into the epidural space in your spine. An IV (intravenous) will be started in your arm prior to the procedure.

The pain specialist will insert a needle into the epidural space in your spine. An assistant will then draw blood from your arm through the IV. This is done in sterile conditions. Your blood is then injected through the needle in your back. That needle is removed. The blood remains in your epidural space where it will clot or "patch" the hole/tear.

What to Expect After a Procedure

Different injection procedures will have all, some or none of the following considerations. The antiseptic solution will usually be washed off of the area that was injected, and a small dressing (band-aid®) will be placed over the injection site. Your provider may monitor your vital signs (blood pressure, pulse, respirations, etc.) for a period of time. If you had an IV, it will be removed. You will be given instructions of what to expect when you go home, which might include:

- *Numbness* – common if a local anesthetic was used. Use caution with any area that is numb. Do not walk or drive with a numb leg, or apply heat or ice to the area until all feeling has returned.
- *Soreness* – common at the injection site after any type of injection. You may put ice on the area.
- *Low Blood Pressure* – may be common for a short period of time if you have had a sympathetic block. You will be monitored until your blood pressure is within your normal limits.
- *Mild to Moderate Headache* – may be from steroids if they were used. An over-the-counter medication of your choice may be used. If you have a severe headache, with or without nausea and vomiting, please call your pain specialist as soon as possible.
- *Increase in pain level or change in pain location* – common for the first 24 hours after the injection/block.
- *Hot flashes, facial redness, mood changes, increased appetite and menstrual irregularities* – common for the first few days to weeks post injection/block. This is due to the effects of the steroid that was injected. These will go away with time.
- *Increased blood sugar* – If you are a diabetic, your blood sugar may be higher than normal for the first 3-5 days after an injection/block. Please contact the healthcare provider who treats your diabetes for any advice before the procedure is scheduled to make plans on what to do when/if this happens after the procedure.
- *Activity* – after a Blood Patch, your activity should be minimal for the first 24 hours. Rest is necessary so as not to dislodge the patch. All other injections/blocks often do not restrict activity. Use your judgment and be careful not to overdue it just because you may be feeling better; this can prevent re-injury.



Please call your pain specialist if you experience any of the following:

- Redness, swelling or drainage around/from the injection/block site
- Persistent bleeding from injection/block site
- Severe headache (may or may not be accompanied by nausea and vomiting)
- Fever
- Stiff neck
- Weakness not present prior to the injection

NEUROABLATIVE THERAPIES

Neuroablative therapies usually produce a longer lasting effect than nerve blocks. These therapies use thermal (heat or cold) or chemical agents (alcohol or phenol) to "destroy" certain nerves or nerve chain pain pathways, thereby providing you with prolonged pain relief. Your pain specialist might choose one of the following therapies if your pain is severe, expected to persist, and cannot be lessened by other therapies. However, in some cases, special cautions must be given about potential nerve damage and return of pain that can be the same or even worse than before.

THERMAL THERAPIES

● Radiofrequency Facet Rhizotomy

A facet rhizotomy destroys facet nerve(s) either in the lower back (lumbar) or the neck (cervical) region, using radiofrequency (heat) waves. This procedure is done if you have pain due to disease in the facet joints of your spine, and you have had pain relief from your facet nerve blocks.

You will be placed in the prone position. Your back or neck will be cleaned with an antiseptic solution and the skin area will be numbed with a local anesthetic.

Fluoroscopy is used to guide the placement of the needle probe to the area of the facet nerve. Radiofrequency waves are transmitted to lesion (destroy with heat) the involved nerve(s). This temporarily stops sensation from that area, which may last for an average of 6 months or more.

● IntraDiscal ElectroThermal Therapy (IDET)

IDET may be considered if you have "cracks" or fissures in the wall of one of your spinal discs, or if the inner disc tissue has "herniated" into the fissure. Since these fissures are filled with small nerve endings, this may be a source of chronic back pain.

IDET is the application of thermal energy (heat) to a section of a spinal disc wall. This may result in the contraction or closure of that "crack" in the spinal disc wall or a reduction in the bulge of the inner disc material.

An IV will be placed in your arm and you will be given sedation. You will be placed in the prone position on an X-ray table. Fluoroscopy is used to guide a needle into place. An electrothermal treatment catheter is inserted through the needle, and the heating element is started. Once the heating is done, the catheter and needle are removed.

You should be given special instructions after this procedure with regard to activity, physical rehabilitation and other considerations.

● Cryoanalgesia

Cryoanalgesia is the application of thermal energy (cold) to a nerve or nerve chain to "freeze" it with nitrous oxide or carbon dioxide gas. Cryoanalgesia may still be available in some pain specialty practices, but it is limited due to the unavailability of equipment from old or new manufacturers.

Cryoanalgesia may be done if you have rib pain, pain after lung/chest surgery, facial pain or pain from a neuroma.

Your positioning will depend on the area being treated. The cryoanalgesia probe will be placed around the nerve to be "frozen" when the gas is activated. This process forms an "ice ball" around the nerve to freeze it. This temporarily stops sensation from that area, which may last for an average of 3-6 months and sometimes more.

CHEMICAL THERAPIES

● Celiac Plexus (Destructive) Block

A celiac plexus destructive block is the injection of an alcohol or phenol in the area of a group of nerves which innervate (supply) the abdominal organs. It is performed most commonly for the treatment of upper abdominal pain due to chronic pancreatitis or cancer, and *usually after you have had pain relief from a diagnostic celiac plexus block*.

After the needle is in the proper area, alcohol or phenol will be injected in the area of the celiac plexus or hypogastric plexus nerves.

● Lumbar Sympathetic (Destructive) Block

A lumbar sympathetic block is the injection of alcohol or phenol around a group of nerves (lumbar sympathetic nerve chain) in your low back (lumbar) region. This may be done if you have Complex Regional Pain Syndrome/RSD, severe peripheral vascular disease, or neuropathic pain (pain coming from the nerves) and *you have had pain relief from a diagnostic lumbar sympathetic block*.

Fluoroscopy is used to guide placement of a needle to the grouping of nerves in your low back. After correct needle placement, alcohol or phenol will be injected.

MINIMALLY INVASIVE SURGERY

● Vertebroplasty (therapeutic)

Percutaneous **vertebroplasty** is a procedure that allows health professionals to stabilize vertebrae damaged by compression fractures by injecting bone cement into the collapsed vertebrae. The aim of a vertebroplasty is to improve the strength and stability of the injured vertebrae and to eliminate pain.

When conservative treatment fails to alleviate pain associated with vertebral





compression fractures, this method may be suggested. The most common complication following vertebroplasty is a transient increase in pain at the injected level. This is readily treated with NSAIDs and typically resolves within 48 hours.

Your care after any of these procedures will be similar to that after having an injection/nerve block. Your pain specialist may provide you with additional instructions depending on the type of procedure performed.

● **Kyphoplasty**

Like Vertebroplasty, kyphoplasty is used to treat bone fractures due to osteoporosis — the loss of calcium from bones resulting in weakened bone structure that increases the risk of fracture. Kyphoplasty includes an additional step when compared to vertebroplasty. Prior to injecting the cement-like material, a special balloon is inserted and gently inflated inside the fractured vertebrae. The goal of this step is to restore height to the bone thus reducing deformity of the spine. Pain is reduced which allows you to return to normal daily activities after either procedure.

INFUSION THERAPIES

Infusion therapies, especially intravenous (IV) drug delivery, are a convenient and effective way to control your pain. Giving pain medications through a catheter placed in your vein or spine means you may get faster and more effective pain relief, especially after surgery, injury or trauma. The following are common infusion therapies.

● **Subcutaneous (SC)**

The SC route is usually used for chronic pain, not acute pain because pain medication given this way will take longer to work. A small needle is placed under your skin into your subcutaneous or "fatty" tissue. The needle is connected to a hollow tubing and infusion pump, which will deliver the pain medication into the SC tissue. The medication is then absorbed by your body and distributed to relieve your pain. SC infusion can successfully be used in the home setting, but require visits from home health personnel.

● **IV Bolus**

Small amounts of pain medication are given through an IV catheter by a doctor or nurse. IV boluses are good for fast control of severe or acute pain on a short-term basis. IV boluses can provide immediate pain relief, but this might only last for 45-60 minutes, so additional boluses will have to be given. IV boluses are usually only used in a hospital setting.

● IV Continuous Infusion

When moderate to severe pain over a long period of time (i.e. a few days after surgery) is expected, a continuous infusion may be used. A continuous dose of pain medication is delivered through an IV by an infusion pump, which means you will have a constant level of pain relief. This is usually started after your pain has been controlled with IV boluses. IV continuous infusions are usually only used in a hospital setting, where a healthcare provider can monitor you.

● IV Patient-controlled Analgesia (PCA)

IV PCA is a method of pain relief to help you feel comfortable. It is routinely used after surgery or during a painful illness. By pushing the patient control button for the PCA infusion pump, you can give yourself small amounts of pain medication. Your doctor will order the amount of pain medication and indicate how often you can have it. The benefits of PCA are rapid pain relief when you need it, the possibility of using less pain medicine and having fewer side effects, and a sense of control over your pain. You will be given specific instructions on using PCA by your provider. IV PCA is usually used in a hospital setting, but may be used at home for severe, chronic pain.

● Intraspinal Drug Delivery

Infusing pain medications and/or local anesthetics directly into the epidural — in front of the spinal fluid space (epidural analgesia) or spinal fluid space (intrathecal analgesia) — is a method of pain relief used after surgery, painful injury or illness. This can help you get better pain relief and help you move better after surgery. It is also possible to use less pain medicine and have fewer side effects, which should help your recovery. With epidural analgesia, a small hollow tube (catheter) is placed in the space between the covering around the spinal cord and the bones of the spine; with intrathecal analgesia, the catheter is placed in the spinal fluid. The catheter may be inserted in the operating room before surgery, on a hospital floor/intensive care unit, or as an outpatient in a pain center or outpatient surgical center. A dressing will be put over the area where the catheter goes into your skin, and the catheter will be taped along your back up to your shoulder. An anesthesiologist (doctor specializing in giving anesthesia), or pain management specialist will order the amount of pain medicine to be given by a specialized infusion pump. Special training is required for nurses who assist in the monitoring and care of this infusion system.

Epidural/intrathecal analgesia is usually used in a hospital setting, but may be used at home for cancer pain.





● **IV Regional Blocks**

IV regional blockade, also known as a Bier Block, is a method of producing pain relief (analgesia) in an arm or leg by injecting medications intravenously, while the blood supply (circulation) in the arm or leg is cut off (occluded). This may cause temporary numbing (anesthesia) of the extremity, if a local anesthetic drug is used. Many patients are sent for physical therapy after the block, so their arm or leg can be exercised without pain. Your doctor may recommend this type of block if you have severe pain from Complex Regional Pain Syndrome or nerve injury.

● **Anesthetic Infusions**

IV Anesthetic Infusion is the infusion of a local anesthetic such as lidocaine through an IV catheter. This method can be used to treat chronic neuropathic pain (pain coming from nerves). The local anesthetic is given over a 30-60 minute period of time; you will be monitored for a period of time after that determined by your pain specialist. This may be done in an outpatient or ambulatory care setting.

● **Disposable Anesthetic Systems**

PainBuster and ON~Q are two of the systems available that provide a continuous infusion of local anesthetic directly into the surgical wound. Your healthcare provider might recommend this method of pain control if you are having knee, hip, shoulder or abdominal surgery. The advantage to this system is it can be used on an outpatient basis. A small catheter is placed directly into the surgical site, and your skin closed around the catheter. A small device will deliver local anesthetic to the wound site for 24-48 hours. You will be instructed on care and removal of the catheter.



Implantable Devices and Surgical Interventions



IMPLANTABLES

Advances in medical technology have greatly impacted pain management delivery systems. Pumps and stimulators have been designed so they can be surgically placed under the skin. This helps reduce the risk of infections that is more common with external devices and provides targeted pain relief to major nerves and the spinal cord, depending on the system selected. External devices tend to be recommended for short-term pain problems when pain relief is expected to decrease over time. Internal (implantable) devices may be more appropriate for persistent pain problems that require long-term pain reduction.

SPINAL CORD STIMULATION (SCS)

SCS therapy may be used to treat chronic pain that has been objectively confirmed in the neck or arms, chest, mid to low back or legs. It is most effective in treating pain coming from the nerves (nerve damage). Your pain specialist will perform a SCS "trial," a test to see if the therapy will help to relieve your pain. If the trial is successful, a surgical procedure will be required to "implant" the SCS system.

Physicians require special training to insert either temporary or permanent SCS. Often, nurses who specialize in pain management are trained in adjusting and monitoring these systems following placement.

SCS uses a small battery-type device, called a pulse generator or receiver, to deliver electrical impulses to a "lead" (catheter with electrodes along the tip), which is placed near nerves along the spinal cord. The electrical impulses, or stimulation, interfere with the transmission of pain signals to the brain. In successful cases, the brain perceives the more pleasant tingling sensation (stimulation) and not the pain sensation.

SCS therapy may be used to treat: chronic pain in the neck or arms, chest, mid to low back and legs that has been objectively confirmed. It is most effective in treating pain coming from the nerves (nerve damage). Your pain specialist will perform a SCS "trial," a test to see if the therapy will help to relieve your pain. If the trial is successful, a surgical procedure will be required to "implant" the SCS system.

There are two types of SCS systems, *Implantable Pulse Generator (IPG)* or *Radiofrequency (RF)*.

The IPG system is known as an internal system; all components (generator connected to the lead) are implanted under your skin. The IPG is typically implanted in your buttock or abdomen, with the lead in your spine. You or your pain specialist may program the system using a programmer held over the generator. In older systems, the IPG will need to be replaced when the generator becomes depleted (battery wears out). This usually requires an outpatient surgical procedure. Newer systems have battery/generators that are rechargeable by placing a small device over the generator. Many patients prefer this system, which is advantageous in terms of not having to have repeat surgery for battery changes. The IPG systems offer great advantages in supporting daily activity (can be used while showering, bathing, swimming) along with cosmetic features (nothing can be seen on the outside).

The RF system, on the other hand, is known as an external system. It uses a rechargeable type battery, located in a small controller called a transmitter. The transmitter is connected to an antenna, which must be placed on your skin over a receiver (usually implanted in your buttock or abdomen). The receiver is then connected to the lead, which is placed in your spine. Some advantages to this system include: no additional surgical procedures required and higher power outputs may be possible.

Disadvantages are that it cannot be used while showering, bathing, or swimming, the transmitter and antenna must be worn continuously outside the body to receive the stimulation, and wardrobe issues may be present.

Prior to undergoing a SCS trial, your pain specialist should provide you with detailed information on the therapy, system components, benefits and risks, and potential complications. This information can help you decide if SCS is right for you.

IMPLANTED INTRASPINAL DRUG DELIVERY SYSTEMS

Intraspinal Drug Delivery is the continuous infusion of pain medications, possibly including opioids, local anesthetic drugs, baclofen, or other drugs into your spinal fluid via a catheter and implanted infusion pump. Physicians require special training to insert implantable systems. Often, nurses who specialize in pain management are trained in filling, adjusting and monitoring these systems following placement.

Your pain specialist may choose this type of advanced pain treatment therapy if you have chronic pain due to cancer, or other chronic pain condition that has been objectively diagnosed. As in SCS therapy, this option should be considered only after conservative methods have been tried and failed. There are many similarities to SCS therapy: a trial infusion of the opiate medication will usually be done to assess your response; a surgical procedure will be required to implant the system; the system lies totally beneath the skin; from time to time the infusion pump must be replaced when the battery is depleted.

The implanted drug delivery system consists of a small flexible catheter, placed in the spinal fluid, connected to a drug infusion pump, and implanted in your abdomen. The medication is placed into the pump via a small port (covered opening) in the top of the pump. Your pain specialist will decide which drug is right for you based on your trial.

A computerized program is used to tell the pump which drug is being used and how much of the drug you are to receive per day.

Prior to undergoing a drug infusion trial, your pain specialist should provide you with detailed information on the therapy, system components, benefits and risks, and potential complications. This information can help you decide if intraspinal drug delivery is right for you.

Looking Forward with Hope



LOOKING FORWARD WITH HOPE!

What's in the Pipeline?

Over the years, new medications and technologies have emerged for the treatment of pain. A variety of pharmaceutical and medical technology companies have been carefully working within their research and development departments to improve drugs and delivery systems and create new treatment options for pain. They work closely with some of the best and brightest pain researchers and pain clinicians. As pain research advances, new ideas are generated and explored. There is hope in the future!

We have seen new preparations of "old" opioids expand with the introduction of longer acting versions in pill form. Work continues so that eventually every opioid that traditionally comes in a short-acting form will have a long-acting version. Today, we have morphine and oxycodone options. Next, hydrocodone, oxymorphone and hydromorphone will be an option. Also, new combination drugs that contain opioids along with other medications are entering clinical trials. Some of these preparations are expected to enhance pain relieving effects. Others are expected to eliminate the "sought after" pleasurable effects when long-acting versions are improperly altered by those who would misuse.

Patch therapy has gained popularity, whether in the form of an opioid, NSAID or anesthetic. Generic versions of fentanyl have entered the market. Hopefully, offering other medications or combination of medications in patch form will be created. The introduction of transbuccal delivery systems for fentanyl has launched a new concept. Some companies are working on improving the onset of oral drug action by speeding it up. Research is underway that uses an effervescent delivery system to create more rapid onset versions of short-acting drugs. One such preparation has been reported to taste like taking a teaspoon of a gentle carbonated cola or soda (pop). This may be very appealing to those who experience breakthrough pain and would prefer faster relief.

Although two of the three COX-2 inhibitors have been taken off the market because they increased the risk of heart attack and stroke in some persons, research is in process to improve the safety of these drugs. It wouldn't be surprising to find new preparations of NSAIDs become available in the next few years.

New adjuvants, such as gabapentin, pregabalin and duloxetine for neuropathic pain, are showing great promise as they may provide better pain relief with fewer side effects. Anesthetic patches, creams and solutions have helped with local pain problems, such as open wounds, diabetic neuropathy and shingles pain. The release of a shingles vaccine was announced in May 2006. This approach is expected to decrease the occurrence of shingles in older or immune-compromised individuals and hopefully reduce the incidence and severity of shingles pain. More research in neuropathic pain will generate new treatment options.

We can expect the introduction of drugs that work by unique mechanisms. For example, Ziconotide, from a snail toxin, was introduced in 2004. Though this must be given through an implantable infusion pump, it has helped in the treatment of severe pain disorders that have not responded to other therapies. More substances that block pain in newly discovered ways are being investigated. Drugs that work on nicotine and capsaicin receptor sites in the nervous system might be the next breakthrough. Others are investigating drugs to "turn off" parts of nerve cells that become "irritated" in the presence of pain stimuli or when some pain relieving drugs, like morphine have been used for a long period of time.

Emerging medical technology is another promise of hope. Creating new and improving current infusion devices and stimulators is on the rise. Recently, a rechargeable battery for implantable pumps was introduced to the marketplace. This should help to decrease the need to replace pumps every five years. That is a cost savings in pain, suffering and healthcare dollars. The creation of smaller, more compact pumps and stimulator systems will not only help decrease the discomfort of implantation, but expand this option for very thin persons and the younger population living with persistent, complex pain. New stimulator devices for the brain and the periphery are undergoing clinical trials now.

There is much to look forward to, but for those in pain the future cannot come fast enough.



CONCLUSION

In summary, understanding and effectively managing pain can be challenging. Since you may have consulted several medical professionals already, you are well aware of the difficulty in receiving adequate pain diagnosis and care. It is very important for you and your healthcare providers to work as a TEAM to treat your pain effectively. Asking for help from professionals who have more experience in specialized areas may be recommended. That way, a pain management program can be designed to meet your needs.

As part of the pain "investigation," a comprehensive pain assessment should be completed. Knowing as much information as possible about your pain experience will make it easier for your provider to diagnose and decide if your pain condition is treatable by behavioral changes, medication adjustments and/or the inclusion of other specialists or techniques.

When there is a challenging pain problem to address, working with well-trained and experienced pain management specialists is ideal. There are many more complicated therapies than those discussed here that could be helpful to some.

Fortunately, there are also some pain problems that are easily managed, and a primary care provider often can handle the problem very well. The main point is to understand that most pain can be managed, and that all people have the right to have their pain problems addressed.

Disability Determination

The overall goal for pain management is to reduce pain and improve function so that each individual living with persistent pain may regain a quality of life. When pain cannot be adequately reduced or when function is impaired, other options may need to be pursued. Pain experts in rehabilitative medicine (See *Rehabilitative section*) are often trained experts in the evaluation of those who may require some form of disability classification. This process is better known as a disability determination. More information about disability evaluations and the government sponsored program under Social Security can be found at <http://www.ssa.gov/disability/professionals/bluebook/> or by calling **1-800-772-1213**.

Common Pain Terms

Pain: an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (IASP/APS 1992); The inability to identify tissue damage sufficient to explain the pain is not proof that the pain is of psychological origin (Portenoy, Kanner 1996); Pain is whatever the experiencing person says it is, existing whenever said it does (McCaffery 1968). Pain is personal and subjective (APS 1999), therefore, the individual's self-report on pain is the single most reliable indicator of pain (AHCPR 1992).

Acute Pain: pain of sudden onset usually from a single, "fixable" event commonly seen with surgery, accidental injury or inflammation, however, can be from unknown cause; short duration from days to less than 3-6 months as associated with healing; considered our biological red flag that sends warning signals through the nervous system that something is either wrong within the body or that a hurtful activity should be avoided to prevent further or repeat damage.

Allodynia: pain caused by a stimulus or action that does not normally cause pain, like light touch or pressure, subtle temperature change, gentle breeze on skin (Mersky 1986).

Breakthrough Pain: pain that flares up or emerges through the comfort state obtained from drug and/or non-drug pain relief methods.

Central pain: pain started or caused by damage to the central nervous system (spinal cord, brain); this is a disorder of the nervous system or a disruption of normal nervous system activity.

Chronic Pain: pain lasting longer than expected healing time, may last for many months, years or a lifetime, may be constant or in intervals; cause may be unknown or result of recent or previous acute pain episode; may be related to another chronic disorder, such as arthritis, peripheral vascular disease, diabetes, or cancer (disease, treatment or aftermath as a survivor); often cancer-related pain and non-cancer-related pain are discussed as separate, distinct pain problems.

Deafferentation Pain: pain due to alteration or damage to the central nervous system (central pain or neuropathic pain) or may be alteration of nervous system within larger nerves or nerve roots before entry into central nervous system.

Escape Pain: another term used to describe breakthrough pain.

Hyperalgesia: an increased response to a stimulus that normally would induce a mild discomfort (Mersky 1986).

Intractable Pain: old term (outdated) used to describe chronic pain resistant to pain treatment; may be seen as diagnosis of those experiencing chronic persistent pain.

Lacinating Pain: stabbing, knifelike pain (Portenoy and McCaffery 1999).

Neuralgia: pain along a nerve or nerves (Mersky 1986).

Neuritis: pain caused from the inflammation of a nerve or nerves (Mersky 1986).

Neuropathic Pain: pain started or caused from alteration of the nervous system (McCaffery and Pasero, 1999).

Nociceptive Pain: another term used to describe acute pain as a response to a noxious (unpleasant) stimulus activating nerve cells to send pain signals along the nervous system for recognition and response. The nervous system is working appropriately.

Pain Flares: pain that suddenly erupts or emerges with or without an aggravating event or activity.

Pain Perception: the natural process of recognizing, defining and responding to pain (McCaffery and Pasero, 1999).

Pain Threshold: the least experience of pain that is recognized (or) the lowest level of stimulus that is perceived as painful (Mersky 1986).

Pain Tolerance: the greatest level of pain that an individual is prepared to (or willing to) tolerate (Mersky 1986).

Paroxysmal Pain: pain that occurs in waves or patterns, intermittent in nature; may be related to muscle spasm or visceral pain disorders.

Peripheral Neuropathic Pain: pain started or caused from alteration of nerves or nerve roots (McCaffery and Pasero, 1999).

Persistent Pain: pain that lasts 12 or more hours every day.

Radicular Pain (Radiculopathy): pain from an alteration within one or more nerve roots (Bonica 1990).

Somatic Pain: pain within the muscles and/or bones (McCaffery and Pasero 1999).

Visceral Pain: pain within internal organs (McCaffery and Pasero 1999).

REFERENCES

Definitions Related to the Use of Opioids for the Treatment of Pain
American Society of Addiction Medicine
<http://www.asam.org/pain/definitions2.pdf>

MedlinePlus
National Library of Medicine
<http://medlineplus.gov/>

National Center for Complementary & Alternative Medicine
National Institutes of Health
<http://nccam.nih.gov/health/>

National Institutes of Health
<http://www.nih.gov/>

Pain & Policy Studies Group
University of Wisconsin
<http://www.medsch.wisc.edu/painpolicy/>

Pain Management Guidelines for the Older Persons
American Geriatric Society
<http://www.americangeriatrics.org/products/positionpapers/JGS5071.pdf>

RxList: The Internet Drug Index
<http://www.rxlist.com/>

Use of Opioids for the Treatment of
Chronic Pain
American Pain Society
<http://www.ampainsoc.org/advocacy/opioids.htm>

Note: Many resources and a more comprehensive list of links relating to this Treatment Options Book can be found through the American Pain Foundation's Web site or toll-free telephone information service.

RESOURCES - FIND A PAIN SPECIALIST

American Academy of Medical Acupuncture
(323) 937-5514

http://www.medicalacupuncture.org/acu_info/generalinfo.html

American Academy of Pain Management
(209) 533-9744
<http://www.aapainmanage.org/info/Patients.php>

American Academy of Pain Medicine
<http://www.painmed.org/membership/>

American Academy of Physical Medicine and Rehabilitation
(312) 464-9700
<http://www.aapmr.org/>

American Association of Naturopathic Physicians
(866) 538-2267
<http://www.naturopathic.org/>

American Chiropractic Association
(703) 276-8800
http://www.amerchiro.org/level1_css.cfm?T1ID=13

American Holistic Medical Association
(505) 292-7788
<http://www.holisticmedicine.org/public/public.shtml>

American Holistic Nurses Association
(800) 278-2462
<http://www.ahna.org/practitioners/index.html>

American Osteopathic Association
(800) 621-1773
http://www.osteopathic.org/index.cfm?PageID=findado_main

American Pain Society
(847) 375-4715
<http://www.ampainsoc.org>

American Society of Addiction Medicine
(301) 656-3920
<http://www.asam.org/search/search2.html>

American Society of Interventional Pain Physicians
(270) 554-9412
<http://www.asipp.org/>

American Society for Pain Management Nursing
(888) 34-ASPMN / (888) 342-7766
<http://www.aspnn.org/>

American Society of Regional Anesthesia & Pain Medicine
(847) 825-7246
<http://www.asra.com/>

RESOURCES

American Alliance of Cancer Pain Initiatives
(608) 265-4013
<http://www.aaci.wisc.edu/>

American Cancer Society
(800) ACS-2345
<http://www.cancer.org>

American Chronic Pain Association
(800) 533-3231
<http://www.theacpa.org/>

American Pain Foundation
(888) 615-PAIN (7246)
<http://www.painfoundation.org>

Beth Israel Medical Center
Department of Pain Medicine and Palliative Care
<http://www.stopain.org/>

CancerCare
(800) 813-HOPE (4673)
<http://www.cancercare.org>

City of Hope Pain/Palliative Care Resource Center
<http://www.cityofhope.org/prc/>

Mayday Pain Project
<http://www.painandhealth.org/index.html>

National Chronic Pain Society
(281) 357-HOPE (4673)
<http://www.ncps-cpr.org/>

National Family Caregivers Association
(800) 896-3650
<http://www.thefamilycaregiver.org/>

National Pain Foundation
(303) 783-8899
<http://www.nationalpainfoundation.org/>

Pain Assessment Scales
<http://www.partnersagainstpain.com/index-mp.aspx?sid=3&aid=7825>

Pain Assessment Scales for Children
<http://www.childcancerpain.org/content.cfm?content=assess07>

Pain Assessment Scales in Multiple Languages
<http://www.partnersagainstpain.com/index-mp.aspx?sid=3&aid=7692>

Pain Clinical Trials Resource Center
<http://www.centerwatch.com/ctr/PainFoundation/default.asp>

Pain.com
<http://www.pain.com/>

Partnership for Prescription Assistance
(888) 4PPA-NOW / (888) 477-2669
<https://www.pparx.org/Intro.php>

Patient Advocate Foundation
(800) 532-5274
<http://www.patientadvocate.org/>

Spine Universe
<http://www.spineuniverse.com/>

Whole Health MD Therapies Reference Library
<http://www.wholehealthmd.com/ME2/Default.asp>

Yoga for Chronic Pain
<http://www.painfoundation.org/page.asp?file=ManageYourPain/Yoga/Intro.htm>

BOOKS

Managing Pain Before It Manages You, Revised Edition – M.A. Caudill-Slosberg (Guilford Press, 2001).

The War on Pain – S. Fishman & L. Berger, (Harper Collins, 2001).

The Savvy Woman Patient: How and Why Your Sex Matters to Your Health - P. Greenberger & J. Wider, Eds. (Capital Books, 2006)

Pain: Clinical Manual, 2nd edition – M. McCaffrey, & C. Pasero (Mosby, 1999).

Mayo Clinic on Chronic Pain, 2nd edition – J. Rome, Ed. (Mayo Clinic Health Information, 2002).

The Truth About Chronic Pain: Patients And Professionals On How To Face It, Understand It, Overcome It – A. Rosenfeld (Basic Books, 2004).

Cognitive Therapy for Chronic Pain: A Step-by-Step Guide – B.E. Thorn (Guilford Press, 2004).

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An amazing document.

—Jackie Levin RN, MS

First, let me say how much I enjoyed reading this publication—it is very well developed and informative. I couldn't think of a thing that might have been missed. I think it will be very well-received by the general public. Y'all have done an exemplary job!!

— MaryAnn Stabile, Person Living with Pain

REFRIGERATOR REMINDER

Medication Schedule For: _____

Date: _____

www.painfoundation.org

1-888-615 PAIN (7246)

This is a very good resource for the pain patient.

— Russell Portenoy, MD

What a great job! Finally; a full consumer resource created for patients with pain. A “must have”for every physician’s waiting room. — Scott Fishman, MD

This is one heck of a guide. Most of the therapies I have had or heard of but there were a few that popped in that I had not heard about. It is a great overall introduction, explanation and summary of complex issues and multi-disciplinary approaches to pain treatment. — Nick Wilson, Person Living with Pain

This book is just AWESOME, AWESOME, AWESOME. It makes me so mad I didn’t have this when my family and I were trying to understand different therapies and getting hopelessly confused!

*You all should be SO proud of what you have done here.
— Mary Vargas, Person Living with Pain*



American Pain Foundation

Dedicated to eliminating the undertreatment of pain in America.

American Pain Foundation
201 North Charles Street,
Suite 710
Baltimore, MD 21201-4111

EXHIBIT 27

Watch YouTube videos with Chrome. [Yes, get Chrome now.](#)

"Let's talk pain"

K



Episode 1: Safe Use of Opioids (PainSAFE)

LetsTalkPain



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Published on Sep 28, 2010

APF Action Network leader and patient advocate Teresa Shaffer talks with Al Anderson, M.D. and member of the AAPM Board of Directors, about how her medication program has helped improve her ability to walk without a wheelchair. Dr. Anderson emphasizes the important role of physicians in prescribing opioids to

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COMMENTS

EXHIBIT 28

Evidence Report/Technology Assessment

Number 218



The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain



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Evidence-Based
Practice

Evidence Report/Technology Assessment

Number 218

The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain

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This report is based on research conducted by the Pacific Northwest Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2012-00014-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

This report may periodically be assessed for the urgency to update. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at: www.effectivehealthcare.ahrq.gov. Search on the title of the report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Key Informants

This topic was nominated to AHRQ from the National Institutes of Health. Therefore, in place of Key Informants, a National Institutes of Health Working Group Planning Meeting was conducted to provide input into the key questions and the scope of the report.

Technical Expert Panel

In designing the review questions and methodology at the outset of this report, the EPC consulted several technical and content experts, reflecting a variety of viewpoints relevant to this topic. Technical experts consulted are expected to have divergent and possibly conflicting opinions. This diversity is helpful in achieving a well-rounded report. The study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

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University of California, Los Angeles
Los Angeles, CA

The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain

Structured Abstract

Objectives. Chronic pain is common and use of long-term opioid therapy for chronic pain has increased dramatically. This report reviews the current evidence on effectiveness and harms of opioid therapy for chronic pain, focusing on long-term (≥ 1 year) outcomes.

Data sources. A prior systematic review (searches through October 2008), electronic databases (Ovid MEDLINE, Scopus, and the Cochrane Libraries January 2008 to August 2014), reference lists, and clinical trials registries.

Review methods. Using predefined criteria, we selected randomized trials and comparative observational studies of patients with cancer or noncancer chronic pain being considered for or prescribed long-term opioid therapy that addressed effectiveness or harms versus placebo, no opioid use, or nonopioid therapies; different opioid dosing methods; or risk mitigation strategies. We also included uncontrolled studies ≥ 1 year that reported rates of abuse, addiction, or misuse, and studies on the accuracy of risk prediction instruments for predicting subsequent opioid abuse or misuse. The quality of included studies was assessed, data were extracted, and results were summarized qualitatively.

Results. Of the 4,209 citations identified at the title and abstract level, a total of 39 studies were included. For a number of Key Questions, we identified no studies meeting inclusion criteria. Where studies were available, the strength of evidence was rated no higher than low, due to imprecision and methodological shortcomings, with the exception of buccal or intranasal fentanyl for pain relief outcomes within 2 hours after dosing (strength of evidence: moderate). No study evaluated effects of long-term opioid therapy versus no opioid therapy. In 10 uncontrolled studies, rates of opioid abuse were 0.6 percent to 8 percent and rates of dependence were 3.1 percent to 26 percent in primary care settings, but studies varied in methods used to define and ascertain outcomes. Rates of aberrant drug-related behaviors ranged from 5.7 percent to 37.1 percent. Compared with nonuse, long-term opioid therapy was associated with increased risk of abuse (one cohort study), overdose (one cohort study), fracture (two observational studies), myocardial infarction (two observational studies), and markers of sexual dysfunction (one cross-sectional study), with several studies showing a dose-dependent association. One randomized trial found no difference between a more liberal opioid dose escalation strategy and maintenance of current dose in pain or function, but differences between groups in daily opioid doses at the end of the trial were small. One cohort study found methadone associated with lower risk of mortality than long-acting morphine in a Veterans Affairs population in a propensity adjusted analysis (adjusted HR 0.56, 95 percent CI 0.51 to 0.62). Estimates of diagnostic accuracy for the Opioid Risk Tool were extremely inconsistent and other risk assessment instruments were evaluated in only one or two studies. No study evaluated the effectiveness of risk mitigation strategies on outcomes related to overdose, addiction, abuse, or misuse. Evidence was insufficient to evaluate benefits and harms of long-term opioid therapy in high-risk patients or in other subgroups.

Conclusions. Evidence on long-term opioid therapy for chronic pain is very limited but suggests an increased risk of serious harms that appears to be dose-dependent. More research is needed to understand long-term benefits, risk of abuse and related outcomes, and effectiveness of different opioid prescribing methods and risk mitigation strategies.

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Executive Summary

Introduction

Background

Chronic pain, often defined as pain lasting longer than 3 months or past the time of normal tissue healing,¹ is extremely common. According to a recent Institute of Medicine report, up to one-third of U.S. adults report chronic pain.² Chronic pain is a major cause of decreased quality of life and disability and is often refractory to treatment.^{3,4} There has been a dramatic increase over the past 10 to 20 years in the prescription of opioid medications for chronic pain,⁵⁻⁷ despite limited evidence showing long-term beneficial effects.^{8,9} In addition, accumulating evidence indicates that prescription opioids may be associated with important harms, including accidental overdose, abuse, addiction, diversion, and accidents involving injuries (such as falls and motor vehicle accidents).¹⁰⁻²⁰ Perhaps of most concern is the dramatic increase in overdose deaths associated with opioids. In 2011, there were 16,917 fatal overdoses involving prescription opioids.²¹ Prescription opioid misuse and abuse resulted in almost 660,000 emergency department visits in 2010, over twice as many as in 2004.¹³ Substance abuse treatment admissions for opiates other than heroin increased more than six-fold from 1999 to 2009.¹² Opioids are also associated with adverse effects such as constipation, nausea, and sedation.²² Finally, data indicate potential associations between long-term opioid therapy and other harms, such as adverse endocrinological effects and hyperalgesia.²³⁻²⁵

These data underscore the complexity of clinical decisionmaking around long-term opioid therapy, which requires individualized assessments of the balance between benefits and harms; appropriate opioid selection, dose initiation, and titration strategies; integration of risk assessment and mitigation strategies; and consideration of the use of alternative, nonopioid therapies.⁹ Risk mitigation strategies that have been suggested for patients prescribed long-term opioids include use of opioid medication agreements, application of dose thresholds that warrant increased caution, regular clinical followup and monitoring, urine drug screens, use of abuse-deterrent opioid formulations, and use of data from prescription drug monitoring programs.⁹

Understanding benefits and harms of long-term opioid therapy for chronic pain is a challenge because effects may vary depending on patient characteristics (e.g., age, sex, pain condition, psychosocial factors, comorbidities), opioid characteristics (e.g., specific opioid, short- versus long-acting opioid, mode of administration, dose), dosing strategies (e.g., round-the-clock versus as-needed dosing, application of dose thresholds), concomitant therapies (e.g., use of benzodiazepines or other drugs that may interact with opioids), and characteristics of the clinical setting. Other challenges in interpreting the literature include potential limitations in generalizability due to study design and other methodological shortcomings (e.g., duration of followup, exclusion of patients at higher risk for harms, under-representation of certain sociodemographic groups, and high dropout rates), and gaps in research on important scientific questions.²⁶ Although guidelines on use of opioids for chronic pain are available, most recommendations are based on weak or limited evidence.^{9,27} The increase in use of long-term opioid therapy for chronic pain, new information concerning harms associated with long-term opioid therapy, continued wide variations in practice related to long-term opioid therapy, and the availability of new evidence underscore the need for a current systematic review in this area.

The purpose of this report is to systematically review the current evidence on long-term opioid therapy for chronic pain, which will be used by the National Institutes of Health (NIH) to inform a Pathways to Prevention Workshop on the role of opioids in the treatment of chronic pain. Although guidelines have been published from the American Pain Society (APS)/American Academy of Pain Medicine,⁹ the Veterans Affairs (VA)/Department of Defense,²⁸ and other groups, the availability of new evidence warrants a new systematic review that could be used to inform updated or new guidelines, guide quality improvement efforts, and define and update priorities for further research in this area.²⁶ This review updates a prior systematic review on opioid therapy for chronic pain funded by the APS.²⁹ Differences between this review and the 2009 APS review are that it focuses specifically on benefits and harms associated with long-term use of opioid therapy and evaluates an additional Key Question on dose escalation versus maintenance of doses in patients on long-term opioid therapy, additional outcomes (e.g., cardiovascular events, infection, and psychological outcomes), and additional risk mitigation strategies (e.g., abuse-deterring formulations and use of data from prescription drug monitoring programs).

Scope of Review and Key Questions

The Key Questions and analytic framework (Figure A) used to guide this report are shown below. The analytic framework shows the target populations, interventions, and outcomes that we examined.

Key Question 1. Effectiveness and Comparative Effectiveness

- a. In patients with chronic pain, what is the effectiveness of long-term opioid therapy versus placebo or no opioid therapy for long-term (≥ 1 year) outcomes related to pain, function, and quality of life?
- b. How does effectiveness vary depending on: (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including low back pain], fibromyalgia, sickle cell disease, inflammatory pain, and headache disorders); (2) patient demographics (e.g., age, race, ethnicity, gender); (3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities and high risk for addiction)?
- c. In patients with chronic pain, what is the comparative effectiveness of opioids versus nonopioid therapies (pharmacological or nonpharmacological) on outcomes related to pain, function, and quality of life?
- d. In patients with chronic pain, what is the comparative effectiveness of opioids plus nonopioid interventions (pharmacological or nonpharmacological) versus opioids or nonopioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used?

Key Question 2. Harms and Adverse Events

- a. In patients with chronic pain, what are the risks of opioids versus placebo or no opioid on: (1) opioid abuse, addiction, and related outcomes; (2) overdose; and (3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?

- b. How do harms vary depending on: (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including back pain], fibromyalgia, sickle cell disease, inflammatory pain, headache disorders); (2) patient demographics; (3) patient comorbidities (including past or current substance use disorder or at high risk for addiction); (4) the dose of opioids used?

Key Question 3. Dosing Strategies

- a. In patients with chronic pain, what is the comparative effectiveness of different methods for initiating and titrating opioids for outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?
- b. In patients with chronic pain, what is the comparative effectiveness of short- versus long-acting opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?
- c. In patients with chronic pain, what is the comparative effectiveness of different long-acting opioids on outcomes related to pain, function, and quality of life; and risk of overdose, addiction, abuse, or misuse?
- d. In patients with chronic pain, what is the comparative effectiveness of short- plus long-acting opioids versus long-acting opioids alone on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?
- e. In patients with chronic pain, what is the comparative effectiveness of scheduled, continuous versus as-needed dosing of opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?
- f. In patients with chronic pain on long-term opioid therapy, what is the comparative effectiveness of dose escalation versus dose maintenance or use of dose thresholds on outcomes related to pain, function, and quality of life?
- g. In patients on long-term opioid therapy, what is the comparative effectiveness of opioid rotation versus maintenance of current opioid therapy on outcomes related to pain, function, and quality of life; and doses of opioids used?
- h. In patients on long-term opioid therapy, what is the comparative effectiveness of different strategies for treating acute exacerbations of chronic pain on outcomes related to pain, function, and quality of life?
- i. In patients on long-term opioid therapy, what are the effects of decreasing opioid doses or of tapering off opioids versus continuation of opioids on outcomes related to pain, function, quality of life, and withdrawal?
- j. In patients on long-term opioid therapy, what is the comparative effectiveness of different tapering protocols and strategies on measures related to pain, function, quality of life, withdrawal symptoms, and likelihood of opioid cessation?

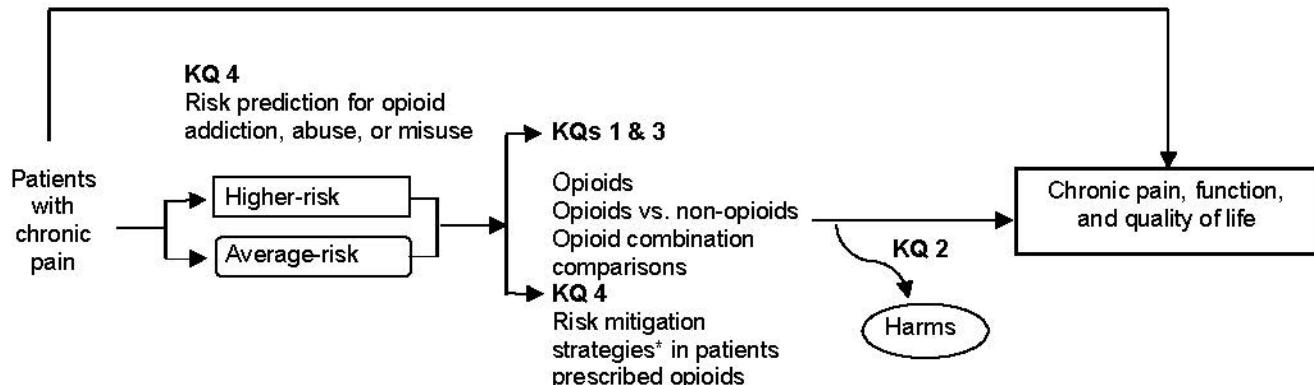
Key Question 4. Risk Assessment and Risk Mitigation Strategies

- a. In patients with chronic pain being considered for long-term opioid therapy, what is the accuracy of instruments for predicting risk of opioid overdose, addiction, abuse, or misuse?
- b. In patients with chronic pain, what is the effectiveness of use of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse?
- c. In patients with chronic pain prescribed long-term opioid therapy, what is the effectiveness of risk mitigation strategies, including (1) opioid management plans, (2) patient education, (3) urine drug screening, (4) use of prescription drug monitoring

program data, (5) use of monitoring instruments, (6) more frequent monitoring intervals, (7) pill counts, and (8) use of abuse-deterrent formulations on outcomes related to overdose, addiction, abuse, or misuse?

- d. What is the comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids on outcomes related to overdose, abuse, misuse, pain, function, and quality of life?

Figure A. Analytic framework



KQ, Key Question.

*Including opioid management plans, patient education, urine drug screening, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, and use of abuse-deterrent formulations.

Methods

The methods for this Comparative Effectiveness Review (CER) follow the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.³⁰ All methods were determined a priori.

Topic Refinement and Review Protocol

This topic was selected for review based on a nomination from NIH. The initial Key Questions for this CER were developed with input from an NIH working group. The Key Questions and scope were further developed with input from a Technical Expert Panel (TEP) convened for this report. The TEP provided high-level content and methodological guidance to the review process and consisted of experts in health services research, internal medicine, psychology, pain medicine, pharmacology, neurology, occupational medicine, pediatrics, and epidemiology. TEP members disclosed all financial or other conflicts of interest prior to participation. The AHRQ Task Order Officer and the investigators reviewed the disclosures and determined that the TEP members had no conflicts of interest that precluded participation.

The protocol for this CER was developed prior to initiation of the review, and was posted on the AHRQ Web site on December 19, 2013 at:
<http://effectivehealthcare.ahrq.gov/ehc/products/557/1837/chronic-pain-opioid-treatment-protocol-131219.pdf>. The protocol was also registered in the PROSPERO international database of prospectively registered systematic reviews.³¹

Literature Search Strategy

A research librarian conducted searches in Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, PsychINFO, and CINAHL from 2008 to August 2014 (see Appendix A for full search strategies). We restricted search start dates to January 2008 because the searches in the prior APS review, which we used to identify potentially relevant studies, went through October 2008.²⁹ For outcomes (cardiovascular, infections, and psychological harms) and interventions (abuse-deterrent formulations, and use of prescription monitoring program data) not addressed in the APS review, we searched the same databases and did not apply any search date start restrictions.

We also hand-searched the reference lists of relevant studies and searched for unpublished studies in ClinicalTrials.gov. Scientific information packets (SIPs) with relevant published and unpublished studies were requested from 19 current application holders from the U.S. Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategy (REMS) Extended-Release and Long-Acting (ER/LA) Opioid Analgesics List.³² We received five SIP submissions.

Study Selection

We developed criteria for inclusion and exclusion of articles based on the Key Questions and the populations, interventions, comparators, outcomes, timing, and setting (PICOTS) approach (Appendix B). Articles were selected for full-text review if they were about long-term opioid therapy for chronic pain, were relevant to a Key Question, and met the predefined inclusion criteria as shown below. We excluded studies published only as conference abstracts, restricted inclusion to English-language articles, and excluded studies of nonhuman subjects. Studies had to report original data to be included.

Each abstract was independently reviewed for potential inclusion and full-text review by two investigators. Two investigators independently reviewed all full-text articles for final inclusion. Discrepancies were resolved through discussion and consensus. A list of the included articles is available in Appendix C; excluded articles are shown Appendix D with primary reasons for exclusion.

We selected studies of adults (age ≥ 18 years) with chronic pain (defined as pain lasting >3 months) being considered for long-term opioid therapy (Key Questions 4a and 4b) or prescribed long-term opioid therapy (all other Key Questions). We defined long-term opioid therapy as use of opioids on most days for >3 months; this threshold was selected to differentiate ongoing opioid therapy (as often used for chronic pain) from short-term therapy. We included studies that did not explicitly report the duration of pain if the average duration of opioid therapy was >3 months. We included studies that did not explicitly report the duration of opioid therapy if patients were prescribed long-acting opioids, as these are not typically prescribed for short-term use. We included studies with patients with chronic pain related to current or previously treated cancer, but excluded studies with patients with pain at end of life (e.g., patients with cancer in hospice care). We excluded studies with patients with acute pain, pregnant or breastfeeding women, and patients treated with opioids for addiction.

We included studies of patients prescribed any long- or short-acting opioid used as long-term therapy, either alone or in combination with another agent (Key Question 1d). We included tapentadol, a dual mechanism medication with strong opioid mu-receptor affinity, but excluded tramadol, which is also a dual mechanism medication but with weak opioid mu-receptor affinity that has not been identified as a cause of unintentional prescription drug overdose deaths.³³ We also excluded studies of parenteral opioids.

We included studies that compared long-term opioid therapy versus placebo, no therapy, or another drug or nondrug therapy; studies that evaluated different dose initiation, titration, or rotation strategies; studies of different methods for tapering or discontinuing opioids; studies on methods for treating acute exacerbations of pain in people with chronic pain; and studies on various risk mitigation strategies for reducing harms associated with opioids. Risk mitigation strategies included opioid management plans, patient education, urine drug screening, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, and use of abuse-deterrent formulations. We also included studies that compared the predictive accuracy of risk prediction instruments in people with chronic pain prior to initiation of opioids for predicting outcomes related to future misuse, abuse, or addiction, and studies on the effects of risk prediction instruments on clinical outcomes.

Outcomes were pain (intensity, severity, bothersomeness), function (physical disability, activity limitations, activity interference, work function), quality of life (including depression), and doses of opioids used. Evaluated harms included overdose, opioid use disorder, addiction, abuse, and misuse, as well as other opioid-related harms (including gastrointestinal harms, fractures, falls, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms [e.g., depression]). We focused on outcomes reported after at least 1 year of opioid therapy, with the exception of outcomes related to overdose and injuries (fractures, falls, and motor vehicle accidents), studies on treatment of acute exacerbations of chronic pain, studies on dose initiation and titration, and studies on discontinuation of opioid therapy, for which we included studies of any duration.

For all Key Questions, we included randomized trials and controlled observational studies (cohort studies, cross-sectional studies, and case-control studies) that performed adjustment on

potential confounders. We included uncontrolled observational studies of patients with chronic pain prescribed opioid therapy for at least 1 year that reported abuse, misuse, or addiction as a primary outcome and described predefined methods to assess these outcomes. Otherwise, we excluded uncontrolled observational studies, case series, and case reports. We reviewed systematic reviews for potentially relevant references.

Data Extraction

We extracted the following information from included studies into evidence tables using Excel spreadsheets: study design, year, setting, inclusion and exclusion criteria, population characteristics (including sex, age, race, pain condition, and duration of pain), sample size, duration of followup, attrition, intervention characteristics (including specific opioid and formulation, dose, and duration of therapy), results, and funding sources.

For studies on the predictive accuracy of risk prediction instruments, we attempted to create two-by-two tables from information provided (sample size, prevalence, sensitivity, and specificity) and compared calculated measures of diagnostic accuracy based on the two-by-two tables with reported results. We noted discrepancies between calculated and reported results when present. When reported, we also recorded the area under the receiver operating characteristic curve (AUROC).^{34,35}

For studies of interventions, we calculated relative risks (RR) and associated 95 percent confidence intervals (CI) based on the information provided (sample sizes and incidence of outcomes of interest in each intervention group). We noted discrepancies between calculated and reported results when present.

Data extraction for each study was performed by two investigators. The first investigator extracted the data, and the second investigator independently reviewed the extracted data for accuracy and completeness.

Assessing Methodological Risk of Bias of Individual Studies

We assessed risk of bias (quality) for each study using predefined criteria. We used the term “quality” rather than the alternate term “risk of bias;” both refer to internal validity. Randomized trials were evaluated with criteria and methods developed by the Cochrane Back Review Group.³⁶ Cohort studies, case-control studies, and cross-sectional studies were rated using criteria from the U.S. Preventive Services Task Force.³⁷ Risk prediction instrument studies were rated using criteria from various sources.³⁸⁻⁴⁰ These criteria were applied in conjunction with the approach recommended in the chapter, Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions,⁴¹ in the AHRQ Methods Guide. Studies of predictive accuracy of risk prediction instruments were assessed using an approach adapted from the AHRQ Methods Guide for Medical Test Reviews,³⁸ which is based on methods developed by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) group.³⁹ We reassessed the quality of studies included in the prior APS review to ensure consistency in quality assessment. Two investigators independently assessed the quality of each study. Discrepancies were resolved through discussion and consensus.

Individual studies were rated as having “poor,” “fair,” or “good” quality. We rated the quality of each randomized trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; whether attrition was adequately reported and acceptable; similarity in use of cointerventions; compliance to allocated treatments; the use of intent-to-treat analysis; and avoidance of selective outcomes reporting.^{36,37}

We rated the quality of each cohort study based on whether it enrolled a consecutive or random sample of patients meeting inclusion criteria; whether it evaluated comparable groups; whether rates of loss to followup were reported and acceptable; whether it used accurate methods for ascertaining exposures, potential confounders, and outcomes; and whether it performed adjustment for important potential confounders.³⁷ For cross-sectional studies, we used criteria for cohort studies, but did not rate criteria related to loss to followup. For uncontrolled studies on risk of abuse or related outcomes, we evaluated whether it enrolled a consecutive or random sample, whether outcome assessors were blinded to patient characteristics, whether rates of loss to followup were reported (for longitudinal studies) and acceptable, and whether pre-specified outcomes were assessed in all patients.

We rated the quality of each case-control study based on whether it enrolled a consecutive or random sample of cases meeting predefined criteria; whether controls were derived from the same population as cases; whether cases and controls were comparable on key prognostic factors; whether it used accurate methods to ascertain outcomes, exposures, and potential confounders; and whether it performed adjustment for important potential confounders.³⁷

We rated the quality of each study on the predictive value of risk prediction instruments based on whether it evaluated a consecutive or random sample of patients meeting pre-defined criteria, whether the patient population evaluated in the study was adequately described, whether the screening instrument included appropriate criteria, and whether outcomes were assessed in all patients independent of the results of the risk assessment instrument using adequately described methods.^{38,39} We also evaluated whether the study was to develop a risk prediction instrument or to validate a previously developed instrument.⁴⁰

Studies rated “good quality” were considered to have the least risk of bias and their results are likely to be valid. Studies rated “fair quality” have some methodological shortcomings, but no flaw or combination of flaws judged likely to cause major bias. In some cases, the article did not report important information, making it difficult to assess its methods or potential limitations. The moderate risk of bias category is broad and studies with this rating vary in their strengths and weaknesses; the results of some studies assessed to have moderate risk of bias are likely to be valid, while others may be only possibly valid. Studies rated “poor quality” have significant flaws that may invalidate the results. They have a serious or “fatal” flaw or combination of flaws in design, analysis, or reporting; large amounts of missing information; or serious discrepancies in reporting. The results of these studies are at least as likely to reflect flaws in the study design as the differences between the compared interventions. We did not exclude studies rated as having high risk of bias a priori, but they were considered the least reliable when synthesizing the evidence, particularly when discrepancies between studies were present.

Assessing Research Applicability

We recorded factors important for understanding the applicability of studies, such as whether the publication adequately described the study sample, the country in which the study was conducted, the characteristics of the patient sample (e.g., age, sex, race, pain condition, duration or severity of pain, medical comorbidities, and psychosocial factors), the characteristics of the interventions used (e.g., specific opioid, dose, mode of administration, or dosing strategy), the clinical setting (e.g., primary care or specialty setting), and the magnitude of effects on clinical outcomes.⁴² We also recorded the funding source and role of the sponsor. We did not assign a rating of applicability (such as high or low) because applicability may differ based on the user of the report.

Evidence Synthesis and Rating the Body of Evidence

We constructed evidence tables summarizing study characteristics, results, and quality ratings for all included studies. We summarized evidence for each Key Question qualitatively used a hierarchy-of-evidence approach, where the best evidence was the focus of our synthesis for each Key Question. In the evidence tables, we included relevant studies from the prior APS review as well as new studies meeting inclusion criteria. Results were organized by Key Question. We did not attempt meta-analyses because of the small number of studies available for each Key Question; variability in study designs, patient samples, interventions, and measures; and methodological shortcomings in the available studies.

We assessed the overall strength of evidence (SOE) for each Key Question and outcome using the approach described in the AHRQ Methods Guide.³⁰ We synthesized the quality of the studies; the consistency of results within and between study designs; the directness of the evidence linking the intervention and health outcomes; and the precision of the estimate of effect (based on the number and size of studies and CIs for the estimates). We were not able to formally assess for publication bias due to small number of studies, methodological shortcomings, or differences across studies in designs, measured outcomes, and other factors. Rather, as described above, we searched for unpublished studies through searches of clinical trials registries and regulatory documents and by soliciting SIPs.

The SOE was based on the overall quality of each body of evidence, based on the risk of bias (graded low, moderate, or high); the consistency of results across studies (graded consistent, inconsistent, or unable to determine when only one study was available); the directness of the evidence linking the intervention and health outcomes (graded direct or indirect); and the precision of the estimate of effect, based on the number and size of studies and CIs for the estimates (graded precise or imprecise). We did not grade supplemental domains for cohort studies evaluating intermediate and clinical outcomes because too few studies were available for these factors to impact the SOE grades.

We graded the SOE for each Key Question using the four key categories recommended in the AHRQ Methods Guide.³⁰ A “high” grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect. A “moderate” grade indicates moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate. A “low” grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. An “insufficient” grade indicates evidence either is unavailable or is too limited to permit any conclusion, due to the availability of only poor-quality studies, extreme inconsistency, or extreme imprecision.

Peer Review and Public Commentary

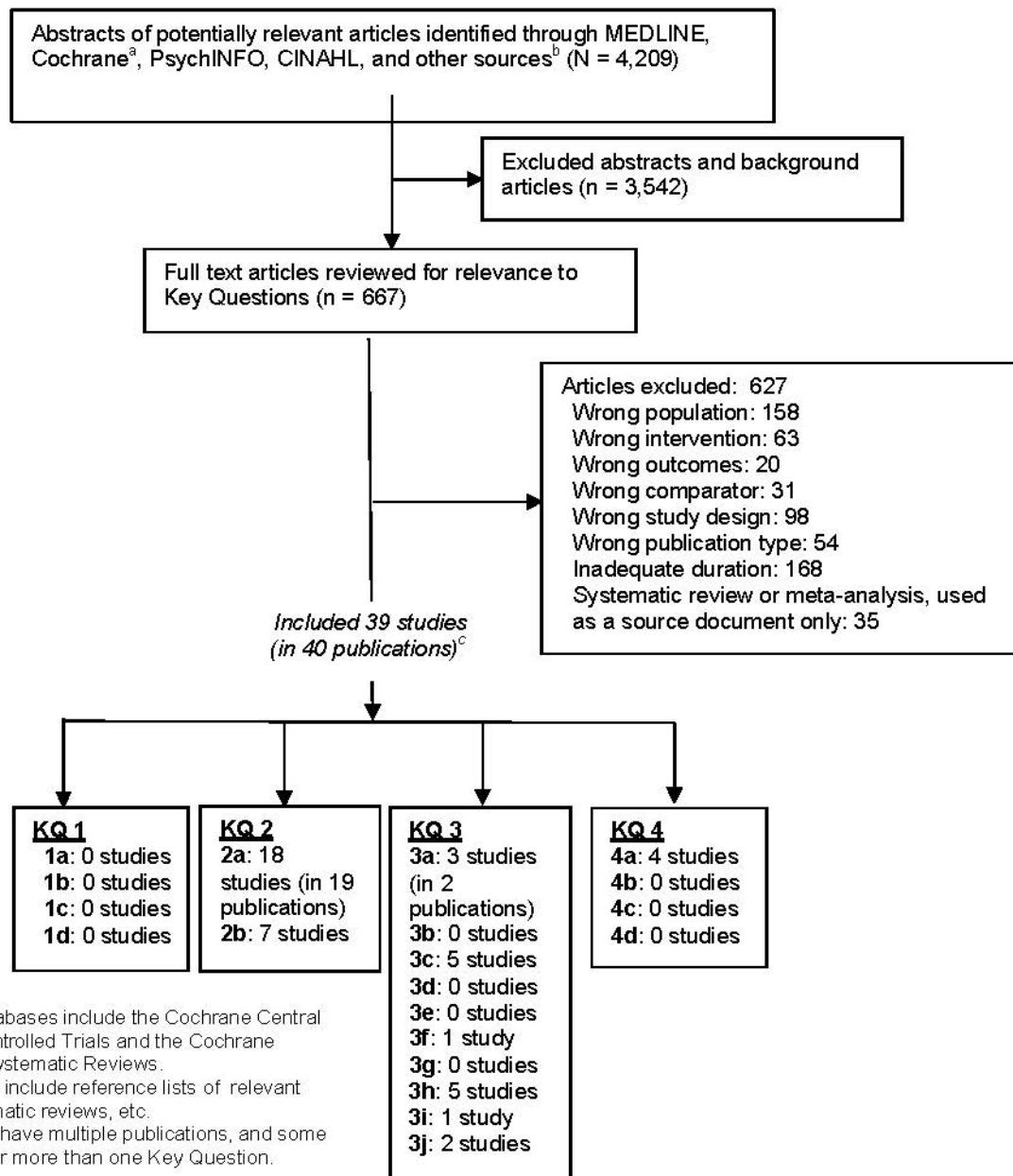
Experts in chronic pain and opioid therapy, as well as individuals representing important stakeholder groups, were invited to provide external peer review of this CER. The AHRQ Task Order Officer and a designated EPC Associate Editor also provided comments and editorial review. To obtain public comment, the draft report was posted on the AHRQ Web site for 4 weeks. A disposition of comments report detailing the authors' responses to the peer and public review comments will be made available after AHRQ posts the final CER on the public Web site.

Results

Overview

The search and selection of articles are summarized in the study flow diagram (Figure B). Database searches resulted in 4,209 potentially relevant articles. After dual review of abstracts and titles, 667 articles were selected for full-text review, and 39 studies (in 40 publications) were determined by dual review at the full-text level to meet inclusion criteria and were included in this review. Data extraction and quality assessment tables for all included studies per Key Question are available in Appendixes E and F.

Figure B. Literature flow diagram



Key Question 1. Effectiveness and Comparative Effectiveness

No study evaluated the effectiveness or comparative effectiveness of long-term opioid therapy versus placebo or no opioid therapy for long-term (≥ 1 year) outcomes related to pain, function, or quality of life in patients with chronic pain (SOE: insufficient).

Key Question 2. Harms and Adverse Events

In patients with chronic pain, 10 uncontrolled studies of patients on opioid therapy for at least 1 year that used predefined methods for ascertaining rates of abuse and related outcomes, rates of opioid abuse were 0.6 percent to 8 percent and rates of dependence were 3.1 percent to 26 percent in primary care settings, and rates of abuse were 14.4 percent, misuse 8 percent, and addiction 1.9 percent in pain clinic settings, but studies varied in methods used to define and ascertain outcomes. Rates of aberrant drug-related behaviors (e.g., positive urine drug tests, medication agreement violations) ranged from 5.7 percent to 37.1 percent (SOE: insufficient). In controlled observational studies, opioids were associated with increased risk of abuse (one study), overdose (one study), fracture (two studies), myocardial infarction (two studies), and use of testosterone replacement or medications for erectile dysfunction (one study) versus no opioid use (strength of evidence: low). No study evaluated effects of opioids versus placebo or no opioid on gastrointestinal harms, motor vehicle accidents, infections, and psychological or cognitive harms. In patients with chronic pain prescribed long-term opioid therapy, observational studies reported an association between higher doses of opioids and risk of abuse (one study), overdose (two studies), fracture (one study), myocardial infarction (one study), motor vehicle accidents (one study), and use or testosterone replacement or medications for erectile dysfunction (one study) (SOE: low). No study examined how harms vary depending on the specific type or cause of pain, patient demographics, or patient comorbidities (including past or current substance abuse disorder or being at high risk for addiction).

Key Question 3. Dosing Strategies

Three randomized, head-to-head trials of various long-acting opioids found no differences in long-term outcomes related to pain or function (SOE: low). One retrospective cohort study conducted in a Veterans Affairs setting that used a propensity-adjusted analysis found methadone associated with lower mortality risk than sustained-release morphine (SOE: low). One randomized trial found no difference between more liberal dose escalation versus maintenance of current doses on outcomes related to pain, function, or withdrawal due to opioid use, but doses of opioids at the end of the trial in the two groups were similar (52 versus 40 mg MED/day) (SOE: low). Five randomized trials found buccal or nasal fentanyl more effective than placebo or oral opioids for acute exacerbations of pain in patients with chronic pain, but focused on immediate (within 2 hours) outcomes (SOE: moderate). Studies on different methods for initiating and titrating opioids (three studies), decreasing doses or tapering off versus continuation (one study), and different tapering protocols and strategies (two studies), were limited in number, had methodological shortcomings, and showed no clear differences on outcomes related to pain and function (SOE: insufficient). No study examined effects of short- versus long-acting opioids, short- plus long-acting opioids versus long-acting opioids alone, scheduled, continuous versus as-needed dosing, or opioid rotation versus maintenance of current therapy in patients with chronic pain on long-term opioid therapy.

Key Question 4. Risk Assessment and Risk Mitigation Strategies

Four studies examined the accuracy of instruments for predicting risk of opioid overdose, addiction, abuse, or misuse in patients with chronic pain being considered for long-term opioid therapy. Three studies reported sensitivities for the Opioid Risk Tool that ranged from 0.20 to 0.99 (three studies) and specificities of 0.88 and 0.16 (two studies) (SOE: insufficient). Two studies found no clear differences between different risk assessment instruments in diagnostic accuracy. No study evaluated the effectiveness of the use of risk prediction instruments or other risk mitigation strategies, or the comparative effectiveness of treatment strategies for managing patients with a history of addiction on overdose, addiction, abuse, misuse, and related outcomes.

Key findings and SOE grades are summarized in the summary of evidence table (Table A). The factors used to determine the overall SOE grades are available in Appendix G.

Table A. Summary of evidence

Key Question Outcome	Strength of Evidence Grade	Conclusion
1. Effectiveness and comparative effectiveness		
a. In patients with chronic pain, what is the effectiveness of long-term opioid therapy versus placebo or no opioid therapy for long-term (≥ 1 year) outcomes related to pain, function, and quality of life?		
Pain, function, quality of life	Insufficient	No study of opioid therapy versus placebo or no opioid therapy evaluated long-term (≥ 1 year) outcomes related to pain, function, or quality of life
b. How does effectiveness vary depending on: 1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including low back pain], fibromyalgia, sickle cell disease, inflammatory pain, and headache disorders); 2) patient demographics (e.g., age, race, ethnicity, gender); 3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities and high risk for addiction)?		
Pain, function, quality of life	Insufficient	No studies
c. In patients with chronic pain, what is the comparative effectiveness of opioids versus nonopioid therapies (pharmacological or nonpharmacological) on outcomes related to pain, function, and quality of life?		
Pain, function, quality of life	Insufficient	No studies
d. In patients with chronic pain, what is the comparative effectiveness of opioids plus nonopioid interventions (pharmacological or nonpharmacological) versus opioids or nonopioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used?		

Table A. Summary of evidence (continued)

Key Question Outcome	Strength of Evidence Grade	Conclusion
Pain, function, quality of life	Insufficient	No Studies
2. Harms and adverse events		
a. In patients with chronic pain, what are the risks of opioids versus placebo or no opioid on: 1) opioid abuse, addiction, and related outcomes; 2) overdose; and 3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?		
Abuse, addiction	Low	No randomized trial evaluated risk of opioid abuse, addiction, and related outcomes in patients with chronic pain prescribed opioid therapy. One retrospective cohort study found prescribed long-term opioid use associated with significantly increased risk of abuse or dependence versus no opioid use.
Abuse, addiction	Insufficient	In 10 uncontrolled studies, estimates of opioid abuse, addiction, and related outcomes varied substantially even after stratification by clinic setting
Overdose	Low	Current opioid use was associated with increased risk of any overdose events (adjusted HR 5.2, 95% CI 2.1 to 12) and serious overdose events (adjusted HR 8.4, 95% CI 2.5 to 28) versus current nonuse
Fractures	Low	Opioid use associated with increased risk of fracture in 1 cohort study (adjusted HR 1.28, 95% CI 0.99 to 1.64) and 1 case-control study (adjusted OR 1.27, 95% CI 1.21 to 1.33)
Myocardial infarction	Low	Current opioid use associated with increased risk of myocardial infarction versus nonuse (adjusted OR 1.28, 95% CI 1.19 to 1.37 and incidence rate ratio 2.66, 95% CI 2.30 to 3.08)
Endocrine	Low	Long-term opioid use associated with increased risk of use of medications for erectile dysfunction or testosterone replacement versus nonuse (adjusted OR 1.5, 95% CI 1.1 to 1.9)
Gastrointestinal harms, motor vehicle accidents, infections, psychological harms, cognitive harms	Insufficient	No studies
b. How do harms vary depending on: 1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including back pain], fibromyalgia, sickle cell disease, inflammatory pain, headache disorders); 2) patient demographics; 3) patient comorbidities (including past or current substance use disorder or at high risk for addiction)?		

Table A. Summary of evidence (continued)

Key Question Outcome	Strength of Evidence Grade	Conclusion
Various harms	Insufficient	No studies
b. How do harms vary depending on the dose of opioids used?		
Abuse, addiction	Low	One retrospective cohort study found higher doses of long-term opioid therapy associated with increased risk of opioid abuse or dependence than lower doses. Compared to no opioid prescription, the adjusted odds ratios were 15 (95 percent CI 10 to 21) for 1-36 MED/day, 29 (95 percent CI 20 to 41) for 36-120 MED/day, and 122 (95 percent CI 73 to 205) for \geq 120 MED/day.
Overdose	Low	Versus 1 to 19 mg MED/day, 1 cohort study found an adjusted HR for an overdose event of 1.44 (95% CI 0.57 to 3.62) for 20 to 49 mg MED/day that increased to 11.18 (95% CI 4.80 to 26.03) at >100 mg MED/day; 1 case-control study found an adjusted OR for an opioid-related death of 1.32 (95% CI 0.94 to 1.84) for 20 to 49 mg MED/day that increased to 2.88 (95% CI 1.79 to 4.63) at \geq 200 mg MED/day
Fracture	Low	Risk of fracture increased from an adjusted HR of 1.20 (95% CI 0.92 to 1.56) at 1 to $<$ 20 mg MED/day to 2.00 (95% CI 1.24 to 3.24) at \geq 50 mg MED/day; the trend was of borderline statistical significance
Myocardial infarction	Low	Relative to a cumulative dose of 0 to 1350 mg MED over 90 days, the incidence rate ratio for myocardial infarction for 1350 to $<$ 2700 mg was 1.21 (95% CI 1.02 to 1.45), for 2700 to $<$ 8100 mg was 1.42 (95% CI 1.21 to 1.67), for 8100 to $<$ 18,000 mg was 1.89 (95% CI 1.54 to 2.33), and for $>$ 18,000 mg was 1.73 (95% CI 1.32 to 2.26)
Motor vehicle accidents	Low	No association between opioid dose and risk of motor vehicle accidents.
Endocrine	Low	Relative to 0 to $<$ 20 mg MED/day, the adjusted OR for daily opioid dose of \geq 120 mg MED/day for use of medications for erectile dysfunction or testosterone replacement was 1.6 (95% CI 1.0 to 2.4)

Table A. Summary of evidence (continued)

Key Question Outcome	Strength of Evidence Grade	Conclusion
3. Dosing strategies		
a. In patients with chronic pain, what is the comparative effectiveness of different methods for initiating and titrating opioids for outcomes related to pain, function, and quality of life; risks of overdose, addiction, abuse, or misuse; and doses of opioids used?		
Pain	Insufficient	Evidence from three trials on effects of titration with immediate-release versus sustained-release opioids reported inconsistent results on outcomes related to pain and are difficult to interpret due to additional differences between treatment arms in dosing protocols (titrated vs. fixed dosing) and doses of opioids used
Function, quality of life, outcomes related to abuse	Insufficient	No studies
b. In patients with chronic pain, what is the comparative effectiveness of short- versus long-acting opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?		

Table A. Summary of evidence (continued)

Key Question Outcome	Strength of Evidence Grade	Conclusion
Pain, function, quality of life, outcomes related to abuse	Insufficient	No studies
c. In patients with chronic pain, what is the comparative effectiveness of different long-acting opioids on outcomes related to pain, function, and quality of life; and risk of overdose, addiction, abuse, or misuse?		
Pain and function	Low	No difference between various long-acting opioids
Assessment of risk of overdose, addiction, abuse, or misuse	Insufficient	No studies were designed to assess risk of overdose, addiction, abuse, or misuse
Overdose (as indicated by all-cause mortality)	Low	One cohort study found methadone to be associated with lower all-cause mortality risk than sustained-release morphine in a propensity adjusted analysis
Abuse and related outcomes	Insufficient	Another cohort study found some differences between long-acting opioids in rates of adverse outcomes related to abuse, but outcomes were nonspecific for opioid-related adverse events, precluding reliable conclusions
d. In patients with chronic pain, what is the comparative effectiveness of short- plus long-acting opioids vs. long-acting opioids alone on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?		
Pain, function, quality of life, outcomes related to abuse	Insufficient	No studies
e. In patients with chronic pain, what is the comparative effectiveness of scheduled, continuous versus as-needed dosing of opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?		
Pain, function, quality of life, outcomes related to abuse	Insufficient	No studies
f. In patients with chronic pain on long-term opioid therapy, what is the comparative effectiveness of dose escalation versus dose maintenance or use of dose thresholds on outcomes related to pain, function, and quality of life?		
Pain, function, withdrawal due to opioid misuse	Low	No difference between more liberal dose escalation versus maintenance of current doses in pain, function, or risk of withdrawal due to opioid misuse, but there was limited separation in opioid doses between groups (52 vs. 40 mg MED/day at the end of the trial)
g. In patients on long-term opioid therapy, what is the comparative effectiveness of opioid rotation versus maintenance of current opioid therapy on outcomes related to pain, function, and quality of life; and doses of opioids used?		
Pain, function, quality of life, outcomes related to abuse	Insufficient	No studies

Table A. Summary of evidence (continued)

Key Question Outcome	Strength of Evidence Grade	Conclusion
h. In patients on long-term opioid therapy, what is the comparative effectiveness of different strategies for treating acute exacerbations of chronic pain on outcomes related to pain, function, and quality of life?		
Pain	Moderate	Two randomized trials found buccal fentanyl more effective than placebo for treating acute exacerbations of pain and three randomized trials found buccal fentanyl or intranasal fentanyl more effective than oral opioids for treating acute exacerbations of pain in patients on long-term opioid therapy, based on outcomes measured up to 2 hours after dosing
Abuse and related outcomes	Insufficient	No studies
i. In patients on long-term opioid therapy, what are the effects of decreasing opioid doses or of tapering off opioids versus continuation of opioids on outcomes related to pain, function, quality of life, and withdrawal?		
Pain, function	Insufficient	Abrupt cessation of morphine was associated with increased pain and decreased function compared to continuation of morphine
j. In patients on long-term opioid therapy, what is the comparative effectiveness of different tapering protocols and strategies on measures related to pain, function, quality of life, withdrawal symptoms, and likelihood of opioid cessation?		
Opioid abstinence	Insufficient	No clear differences between different methods for opioid discontinuation or tapering in likelihood of opioid abstinence after 3 to 6 months
4. Risk assessment and risk mitigation strategies		
a. In patients with chronic pain being considered for long-term opioid therapy, what is the accuracy of instruments for predicting risk of opioid overdose, addiction, abuse, or misuse?		
Diagnostic accuracy: Opioid Risk Tool	Insufficient	Based on a cutoff of >4, three studies (one poor-quality, two poor-quality) reported very inconsistent estimates of diagnostic accuracy, precluding reliable conclusions
Diagnostic accuracy: Screening and Opioid Assessment for Patients with Pain (SOAPP) version 1	Low	Based on a cutoff score of ≥8, sensitivity was 0.68 and specificity of 0.38 in 1 study, for a PLR of 1.11 and NLR of 0.83. Based on a cutoff score of >6, sensitivity was 0.73 in 1 study
b. In patients with chronic pain, what is the effectiveness of use of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse?		
Outcomes related to abuse	Insufficient	No study evaluated the effectiveness of risk prediction instruments for reducing outcomes related to overdose, addiction, abuse, or misuse

Table A. Summary of evidence (continued)

Key Question Outcome	Strength of Evidence Grade	Conclusion
c. In patients with chronic pain prescribed long-term opioid therapy, what is the effectiveness of risk mitigation strategies, including 1) opioid management plans, 2) patient education, 3) urine drug screening, 4) use of prescription drug monitoring program data, 5) use of monitoring instruments, 6) more frequent monitoring intervals, 7) pill counts, and 8) use of abuse-deterrent formulations on outcomes related to overdose, addiction, abuse, or misuse?		
Outcomes related to abuse	Insufficient	No studies
d. What is the comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids on outcomes related to overdose, abuse, misuse, pain, function, and quality of life?		
Outcomes related to abuse	Insufficient	No studies

Abbreviations: CI=confidence interval, HR=hazard ratio, MED= morphine equivalent dose, mg=milligrams, NLR=negative likelihood ratio, OR=odds ratio, PLR=positive likelihood ratio, SOAPP= Screening and Opioid Assessment for Patients with Pain.

Discussion

Key Findings and Strength of Evidence

The key findings of this review are summarized in the summary of evidence table (Table A) and the factors used to determine the overall SOE grades are summarized in Appendix G. For a number of Key Questions, we identified no studies meeting inclusion criteria. For Key Questions where studies were available, the SOE was rated no higher than low, due to small numbers of studies and methodological shortcomings, with the exception of buccal or intranasal fentanyl for pain relief outcomes within 2 hours after dosing, for which the SOE was rated moderate.

For effectiveness and comparative effectiveness, we identified no studies of long-term opioid therapy in patients with chronic pain versus no opioid therapy or nonopioid alternative therapies that evaluated outcomes at 1 year or longer. No studies examined how effectiveness varies based on various factors, including type of pain and patient characteristics. Most placebo-controlled randomized trials were shorter than 6 weeks in duration⁴³ and no cohort studies on the effects of long-term opioid therapy versus no opioid therapy on outcomes related to pain, function, or quality of life were found. Although uncontrolled studies of patients prescribed opioids are available,⁸ findings are difficult to interpret due to the lack of a nonopioid comparison group.

Regarding harms, new evidence (published since the APS review) from observational studies suggests that being prescribed long-term opioids for chronic pain is associated with increased risk of abuse,⁴⁴ overdose,⁴⁵ fractures,^{18,46} and myocardial infarction,⁴⁷ versus not currently being prescribed opioids. In addition, several recent studies suggest that the risk is dose-dependent, with higher opioid doses associated with increased risk.^{11,18,44,45,48,49} Although two studies found an association between opioid dose and increased risk of overdose starting at relatively low doses (20 to 49 mg MED/day), estimates at higher doses were variable (adjusted HR 11.18 at >100 mg MED/day versus adjusted OR 2.88 for ≥200 mg MED/day).^{45,49} However, few studies evaluated each outcome and the population evaluated and duration of opioid therapy were not always well characterized. In addition, as in all observational studies, findings are susceptible to residual confounding despite use of statistical adjustment and other techniques such as matching. A study also found long-term opioid therapy associated with increased likelihood of receiving prescriptions for erectile dysfunction or testosterone, which may be markers for sexual dysfunction due to presumed endocrinological effects of opioids.¹¹ However, it did not directly measure sexual dysfunction, and patients may seek or receive these medications for other reasons.

No study assessed the risk of abuse, addiction, or related outcomes associated with long-term opioid therapy use versus placebo or no opioid therapy. In uncontrolled studies, rates of abuse and related outcomes varied substantially, even after restricting inclusion to studies that evaluated patients on opioid therapy for at least one year and used pre-defined methods for ascertaining these outcomes, and stratifying studies according to whether they evaluated primary care populations or patients evaluated in pain clinic settings.⁵⁰⁻⁶⁰ An important reason for the variability in estimates is differences in patient samples and in how terms such as addiction, abuse, misuse, and dependence were defined in the studies, and in methods used to identify these outcomes (e.g., formal diagnostic interview with patients versus chart review or informal assessment). In one study, estimates of opioid misuse were lower based on independent review than based on assessments by the treating physician.⁵⁹ No study evaluated patients with “opioid use disorder” as recently defined in the new DSM-V.⁶¹

Evidence on the effectiveness of different opioid dosing strategies is also extremely limited. One new trial of a more liberal dose escalation strategy versus maintenance of current doses found no differences in outcomes related to pain, function, or risk of withdrawal from the study due to opioid misuse, but the difference in opioid doses between groups at the end of the trial was small (52 versus 40 mg MED/day).⁶² One study from Washington State reported a decrease in the number of opioid-associated overdose deaths after implementing a dose threshold,⁶³ but did not meet inclusion criteria for this review because it was an ecological, before-after study, and it is not possible to reliably determine whether changes in the number of opioid overdose deaths were related to other factors that could have impacted opioid prescribing practices. Evidence on benefits and harms of different methods for initiating and titrating opioids, short-versus long-acting opioids, scheduled and continuous versus as-needed dosing of opioids, use of opioid rotation, and methods for titrating or discontinuing patients off opioids was not available or too limited to reach reliable conclusions.

We also found limited evidence on the comparative benefits and harms of specific opioids. Three head-to-head trials found few differences in pain relief between various long-acting opioids at 1 year followup,⁶⁴⁻⁶⁶ but the usefulness of these studies for evaluating comparative effectiveness may be limited because patients in each arm had doses titrated to achieve adequate pain control. None of the trials was designed to evaluate abuse, addiction, or related outcomes.

Methadone has been an opioid of particular interest because it is disproportionately represented in case series and epidemiological studies of opioid-associated deaths.⁶⁷ Characteristics of methadone that may be associated with increased risk of serious harms are its long and variable half-life, which could increase the risk for accidental overdose, and its association with electrocardiographic QTc interval prolongation, which could increase the risk of potentially life-threatening ventricular arrhythmia.⁶⁸ However, the highest-quality observational study, which was conducted in VA patients with chronic pain and controlled well for confounders using a propensity-adjusted analysis, found methadone to be associated with lower risk of mortality as compared with sustained-release morphine.⁶⁹ These results suggest that in some settings, methadone may not be associated with increased mortality risk, though research is needed to understand the factors that contribute to safer prescribing in different clinical settings.

Although five randomized trials found buccal or intranasal fentanyl more effective than placebo or oral opioids for treating acute exacerbations of chronic pain, all focused on short-term treatment and immediate outcomes in the minutes or hours after administration.⁷⁰⁻⁷⁴ No study was designed to assess long-term benefits or harms, including accidental overdose, abuse, or addiction. In 2007, the U.S. FDA released a public health advisory due to case reports of deaths and other life-threatening adverse effects in patients prescribed buccal fentanyl.⁷⁵

Evidence also remains limited on the utility of opioid risk assessment instruments, used prior to initiation of opioid therapy, for predicting likelihood of subsequent opioid abuse or misuse. In three studies of the ORT, estimates were extremely inconsistent (sensitivity ranged from 0.20 to 0.99).⁷⁶⁻⁷⁸ A study that directly compared the accuracy of the ORT and two other risk assessment instruments reported weak likelihood ratios for predicting future abuse or misuse (PLR 1.27 to 1.65 and NLR 0.86 to 0.91).⁷⁶ Risk prediction instruments other than the ORT (such as the SOAPP version 1, revised SOAPP, or DIRE) were only evaluated in one or two studies, and require further validation. Studies on the accuracy of risk instruments for identifying aberrant behavior in patients already prescribed opioids are available,^{53,56,76,79-85} but were outside the scope of this review.

No study evaluated the effectiveness of risk mitigation strategies, such as use of risk assessment instruments, opioid management plans, patient education, urine drug screening, prescription drug monitoring program data, monitoring instruments, more frequent monitoring intervals, pill counts, or abuse-deterrent formulations on outcomes related to overdose, addiction, abuse or misuse. Studies on effects of risk mitigation strategies were primarily focused on ability to detect misuse (e.g., urine drug testing and prescription monitoring program data) or on effects on markers of risky prescribing practices or medication-taking behaviors,⁸⁶ and did not meet inclusion criteria for this review, which focused on effects on clinical outcomes. One study found that rates of poison center treatment incidents and opioid-related treatment admissions increased at a lower rate in States with a prescription drug monitoring program than in States without one, but used an ecological design, did not evaluate a cohort of patients prescribed opioids for chronic pain, and was not designed to account for other factors that could have impacted opioid prescribing practices.⁸⁶

Although evidence indicates that patients with a history of substance abuse or at higher risk for abuse or misuse due to other risk factors are more likely to be prescribed opioids than patients without these risk factors,⁸⁷⁻⁹⁰ we identified no study on the effectiveness of methods for mitigating potential harms associated with long-term opioid therapy in high-risk patients.

Findings in Relationship to What is Already Known

Our findings are generally consistent with prior systematic reviews of opioid therapy for chronic pain that also found no long-term, placebo-controlled randomized trials.^{8,43} One systematic review of outcomes associated with long-term opioid therapy concluded that many patients discontinue treatment due to adverse events or insufficient pain relief, though patients who continue opioid therapy experience clinically significant pain relief.⁸ However, results of the studies included in this review are difficult to interpret because the studies had no nonopioid therapy control group, reported substantial between-study heterogeneity, and were susceptible to potential attrition and selection bias. Our findings are also consistent with a systematic review on comparative benefits and harms of various long-acting opioids and short- versus long-acting opioids, which found no clear differences, primarily based on short-term randomized trials.⁹¹

Our review reported rates of abuse and related outcomes that are higher than a previously published systematic review of long-term opioid therapy that reported a very low rate of opioid addiction (0.27 percent).⁸ Factors that may explain this discrepancy are that the prior review included studies that did not report predefined methods for ascertaining opioid addiction, potentially resulting in underreporting, and primarily included studies that excluded high-risk patients. Like a previous systematic review, we found variability in estimates of abuse and related outcomes, with some potential differences in estimates based on clinical setting (primary care versus pain clinic) and patient characteristics (e.g., exclusion of high-risk patients).⁹²

Regarding risk mitigation strategies, our findings were similar to a previously published systematic review that found weak evidence with which to evaluate risk prediction instruments.⁹³ Unlike our review, which found no evidence on effects of risk mitigation strategies on risk of abuse, addiction, or related outcomes, a previously published review found use of opioid management plans and urine drug screens to be associated with decreased risk of misuse behaviors.¹⁴ However, this conclusion was based on four studies that did not meet inclusion criteria for our review because effects of opioid management plans and urine drug screens could not be separated from other concurrent opioid prescribing interventions,^{94,95} use of a historical control group,^{96,97} or before-after study design.⁹⁴

Applicability

A number of issues could impact the applicability of our findings. One challenge was difficulty in determining whether studies focused on patients with chronic pain. Although a number of large observational studies reported harms based on analyses of administrative databases, they were frequently limited in their ability to assess important clinical factors such as the duration or severity of pain. For some of these studies, we inferred the presence of chronic pain from prescribing data, such as the number of prescriptions over a defined period or the use of long-acting opioid preparations. Some potentially relevant studies were excluded because it was not possible to determine whether the sample evaluated had chronic pain or received long-term therapy.^{16,98-103}

Another issue that could impact applicability is the type of opioid used in the studies. Both long-acting and short-acting opioids are often prescribed for chronic pain. In some studies, use of short-acting opioids predominated.^{11,18,49} Results of studies of short-acting opioids may not generalize to patients prescribed long-acting opioids.

Selection of patients could also impact applicability. The few randomized trials that met inclusion criteria typically excluded patients at high risk of abuse or misuse and frequently used run-in periods prior to allocating treatments. The use of a run-in period preselects patients who respond to and tolerate initial exposure to the studied treatment. Therefore, benefits observed in the trials might be greater and harms lower than seen in actual clinical practice.¹⁰⁴

Another factor impacting applicability is that most trials were not designed or powered to assess risk of abuse, addiction, or related outcomes. For example, trials of buccal fentanyl for acute exacerbations of chronic pain focused exclusively on immediate (episode-based) outcomes and were not designed to assess long-term outcomes, including outcomes related to the potential for abuse.⁷⁰⁻⁷⁴ Long-term head-to-head trials of long-acting opioids excluded patients at high risk for these outcomes and reported no events.⁶⁴⁻⁶⁶

The setting in which studies were conducted could also impact applicability. As noted in other sections of this report, rates of overdose, abuse, addiction, and related outcomes are likely to vary based on the clinical setting. Therefore, we stratified studies reporting rates of abuse according to whether they were performed in primary care or pain clinic settings. The highest-quality comparative study of methadone versus another opioid (long-acting morphine) found decreased mortality risk but was conducted in a VA setting,⁶⁹ which could limit applicability to other settings, due to factors such as how clinicians were trained in methadone use, policies on opioid prescribing, availability of resources to manage opioid prescribing, or other factors.

Implications for Clinical and Policy Decisionmaking

Our review has important implications for clinical and policy decisionmaking. Based on our review, most clinical and policy decisions regarding use of long-term opioid therapy must necessarily still be made on the basis of weak or insufficient evidence. This is in accordance with findings from a 2009 U.S. guideline on use of opioids for chronic pain, which found 21 of 25 recommendations supported by only low-quality evidence,¹⁰⁵ and a 2010 Canadian guideline,¹⁰⁶ which classified 3 of 24 recommendations as based on (short-term) randomized trials and 19 recommendations as based solely or partially on consensus opinion. Although randomized trials show short-term, moderate improvements in pain in highly selected, low-risk populations with chronic pain, such efficacy-based evidence is of limited usefulness for informing long-term opioid prescribing decisions in clinical practice.

Given the marked increase in numbers of overdose deaths and other serious adverse events that have occurred following the marked increase in opioid prescribing for chronic pain, recent policy efforts have focused on safer prescribing of opioids. A recent review of opioid guidelines found broad agreement regarding a number of risk mitigation strategies despite weak evidence, such as risk-assessment guided patient assessment for opioid therapy, urine drug testing, use of prescription monitoring program data, abuse-deterrent formulations, and opioid management plans.¹⁰⁷ Based on low-quality evidence regarding harms associated with long-term opioid therapy, our review provides some limited support for clinical policy efforts aimed at reducing harms. One area in which there has been less agreement across guidelines is whether dose thresholds that warrant more intense monitoring or used to define maximum ceiling doses should be implemented, and if so, what is the appropriate threshold. Some evidence is now available on dose-dependent harms associated with opioids,^{45,49} which could help inform policies related to dose thresholds. However, research on the effects of implementing dose thresholds on clinical outcomes is limited to a single ecological study.⁶³ In addition, although two observational studies were consistent in reporting a relationship between higher opioid dose and risk of overdose, estimates were highly variable at similar doses.^{45,49} This makes it difficult to determine an optimal maximum dose threshold based on an objective parameter, such as a dose inflection point where risk rises markedly. Other studies have begun to characterize cardiovascular, endocrinological, and injury-related harms associated with long-term opioid therapy and could be used to inform clinical decisions, though using such information in balanced assessments to inform clinical and policy decisionmaking remains a challenge given the lack of evidence regarding long-term benefits.

Limitations of the Review Process

We excluded non-English language articles and did not search for studies published only as abstracts. We did not attempt meta-analysis or assess for publication bias using graphical or statistical methods to detect small sample effects due to the paucity of evidence. Although we found no evidence of unpublished studies through searches on clinical trial registries and regulatory documents and solicitation of unpublished studies through SIP requests, the usefulness of such methods for identifying unpublished observational studies may be limited, as such studies are often not registered. We identified no unpublished randomized trials meeting inclusion criteria. We focused on studies that reported outcomes after at least one year of opioid therapy, though applying a shorter duration threshold for inclusion could have provided additional evidence. However, we identified no placebo-controlled trials of opioid therapy for at least 6 months.

Limitations of the Evidence Base

As noted previously, the critical limitation of our review is the lack of evidence in the target population (patients with chronic pain) and intervention (long-term opioid therapy), despite broadening of inclusion criteria to incorporate studies in which we assumed that patients were being treated for chronic pain due to the type of opioid prescribed (long-acting opioid) or number of prescriptions. We were also unable to determine how benefits and harms vary in subgroups, such as those defined by demographic characteristics, characteristics of the pain condition, and other patient characteristics (e.g., medical or psychological comorbidities). Due to the lack of evidence and methodological shortcomings in the available studies, no body of evidence (with

the exception of buccal or intranasal fentanyl for immediate pain relief) was rated higher than low, meaning that conclusions are highly uncertain.

Research Gaps

Many research gaps limit the full understanding of the effectiveness, comparative effectiveness, and harms of long-term opioid therapy, as well as of the effectiveness of different dosing methods and risk mitigation strategies, and effectiveness in special populations. Longer-term studies of patients clearly with chronic pain comparing those who are prescribed long-term opioid therapy with those receiving other pharmacological and non-pharmacological therapies are needed. Studies that include higher-risk patients, commonly treated with opioids in clinical practice, and that measure multiple important outcomes, including pain, physical and psychological functioning, as well as misuse and abuse, would be more helpful than efficacy studies focused solely on pain intensity. Greater standardization of methods for defining and identifying abuse-related outcomes in studies that report these outcomes are needed. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group recently issued recommendations on measuring abuse liability in analgesic clinical trials.¹⁰⁸

Additional research is also needed to develop and validate risk prediction instruments, and to determine how using them impacts treatment decisions and, ultimately, patient outcomes. More research is needed on the comparative benefits and harms of different opioids or formulations and different prescribing methods. Studies comparing effectiveness and harms of methadone versus other long-acting opioids, to determine if findings from a study⁶⁹ conducted in a VA setting are reproducible in other settings, and to better understand factors associated with safer methadone prescribing.

Research is also needed to understand the effects of risk mitigation strategies such as urine drug screening, use of prescription drug monitoring program data, and abuse-deterrent formulations on clinical outcomes such as rates of overdose, abuse, addiction, and misuse. In one before-after study, the introduction of an abuse-deterrent opioid was followed by patients switching to other prescription opioids or illicit opioids,¹⁰⁹ underscoring the need for research to understand both the positive and negative clinical effects of risk mitigation strategies.

Long-term randomized trials of opioid therapy are difficult to implement due to attrition, challenges in recruitment, or ethical factors (e.g., long-term allocation of patients with pain to placebo or allocation to non-use of risk mitigation strategies recommended in clinical practice guidelines). Nonetheless, pragmatic and other non-traditional randomized trial approaches could be used to address these challenges.¹¹⁰ Observational studies could also help address a number of these research questions, but should be specifically designed to evaluate patients with chronic pain prescribed long-term opioid therapy and appropriately measure and address potential confounders. Well-designed clinical registries that enroll patients with chronic pain prescribed and not prescribed chronic opioids could help address the limitations of studies based solely or primarily on administrative databases, which are often unable to fully characterize the pain condition (e.g., duration, type, and severity) or other clinical characteristics and frequently do not have information regarding outcomes related to pain, function, and quality of life. Such registry studies could be designed to extend the observations from randomized trials of opioids versus placebo or other treatments, but would differ from currently available studies by following patients who discontinue or do not start opioids, in addition to those who continue on or start opioid therapy.

Conclusions

Evidence on long-term opioid therapy for chronic pain is very limited, but suggests an increased risk of serious harms that appears to be dose-dependent. Based on our review, most clinical and policy decisions regarding use of long-term opioid therapy must necessarily still be made on the basis of weak or insufficient evidence. More research is needed to understand long-term benefits, risk of abuse and related outcomes, and effectiveness of different opioid prescribing methods and risk mitigation strategies.

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Introduction

Background

Chronic pain, often defined as pain lasting longer than 3 months or past the time of normal tissue healing,¹ is extremely common. According to a recent Institute of Medicine report, up to one-third of U.S. adults report chronic pain.² Chronic pain is a major cause of decreased quality of life and disability and is often refractory to treatment.^{3,4} There has been a dramatic increase over the past 10 to 20 years in the prescription of opioid medications for chronic pain,⁵⁻⁷ despite limited evidence showing long-term beneficial effects.^{8,9} In addition, accumulating evidence indicates that prescription opioids may be associated with important harms, including accidental overdose, abuse, addiction, diversion, and accidents involving injuries (such as falls and motor vehicle accidents).¹⁰⁻²⁰ Perhaps of most concern is the dramatic increase in overdose deaths associated with opioids. In 2011, there were 16,917 fatal overdoses involving prescription opioids.²¹ Prescription opioid misuse and abuse resulted in almost 660,000 emergency department visits in 2010, over twice as many as in 2004.¹³ Substance abuse treatment admissions for opiates other than heroin increased more than six-fold from 1999 to 2009.¹² Opioids are also associated with adverse effects such as constipation, nausea, and sedation.²² Finally, data indicate potential associations between long-term opioid therapy and other harms, such as adverse endocrinological effects and hyperalgesia.²³⁻²⁵

These data underscore the complexity of clinical decisionmaking around long-term opioid therapy, which requires individualized assessments of the balance between benefits and harms; appropriate opioid selection, dose initiation, and titration strategies; integration of risk assessment and mitigation strategies; and consideration of the use of alternative, nonopioid therapies.⁹ Risk mitigation strategies that have been suggested for patients prescribed long-term opioids include use of opioid medication agreements, application of dose thresholds that warrant increased caution, regular clinical followup and monitoring, urine drug screens, use of abuse-deterrent opioid formulations, and use of data from prescription drug monitoring programs.⁹

Understanding benefits and harms of long-term opioid therapy for chronic pain is a challenge because effects may vary depending on patient characteristics (e.g., age, sex, pain condition, psychosocial factors, comorbidities), opioid characteristics (e.g., specific opioid, short- versus long-acting opioid, mode of administration, dose), dosing strategies (e.g., round-the-clock versus as-needed dosing, application of dose thresholds), concomitant therapies (e.g., use of benzodiazepines or other drugs that may interact with opioids), and characteristics of the clinical setting. Other challenges in interpreting the literature include potential limitations in generalizability due to study design and other methodological shortcomings (e.g., duration of followup, exclusion of patients at higher risk for harms, under-representation of certain sociodemographic groups, and high dropout rates), and gaps in research on important scientific questions.²⁶ Although guidelines on use of opioids for chronic pain are available, most recommendations are based on weak or limited evidence.^{9,27} The increase in use of long-term opioid therapy for chronic pain, new information concerning harms associated with long-term opioid therapy, continued wide variations in practice related to long-term opioid therapy, and the availability of new evidence underscore the need for a current systematic review in this area.

The purpose of this report is to systematically review the current evidence on long-term opioid therapy for chronic pain, which will be used by the National Institutes of Health (NIH) to inform a Pathways to Prevention Workshop on the role of opioids in the treatment of chronic pain. Although guidelines have been published from the American Pain Society (APS)/

American Academy of Pain Medicine,⁹ the Veterans Affairs (VA)/Department of Defense,²⁸ and other groups, the availability of new evidence warrants a new systematic review that could be used to inform updated or new guidelines, guide quality improvement efforts, and define and update priorities for further research in this area.²⁶ This review updates a prior systematic review on opioid therapy for chronic pain funded by the APS.²⁹ Differences between this review and the 2009 APS review are that it focuses specifically on benefits and harms associated with long-term use of opioid therapy and evaluates an additional Key Question on dose escalation versus maintenance of doses in patients on long-term opioid therapy, additional outcomes (e.g., cardiovascular events, infection, and psychological outcomes), and additional risk mitigation strategies (e.g., abuse-deterrent formulations and use of data from prescription drug monitoring programs).

Scope of Review and Key Questions

The Key Questions and analytic framework (Figure 1) used to guide this report are shown below. The analytic framework shows the target populations, interventions, and outcomes that we examined.

Key Question 1. Effectiveness and Comparative Effectiveness

- a. In patients with chronic pain, what is the effectiveness of long-term opioid therapy versus placebo or no opioid therapy for long-term (≥ 1 year) outcomes related to pain, function, and quality of life?
- b. How does effectiveness vary depending on: (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including low back pain], fibromyalgia, sickle cell disease, inflammatory pain, and headache disorders); (2) patient demographics (e.g., age, race, ethnicity, gender); (3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities and high risk for addiction)?
- c. In patients with chronic pain, what is the comparative effectiveness of opioids versus nonopioid therapies (pharmacological or nonpharmacological) on outcomes related to pain, function, and quality of life?
- d. In patients with chronic pain, what is the comparative effectiveness of opioids plus nonopioid interventions (pharmacological or nonpharmacological) versus opioids or nonopioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used?

Key Question 2. Harms and Adverse Events

- a. In patients with chronic pain, what are the risks of opioids versus placebo or no opioid on: (1) opioid abuse, addiction, and related outcomes; (2) overdose; and (3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?
- b. How do harms vary depending on: (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including back pain], fibromyalgia, sickle cell disease, inflammatory pain, headache disorders); (2) patient demographics; (3) patient comorbidities (including past or current substance use disorder or at high risk for addiction); 4) the dose of opioids used?

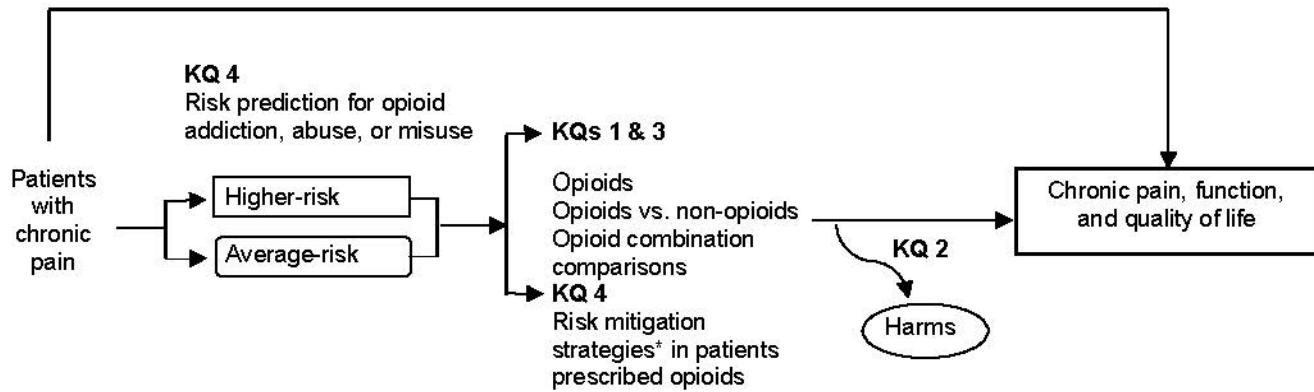
Key Question 3. Dosing Strategies

- a. In patients with chronic pain, what is the comparative effectiveness of different methods for initiating and titrating opioids for outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?
- b. In patients with chronic pain, what is the comparative effectiveness of short- versus long-acting opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?
- c. In patients with chronic pain, what is the comparative effectiveness of different long-acting opioids on outcomes related to pain, function, and quality of life; and risk of overdose, addiction, abuse, or misuse?
- d. In patients with chronic pain, what is the comparative effectiveness of short- plus long-acting opioids versus long-acting opioids alone on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?
- e. In patients with chronic pain, what is the comparative effectiveness of scheduled, continuous versus as-needed dosing of opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?
- f. In patients with chronic pain on long-term opioid therapy, what is the comparative effectiveness of dose escalation versus dose maintenance or use of dose thresholds on outcomes related to pain, function, and quality of life?
- g. In patients on long-term opioid therapy, what is the comparative effectiveness of opioid rotation versus maintenance of current opioid therapy on outcomes related to pain, function, and quality of life; and doses of opioids used?
- h. In patients on long-term opioid therapy, what is the comparative effectiveness of different strategies for treating acute exacerbations of chronic pain on outcomes related to pain, function, and quality of life?
- i. In patients on long-term opioid therapy, what are the effects of decreasing opioid doses or of tapering off opioids versus continuation of opioids on outcomes related to pain, function, quality of life, and withdrawal?
- j. In patients on long-term opioid therapy, what is the comparative effectiveness of different tapering protocols and strategies on measures related to pain, function, quality of life, withdrawal symptoms, and likelihood of opioid cessation?

Key Question 4. Risk Assessment and Risk Mitigation Strategies

- a. In patients with chronic pain being considered for long-term opioid therapy, what is the accuracy of instruments for predicting risk of opioid overdose, addiction, abuse, or misuse?
- b. In patients with chronic pain, what is the effectiveness of use of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse?
- c. In patients with chronic pain prescribed long-term opioid therapy, what is the effectiveness of risk mitigation strategies, including (1) opioid management plans, (2) patient education, (3) urine drug screening, (4) use of prescription drug monitoring program data, (5) use of monitoring instruments, (6) more frequent monitoring intervals, (7) pill counts, and (8) use of abuse-deterrent formulations on outcomes related to overdose, addiction, abuse, or misuse?
- d. What is the comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids on outcomes related to overdose, abuse, misuse, pain, function, and quality of life?

Figure 1. Analytic framework



KQ, Key Question.

*Including opioid management plans, patient education, urine drug screening, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, and use of abuse-deterrent formulations.

Methods

The methods for this Comparative Effectiveness Review (CER) follows the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.³⁰ All methods were determined a priori.

Topic Refinement and Review Protocol

This topic was selected for review based on a nomination from NIH. The initial Key Questions for this CER were developed with input from an NIH working group. The Key Questions and scope were further developed with input from a Technical Expert Panel (TEP) convened for this report. The TEP provided high-level content and methodological guidance to the review process and consisted of experts in health services research, internal medicine, psychology, pain medicine, pharmacology, neurology, occupational medicine, pediatrics, and epidemiology. TEP members disclosed all financial or other conflicts of interest prior to participation. The AHRQ Task Order Officer and the investigators reviewed the disclosures and determined that the TEP members had no conflicts of interest that precluded participation.

The protocol for this CER was developed prior to initiation of the review, and was posted on the AHRQ Web site on December 19, 2013 at:
<http://effectivehealthcare.ahrq.gov/ehc/products/557/1837/chronic-pain-opioid-treatment-protocol-131219.pdf>. The protocol was also registered in the PROSPERO international database of prospectively registered systematic reviews.³¹

Literature Search Strategy

A research librarian conducted searches in Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, PsychINFO, and CINAHL from 2008 to August 2014 (see Appendix A for full search strategies). We restricted search start dates to January 2008 because the searches in the prior APS review, which we used to identify potentially relevant studies, went through October 2008.²⁹ For outcomes (cardiovascular, infections, and psychological harms) and interventions (abuse-deterrent formulations, and use of prescription monitoring program data) not addressed in the APS review, we searched the same databases and did not apply any search date start restrictions.

We also hand-searched the reference lists of relevant studies and searched for unpublished studies in ClinicalTrials.gov. Scientific information packets (SIPs) with relevant published and unpublished studies were requested from nineteen current application holders from the U.S. Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategy (REMS) Extended-Release and Long-Acting (ER/LA) Opioid Analgesics List.³² We received five SIP submissions.

Study Selection

We developed criteria for inclusion and exclusion of articles based on the Key Questions and the populations, interventions, comparators, outcomes, timing, and setting (PICOTS) approach (Appendix B). Articles were selected for full-text review if they were about long-term opioid therapy for chronic pain, were relevant to a Key Question, and met the predefined inclusion criteria as shown below. We excluded studies published only as conference abstracts, restricted

inclusion to English-language articles, and excluded studies of nonhuman subjects. Studies had to report original data to be included.

Each abstract was independently reviewed for potential inclusion and full-text review by two investigators. Two investigators independently reviewed all full-text articles for final inclusion. Discrepancies were resolved through discussion and consensus. A list of the included articles is available in Appendix C; excluded articles are shown Appendix D with primary reasons for exclusion.

We selected studies of adults (age ≥ 18 years) with chronic pain (defined as pain lasting >3 months) being considered for long-term opioid therapy (Key Questions 4a and 4b) or prescribed long-term opioid therapy (all other Key Questions). We defined long-term opioid therapy as use of opioids on most days for >3 months; this threshold was selected to differentiate ongoing opioid therapy (as often used for chronic pain) from short-term therapy. We included studies that did not explicitly report the duration of pain if the average duration of opioid therapy was >3 months. We included studies that did not explicitly report the duration of opioid therapy if patients were prescribed long-acting opioids, as these are not typically prescribed for short-term use. We included studies with patients with chronic pain related to current or previously treated cancer, but excluded studies with patients with pain at end of life (e.g., patients with cancer in hospice care). We excluded studies with patients with acute pain, pregnant or breastfeeding women, and patients treated with opioids for addiction.

We included studies of patients prescribed any long- or short-acting opioid used as long-term therapy, either alone or in combination with another agent (Key Question 1d). We included tapentadol, a dual mechanism medication with strong opioid mu-receptor affinity, but excluded tramadol, which is also a dual mechanism medication but with weak opioid mu-receptor affinity that has not been identified as a cause of unintentional prescription drug overdose deaths.³³ We also excluded studies of parenteral opioids.

We included studies that compared long-term opioid therapy versus placebo, no therapy, or another drug or nondrug therapy; studies that evaluated different dose initiation, titration, or rotation strategies; studies of different methods for tapering or discontinuing opioids; studies on methods for treating acute exacerbations of pain in people with chronic pain; and studies on various risk mitigation strategies for reducing harms associated with opioids. Risk mitigation strategies included opioid management plans, patient education, urine drug screening, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, and use of abuse-deterrent formulations. We also included studies that compared the predictive accuracy of risk prediction instruments in people with chronic pain prior to initiation of opioids for predicting outcomes related to future misuse, abuse, or addiction, and studies on the effects of risk prediction instruments on clinical outcomes.

Outcomes were pain (intensity, severity, bothersomeness), function (physical disability, activity limitations, activity interference, work function), quality of life (including depression), and doses of opioids used. Evaluated harms included overdose, opioid use disorder, addiction, abuse, and misuse, as well as other opioid-related harms (including gastrointestinal, fractures, falls, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms [e.g., depression]). We focused on outcomes reported after at least 1 year of opioid therapy, with the exception of outcomes related to overdose and injuries (fractures, falls, and motor vehicle accidents), studies on treatment of acute exacerbations of chronic pain, studies on dose initiation and titration, and studies on discontinuation of opioid therapy, for which we included studies of any duration.

For all Key Questions, we included randomized trials and controlled observational studies (cohort studies, cross-sectional studies, and case-control studies) that performed adjustment on potential confounders. We included uncontrolled observational studies of patients with chronic pain prescribed opioid therapy for at least 1 year that reported abuse, misuse, or addiction as a primary outcome and described predefined methods to assess these outcomes. Otherwise, we excluded uncontrolled observational studies, case series, and case reports. We reviewed systematic reviews for potentially relevant references.

Data Extraction

We extracted the following information from included studies into evidence tables using Excel spreadsheets: study design, year, setting, inclusion and exclusion criteria, population characteristics (including sex, age, race, pain condition, and duration of pain), sample size, duration of followup, attrition, intervention characteristics (including specific opioid and formulation, dose, and duration of therapy), results, and funding sources.

For studies on the predictive accuracy of risk prediction instruments, we attempted to create two-by-two tables from information provided (sample size, prevalence, sensitivity, and specificity) and compared calculated measures of diagnostic accuracy based on the two-by-two tables with reported results. We noted discrepancies between calculated and reported results when present. When reported, we also recorded the area under the receiver operating characteristic curve (AUROC).^{34, 35}

For studies of interventions, we calculated relative risks (RR) and associated 95 percent confidence intervals (CI) based on the information provided (sample sizes and incidence of outcomes of interest in each intervention group). We noted discrepancies between calculated and reported results when present.

Data extraction for each study was performed by two investigators. The first investigator extracted the data, and the second investigator independently reviewed the extracted data for accuracy and completeness.

Assessing Methodological Risk of Bias of Individual Studies

We assessed risk of bias (quality) for each study using predefined criteria. We used the term “quality” rather than the alternate term “risk of bias;” both refer to internal validity. Randomized trials were evaluated with criteria and methods developed by the Cochrane Back Review Group.³⁶ Cohort studies, case-control studies, and cross-sectional studies were rated using criteria from the U.S. Preventive Services Task Force.³⁷ Risk prediction instrument studies were rated using criteria from various sources.³⁸⁻⁴⁰ These criteria were applied in conjunction with the approach recommended in the chapter, Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions,⁴¹ in the AHRQ Methods Guide. Studies of predictive accuracy of risk prediction instruments were assessed using an approach adapted from the AHRQ Methods Guide for Medical Test Reviews,³⁸ which is based on methods developed by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) group.³⁹ We reassessed the quality of studies included in the prior APS review to ensure consistency in quality assessment. Two investigators independently assessed the quality of each study. Discrepancies were resolved through discussion and consensus.

Individual studies were rated as having “poor,” “fair,” or “good” quality. We rated the quality of each randomized trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; whether attrition was

adequately reported and acceptable; similarity in use of cointerventions; compliance to allocated treatments; the use of intent-to-treat analysis; and avoidance of selective outcomes reporting.^{36, 37}

We rated the quality of each cohort study based on whether it enrolled a consecutive or random sample of patients meeting inclusion criteria; whether it evaluated comparable groups; whether rates of loss to followup were reported and acceptable; whether it used accurate methods for ascertaining exposures, potential confounders, and outcomes; and whether it performed adjustment for important potential confounders.³⁷ For cross-sectional studies, we used criteria for cohort studies, but did not rate criteria related to loss to followup. For uncontrolled studies on risk of abuse or related outcomes, we evaluated whether it enrolled a consecutive or random sample, whether outcome assessors were blinded to patient characteristics, whether rates of loss to followup were reported (for longitudinal studies) and acceptable, and whether pre-specified outcomes were assessed in all patients.

We rated the quality of each case-control study based on whether it enrolled a consecutive or random sample of cases meeting predefined criteria; whether controls were derived from the same population as cases; whether cases and controls were comparable on key prognostic factors; whether it used accurate methods to ascertain outcomes, exposures, and potential confounders; and whether it performed adjustment for important potential confounders.³⁷

We rated the quality of each study on the predictive value of risk prediction instruments based on whether it evaluated a consecutive or random sample of patients meeting pre-defined criteria, whether the patient population evaluated in the study was adequately described, whether the screening instrument included appropriate criteria, and whether outcomes were assessed in all patients independent of the results of the risk assessment instrument using adequately described methods.^{38, 39} We also evaluated whether the study was to develop a risk prediction instrument or to validate a previously developed instrument.⁴⁰

Studies rated “good quality” were considered to have the least risk of bias and their results are likely to be valid. Studies rated “fair quality” have some methodological shortcomings, but no flaw or combination of flaws judged likely to cause major bias. In some cases, the article did not report important information, making it difficult to assess its methods or potential limitations. The moderate risk of bias category is broad and studies with this rating vary in their strengths and weaknesses; the results of some studies assessed to have moderate risk of bias are likely to be valid, while others may be only possibly valid. Studies rated “poor quality” have significant flaws that may invalidate the results. They have a serious or “fatal” flaw or combination of flaws in design, analysis, or reporting; large amounts of missing information; or serious discrepancies in reporting. The results of these studies are at least as likely to reflect flaws in the study design as the differences between the compared interventions. We did not exclude studies rated as having high risk of bias a priori, but they were considered the least reliable when synthesizing the evidence, particularly when discrepancies between studies were present.

Assessing Research Applicability

We recorded factors important for understanding the applicability of studies, such as whether the publication adequately described the study sample, the country in which the study was conducted, the characteristics of the patient sample (e.g., age, sex, race, pain condition, duration or severity of pain, medical comorbidities, and psychosocial factors), the characteristics of the interventions used (e.g., specific opioid, dose, mode of administration, or dosing strategy), the clinical setting (e.g., primary care or specialty setting), and the magnitude of effects on clinical outcomes.⁴² We also recorded the funding source and role of the sponsor. We did not assign a

rating of applicability (such as high or low) because applicability may differ based on the user of the report.

Evidence Synthesis and Rating the Body of Evidence

We constructed evidence tables summarizing study characteristics, results, and quality ratings for all included studies. We summarized evidence for each Key Question qualitatively used a hierarchy-of-evidence approach, where the best evidence was the focus of our synthesis for each Key Question. In the evidence tables, we included relevant studies from the prior APS review as well as new studies meeting inclusion criteria. Results were organized by Key Question. We did not attempt meta-analyses because of the small number of studies available for each Key Question; variability in study designs, patient samples, interventions, and measures; and methodological shortcomings in the available studies.

We assessed the overall strength of evidence (SOE) for each Key Question and outcome using the approach described in the AHRQ Methods Guide.³⁰ We synthesized the quality of the studies; the consistency of results within and between study designs; the directness of the evidence linking the intervention and health outcomes; and the precision of the estimate of effect (based on the number and size of studies and CIs for the estimates). We were not able to formally assess for publication bias due to small number of studies, methodological shortcomings, or differences across studies in designs, measured outcomes, and other factors. Rather, as described above, we searched for unpublished studies through searches of clinical trials registries and regulatory documents and by soliciting SIPs.

The SOE was based on the overall quality of each body of evidence, based on the risk of bias (graded low, moderate, or high); the consistency of results across studies (graded consistent, inconsistent, or unable to determine when only one study was available); the directness of the evidence linking the intervention and health outcomes (graded direct or indirect); and the precision of the estimate of effect, based on the number and size of studies and CIs for the estimates (graded precise or imprecise). We did not grade supplemental domains for cohort studies evaluating intermediate and clinical outcomes because too few studies were available for these factors to impact the SOE grades.

We graded the SOE for each Key Question using the four key categories recommended in the AHRQ Methods Guide.³⁰ A “high” grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect. A “moderate” grade indicates moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate. A “low” grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. An “insufficient” grade indicates evidence either is unavailable or is too limited to permit any conclusion, due to the availability of only poor-quality studies, extreme inconsistency, or extreme imprecision.

Peer Review and Public Commentary

Experts in chronic pain and opioid therapy, as well as individuals representing important stakeholder groups, were invited to provide external peer review of this CER. The AHRQ Task Order Officer and a designated EPC Associate Editor also provided comments and editorial review. To obtain public comment, the draft report was posted on the AHRQ Web site for 4 weeks. A disposition of comments report detailing the authors' responses to the peer and public

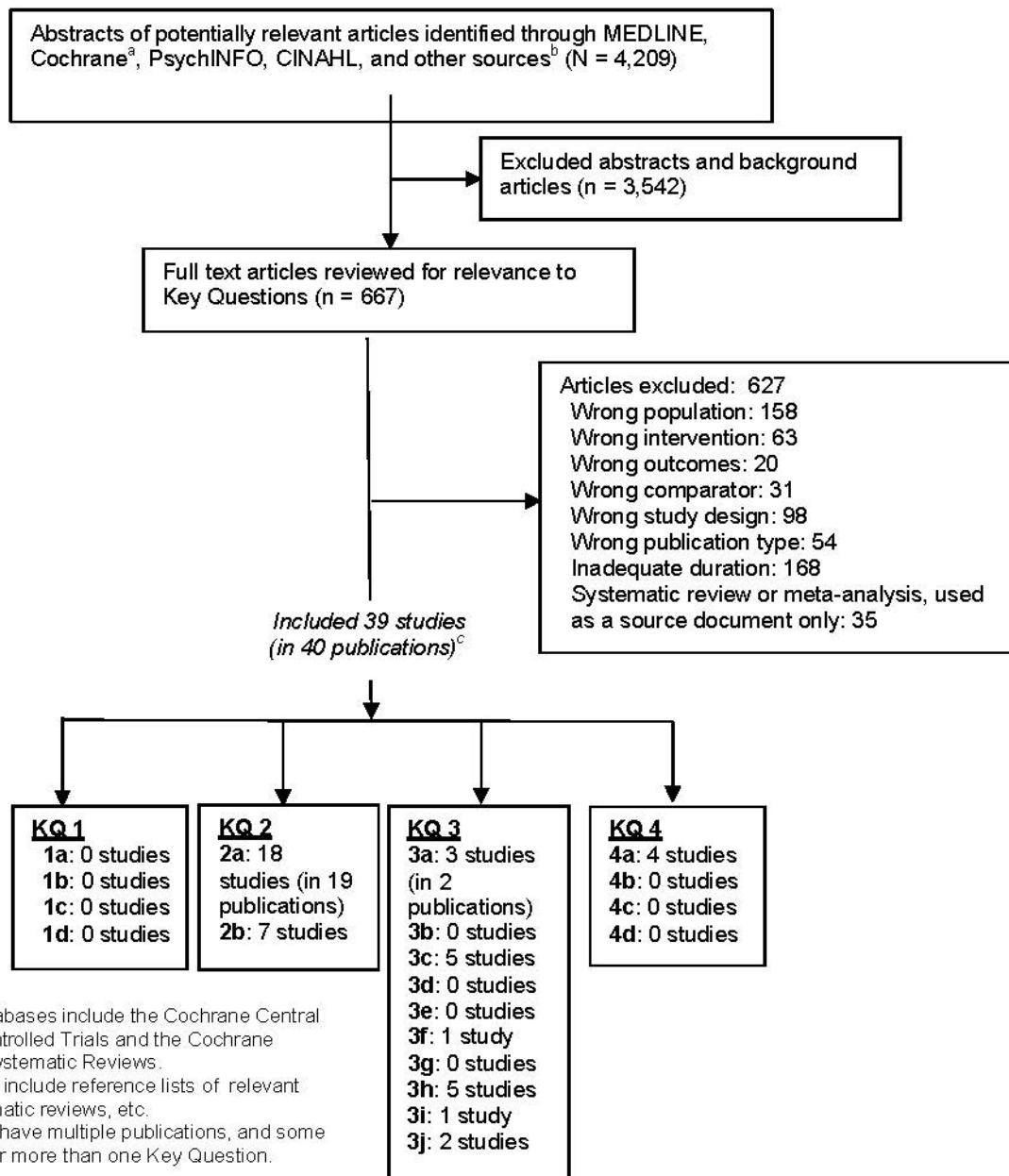
review comments will be made available after AHRQ posts the final CER on the public Web site.

Results

Overview

The search and selection of articles are summarized in the study flow diagram (Figure 2). Database searches resulted in 4,209 potentially relevant articles. After dual review of abstracts and titles, 667 articles were selected for full-text review, and 39 studies (in 40 publications) were determined by dual review at the full-text level to meet inclusion criteria and were included in this review. Data extraction and quality assessment tables for all included studies per Key Question are available in Appendixes E and F.

Figure 2. Literature flow diagram



^aCochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.

^bOther sources include reference lists of relevant articles, systematic reviews, etc.

^cSome studies have multiple publications, and some are included for more than one Key Question.

Key Question 1a

In patients with chronic pain, what is the effectiveness of long-term opioid therapy versus placebo or no opioid therapy for long-term (≥ 1 year) outcomes related to pain, function, and quality of life?

Key Points

- No study of opioid therapy versus placebo or no opioid therapy evaluated long-term (≥ 1 year) outcomes related to pain, function, or quality of life (SOE: Insufficient).

Detailed Synthesis

All studies in the 2009 APS review evaluated outcomes related to pain, function, and quality of life at less than 1 year (typically at ≤ 12 weeks) and did not meet inclusion criteria for the current review. We also identified no studies published since the 2009 APS review that met inclusion criteria. Although a systematic review⁸ of long-term opioid therapy included 10 studies of oral opioids and five studies of transdermal opioids that evaluated outcomes after at least 6 months, all were case series or uncontrolled long-term continuations of patients enrolled in clinical trials, with the exception of one head-to-head randomized trial that compared two long-acting opioids (see Key Question 3c).⁴³ In the systematic review, the pooled estimate for discontinuation due to insufficient pain relief was 10.3 percent (95 percent CI 7.6 to 13.9 percent) with oral opioids and 5.8 percent (95 percent CI 4.2 to 7.9) with transdermal opioids. Among patients who remained on oral opioids for at least 6 months, pain scores were generally reduced, but estimates varied substantially. Effects on quality of life and functional status were inconclusive. Findings of this review are difficult to interpret due to the lack of a nonopioid comparison group in the included studies, marked statistical heterogeneity, and other methodological shortcomings of the studies.

Key Question 1b

How does effectiveness vary depending on: (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including low back pain], fibromyalgia, sickle cell disease, inflammatory pain, and headache disorders); (2) patient demographics (e.g., age, race, ethnicity, gender); (3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities and high risk for addiction)?

Key Points

- No study met inclusion criteria (see Key Question 1a) (SOE: Insufficient).

Detailed Synthesis

No study met inclusion criteria (see Key Question 1a). Although one systematic review⁴⁴ reported similar short-term effects of opioids versus placebo on improvement in pain scores for

nociceptive (31 studies) and neuropathic (13 studies) pain, the studies included in the review did not meet inclusion criteria due to the short duration of followup. In the review, 61 of 62 included randomized trials were 16 weeks or shorter in duration, and the other trial was 24 weeks. There were too few trials of fibromyalgia (two studies) or mixed pain conditions (one study) to reliably estimate effects of opioids for these pain conditions.

Key Question 1c

In patients with chronic pain, what is the comparative effectiveness of opioids versus nonopioid therapies (pharmacological or nonpharmacological) on outcomes related to pain, function, and quality of life?

Key Points

- No study met inclusion criteria (SOE: Insufficient).

Detailed Synthesis

We identified no study on the comparative effectiveness of long-term opioid therapy versus nonopioid therapies on long-term outcomes related to pain, function, and quality of life.

Key Question 1d

In patients with chronic pain, what is the comparative effectiveness of opioids plus nonopioid interventions (pharmacological or nonpharmacological) versus opioids or nonopioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used?

Key Points

- No study met inclusion criteria (SOE: Insufficient).

Detailed Synthesis

We identified no study on the comparative effectiveness of long-term opioid therapy plus nonopioid interventions versus opioids or nonopioid interventions alone on long-term outcomes related to pain, function, and quality of life.

Key Question 2a

In patients with chronic pain, what are the risks of opioids versus placebo or no opioid on: (1) opioid abuse, addiction, and related outcomes; (2) overdose; and (3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?

Key Points

- One fair-quality retrospective review of a large database of claims from commercial health plans found long-term (≥ 91 days supply) prescribed opioid use associated with significantly increased risk of opioid abuse or dependence diagnosis versus no opioid use (1-36 MED/day: OR 15, 95 percent CI 10 to 21; 36-120 MED/day: OR 29, 95 percent CI 20 to 41; ≥ 120 MED/day: OR 122, 95 percent CI 73 to 206) (SOE: Low).
- In 10 uncontrolled studies, estimates of opioid abuse, addiction, and related outcomes varied substantially even after stratification by clinic setting. Rates of diagnosed opioid abuse were 0.6 percent to 8 percent and rates of dependence were 3 percent to 26 percent in primary care settings. In pain clinic settings, rates of misuse were 8 to 16 percent and addiction 2 to 14 percent, but studies varied in methods used to define and ascertain outcomes. Rates of (variably-defined) aberrant drug-related behaviors (e.g., positive urine drug tests, medication agreement violations) ranged from 5.7 percent to 37.1 percent (SOE: Insufficient).
- One fair-quality retrospective cohort study found recent opioid use to be associated with increased risk of any overdose events (adjusted hazard ratio [HR] 5.2, 95 percent CI 2.1 to 12) and serious overdose events (adjusted HR 8.4, 95 percent CI 2.5 to 28) versus current nonuse in chronic pain patients who had received opioids at some point (SOE: Low).
- One fair-quality cohort study and one good-quality case-control study found use of opioids to be associated with increased risk of fracture (adjusted HR 1.28, 95 percent CI 0.99 to 1.64 and adjusted OR 1.27, 95 percent CI 1.21 to 1.33) though the estimate was not statistically significant in the cohort study and the risk was no longer present with more than 20 cumulative prescriptions in the other (SOE: Low).
- One good-quality case-control study found current opioid use versus nonuse to be associated with increased risk of myocardial infarction (adjusted OR 1.28, 95 percent CI 1.19 to 1.37). The risk was highest with 11 to 50 cumulative prescriptions (OR 1.38, 95 percent CI 1.28 to 1.49). A fair-quality cohort study found chronic opioid therapy, compared to the general population, to be associated with increased risk of myocardial infarction (adjusted incidence rate ratio [IRR] 2.66, 95 percent CI 2.30 to 3.08) and of myocardial infarction or revascularization (adjusted IRR 2.38, 95 percent CI 2.15 to 2.63) (SOE: Low).
- One fair-quality cross-sectional study of men with back pain (n=11,327) found long-term opioid use versus nonuse of opioids to be associated with increased risk for use of

medications for erectile dysfunction or testosterone replacement (adjusted OR 1.5, 95 percent CI 1.1 to 1.9) (SOE: Low)

- No study evaluated the association between long-term opioid therapy for chronic pain versus no opioid therapy and risk of motor vehicle accidents, infections, psychological harms, or cognitive harms.

Detailed Synthesis

Opioid Abuse, Addiction, and Related Outcomes

The 2009 APS review included two systematic reviews on use of opioids for chronic pain and rates of opioid abuse, addiction, or related outcomes.^{45, 46} One systematic review that restricted inclusion to studies with at least 1 year of followup reported signs of opioid addiction in 0.27 percent of patients prescribed opioids in studies that reported this outcome.⁴⁵ However, none of the studies met inclusion criteria for the current review because addiction was not the primary outcome and they did not describe pre-specified methods for defining or ascertaining these outcomes. The other systematic review focused on patients with low back pain and reported rates of aberrant medication-taking behaviors that ranged from 5 to 24 percent.⁴⁶ The studies did not meet inclusion criteria for the current review because they did not include patients with at least 1 year of followup, did not clearly separate abuse and addiction related to opioid use versus other substances, or did not report pre-specified methods for the outcomes, with the exception of one retrospective cohort study.⁴⁷ It reported rates of opioid abuse behaviors in patients with chronic pain in primary care settings, based on chart review findings of one or more reports of lost or stolen opioid medications, documented use of other sources to obtain opioid medications, or requests for two or more early refills. Rates of opioid abuse behaviors were 24 percent (12/50) in a VA primary care setting and 31 percent (15/48) in a non-VA, urban hospital-based primary care setting. Factors associated with decreased risk of opioid abuse behaviors were no history of substance use disorder (adjusted OR 0.72, 95 percent CI 0.45 to 1.1) and older age (adjusted OR 0.94, 95 percent CI 0.94 to 0.99).

We identified no randomized trial published since the APS review on risk of opioid abuse, addiction, and related outcomes in patients with chronic pain prescribed long-term opioid therapy. One fair-quality retrospective study of patients in a large administrative database newly diagnosed with chronic (non-cancer) pain and followed for 18 months found prescribed long-term opioid use (receipt of ≥ 91 days' supply of opioids within a 12-month period), versus no prescribed opioids, associated with increased risk of opioid use disorder (defined as opioid abuse and dependence based on ICD-9 codes) (Appendix E1 and F1).⁴⁸ Rates of opioid abuse or dependence were 0.72, 1.28 and 6.1 percent in those prescribed low (1-36 mg MED/day), medium (36-120 mg MED/day) and high (≥ 120 mg MED/day) opioid doses, respectively, during the 12 months after the new chronic pain diagnosis, versus 0.004 percent in those with no opioid prescription. Compared to no opioid prescription and after adjustment for age, sex, history of substance abuse/dependence diagnosis and other comorbidities, chronic opioid use was associated with significantly increased risk of abuse or dependence for all doses of opioids (low dose: OR 15, 95 percent CI 10 to 21; medium dose: OR 29, 95 percent CI 20 to 41; high dose: OR 122, 95 percent CI 73 to 206).

Ten additional uncontrolled studies (in 11 publications) of patients with chronic pain, the majority of whom were prescribed opioids for at least 1 year, evaluated abuse and related outcomes as a primary outcome using explicit, predefined criteria (Table 1 below; Appendix E1

and F2).⁴⁹⁻⁵⁸ All were rated fair-quality; none of the studies reported blinding of outcome assessors to patient characteristics, such as risk factors for substance abuse or psychological comorbidities. Another shortcoming in some studies was failure to assess the predefined outcomes in all patients.

Four of the new studies were performed exclusively or primarily in U.S. primary care settings.^{47, 49, 50, 53} One study⁵³ found that 0.6 percent of primary care clinic patients receiving daily prescription opioids (96 percent for more than a year; total n=801) met the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria for opioid abuse disorder and 3.1 percent for opioid dependence, based on formal diagnostic interviews.

Behaviors indicative of opioid misuse were more common. Thirty-seven percent reported increasing doses on their own, 33 percent feeling intoxicated from pain medication, 24 percent purposeful oversedation, 16 percent using opioids for purposes other than pain management, and 20 percent drinking alcohol to relieve pain. Twenty-four percent of patients had urine drug screens positive for illicit drugs (mostly cannabinoids).⁵³ A retrospective study of chronic pain patients receiving long-term opioid therapy in an integrated managed care health system (n=704) found that 13 percent met DSM-IV criteria for opioid dependence and 8 percent met criteria for opioid abuse without dependence, based on structured phone interviews.⁴⁹ Another study, which performed diagnostic interviews in 9 primary care and 3 specialty clinics with patients who received 4 or more opioid prescriptions over a year (n=705), found that 26 percent met DSM-IV criteria for current opioid dependence.⁵⁰ In multivariate logistic regression models, factors associated with current opioid dependence were age less than 65 years (OR 2.3, 95 percent CI

1.6 to 3.5), history of opioid abuse (OR 3.8, 95 percent CI 2.6 to 5.7), higher lifetime opioid dependence severity (OR 1.9, 95 percent CI 1.4 to 2.5), history of major depression (OR 1.3, 95 percent CI 1.1 to 1.6), and current use of psychotropic medications (OR 1.7, 95 percent CI 1.2 to 2.5). Rates of opioid abuse or misuse behaviors were not reported.

Six other studies were performed in pain clinic settings. Pain clinics may have a higher proportion of patients with opioid abuse and related problems because of referral patterns. Despite initial screening to exclude current substance abuse on entry, one study from a VA pain clinic found that after 1 year of followup, 28 percent of patients prescribed opioids (n=135) were discontinued from the clinic because of medication agreement violations.⁵¹ Among these were 8 percent with specific opioid misuse behaviors such as unsanctioned dose increases or use of opioids other than those prescribed. In a cross-sectional study of Danish pain clinic patients with cancer and noncancer pain (mean duration of opioid use among those taking opioids = 6.8 years), 14.4 percent of those using opioids (n=187) met International Classification of Diseases (ICD-10) criteria for “addiction to opioids,” which correspond most closely to the DSM-IV criteria for opioid abuse.⁵⁴ A cross-sectional study of UK NHS hospital pain clinic patients who had been prescribed opioids (n=104) found that 1.9 percent of the patients self-reported addiction using the Substance Use Questionnaire, 2.9 percent reported that they had craved opioids and 0.9 percent reported that they used alcohol to enhance the effects of opioids.⁵² A prospective registry study of patients who had participated in five clinical trials of CR oxycodone and who continued to take this medication (n=227) found that 5.7 percent of the patients were identified by their physicians as exhibiting problematic drug-related behaviors, based on a brief physician-completed questionnaire.⁵⁵ However, verification by an independent panel resulted in a lower rate of 2.2 percent. A chart review conducted in a single pain clinic (n=197) reported that 15.7 percent of patients had aberrant drug-related behaviors noted in their charts and 8.7 percent had positive urine drug tests.⁵⁷ Finally, a cross-sectional study of patients attending five pain clinics (n=622) found that 37.1 percent had positive urine drug tests (defined as presence of an illicit substance or unprescribed opioid), while 24 percent had positive scores ≥ 2 (the cutoff for “high risk”) on the Prescription Opioid Therapy

Questionnaire and 29.1 percent had scores ≥ 11 (the cutoff for “at risk”) on the Prescription Drug Use Questionnaire.⁵⁸

A challenge in interpreting the evidence on rates of opioid abuse, addiction, and related outcomes is inconsistency in how these outcomes were defined, as well as variability in methods used to ascertain these outcomes. In addition, definitions and usage of these terms have changed over time. The studies described above were all conducted prior to the American Psychiatric Association’s new DSM-V⁵⁹ diagnostic criteria for current opioid use disorder.

Overall, because of methodological limitations in the available studies and because estimates for opioid abuse, addiction, and related outcomes were highly variable even after stratifying by clinical setting, the SOE was rated Insufficient.

Table 1. Uncontrolled studies of long-term opioid use and abuse, misuse, and related outcomes

Author, Year Duration, If Applicable	Sample Characteristics Opioid Dose, Opioid Duration, and Pain Type	Method of Ascertaining and Defining Abuse/Misuse	Main Results
Banta-Green, 2009 ⁴⁹ Cross-sectional	n=704 Integrated group practice patients in a nonprofit healthcare system in Washington State Mean age: 55 years Female sex: 62% Race: 89% non-Hispanic White Dose: mean 50 mg/day MED, past year Duration: NR Pain type: NR	Composite International Diagnostic Interview (CIDI) for DSM-IV opioid diagnoses	Opioid dependence: 13% (91/704) Opioid abuse without dependence: 8% (56/704)
Boscarino, 2010 ⁵⁰ Cross-sectional	n=705 Primary and specialty care patients in integrated healthcare system in Pennsylvania who received 4+ opioid prescriptions in past 12 months Age: 18-64 years: 79% 65+ years: 21% Female sex: 61% White race: 98% Dose: NR Duration: mean of 10.7 opioid prescriptions over 1 year Pain type: non-cancer, otherwise not described	Composite International Diagnostic Interview (CIDI) for DSM-IV criteria for opioid dependence UDT: not examined	25.8% (95% CI: 22.0-29.9) met criteria for current opioid dependence; 35.5% (95% CI: 31.1-40.2) met criteria for lifetime dependence Factors associated with current dependence: Age <65 years (OR 2.3, 95% CI 1.6 to 3.5) History of opioid abuse (OR 3.8, 95% CI 2.6 to 5.7) History of high dependence severity (OR 1.9, 95% CI 1.4 to 2.5) History of major depression (OR 1.3, 95% CI 1.1 to 1.6) Current use of psychotropic medications (OR 1.7, 95% CI 1.2 to 2.5)

Table 1. Uncontrolled studies of long-term opioid use and abuse, misuse, and related outcomes (continued)

Author, Year	Sample Characteristics Opioid Dose, Opioid Duration, and Pain Type	Method of Ascertaining and Defining Abuse/Misuse	Main Results
Carrington Reid, 2002 ⁴⁷ Retrospective cohort	n=98 (50 at VA and 48 at urban primary care clinic) patients with 6+ months of opioid prescriptions during 1 year VA primary care clinic vs. urban hospital primary care clinic Median age: 54 vs. 55 years Female sex: 8% vs. 67% Race: 88% White, 12% Black vs. 52% White, 36% Black, 10% Hispanic Median duration of pain: 10 vs. 13 years Dose: NR Duration: 6+ months of opioid prescriptions during past year Pain type: Non-cancer, Various (low back 44% vs 25%)	Chart review for reports of lost or stolen opioids, documented use of other sources to obtain opioids, and requests for ≥2 early refills UDT: not examined	VA site vs. urban primary care site Opioid abuse behaviors: 24% (12/50) vs. 31% (15/48) Median time to onset of abuse behaviors: 24 months Factors associated with odds of opioid abuse behaviors: History of substance use disorder (adjusted OR 3.8, 95% CI 1.4 to 10.8) Age (adjusted OR 0.4, 95% CI 0.9 to 1.0) Number of medical diseases (adjusted OR 0.7, 95% CI 0.5-1.1)
Compton, 2008 ⁵¹ 1 year	n=135 veterans at a VA pain clinic Mean age: 53 years Female sex: 6% Race: NR Baseline mean usual pain VAS (0-10) rating: 6.75 Dose: NR Duration: NR Pain type: 77% musculoskeletal, 19% neuropathic, 4% multi-category	Chart review for opioid discontinuation due to medication agreement violation (including for opioid misuse or abuse) UDT: not examined	Discontinuation due to medication agreement violation: 28% (38/135) Discontinuation due to specific problematic opioid misuse behaviors: 8% (11/135)
Cowan, 2003 ⁵² Cross-sectional	n=104 patients who had been prescribed opioids at a pain clinic in a UK NHS hospital Mean age: 55.4 years Female sex: 39% Race: NR Mean duration of pain: 10.5 years Dose: NR Duration: mean 14.1 months; 57% of the 104 patients had permanently stopped opioid therapy Pain type: 34% degenerative disease other than OA, 24% failed back/neck surgery syndrome, 10% complex regional pain syndrome, 10% osteoarthritis	SUQ UDT: not examined	Self-reported addiction: 1.9% (2/104) Craving opioids: 2.9% (3/104) Has taken drugs to enhance the effect of opioids: 0.9% (1/104) Has used alcohol to enhance the effect of opioids: 0.9% (1/104)

Table 1. Uncontrolled studies of long-term opioid use and abuse, misuse, and related outcomes (continued)

Author, Year	Sample Characteristics Opioid Dose, Opioid Duration, and Pain Type	Method of Ascertaining and Defining Abuse/Misuse	Main Results
Fleming, 2007 ⁵³ See also: Saffier, 2007 ⁵⁶ Cross-sectional	n=801 primary care patients on daily opioid therapy Mean age: 48.6 years Female sex: 68% Race: 75.6% White; 23.1% African American; 1% other Disability income: 48% Mean daily dose: 92 mg MED Duration: 96% prescribed COT for ≥12 mos. Pain type: Degenerative aarthritis: 24%; low back pain: 21%; migraine headache 8%; neuropathy 5.5%	In-person interviews with Addiction Severity Index (ASI); Substance Dependence Severity Scale (SDSS); Aberrant Behavior 12-item List UDT: sample collected at end of interview	Met DSM-IV criteria for opioid dependence: 3.1% Met DSM-IV criteria for opioid abuse: 0.6% Any illicit drug on UDT: 24% (mostly marijuana) Purposefully over-sedated: 24% (186/785) Felt intoxicated from pain medication: 33% (260/785) Requested early refills: 45% (359/785) Increased dose on own: 37% (288/785) Medications lost or stolen: 30% (236/785) Used opioid for purpose other than pain: 16% (125/785) Drank alcohol to relieve pain: 20% (154/785)
Hojsted, 2010 ⁵⁴ Cross-sectional	n=253 patients at a pain clinic (236 non-cancer and 17 cancer pain) Mean age: 52 years Female sex: 64% Race: NR Receiving opioids: 74% (187/253) Dose: Median daily dose = 90 mg MED among those taking opioids Duration: mean 6.8 years among those taking opioids who returned a questionnaire Pain type: 28% nociceptive pain, 33% neuropathic pain, 39% mixed nociceptive and neuropathic	Addiction screening by physician and nurse (blinded to each other) using the ICD-10 and Portenoy's Criteria; a positive screen by either provider was considered positive UDT: not examined	Addiction to opioids or hypnotics, ICD-10: total sample 11% (28/253); among those taking addictive drugs 13%; among those taking opioids 14% Addiction to opioids, ICD-10, among those taking opioids: 14.4% (27/187) Addiction to opioids or hypnotics, Portenoy's Criteria, among those taking opioids: 19% (36/187) Addiction to opioids, Portenoy's Criteria: 19% (36/187)

Table 1. Uncontrolled studies of long-term opioid use and abuse, misuse, and related outcomes (continued)

Author, Year	Sample Characteristics Opioid Dose, Opioid Duration, and Pain Type	Method of Ascertaining and Defining Abuse/Misuse	Main Results
Portenoy, 2007 ⁵⁵ 3 years	n=227 patients enrolled in a registry study of patients who had participated in a previous controlled clinical trial of CR oxycodone for noncancer pain and who continued to take CR oxycodone Mean age: 56 years Female sex: 57% Race: 90% White BPI average pain score: 6.4 Dose: mean 52.5 mg MED/day Duration: mean 541 days Pain type: 38% osteoarthritis pain, 31% diabetic neuropathy, 31% low back pain	Physician-completed brief questionnaire assessing problematic drug-related behavior with verification by an independent panel of experts UDT: not examined	Problematic drug-related behavior identified by physicians: 5.7% (13/227) Problematic drug-related behavior adjudicated by expert panel as meeting DSM-IV criteria for drug abuse or dependence: 0 Problematic drug-related behavior adjudicated by expert panel as positive: 2.2% (5/227) Problematic drug-related behavior adjudicated by expert panel as possible: 0.4% (1/227) Problematic drug-related behavior adjudicated by expert panel as withdrawal but no indication of abuse: 0.4% (1/227) Problematic drug-related behavior adjudicated by expert panel as suspected abuse/dependence but insufficient information to draw definitive conclusion: 2.2% (5/227) Problematic drug-related behavior adjudicated by expert panel as no evidence of abuse, dependence, or euphoria: 0.4% (1/227) Overdose deaths: 1 (phenylpropanolamine, oxycodone, and alcohol)

Table 1. Uncontrolled studies of long-term opioid use and abuse, misuse, and related outcomes (continued)

Author, Year Duration, If Applicable	Sample Characteristics Opioid Dose, Opioid Duration, and Pain Type	Method of Ascertaining and Defining Abuse/Misuse	Main Results
Schneider, 2010 ⁵⁷ Retrospective chart review	n=197 patients treated by a pain specialist for at least one year Mean age: 49 years Female sex: 67% Race: NR Dose: mean 180 mg/day MED (long-acting), 49 mg/day MED (short-acting) Duration: mean 4.7 years Pain type: 51% back pain, 10% neck pain, 9% fibromyalgia, 8% other myofascial pain	UDT: immunoassay followed by confirmatory GC/MS	Positive UDT: 8.7% (14/161) Aberrant drug-related behaviors noted in chart: 15.7% (31/197)
Wasan, 2009 ⁵⁸ Cross-sectional	n=622 chronic noncancer pain patients from pain management centers on long-term opioid therapy Mean age: 50.4 years Female sex: 55% Race: 80% White Mean pain rating (0-10): 5.96 Dose: NR Duration: mean 6.2 years Pain type: 61% low back pain	POTQ, PDUQ, and UDT (immunoassay and confirmatory GCMS)	Positive scores of ≥ 2 on POTQ: 24% (115/480) Score ≥ 11 on PDUQ: 29.1% (130/447) Positive UDT: 37.1% (134/356)

Abbreviations: ASI= Addiction Severity Index, CI=confidence interval, CIDI=Composite International Diagnostic Interview, DSM-IV=Diagnostic and Statistical Manual Fifth Edition, GC/MS=gas chromatography mass spectrometry, ICD-10=International Statistical Classification of Diseases and Related Health Problems Version 10, MED=morphine-equivalent dose, NA=not applicable, NR= not reported, OR=odds ratio, PDUQ=Prescription Drug Use Questionnaire, POTQ=Prescription Opioid Therapy Questionnaire, SDSS=Dependence Severity Scale, SUQ=Self-report Substance Use Questionnaire, UDT=urine drug test, VA=Veterans Affairs.

Overdose

The 2009 APS review identified no studies on the risk of overdose in patients with chronic pain prescribed long-term opioid therapy versus placebo or no opioid. Epidemiological studies that reported opioid-related deaths did not have a nonopioid control group, did not have denominators for the numbers of people prescribed opioids, were not designed to distinguish deaths related to prescribed opioids from deaths related to illicit use of opioids, or did not focus on patients on long-term opioid therapy.⁶⁰

We identified one fair-quality retrospective cohort study published since the APS review that reported risk of overdose with opioid use versus nonuse in patients (n=9,940) in a U.S. integrated health care system with a new episode of opioid use (defined as no opioid prescription in the past 6 months), a chronic noncancer pain diagnosis within 2 weeks before the initial opioid prescription, and at least 3 opioid prescriptions in the first 90 days of the episode (Appendix E2 and F1).⁶¹ The mean duration of followup was 42 months, and short-acting opioids were the most frequently prescribed type; only 10 percent of the patients received predominantly long- acting opioids. Overdoses were identified through ICD-9 codes and a State mortality registry, with verification through medical record review. Risk estimates were based on recently dispensed opioids at the time of the overdose event. Therefore, results may be interpreted as risk of overdose with current use versus nonuse in people previously prescribed opioid therapy for several months.

The annual overdose rate was 256 per 100,000 person-years in patients who recently received prescribed opioids versus 36 per 100,000 person-years in people who did not. After adjustment for smoking, depression, substance abuse, comorbid conditions, pain site, age, sex, recent sedative-hypnotic prescription, and recent initiation of opioid use, recent receipt of any prescribed opioids, compared to no opioid receipt, was associated with increased risk of any overdose events (HR 5.2, 95 percent CI 2.1 to 12.5) and serious overdose events (HR 8.4, 95 percent CI 2.5 to 28) (SOE: Low).

Gastrointestinal Harms

The APS review identified no studies on risk of gastrointestinal harms with long-term opioid therapy versus placebo or nonuse, and we identified no studies published since the APS review meeting inclusion criteria. Systematic reviews included in the APS review were based on short-term trials that reported frequent nausea, constipation, and vomiting in patients prescribed opioids.^{22, 62, 63}

Fractures

The APS review included a systematic review of six observational studies of the association between opioid use and fracture. All six studies reported a statistically significant association, with a pooled RR of 1.38 (95 percent CI 1.15 to 1.66).⁶⁴ The APS review also included a case-control study not in the systematic review that also found use of various opioids to be associated with increased risk of fracture (OR estimates ranged from 1.1 to 2.2).⁶⁵ However, none of these studies meet inclusion criteria for the current review, because they did not specifically evaluate patients with chronic pain or on long-term opioid therapy. In addition, the studies had important methodological limitations, including failure to adjust for important confounders. Other studies published since the 2009 APS review also evaluated the association between opioid use and fractures, but did not meet inclusion criteria for similar reasons.⁶⁶⁻⁷⁰

We identified one cohort study¹⁸ and one case-control study⁷¹ published since the APS review on the association between opioid use and fracture in patients with chronic pain or on long-term opioid therapy (Appendix E3, F1, and F3). The cohort study identified patients 60 years and older with a diagnosis of noncancer pain initiating a new episode of opioid use (no opioid prescription fills in the prior 6 months) who had at least three opioid prescriptions in the first 90 days of the episode.¹⁸ Patients were followed for a mean of 33 months. The overall annual confirmed nonvertebral fracture rate was 5 percent (6 percent among current opioid users and 4 percent among people not currently using opioids; HR 1.28, 95 percent CI 0.99 to 1.64, adjusted for demographic factors, prior fractures, comorbidities, and concomitant medication use). The most commonly prescribed opioids were hydrocodone (42 percent), oxycodone (24 percent), and codeine combinations (14 percent). The study was rated fair-quality due to failure to report loss to followup and unclear blinding of outcomes assessors.

One good-quality case-control study evaluated 21,739 people with hip, humerus, or wrist fractures from the UK General Practice Research Database and 85,326 nonfracture controls matched on age, sex, date of fracture diagnosis, and practice site.⁷¹ Although the study did not specifically focus on patients with chronic pain, the analysis was stratified by duration of opioid use, based on the cumulative number of opioid prescriptions before the index date. After adjustment for a number of factors, including smoking status, comorbidities, concomitant medications, type of pain, and recent or past opioid use, current opioid therapy was associated with increased risk of fracture versus nonuse (OR 1.27, 95 percent CI 1.21 to 1.33). The risk was

highest with one prescription (OR 2.70, 95 percent CI 2.34 to 3.13) and decreased with higher numbers of prescriptions, with no increased risk for patients with more than 20 cumulative prescriptions, suggesting that increased risk of fracture may be associated with more recent initiation of opioid therapy.

The SOE for the association between opioid use versus non-use and risk of fractures was rated Low.

Motor Vehicle Accidents

The APS review included two systematic reviews^{72, 73} (25 and 48 observational studies) and five other observational studies⁷⁴⁻⁷⁸ on the association between opioid use and driving safety, but none of the studies met inclusion criteria for the current review because they did not report duration of opioid use, included individuals treated for opioid addiction or using opioids illicitly, focused on surrogate markers of driving safety such as simulated driving tests or measures of cognitive performance rather than actual motor vehicle accidents, or did not include a comparison arm of chronic pain patients not prescribed opioids. We identified no studies published since the APS review on risk of motor vehicle accidents in patients with chronic pain on long-term opioid therapy versus no opioid therapy.

Cardiovascular Events

The APS review did not evaluate the association between opioid therapy for chronic pain and risk of cardiovascular events. We identified one cohort study⁷⁹ and one case-control study⁸⁰ on the association between long-term opioid use for chronic pain and risk of myocardial infarction (Appendix E4, F2, and F3). The cohort study included individuals with claims for opioids or a nonselective cyclo-oxygenase-2 (COX-2) inhibitor over a cumulative period of ≥ 180 days over a 3.5 year period.⁷⁹ Individuals were excluded if they had cancer pain or a history of myocardial infarction or cancer and were matched on age, sex and cohort entry date to people in the general population who did not receive ≥ 180 days of opioids or COX-2 selective non-steroidal anti-inflammatory drugs (NSAIDs). Compared to the general population, chronic opioid therapy was associated with increased risk of myocardial infarction (adjusted IRR 2.66, 95 percent CI 2.30 to 3.08) and of myocardial infarction or revascularization (adjusted IRR 2.38, 95 percent CI 2.15 to 2.63), after controlling for age, sex, cardiovascular and other comorbidities, and concomitant medication use. The study was rated fair quality because there was no attempt to match patients on pain condition or severity of pain, or to adjust for these factors.

A good-quality case-control study compared 11,693 people with myocardial infarction from the UK General Practice Research Database to 44,897 controls with no myocardial infarction matched on age, sex, index date, and practice site.⁸⁰ The most commonly prescribed opioids were codeine, propoxyphene, and dihydrocodeine. Although it did not specifically enroll patients with chronic pain, the study included an analysis stratified by duration of opioid use, based on the number of cumulative opioid prescriptions at the time of myocardial infarction. After adjustment for a number of factors, including smoking status, comorbidities, concomitant medications, type of pain, and recent or past opioid use, it found current opioid therapy use associated with increased risk of myocardial infarction versus nonuse (adjusted OR 1.28, 95 percent CI 1.19 to 1.37). Recent (within 31 to 365 days) use was also associated with increased risk (OR 1.17, 95 percent CI 1.10 to 1.24). The risk was highest with 11 to 50 cumulative prescriptions (OR 1.38, 95 percent CI 1.28 to 1.49) but was statistically significant with 1-2, 3-10, or >50 cumulative prescriptions (OR range 1.09 to 1.25).

The SOE for the association between opioid use versus non-use and risk of myocardial infarction was rated Low.

We identified no study on the association between long-term opioid therapy for chronic pain versus no opioid therapy and risk of arrhythmia or sudden death.

Endocrinological Harms

The APS review included four studies on the effects of oral opioid use on endocrinological effects. One cross-sectional study of women with chronic pain (n=37, mean duration of opioid use 31 months) found no association between opioid use versus nonuse and growth hormone, corticotrophin, cortisol, thyroxine, thyrotropin, prolactin, estradiol, follicle stimulating hormone, luteinizing hormone, or testosterone levels, but did not meet inclusion criteria because it did not adjust for potential confounders.⁸¹ Three other cross-sectional studies found opioid use to be associated with decreased levels of gonadal hormone or dehydroepiandrosterone sulfate in men and women, but it was unclear in two of the studies whether patients had chronic pain, the duration of opioid use was not reported, none of the studies adjusted for potential confounders, and it was unclear how patients were selected, making it difficult to determine whether patients on opioids with signs of sexual or endocrinological dysfunction were preferentially enrolled.^{23, 24}

⁸² We identified one study published since the APS review on the association between opioid use versus nonuse and endocrinological harms (Appendix E5 and F2).¹¹ In a cross-sectional analysis of men with back pain (n=11,327) in an integrated health care system, long-term opioid use (defined as ≥120 days or >90 days with 10 or more fills), compared with no opioid use, was associated with increased likelihood of use of medications for erectile dysfunction or testosterone replacement (adjusted OR 1.5, 95 percent CI 1.1 to 1.9), after adjustment for age, co-morbidities, hospitalizations, use of sedative-hypnotics, dose of opioids, type of opioid, depression, and smoking status. Median opioid dose in men on chronic opioids was 30 mg morphine equivalent dose (MED)/day (19 percent received ≥120 mg) and 42 percent received long-acting opioids. A limitation of this study is that the patient sample was a mix of acute, subacute, and chronic back pain, and the study could not control for duration of pain. In all studies, the cross-sectional design makes it impossible to determine whether endocrinological problems preceded opioid use or resulted from opioid use. One other cross-sectional study published since the prior APS review reported an association between long-term opioid use and laboratory markers of endocrinological dysfunction, but did not meet inclusion criteria because it did not perform adjustment for potential confounders.⁸³

The SOE for the association between opioid use versus non-use and risk of endocrinological harms was rated Low.

Other Harms

We identified no studies on the association between long-term opioid therapy for chronic pain versus no opioid use and risk of falls, infections, cognitive harms, or psychological harms. These outcomes were not evaluated in the APS review.

Key Question 2b

How do harms vary depending on: (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including back pain], fibromyalgia, sickle cell disease, inflammatory pain, headache disorders); (2) patient demographics; (3) patient comorbidities (including past or current substance abuse disorder or at high risk for addiction); (4) the dose of opioids used?

Key Points

- No study evaluated how harms associated with long-term opioid therapy vary depending on the specific type or cause of pain, patient demographics, or patient comorbidities (SOE: Insufficient).
- One fair-quality retrospective database study found higher doses of long-term opioid therapy associated with increased risk of opioid abuse or dependence than lower doses. Compared to no opioid prescription, the adjusted odds ratios were 15 (95 percent CI 10 to 21) for 1-36 mg MED/day, 29 (95 percent CI 20 to 41) for 36-120 mg MED/day, and 122 (95 percent CI 73 to 206) for \geq 120 mg MED/day (SOE: Low).
 - One fair-quality retrospective cohort study and one good-quality nested case-control study found an association between higher doses of long-term opioid therapy and risk of overdose. In the cohort study, versus 1 to 19 mg MED/day, the adjusted HR for an overdose event was 1.44 (95 percent CI 0.57 to 3.62) with 20 to 49 mg MED/day and increased with higher doses to 8.87 (95 percent CI 3.99 to 19.72) for \geq 100 mg MED/day. The risk for serious overdose showed a similar pattern, with HRs of 1.19 (95 percent CI 0.4 to 3.6) for 20 to <50 mg MED/day, 3.11 (95 percent CI 1.01 to 9.51) for 50 to 99 mg/day, and 11.18 (95 percent CI 4.80 to 26.03) for \geq 100 mg/day (all relative to 1-19 mg/day). In the case-control study, versus 1 to 19 mg MED/day, the adjusted OR for an opioid-related death was 1.32 (95 percent CI 0.94 to 1.84) for 20 to 49 mg MED/day and increased to 2.88 (95 percent CI 1.79 to 4.63) for \geq 200 mg MED/day (SOE: Low).
 - One fair-quality cohort study found that risk of fracture increased from an adjusted HR of 1.20 (95 percent CI 0.92 to 1.56) at 1 to <20 mg MED/day to 2.00 (95 percent CI 1.24 to 3.24) at \geq 50 mg MED/day; the overall test for dose response did not reach statistical significance ($P = 0.06$) (SOE: Low).
 - One fair-quality cohort study found that relative to a cumulative dose of 0 to <1350 mg MED over 90 days, the adjusted IRR for myocardial infarction for 1350 to <2700 mg was 1.21 (95 percent CI 1.02 to 1.45), for 2700 to <8100 mg was 1.42 (95 percent CI 1.21 to 1.67), for 8100 to <18,000 mg was 1.89 (95 percent CI 1.54 to 2.33), and for \geq 18,000 mg was 1.73 (95 percent CI 1.32 to 2.26) (SOE: Low).
 - One good-quality case-control study found no association between opioid dose and odds of road trauma injury among drivers and passengers.

Doses of opioids $>$ 20 mg MED/day were associated with increased odds of road trauma injury when the analysis was restricted to drivers. There was no dose-dependent association at doses higher than 20 mg MED/day. Relative to 1 to <20 mg MED/day, the adjusted odds of road trauma injury among drivers were 1.21 (1.02 to 1.42) for 20 to 49 (1.02 to 1.49) for $>$ 200 mg. (SOE: Low).

One fair-quality cross-sectional study of men found a daily opioid dose of ≥ 120 mg MED/day to be associated with increased odds of use of medications for erectile dysfunction or testosterone replacement versus 0 to < 20 mg MED/day (adjusted OR 1.6, 95 percent CI 1.03 to 2.4). Odds were not increased at doses of 20 to < 120 mg MED/day (SOE: Low).

Detailed Synthesis

We identified no study on how harms associated with long-term opioid therapy vary depending on the specific type or cause of pain, patient demographics, or patient comorbidities, including those with a history of or at high risk for addiction.

The APS review identified no studies on the association between opioid dose and risk of harms in patients with chronic pain on long-term opioid therapy. We identified six studies published since the APS review on the association between opioid dose and risk of opioid-related deaths or overdose,^{61,84} fractures,¹⁸ myocardial infarction,⁷⁹ motor vehicle accidents,²⁰ and endocrinological effects.¹¹

Opioid Abuse, Addiction, and Related Outcomes

A previously described (see KQ 2a) fair-quality retrospective database study found a dose-dependent association between dose of long-term opioid therapy for chronic pain and risk of abuse or dependence.⁴⁸ Based on ICD-9 diagnosis codes, rates of abuse or dependence were 0.7 percent with low-dose opioids (1-36 mg MED/day), 1.3 percent with medium-dose (36-120 mg MED/day), and 6.1 percent with high-dose (≥ 120 mg MED/day). Compared to no opioid prescription, the odds ratio for abuse or dependence after adjustment for age, sex, history of substance abuse and other comorbidities was 15 (95 percent CI 10 to 21) for low-dose, 29 (95 percent CI 20 to 41) for medium-dose, and 122 (95 percent CI 73 to 205) for high-dose opioids (Appendix E1) (SOE: Low).

Overdose

Two studies found an association between opioid dose and risk of overdose (Appendix E2, F1, and F3).^{61,84} A previously described (see KQ 2a), fair-quality retrospective cohort study of patients (n=9,940) with recently diagnosed noncancer pain and prescribed opioid therapy followed patients for a mean duration of 42 months.⁶¹ Fifty-one patients experienced overdose events (148 per 100,000 person-years); 40 were serious overdose events (116 per 100,000 person-years) and 6 were fatal overdose events (17 per 100,000 person-years). After adjusting for smoking, depression, substance abuse, comorbid conditions, pain site, age, sex, recent sedative-hypnotic prescription, and recent initiation of opioid use, higher opioid dose was associated with increased risk of any overdose event. Relative to 1 to 19 mg MED/day, 20 to 49 mg/day was associated with a HR of 1.44 (0.57-3.62), 50-99 mg/day with a HR of 3.73 (1.47-9.5), and ≥ 100 mg/day with a HR of 8.87 (3.99-19.72). The risk for serious overdose showed a similar pattern, with HRs of 1.19 (95 percent CI 0.4 to 3.6) for 20 to 49 mg MED/day, 3.11 (95 percent CI 1.01 to 9.51) for 50 to 99 mg/day, and 11.18 (95 percent CI 4.80 to 26.03) for ≥ 100 mg/day (all relative to 1-19 mg/day).

A good-quality, population-based, nested case-control study of Canadian patients eligible for publicly funded prescription drug coverage who had received an opioid for noncancer pain identified 498 cases of opioid-associated deaths.⁸⁴ Cases were matched on age, sex, index year, the Charlson comorbidity index, and a disease risk index based on comorbidities to 1714 controls. Opioid-associated deaths were identified using coroner records and defined as deaths in which the coroner identified a combination of drugs including at least one opioid or in which forensic toxicology testing showed an opioid concentration sufficiently high to cause death.

Mean duration of opioid use was 5 years in cases and 4 years in controls. Long-acting opioids were dispensed at some point in the exposure period to 46 percent of cases and 30 percent of controls. After adjusting for previous drugs used, number of drugs, duration of opioid treatment, the number of physicians prescribing opioids, the number of pharmacies dispensing opioids, and prescribing of long-acting opioids, higher doses of opioids were associated with increased odds of opioid-associated mortality. Relative to 1 to 19 mg MED/day, the adjusted OR for opioid-associated mortality was 1.32 (95 percent CI 0.94 to 1.84) for 20 to 49 mg/day, 1.92 (95 percent CI 1.30 to 2.85) for 50 to 99 mg/day, 2.04 (95 percent CI 1.28 to 3.24) for 100 to 199 mg/day, and 2.88 (95 percent CI 1.79 to 4.63) for ≥ 200 mg/day (SOE: Low).

Three other observational studies also found an association between higher opioid doses and risk of opioid overdose-related deaths, but did not meet inclusion criteria because duration of opioid use was not reported,^{16,85} emergency room visits for opioid-related overdose events were combined with emergency room visits for alcohol,⁸⁶ or it did not evaluate patients with chronic pain prescribed long-term opioid therapy.⁸⁵

Fractures

A previously described, fair-quality cohort study (see Key Question 2a) on the association between current use of opioids and risk of fractures in people aged 60 and older found that risk of fracture increased from an adjusted hazard ratio of 1.20 (95 percent CI 0.92 to 1.56) at 1 to <20 mg MED/day to 2.00 (95 percent CI 1.24 to 3.24) at ≥ 50 mg MED/day, although the overall test for dose response did not reach statistical significance ($p = 0.06$) (Appendix E3 and F2) (SOE: Low).¹⁸

Cardiovascular Events

A previously described fair-quality cohort study (see Key Question 2a) on the association between current use of opioids and risk of myocardial infarction in patients using long-term opioid therapy found a trend towards increased risk of myocardial infarction with higher cumulative opioid exposure (Appendix E4 and F1).⁷⁹ Compared to a cumulative dose of 0 to <1350 mg MED over 90 days, the adjusted IRR for myocardial infarction for 1350 to <2700 mg was 1.21 (95 percent CI 1.02 to 1.45), for 2700 to <8100 mg was 1.42 (95 percent CI 1.21 to 1.67), for 8100 to <18,000 mg was 1.89 (95 percent CI 1.54 to 2.33), and for $\geq 18,000$ mg was 1.73 (95 percent CI 1.32 to 2.26) (SOE: Low).

Motor Vehicle Accidents

We identified one good-quality case-control study ($n=10,600$) on the association of opioid dose with risk of motor vehicle accidents in Ontario, Canada among individuals eligible for provincial prescription drug coverage who received at least one opioid prescription (Appendix E6 and F3).²⁰ It identified 5,300 cases who visited an emergency department with an injury related to road trauma. Cases were matched on sex, age, index year, and disease risk index to

5300 controls who did not visit the emergency department for road trauma. Although it did not specifically identify chronic pain patients on long-term opioid therapy, the average duration of opioid use was 7.1 years in cases and 6.8 years in controls. Individuals prescribed methadone were excluded because methadone is typically used to treat addiction in this area. Although there was no association between opioid dose and risk of road trauma in drivers or passengers at the time of the accident, doses of opioids >20 mg MED/day were associated with increased odds of road trauma when the analysis was restricted to drivers. There was no dose-dependent association at doses higher than 20 mg MED/day. Relative to 1 to <20 mg MED/day, the odds of road trauma among drivers after adjustment for age, alcoholism history, concomitant medication use, total number of drugs, and number of physician and emergency department visits was 1.21 (95 percent CI 1.02 to 1.42) for 20 to 49 mg, 1.29 (95 percent CI 1.06 to 1.57) for 50-99 mg, 1.42 (95 percent CI 1.15 to 1.76) for 100 to 199 mg, and 1.23 (95 percent CI 1.02 to 1.49) for \geq 200 mg (SOE: Low).

Endocrinological Harms

One previously described fair-quality study cross-sectional analysis of men with back pain (n=11,327) found a daily opioid dose of \geq 120 mg MED/day associated with increased risk of use of medications for erectile dysfunction or testosterone replacement versus 0 to <20 mg MED/day (OR 1.6, 95 percent CI 1.03 to 2.4), after adjustment for duration of opioid use, age, co-morbidities, hospitalizations, use of sedative-/hypnotics, type of opioid, depression, and smoking status (Appendix E5 and F2) (SOE: Low).¹¹ There was no increased risk at doses of 20 to <120 mg MED/day.

Key Question 3a

In patients with chronic pain, what is the comparative effectiveness of different methods for initiating and titrating opioids for outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?

Key Points

- Evidence from three trials on effects of titration with immediate-release versus sustained-release opioids reported inconsistent results on outcomes related to pain and are difficult to interpret due to additional differences between treatment arms in dosing protocols (titrated versus fixed dosing) and doses of opioids used (SOE: Insufficient).
- No trial was designed to assess risk of addiction, abuse, or misuse (SOE: Insufficient).

Detailed Synthesis

The APS review included three fair-quality, open-label trials of sustained-release versus immediate release opioids for titrating patients to stable pain control (Appendix E7 and F4).^{87, 88} Two trials comparing controlled-release (CR) versus immediate-release (IR) oxycodone were reported in one publication.⁸⁷ The first involved a sample of 48 patients with cancer pain and dose titration for a period up to 21 days.⁸⁷ The second trial titrated 57 patients with low back pain for a period of up to 10 days.⁸⁷ Most patients in both trials were converted to oxycodone from other opioids. Results of both trials showed no difference between CR and IR oxycodone with

respect to the percentage of patients achieving stable pain control, the time to achieve stable pain control, and the degree of pain control achieved. Another trial found titrated doses of sustained-release morphine plus immediate-release oxycodone slightly superior to fixed-dose, immediate-release oxycodone for pain intensity, but no differences on measures of function, sleep, and psychological distress.⁸⁸ Results of this trial are difficult to interpret because maximum doses of opioids varied in the two arms (up to 200 mg MED/day in titrated dose arm, versus up to 20 mg/day in the fixed-dose oxycodone arm), and average doses of opioids were not reported. None of the three trials was designed to assess outcomes related to risk of overdose, addiction, abuse, or misuse. Due to study limitations, inconsistent results, and differences between study arms other than use of sustained-release versus immediate-release opioids, the SOE was rated Insufficient.

We identified no study published since the APS review on the comparative effectiveness of different methods for initiating and titrating opioids.

Key Question 3b

In patients with chronic pain, what is the comparative effectiveness of short- versus long-acting opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?

Key Points

- No study compared effectiveness of short- versus long-acting opioids on long-term outcomes in patients with chronic pain (SOE: Insufficient).

Detailed Synthesis

The APS review included a systematic review⁸⁹ of seven trials^{87, 88, 90-94} of short- versus long-acting opioid formulations, but none of the trials met inclusion criteria for the current review. Six trials^{87, 90-94} were 30 days or shorter in duration and the other⁸⁸ was 16 weeks in duration. Five of the trials found no difference between sustained-release and immediate-release opioid formulations in pain control.^{87, 90, 91, 93, 94} Although two trials found regimens including sustained-release preparations more effective for pain control than regimens restricted to immediate-release preparations, results are difficult to interpret because the regimens were not given at therapeutically equivalent doses.^{88, 92} No trial was designed to evaluate risk of overdose, addiction, abuse, or misuse.

We identified no trials of short- versus long-acting opioids published since the APS review that met inclusion criteria.

Key Question 3c

In patients with chronic pain, what is the comparative effectiveness of different long-acting opioids on outcomes related to pain, function, and quality of life; and risk of overdose, addiction, abuse, or misuse?

Key Points

- Three randomized, head-to-head trials of various long-acting opioids found no differences in long-term outcomes related to pain or function (SOE: Low).
- No trial was designed to assess risk of overdose, addiction, abuse, or misuse (SOE: Insufficient).
- One cohort study found sustained-release methadone to be associated with lower mortality risk (presumably related to accidental overdose) as compared to morphine in a propensity-adjusted analysis (SOE: Low).
- Another cohort study found some differences between long-acting opioids in rates of adverse outcomes related to abuse, but outcomes were nonspecific for opioid-related adverse events, precluding reliable conclusions (SOE: Insufficient).

Detailed Synthesis

The APS review included one fair-quality, open-label randomized trial (n=680) of transdermal fentanyl versus sustained-release morphine in patients with chronic low back pain that evaluated outcomes through 13 months⁴³ (Table 2 below; Appendix E8a, E8b, and F4). The study found no differences between these long-acting opioids in pain relief, pain intensity, use of supplemental analgesic medications, work loss, and quality of life. The study was not designed to assess overdose and addiction or related outcomes, and no cases of these outcomes were reported. The APS review also included a fair-quality retrospective cohort study based on Oregon Medicaid administrative data (n=5,684) that evaluated abuse and other related outcomes in patients with cancer or noncancer pain and at least one new 28-day prescription of methadone, sustained-release oxycodone, sustained-release morphine, or transdermal fentanyl over a 4-year timeframe.⁹⁵ Adverse events were based on clinical encounters and ICD-9 codes and defined as emergency department (ED) visits or hospitalization for opioid-related events, all-cause ED visits or hospitalizations, opioid poisoning, overdose symptoms, and death. After adjusting for opioid dose, co-morbidities, concomitant medications, and other potential confounders, sustained-release oxycodone was associated with lower risk than sustained-release morphine of an ED encounter or hospitalization involving an opioid-related adverse event (HR 0.45, 95 percent CI 0.26 to 0.77) or death (HR 0.71, 95 percent CI 0.54 to 0.94). Among patients with noncancer pain, compared with sustained-release morphine, fentanyl was associated with higher risk of ED encounters (HR 1.27, 95 percent CI 1.02 to 1.59) and methadone was associated with greater risk of overdose symptoms (HR 1.57, 95 percent CI 1.03 to 2.40). There were no significant differences between methadone and long-acting morphine in risk of death (adjusted HR 0.71, 95 percent CI 0.46 to 1.08) or overdose symptoms. Some limitations of this study include large, statistically significant differences in baseline characteristics between patients prescribed different long-acting opioids and analysis of outcomes not specific for opioid-related adverse events. For example, overdose symptoms were defined as alteration of consciousness, malaise, fatigue, lethargy, or respiratory failure.

We identified two randomized trials^{96, 97} and one retrospective cohort study⁹⁸ published since the APS review that compared different long-acting opioids in patients receiving long-term opioid therapy. One large (n=1,117) fair-quality trial of patients with chronic low back pain or osteoarthritis pain found no difference between sustained-release tapentadol and sustained-release oxycodone in pain intensity through 1 year.⁹⁷ Methodological limitations included open-label design and high attrition. A smaller (n=46), poor-quality trial of patients with various types of chronic noncancer pain (61 percent low back pain) found no clear differences between transdermal buprenorphine versus transdermal fentanyl in pain intensity, pain relief, quality of life, function, or psychological symptoms through 1 year.⁹⁶ It was rated poor-quality due to high attrition and open-label design. In addition, statistical analyses comparing results between groups were not reported for most outcomes and the study was not designed to measure efficacy. No deaths were reported in either study, and the studies were not designed to assess risk of addiction, abuse, or misuse. In both trials, opioid doses were titrated to effect.

A fair-quality retrospective cohort study based on national VA system pharmacy data compared all-cause mortality among chronic pain patients prescribed methadone (n=28,554) or long-acting morphine (n=79,938).⁹⁸ The study excluded patients prescribed methadone for opioid dependence or in palliative care settings. The mean daily doses of methadone and long acting morphine were 25.4 mg and 67.5 mg, respectively. Compared to the morphine cohort, the methadone group was younger and had fewer comorbid medical conditions, but higher rates of psychiatric conditions, substance use, and back pain. To help control for these and other differences, the study analyzed patients based on their propensity for being prescribed methadone. The baseline characteristics in each propensity quintile were very similar across the two groups. In both groups, all-cause mortality was highest in propensity quintile 1 (patients with the least propensity to receive methadone and most medically ill) and least in quintile 5 (highest propensity to receive methadone). In the propensity-stratified analysis, overall risk of mortality was lower with methadone than with morphine (adjusted HR 0.56, 95 percent CI 0.51 to 0.62).

For propensity quintile 1, the adjusted HR was 0.36 (95 percent CI 0.26 to 0.49); similar trends were observed for quintiles 2 to 4. For quintile 5, there was no difference between methadone and morphine in risk of all-cause mortality (adjusted HR 0.92, 95 percent CI 0.74 to 1.2). The main limitation of this study is the possibility of residual confounding by indication. Although the study stratified patients based on their propensity for being prescribed methadone and performed adjustment on potential confounders, unmeasured confounders could still have been present. The likely effects of residual confounding on estimates is difficult to predict, because people prescribed methadone had features associated both with decreased risk of mortality (younger age and fewer co-morbid medical conditions) as well as with increased risk (more psychiatric conditions and substance abuse).

The SOE was rated Low for no difference between different long-acting opioids in pain or function, Low for mortality risk associated with methadone versus morphine, and Insufficient for abuse and related outcomes.

Table 2. Head-to-head trials and observational studies of different long-acting opioids

Author Year Study Design Duration	Setting/ Data Source Country	Interventions, N	Results	Quality
Allan, 2005 ⁴³ Randomized trial 13 months	Multicenter (number of sites not clear) Europe	A: Transdermal fentanyl (titrated from 25 mcg/hr) (Mean dose 57 mcg/hr) (N=338) B: Sustained-release morphine (titrated from 30 mg q 12 hrs) (Mean dose: 140 mg) (N=342)	A vs. B Pain score (mean, 0-100 VAS) at 56 weeks (N=608): 56.0 vs. 55.8 Severe pain at rest (per protocol analyses, N=248 and 162): 22/248 (9%) vs. 20/162 (12%), p=0.030 (no significant differences in ITT analysis, but data not provided) Severe pain on movement (per protocol): 70/248 (28%) vs. 43/162 (27%), p=0.611 Severe pain during the day (per protocol): 48/248 (19%) vs. 40/162 (25%), p=0.385 Severe pain at night (per protocol): 25/248 (10%) vs. 26/162 (16%) , p=0.003 (no significant differences in ITT analysis, but data not provided) Rescue strong opioids use: 154/296 (52%) vs. 154/291 (53%) Quality of life (SF-36): No differences between interventions Loss of working days: No differences between interventions Withdrawal due to lack of efficacy: 18/335 (5%) vs. 15/342 (4%)	Fair

Table 2. Head-to-head trials and observational studies of different long-acting opioids (continued)

Author Year Study Design Duration	Setting/ Data Source Country	Interventions, N	Results	Quality
Hartung, 2007 ⁹⁵ Retrospective cohort study Duration not applicable	U.S. Medicaid claims	A. Transdermal fentanyl (n=1,546) B. Methadone (n=974) C. ER oxycodone (n=1,866) D. ER morphine (n=1,298)	A vs. B vs. C (reference: D) Mortality: adjusted HR 0.71 (95% CI 0.46 to 1.08) vs. HR 0.71 (95% CI 0.54 to 0.94) vs. 0.80 (95% CI 0.63 to 1.02) ED encounter or hospitalization involving an opioid-related adverse event (HR 0.45, 95% CI 0.26 to 0.77) Among patients with noncancer pain: Fentanyl associated with higher risk of ED encounters than sustained-release morphine (HR 1.27, 95% CI 1.02 to 1.59) Methadone associated with greater risk of overdose symptoms than sustained-release morphine (HR 1.57, 95% CI 1.03 to 2.40) No significant differences between methadone and long-acting morphine in risk of death (adjusted HR 0.71, 95% CI 0.46 to 1.08)	Fair
Krebs, 2011 ⁹⁸ Retrospective cohort study Duration not applicable	U.S. VA	A: Methadone (n=28,554) B: Long-acting morphine sulfate (MS) (n=79,938)	All-cause mortality: Unadjusted: 3,347 (3.4%) patients died; highest mortality within 1st 30 days (1.2% in methadone and 3.7% in MS); raw death rates from MS higher than methadone for all 30-day intervals; Death rate: Quintile #1 (0.042 vs 0.133); Quintile #2 (0.034 vs 0.078); Quintile #3 (0.025 vs 0.053); Quintile #4 (0.022 vs 0.034); Quintile #5 (0.017 vs 0.020); Propensity adjusted mortality (HR): Overall risk of mortality lower with methadone than morphine (adjusted HR 0.56, 95% CI 0.51 to 0.62) Quintile #1: 0.36 (95% CI: 0.26, 0.49); Quintile #2: 0.46 (0.37, 0.56); Quintile #3: 0.50 (0.41, 0.61); Quintile #4: 0.66 (0.54, 0.81); Quintile #5: 0.92 (0.74, 1.16); Results robust in validation dataset	Fair
Mitra, 2013 ⁹⁶ Randomized trial 12 months	Townsville, Australia (1 site)	A: Transdermal buprenorphine (TDB) initial dose=5 mcg/h (n=22) B: Transdermal fentanyl (TDF) initial dose=12.5 mcg/h (n=24) Both titrated to optimal doses over 4 weeks; increased doses beyond that given as clinically indicated	Sleep quality: No significant difference between groups (data not provided) Pain VAS: 3-point (scale 1-10) reduction in pain in 11% in each treatment group (data not provided) DASS21: TDB had relatively better score at 12 mos (data not provided) PDI: Appears similar (data not provided)	Poor

**Table 2. Head-to-head trials and observational studies of different long-acting opioids
(continued)**

Author Year Study Design Duration	Setting/ Data Source Country	Interventions, N	Results	Quality
Wild, 2010 ⁹⁷ Randomized trial 12 months	53 sites in North America; 36 sites in Europe	A. Tapentadol ER 100-250 mg BID (adjustable) (n=894) B. Oxycodone CR 20-50 mg BID (adjustable) (n=223)	Mean (SE) pain intensity score: decreased from 7.6 (0.05) and 7.6 (0.11) at baseline to 4.4 (0.09) and 4.5 (0.17) Global assessment, very much improved or much improved: 48.1% (394/819) vs 41.2% (73/177) Concomitant nonopioid analgesics (NSAIDS, ASA, acetaminophen): 19.9% (178/894) vs. 17% (38/223)	Fair

Abbreviations: ASA=aspirin, BID=twice daily, CI=confidence interval, CR=controlled release, DASS21=Depression, Anxiety, and Stress Scale-21 Items, ER=extended release, HR=hazard ratio, ITT=intent to treat, MS=long-acting morphine sulfate, NSAID=nonsteroidal anti-inflammatory drug, PDI=Physical Disability Index, q=every, SE=standard error, TDB= transdermal buprenorphine, TDF= transdermal fentanyl, US=United States, VA=Veterans Affairs, VAS=Visual Analogue Scale.

Key Question 3d

In patients with chronic pain, what is the comparative effectiveness of short- plus long-acting opioids versus long-acting opioids alone on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?

The APS review identified no trial of short- plus long-acting opioids versus long-acting opioids alone. We also identified no study published since the APS review that addressed this question (SOE: Insufficient).

Key Question 3e

In patients with chronic pain, what is the comparative effectiveness of scheduled, continuous versus as-needed dosing of opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?

Key Points

- No study compared long-term opioid therapy using scheduled, continuous dosing versus as-needed dosing (SOE: Insufficient).

Detailed Synthesis

The 2009 APS review included one trial of scheduled, around-the-clock dosing of codeine versus as-needed dosing, but it did not meet inclusion criteria for the current review because duration of followup was five days.⁹² In addition, results of this trial were difficult to interpret because the interventions varied on factors other than whether the opioid was dosed around-the-clock, including use of sustained-release versus immediate-release codeine formulations and different doses (200 versus 71 mg/day of codeine).

We identified no study published since the APS review on long-term opioid therapy using scheduled, continuous dosing versus as-needed dosing (SOE: Insufficient).

Key Question 3f

In patients on long-term opioid therapy, what is the comparative effectiveness of dose escalation versus dose maintenance or use of dose thresholds on outcomes related to pain, function, and quality of life?

Key Points

- One fair-quality randomized trial of more liberal dose escalation versus maintenance of current doses found no difference in outcomes related to pain or function, or risk of

withdrawal due to opioid misuse, but achieved limited separation between groups in opioid doses (52 versus 40 mg MED/day at the end of the trial) (SOE: Low).

Detailed Synthesis

The APS review did not address the comparative effectiveness of dose escalation versus dose maintenance or use of dose thresholds. We identified one relevant fair-quality randomized trial (n=140) published since the APS review (Appendix E9 and F4).⁹⁹ It compared more liberal dose escalation (doses increased for inadequate pain relief using preset dosing guidelines) versus maintenance of current doses (doses only increased if medically necessary due to clear dosage tolerance or acute injury). The subjects were VA patients with primarily musculoskeletal chronic pain⁹⁹ (defined as >6 months duration). Over 90 percent of enrollees were male and initial opioid doses were about 30 mg morphine equivalents/day. Both short- and long-acting opioids were prescribed, with long-acting opioids used more at higher doses. Average pain at baseline was about 7 on a 0 to 10 scale, and mean Oswestry Disability Index (ODI) score was about 48 (indicating moderate functional disability). The trial was fair-quality, primarily due to high attrition. Although doses at the end of the 12-month trial were higher in the dose escalation group, an important limitation of this trial is that the difference in opioid doses prescribed at the end of the trial was relatively small (mean 52 versus 40 mg morphine equivalents/day).

The trial found no difference between groups at 12 months in mean Visual Analogue Scale (VAS) pain ratings (5.6 for escalating dose versus 6.2 for stable dose, p=0.11), proportion with ≥ 1.5 point improvement in VAS pain rating (28 percent versus 20 percent, RR 1.4, 95 percent CI 1.76 to 2.5), mean ODI scores (46 versus 45, p=0.85), proportion with ≥ 10 point improvement in ODI score (29 percent versus 23 percent, RR 1.0, 95 percent CI 0.61 to 1.8), or use of various nonopioid medications or physical therapy. There was also no significant difference in all-cause withdrawals (49 percent versus 56 percent, RR 0.88, 95 percent CI 0.64 to 1.2). Withdrawal due to opioid misuse was frequent in both groups, with no difference between groups (24 percent versus 30 percent, RR 0.79, 95 percent 0.46 to 1.4) (SOE: Low).

Key Question 3g

In patients on long-term opioid therapy, what is the comparative effectiveness of opioid rotation versus maintenance of current opioid therapy on outcomes related to pain, function, and quality of life; and doses of opioids used?

Key Points

- No study compared opioid rotation versus maintenance of long-term opioid therapy (SOE: Insufficient).

Detailed Synthesis

The APS review identified no randomized trials or controlled observational studies on opioid rotation versus maintenance of current therapy. We identified no studies published since the APS review that addressed this Key Question (SOE: Insufficient).

Key Question 3h

In patients on long-term opioid therapy, what is the comparative effectiveness of different strategies for treating acute exacerbations of chronic pain on outcomes related to pain, function, and quality of life?

Key Points

- Two good-quality randomized trials found buccal fentanyl more effective than placebo for treating acute exacerbations of pain and three randomized trials found buccal fentanyl or intranasal fentanyl more effective than oral opioids for treating acute exacerbations of pain in patients on long-term opioid therapy, based on outcomes measured up to 2 hours after dosing. (SOE: Moderate).
- No study evaluated long-term benefits or harms (SOE: Insufficient).

Detailed Synthesis

The APS review included two placebo-controlled, randomized trials (n=77 and 79) of buccal fentanyl for acute exacerbations of pain in people prescribed opioid therapy for chronic pain (Table 3 below, Appendix E10 and F4).^{100, 101} Both found buccal fentanyl to be more effective than placebo at relieving acute pain exacerbations based on outcomes measured up to 2 hours after dosing, for up to nine episodes over a 3-week period. Neither trial was designed to evaluate benefits or harms associated with longer-term use of buccal fentanyl, including outcomes related to abuse and associated outcomes. Use of a run-in period in both trials could limit generalizability of findings, as about one-quarter of patients were excluded during an open-label run-in period due to lack of efficacy or adverse events.

We identified three subsequent head-to-head trials of buccal or intranasal fentanyl versus oral opioids for acute exacerbations of chronic pain.¹⁰²⁻¹⁰⁴ As in the prior trials, all were funded by the manufacturer of buccal or intranasal fentanyl or conducted by researchers affiliated with the manufacturer. All used a double-blind, double-dummy crossover design and enrolled patients prescribed ≥60 mg MED/day and with one to four episodes of pain exacerbations per day. Like the prior trials, they focused on immediate outcomes following administration and used a run-in period. Two good-quality trials (n=183 and 137) found fentanyl buccal tablets to be more effective than oxycodone in reducing pain intensity (pain reduction 0.82 versus 0.60 and 0.88 versus 0.76 on a 0-10 scale; both p<0.001) and meaningful pain relief (undefined) (16 percent versus 12 percent at 15 minutes, p<0.05 and 46 percent versus 38 percent at 30 minutes, p<0.01).^{102, 104} The pain condition in most patients in both trials was back or neck pain, osteoarthritis, fibromyalgia, traumatic injury, or complex regional pain syndrome. A fair-quality trial (n=84) of cancer patients found fentanyl pectin nasal spray more effective than immediate-release morphine sulfate at reducing pain intensity by >33 percent at 15 minutes (52 percent versus 44 percent of episodes; p<0.01).¹⁰³ It was unclear how many of the patients in the study were at end of life.

The SOE for the effectiveness of buccal or nasal fentanyl for immediate pain relief was rated Moderate.

Table 3. Trials of different strategies for treating acute exacerbations of chronic pain in patients on long-term opioid therapy

Author, Year Study Design Duration	Sample	Interventions, N	Results	Quality
Ashburn, 2011 ¹⁰² Randomized trial (crossover) Duration: up to 42 days total	n=183 Patients aged 18 to 80 years with >3 months of chronic pain receiving >60 mg/day MED, with 1-4 episodes of breakthrough pain per day Mean age: 48.8 years Female sex: 62% Race: 92% White, 5% Black, 3% other Pain intensity in 24 hours prior to enrollment: 5.1 Indication (most common): 57% back pain, 11% osteoarthritis, 8% neck pain, 9% fibromyalgia, 4% traumatic injury, 4% complex regional pain syndrome	A. Fentanyl buccal tablet (n=183) B. Oxycodone (n=183)	A vs. B Pain intensity difference (from before drug administration; 0-10 scale) at 15 minutes: 0.82 vs. 0.60 (p<0.0001) Pain relief (0-5 scale) at 15 minutes: 0.69 vs. 0.53 (p<0.05) Meaningful pain relief within 15 minutes: 16% vs. 12% of episodes (p<0.05)	Good
Davies, 2011 ¹⁰³ Randomized trial (crossover) 3 to 21 days	n=84 Patients with histologically confirmed cancer, receiving a fixed-schedule opioid regimen at a total daily dose equivalent >60 mg MED, with 1 to 4 episodes of breakthrough pain per day Mean age: 55.9 years Female sex: NR Race: NR	A. Fentanyl pectin nasal spray (n=106 for safety and n=84 for efficacy) B. Immediate-release morphine sulfate (n=106 for safety and n=84 for efficacy)	A vs. B ≥2-point reduction in pain intensity at 10 minutes: 52.4% vs. 45.4% (p<0.05) ≥2 pain relief at 15 minutes: 60.2% vs. 53.4% (p<0.05) Total pain relief ≥33% at 15 minutes: 52.3% vs. 43.5% (p<0.01)	Fair

Table 3. Trials of different strategies for treating acute exacerbations of chronic pain in patients on long-term opioid therapy (continued)

Author, Year Study Design Duration	Sample	Interventions, N	Results	Quality
Portenoy, 2007 ¹⁰⁰ Randomized trial 3 weeks	n=77 Patients aged 18 to 80 years with chronic low back pain Mean age: 47 years Female gender: 55% Nonwhite race: 12% Baseline pain intensity: 5.1 (10 point scale) Primary etiology of low back pain degenerative disc disease: 68%	A. Buccal fentanyl 100 to 800 mcg for an episode of breakthrough pain B. Placebo (n=77) Dose of buccal fentanyl: 800 mcg 56%; 600 mcg 24%; 400 mcg 15%; 200 mcg 5%	A vs. B Sum of the pain intensity differences from 5 through 60 minutes: 8.3 vs. 3.6 Proportion of breakthrough pain episodes with "meaningful" pain reduction: 70% (289/413) vs. 30% (63/207) (p<0.0001) Proportion of breakthrough pain episodes with ≥33% reduction in pain intensity after 30 minutes: 42% (172/413) vs. 18% (18/207) (p<0.0001) Proportion of breakthrough pain episodes with ≥50% reduction in pain intensity after 30 minutes: 30% (122/413) vs. 13% (27/207) (p<0.0001) Proportion of breakthrough pain episodes with ≥33% reduction in pain intensity after 120 minutes: 65% (269/413) vs. 28% (57/207) (p<0.0001) Proportion of breakthrough pain episodes with ≥50% reduction in pain intensity after 120 minutes: 48% (198/413) vs. 16% (33/207) (p<0.0001)	Good

Table 3. Trials of different strategies for treating acute exacerbations of chronic pain in patients on long-term opioid therapy (continued)

Author, Year Study Design Duration	Sample	Interventions, N	Results	Quality
Simpson, 2007 ¹⁰¹ Randomized trial (crossover) 3 weeks	n=79 18 to 80 years old, >3 months history of chronic neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, traumatic injury, or complex regional pain syndrome, on chronic opioids (at least 60 mg/day or morphine or equivalent), pain intensity <7 on a 0 to 10 scale, 1 to 4 daily episodes of breakthrough pain	A. Buccal fentanyl 100 to 800 mcg for an episode of breakthrough pain B. Placebo (n=79) Dose of buccal fentanyl: 800 mcg 54%; 600 mcg 19%; 400 mcg 18%; 200 mcg 5%, 100 mcg 5%	A vs. B Sum of the pain intensity differences from 5 through 60 minutes: 9.63 vs. 5.73 (p<0.001) Proportion of breakthrough pain episodes with 'meaningful' pain reduction: 69% vs. 36% (p<0.0001) Proportion of breakthrough pain episodes with ≥50% reduction in pain intensity after 15 minutes: 12% vs. 5% (p<0.0001), p<0.0001 for each subsequent time point from 30 to 120 minutes Use of supplemental medication: 14% (59/432) vs. 36% (77/213) (OR 0.28, 95% CI 0.18 to 0.42)	Good
Webster, 2013 ¹⁰⁴ Randomized trial (crossover) Up to 42 days	N=274 Mean age: 50.8 years Female sex: 58% Race: 91% white, 7% black, 2% other Pain intensity in 24 hours prior to enrollment: 5.1	A. Fentanyl buccal tablet (n=137) B. Oxycodone (n=137)	A vs. B Pain intensity difference (from before drug) at 15 minutes: 0.88 vs. 0.76 (0-10 scale) (p<0.001) Pain relief at 15 minutes: 38% vs. 34% (p<0.05) Meaningful pain relief within 15 minutes: 17% vs. 16% (p=NS) Meaningful pain relief within 30 minutes: 46% vs. 38% (p<0.01)	Good

Abbreviations: CI=confidence interval, MED=morphine equivalent dose, NR=not reported, NS=not significant, OR=odds ratio.

Key Question 3i

In patients on long-term opioid therapy, what are the effects of decreasing opioid doses or of tapering off opioids versus continuation of opioids on outcomes related to pain, function, quality of life, and withdrawal?

Key Points

- One small (n=10), poor-quality crossover trial found abrupt cessation of morphine to be associated with increased pain and decreased function compared to continuation of morphine (SOE: Insufficient).

Detailed Synthesis

The APS review included one small (n=10), poor-quality crossover trial that found abrupt cessation of morphine to be associated with increased pain and decreased function compared to continuation of morphine (Appendix E11 and F4).¹⁰⁵ Three patients (30 percent) reported opioid withdrawal symptoms following abrupt cessation of morphine, though there were no differences in physiologic parameters (vital signs and pupil size). Average dose of morphine prior to entry into was 42 mg/day (range 30 to 120 mg/day). Results of this trial may not apply to the general population of patients with chronic pain, as patients who did not have pain

adequately controlled by immobilization and alternative medications were excluded from study entry. We identified no study published since the APS review addressing this question.

Key Question 3j

In patients on long-term opioid therapy, what is the comparative effectiveness of different tapering protocols and strategies on measures related to pain, function, quality of life, withdrawal symptoms, and likelihood of opioid cessation?

Key Points

- Two poor-quality, nonrandomized prospective trials found no clear differences between different methods for opioid discontinuation or tapering (inpatient, patient controlled versus fixed reduction schedule or detoxification plus counseling versus detoxification plus maintenance) in likelihood of opioid abstinence after 3 to 6 months (SOE: Insufficient).

Detailed Synthesis

The APS review included two poor-quality, nonrandomized prospective trials that reported similar rates of opioid abstinence after 3 to 6 months in patients allocated to different methods for opioid discontinuation or tapering (Appendix E12 and F4).^{106, 107} In one study (n=108), patients either chose inpatient, patient-controlled reduction of opioids or a fixed reduction schedule.¹⁰⁶ Mean opioid dose on study entry was 36 mg MED/day; duration of opioid therapy was not reported. In the second study, patients (n=42) received detoxification plus counseling or detoxification with maintenance therapy if detoxification was unsuccessful.¹⁰⁷ Mean duration of opioid use was 7.2 years in the detoxification plus counseling group and 9.2 years in the detoxification plus maintenance group; opioid doses ranged widely (e.g., codeine daily doses ranged from 240 to 2400 mg/day). Neither study evaluated effects of different methods for discontinuing opioids on pain, function, quality of life, or withdrawal symptoms.

We identified no study published since the APS review on the comparative effectiveness of different tapering protocols and strategies in chronic pain patients on long-term opioid therapy.

Key Question 4a

In patients with chronic pain being considered for long-term opioid therapy, what is the accuracy of instruments for predicting risk of opioid overdose, addiction, abuse, or misuse?

Key Points

- Three studies (one fair-quality, two poor-quality) evaluated the Opioid Risk Tool (ORT); using a cutoff of ≥ 4 . Estimates of diagnostic accuracy were inconsistent, precluding reliable conclusions. Sensitivities ranged from 0.20 to 0.99; specificities for the two in which this could be calculated were 0.88 and 0.16 (SOE: Insufficient).

- Two studies evaluated the Screening and Opioid Assessment for Patients with Pain (SOAPP) Version 1 instrument. In one fair-quality study, based on a cutoff score of ≥ 8 , sensitivity was 0.68 and specificity was 0.38, for a PLR of 1.11 and NLR of 0.83 for predicting aberrant urine drug test. In one poor-quality study, sensitivity for predicting opioid discontinuation due to aberrant drug-related behavior was 0.73 based on a cutoff score of >6 and other diagnostic accuracy indicators could not be determined. (SOE: Low).
- One poor-quality study evaluated the Diagnosis, Intractability, Risk, and Efficacy Inventory (DIRE), but specificity and other diagnostic accuracy indicators could not be determined as patients who were not discontinued from opioids were not included in this study. (SOE: Insufficient)
- One poor-quality study evaluated the Pain Medication Questionnaire (PMQ), and for a cutoff of scores ≥ 30 , sensitivity was low (0.34), specificity was 0.77, and AUROC was 0.57 for predicting opioid discontinuation due to aberrant drug-related behaviors. (SOE: Insufficient)
- One poor-quality study evaluated the Screening and Opioid Assessment for Patients with Pain-Revised (SOAPP-R). For a cutoff of ≥ 18 , sensitivity was 0.39 and specificity was 0.69 and AUROC was 0.54 for predicting opioid discontinuation and discharge due to aberrant drug-related behavior. (SOE: Insufficient)

Detailed Synthesis

The APS review¹⁰⁸ included two fair-quality prospective studies of instruments to predict risk of opioid abuse or misuse completed by patients before initiation of opioid therapy (Table 4 below; Appendix E13 and F5).^{109, 110} One study¹⁰⁹ evaluated the 14-item, patient self-administered Screening and Opioid Assessment for Patients with Pain (SOAPP) Version 1 instrument¹¹¹ and the other¹¹⁰ evaluated the 10-item, self-administered Opioid Risk Tool (ORT). The SOAPP is scored on a scale of 0 to 56, while ORT scores can range from 0 to 25. For both instruments, higher scores indicate greater risk of opioid misuse and patients with scores ≥ 8 are considered high-risk for abuse. Both studies were performed with samples of patients in pain clinics. Methodological shortcomings of both studies included unclear blinding of outcomes assessors to findings of the screening instrument, use of definitions for aberrant drug-related behaviors that were not well standardized or defined, and failure to distinguish less serious from more serious behaviors. Although the APS review included two other studies used to develop the SOAPP Version 1¹¹¹ and the Revised SOAPP,¹¹² both were conducted using samples of patients already on long-term opioid therapy and did not meet inclusion criteria for the current review. In these studies, sensitivities (0.80 and 0.91) and specificities (0.68 and 0.69) were higher than those reported in the study of the SOAPP Version 1¹⁰⁹ conducted in patients evaluated prior to initiation of treatment.

The study of the SOAPP Version 1 instrument¹¹¹ reported a sensitivity of 0.68 (95 percent CI 0.52 to 0.81) and specificity of 0.38 (95 percent CI 0.29 to 0.49) based on a cutoff score of ≥ 8 , for a PLR of 1.11 (95 percent CI 0.86 to 1.43) and NLR of 0.83 (95 percent CI 0.50 to 1.36) (Table 5 below).¹⁰⁹ Results were difficult to interpret because the only outcome reported was aberrant urine drug test, urine drug screens were not obtained in most patients, and duration of followup was unclear.

In the study¹¹⁰ of the ORT, items in the ORT were chosen and weighted before evaluation of diagnostic test characteristics, and cut-off scores for different risk categories appeared to be selected on an a priori basis. Aberrant drug-related behaviors as documented in medical records over 12 months of follow-up were identified in 6 percent (1/18) of patients categorized as low risk (score 0 to 3), compared with 28 percent (35/123) of patients categorized as moderate risk (score 4 to 7) and 91 percent (41/44) of those categorized as high risk (score ≥ 8), for PLRs of 0.08 (95 percent CI 0.01 to 0.62) for a low-risk score, 0.57 (95 percent CI 0.44 to 0.74) for a moderate-risk score, and 14.34 (95 percent 5.35 to 38) for a high-risk score (Table 5 below).¹¹⁰

We identified two subsequent poor-quality retrospective studies that compared the ability of different risk assessment instruments to predict subsequent opioid abuse or misuse.^{113, 114} One study compared the ORT, the Revised (24-item) SOAPP (SOAPP-R), the Pain Medication Questionnaire (PMQ), and a semi-structured clinical interview.¹¹³ SOAPP-R scores range from 0 to 24 (scores ≥ 18 indicate high risk) and PMQ scores range from 0 to 104 (scores ≥ 30 indicate high risk.) The other compared the SOAPP Version 1, the ORT, the Diagnosis, Intractability, Risk, and Efficacy Inventory (DIRE) instrument, and a semi-structured clinical interview.¹¹⁴ DIRE scores range from 7 to 21, and unlike the other risk assessment instruments, lower scores (≤ 13) indicate high-risk for abuse. Both studies appeared to be conducted in the same pain clinic during different time periods. Methodological shortcomings in both studies included exclusion of patients who were not evaluated with all of the risk assessment instruments (in one study, nearly 300 of 347 patients were excluded for this reason,¹¹³ and in the other the proportion excluded was not reported¹¹⁴) and use of a case-control design. In both studies, cases were based on opioid discontinuations due to abuse, without further specification. One study also evaluated aberrant behaviors, but this outcome was not clearly defined.¹¹⁴

One poor-quality study found the ORT (cutoff >4), PMQ (cutoff ≥ 30) and SOAPP-R (cutoff ≥ 18) associated with sensitivities of 0.20, 0.34, and 0.39, respectively, and specificities of 0.88, 1.77 and 0.69, resulting in weak positive likelihood ratios (PLR; range 1.27 to 1.65) and negative likelihood ratios (NLR; range 0.86 to 0.91).¹¹³ The AUROC ranged from 0.54 to 0.57. Results were similar when cases were based on presence of aberrant behaviors not necessarily resulting in opioid discontinuation. The other poor-quality study reported a higher sensitivity with the SOAPP Version 1 (0.73 at cutoff >6) compared with the ORT (0.45 at cutoff ≥ 4) or DIRE (0.17 at cutoff <14).¹¹⁴ Because patients who were not discontinued from opioids were not included in this study, specificity and other diagnostic accuracy indicators could not be determined. Both studies also included a semi-structured clinician interview that addressed many of the components included in the risk prediction instruments (e.g., pain source and duration, history of drug or alcohol abuse, psychiatric symptoms or comorbidities). In both studies, the predictive accuracy of the clinician interview was at least as good as that of formal risk instruments.

The only instruments evaluated in more than one study were the ORT (3 studies^{110, 113, 114}) and the SOAPP version 1 (two studies).^{109, 114} Across the studies, estimates for diagnostic accuracy were extremely inconsistent. Using a cutoff score of >4 , the sensitivity of the ORT ranged from 0.20 to 0.99 in three studies^{110, 113, 114} and specificity was 0.88 and 0.16 in two studies and could not be calculated in the third study (SOE: Insufficient).^{110, 113} The inconsistency could be due in part to differences in study methods and definitions of opioid abuse or misuse. For the SOAPP, cutoff scores of ≥ 6 and ≥ 8 had similar sensitivities (0.73 and 0.68, respectively) (SOE: Low), but other measures of diagnostic accuracy could not be compared because one of the studies only included cases.¹¹⁴

Table 4. Studies of risk assessment instrument.

Author Year	Population, N	Risk Assessment	Method of Administratio	Reference Standard
Akbik, 2006 ¹⁰⁹	n=155 Mean age 43 years (SD 9.6) 33% female 86% White, other races not reported Pain: 39% back	SOAPP (scale 0-56; high risk ≥8)	Self-report	Positive urine drug test
Jones, 2012 ¹¹³ (Study 2)	n=263 Mean age 48 years (SD 13) 56% female 96% White, other races not reported Pain: 45% low back pain, 21% arthritis or fibromyalgia), 14% joint pain, 10% pelvic or abdominal pain, 7% neck or upper back pain	ORT (scale 0-25; high risk ≥8) PMQ (scale 0-104; high risk ≥30) SOAPP-R (scale 0-24; high risk ≥18) Clinician assessment	Self-report (SOAPP-R, ORT, PMQ); clinician interview	Opioid discontinuation due to abuse
Moore, 2009 ¹¹⁴	n=48 Mean age 44 years (SD 11) 60% female Race not reported Pain not reported	SOAPP (scale 0-56; high risk ≥8) DIRE (scale 7-21; high-risk ≤13) ORT (scale 0-26; high risk ≥8) Clinician assessment	Self-report (SOAPP, DIRE, ORT); clinician interview	Opioid discontinuation due to abuse ^a
Webster, 2005 ¹¹⁰	n=185 Mean age 44 years (SD 13) 58% female Race not reported Pain: 45% back; 18% head; 16% neuropathic; 16% musculoskeletal; 5% visceral	ORT (scale 0-25; high risk ≥8)	Self-report	Documentation in medical record of aberrant behavior during followup

Abbreviations: DIRE= Diagnosis Intractability Risk and Efficacy Inventory, ORT= Opioid Risk Tool, PMQ=Pain Medication Questionnaire,

SD=standard deviation, SOAPP= Screening and Opioid Assessment for Patients with Pain, SOAPP-R= Screening and Opioid Assessment for Patients with Pain-Revised.

Table 5. Predictive value of risk assessment instruments

Scale	Studies	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio	AUROC
DIRE	Moore, 2009 ¹¹⁴	Score <14: 0.17	Not calculable ^a	Not calculable ^a	Not calculable ^a	Not calculable ^a
ORT	Jones, 2012 ¹¹³	Score >4: 0.20 (95% CI 0.15 to 0.27)	Score >4: 0.88 (95% CI 0.82 to 0.93)	Score >4: 1.65 (95% CI 0.78 to 3.51)	Score >4: 0.91 (95% CI 0.78 to 1.06)	0.54
	Moore, 2009 ¹¹⁴	Score ≥4: 0.45	Not calculable ^a	Not calculable ^a	Not calculable ^a	Not calculable ^a
	Webster, 2005 ¹¹⁰	Score ≥4: 0.99 (95% CI 0.92 to 0.99)	Score ≥4: 0.16 (95% CI 0.10 to 0.24)	Score ≥4: 0.99 (95% CI 0.92 to 0.999) Score 1-3: 0.08 (95% CI 0.01 to 0.62) Score 4-7: 0.57 (95% CI 0.44 to 0.74) Score ≥8: 14.34 (95% CI 5.35 to 38)	Score ≥4: 0.16 (95% CI 0.10 to 0.24)	Not reported
PMQ	Jones, 2012 ¹¹³	Score ≥30: 0.34 (95% CI 0.20 to 0.51)	Score ≥30: 0.77 (95% CI 0.69 to 0.80)	Score ≥30: 1.46 (95% CI 0.87 to 2.45)	Score ≥30: 0.86 (95% CI 0.68 to 1.08)	0.57
SOAPP-R	Jones, 2012 ¹¹³	Score ≥18: 0.39 (95% CI 0.26 to 0.54)	Score ≥18: 0.69 (95% CI 0.63 to 0.75)	Score ≥18: 1.27 (95% CI 0.86 to 1.90)	Score ≥18: 0.88 (95% CI 0.70 to 1.10)	0.54
SOAPP	Moore, 2009 ¹¹⁴	Score >6: 0.73	Not calculable ^a	Not calculable ^a	Not calculable ^a	Not calculable
	Akbik, 2006 ¹⁰⁹	Score ≥8: 0.68 (95% CI 0.52 to 0.81)	Score ≥8: 0.38 (95% CI 0.29 to 0.49)	Score ≥8: 1.11 (95% CI 0.86 to 1.43)	Score ≥8: 0.83 (95% CI 0.50 to 1.36)	Not reported

^aRetrospective study; only patients who had discontinued opioids due to aberrant drug-related behavior were included.

Abbreviations: CI=confidence interval, DIRE= Diagnosis Intractability Risk and Efficacy Inventory, ORT= Opioid Risk Tool, PMQ=Pain Medication Questionnaire, SOAPP= Screening and Opioid Assessment for Patients with Pain, SOAPP-R=Screening and Opioid Assessment for Patients with Pain-Revised.

Key Question 4b

In patients with chronic pain, what is the effectiveness of use of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse?

Key Points

- No study evaluated the effectiveness of risk prediction instruments for reducing outcomes related to overdose, addiction, abuse, or misuse (SOE: Insufficient).

Detailed Synthesis

The APS review identified no studies on the effectiveness of risk prediction instruments in reducing outcomes related to overdose, addiction abuse or misuse. We also did not identify any studies published since the APS review addressing this question.

Key Question 4c

In patients with chronic pain prescribed long-term opioid therapy, what is the effectiveness of risk mitigation strategies, including (1) opioid management plans, (2) patient education, (3) urine drug screening, (4) use of prescription drug monitoring program data, (5) use of monitoring instruments, (6) more frequent monitoring intervals, (pill counts, and (8) use of abuse-deterring formulations on outcomes related to overdose, addiction, abuse, or misuse?

Key Points

- No study evaluated the effectiveness of risk mitigation strategies for improving outcomes related to overdose, addiction, abuse, or misuse (SOE: Insufficient).

Detailed Synthesis

Like the APS review, we identified no study on the effectiveness of various risk mitigation strategies for improving outcomes related to overdose, addiction, abuse, or misuse.

Key Question 4d

What is the comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids on outcomes related to overdose, abuse, misuse, pain, function, and quality of life?

Key Points

- No study evaluated the comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids (SOE: Insufficient).

Detailed Synthesis

Like the APS review, we identified no study on the comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids. Short-term randomized trials generally excluded patients with a past or current history of addiction.

Discussion

Key Findings and Strength of Evidence

The key findings of this review are summarized in the summary of evidence table (Table 6 below) and the factors used to determine the overall SOE grades are summarized in Appendix G. For a number of Key Questions, we identified no studies meeting inclusion criteria. For Key Questions where studies were available, the SOE was rated no higher than low, due to small numbers of studies and methodological shortcomings, with the exception of buccal or intranasal fentanyl for pain relief outcomes within 2 hours after dosing, for which the SOE was rated moderate.

For effectiveness and comparative effectiveness, we identified no studies of long-term opioid therapy in patients with chronic pain versus no opioid therapy or nonopioid alternative therapies that evaluated outcomes at 1 year or longer. No studies examined how effectiveness varies based on various factors, including type of pain and patient characteristics. Most placebo-controlled randomized trials were shorter than 6 weeks in duration⁴⁴ and no cohort studies on the effects of long-term opioid therapy versus no opioid therapy on outcomes related to pain, function, or quality of life were found. Although uncontrolled studies of patients prescribed opioids are available,⁸ findings are difficult to interpret due to the lack of a nonopioid comparison group.

Regarding harms, new evidence (published since the APS review) from observational studies suggests that being prescribed long-term opioids for chronic pain is associated with increased risk of abuse,⁴⁸ overdose,⁶¹ fractures,^{18, 71} and myocardial infarction,⁸⁰ versus not currently being prescribed opioids. In addition, several recent studies suggest that the risk is dose-dependent, with higher opioid doses associated with increased risk.^{11, 18, 48, 61, 79, 84} Although two studies found an association between opioid dose and increased risk of overdose starting at relatively low doses (20 to 49 mg MED/day), estimates at higher doses were variable (adjusted HR 11.18 at >100 mg MED/day versus adjusted OR 2.88 for ≥200 mg MED/day).^{61, 84} However, few studies evaluated each outcome and the population evaluated and duration of opioid therapy were not always well characterized. In addition, as in all observational studies, findings are susceptible to residual confounding despite use of statistical adjustment and other techniques such as matching. A study also found long-term opioid therapy associated with increased likelihood of receiving prescriptions for erectile dysfunction or testosterone, which may be markers for sexual dysfunction due to presumed endocrinological effects of opioids.¹¹ However, it did not directly measure sexual dysfunction, and patients may seek or receive these medications for other reasons.

No study assessed the risk of abuse, addiction, or related outcomes associated with long-term opioid therapy use versus placebo or no opioid therapy. In uncontrolled studies, rates of abuse and related outcomes varied substantially, even after restricting inclusion to studies that evaluated patients on opioid therapy for at least one year and used pre-defined methods for ascertaining these outcomes, and stratifying studies according to whether they evaluated primary care populations or patients evaluated in pain clinic settings.^{46, 49-58} An important reason for the variability in estimates is differences in patient samples and in how terms such as addiction, abuse, misuse, and dependence were defined in the studies, and in methods used to identify these outcomes (e.g., formal diagnostic interview with patients versus chart review or informal assessment). In one study, estimates of opioid misuse were lower based on independent review than based on assessments by the treating physician.⁵⁷ No study evaluated patients with “opioid use disorder” as recently defined in the new DSM-V.⁵⁹

Evidence on the effectiveness of different opioid dosing strategies is also extremely limited. One new trial of a more liberal dose escalation strategy versus maintenance of current doses found no differences in outcomes related to pain, function, or risk of withdrawal from the study due to opioid misuse, but the difference in opioid doses between groups at the end of the trial was small (52 versus 40 mg MED/day).⁹⁹ One study from Washington State reported a decrease in the number of opioid-associated overdose deaths after implementing a dose threshold,¹¹⁵ but did not meet inclusion criteria for this review because it was an ecological, before-after study, and it is not possible to reliably determine whether changes in the number of opioid overdose deaths were related to other factors that could have impacted opioid prescribing practices. Evidence on benefits and harms of different methods for initiating and titrating opioids, short-versus long-acting opioids, scheduled and continuous versus as-needed dosing of opioids, use of opioid rotation, and methods for titrating or discontinuing patients off opioids was not available or too limited to reach reliable conclusions.

We also found limited evidence on the comparative benefits and harms of specific opioids. Three head-to-head trials found few differences in pain relief between various long-acting opioids at 1 year followup,^{43, 96, 97} but the usefulness of these studies for evaluating comparative effectiveness may be limited because patients in each arm had doses titrated to achieve adequate pain control. None of the trials was designed to evaluate abuse, addiction, or related outcomes.

Methadone has been an opioid of particular interest because it is disproportionately represented in case series and epidemiological studies of opioid-associated deaths.¹¹⁶ Characteristics of methadone that may be associated with increased risk of serious harms are its long and variable half-life, which could increase the risk for accidental overdose, and its association with electrocardiographic QTc interval prolongation, which could increase the risk of potentially life-threatening ventricular arrhythmia.¹¹⁷ However, the highest-quality observational study, which was conducted in VA patients with chronic pain and controlled well for confounders using a propensity-adjusted analysis, found methadone to be associated with lower risk of mortality as compared with sustained-release morphine.⁹⁸ These results suggest that in some settings, methadone may not be associated with increased mortality risk, though research is needed to understand the factors that contribute to safer prescribing in different clinical settings.

Although five randomized trials found buccal or intranasal fentanyl more effective than placebo or oral opioids for treating acute exacerbations of chronic pain, all focused on short-term treatment and immediate outcomes in the minutes or hours after administration.¹⁰⁰⁻¹⁰⁴ No study was designed to assess long-term benefits or harms, including accidental overdose, abuse, or addiction. In 2007, the U.S. FDA released a public health advisory due to case reports of deaths and other life-threatening adverse effects in patients prescribed buccal fentanyl.¹¹⁸

Evidence also remains limited on the utility of opioid risk assessment instruments, used prior to initiation of opioid therapy, for predicting likelihood of subsequent opioid abuse or misuse. In three studies of the ORT, estimates were extremely inconsistent (sensitivity ranged from 0.20 to 0.99).^{110, 114, 119} A study that directly compared the accuracy of the ORT and two other risk assessment instruments reported weak likelihood ratios for predicting future abuse or misuse (PLR 1.27 to 1.65 and NLR 0.86 to 0.91).¹¹⁹ Risk prediction instruments other than the ORT (such as the SOAPP version 1, revised SOAPP, or DIRE) were only evaluated in one or two studies, and require further validation. Studies on the accuracy of risk instruments for identifying aberrant behavior in patients already prescribed opioids are available,^{51, 54, 112, 119-125} but were outside the scope of this review.

No study evaluated the effectiveness of risk mitigation strategies, such as use of risk assessment instruments, opioid management plans, patient education, urine drug screening, prescription drug monitoring program data, monitoring instruments, more frequent monitoring intervals, pill counts, or abuse-deterring formulations on outcomes related to overdose, addiction, abuse or misuse. Studies on effects of risk mitigation strategies were primarily focused on ability to detect misuse (e.g., urine drug testing and prescription monitoring program data) or on effects on markers of risky prescribing practices or medication-taking behaviors,¹²⁶ and did not meet inclusion criteria for this review, which focused on effects on clinical outcomes. One study found that rates of poison center treatment incidents and opioid-related treatment admissions increased at a lower rate in States with a prescription drug monitoring program than in States without one, but used an ecological design, did not evaluate a cohort of patients prescribed opioids for chronic pain, and was not designed to account for other factors that could have impacted opioid prescribing practices.¹²⁶

Although evidence indicates that patients with a history of substance abuse or at higher risk for abuse or misuse due to other risk factors are more likely to be prescribed opioids than patients without these risk factors,¹²⁷⁻¹³⁰ we identified no study on the effectiveness of methods for mitigating potential harms associated with long-term opioid therapy in high-risk patients.

Table 6. Summary of evidence

Key Question Outcome	Strength of Evidence Grade	Conclusion
1. Effectiveness and comparative effectiveness		
a. In patients with chronic pain, what is the effectiveness of long-term opioid therapy versus placebo or no opioid therapy for long-term (≥ 1 year) outcomes related to pain, function, and quality of life?		
Pain, function, quality of life	Insufficient	No study of opioid therapy versus placebo or no opioid therapy evaluated long-term (≥ 1 year) outcomes related to pain, function, or quality of life
b. How does effectiveness vary depending on: 1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including low back pain], fibromyalgia, sickle cell disease, inflammatory pain, and headache disorders); 2) patient demographics (e.g., age, race, ethnicity, gender); 3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities and high risk for addiction)?		
Pain, function, quality of life	Insufficient	No studies
c. In patients with chronic pain, what is the comparative effectiveness of opioids versus nonopioid therapies (pharmacological or nonpharmacological) on outcomes related to pain, function, and quality of life?		

Table 6. Summary of evidence (continued)

Key Question Outcome	Strength of Evidence Grade	Conclusion
Pain, function, quality of life	Insufficient	No studies
Key Question Outcome	Strength of Evidence Grade	Conclusion
d. In patients with chronic pain, what is the comparative effectiveness of opioids plus nonopioid interventions (pharmacological or nonpharmacological) versus opioids or nonopioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used?		
Pain, function, quality of life	Insufficient	No studies
2. Harms and adverse events		
a. In patients with chronic pain, what are the risks of opioids versus placebo or no opioid on: 1) opioid abuse, addiction, and related outcomes; 2) overdose; and 3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?		
Abuse, addiction	Low	No randomized trial evaluated risk of opioid abuse, addiction, and related outcomes in patients with chronic pain prescribed opioid therapy. One retrospective cohort study found prescribed long-term opioid use associated with significantly increased risk of abuse or dependence versus no opioid use.
Abuse, addiction	Insufficient	In 10 uncontrolled studies, estimates of opioid abuse, addiction, and related outcomes varied substantially even after stratification by clinic setting
Overdose	Low	Current opioid use was associated with increased risk of any overdose events (adjusted HR 5.2, 95% CI 2.1 to 12) and serious overdose events (adjusted HR 8.4, 95% CI 2.5 to 28) versus current nonuse
Fractures	Low	Opioid use associated with increased risk of fracture in 1 cohort study (adjusted HR 1.28, 95% CI 0.99 to 1.64) and 1 case-control study (adjusted OR 1.27, 95% CI 1.21 to 1.33)
Myocardial infarction	Low	Current opioid use associated with increased risk of myocardial infarction versus nonuse (adjusted OR 1.28, 95% CI 1.19 to 1.37 and incidence rate ratio 2.66, 95% CI 2.30 to 3.08)
Endocrine	Low	Long-term opioid use associated with increased risk of use of medications for erectile dysfunction or testosterone replacement versus nonuse (adjusted OR 1.5, 95% CI 1.1 to 1.9)

Table 6. Summary of evidence (continued)

Key Question Outcome	Strength of Evidence Grade	Conclusion
Gastrointestinal harms, motor vehicle accidents, infections, psychological harms, cognitive harms	Insufficient	No studies
b. How do harms vary depending on: 1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including back pain], fibromyalgia, sickle cell disease, inflammatory pain, headache disorders); 2) patient demographics; 3) patient comorbidities (including past or current substance use disorder or at high risk for addiction)?		
Various harms	Insufficient	No studies
b. How do harms vary depending on the dose of opioids used?		
Abuse, addiction	Low	One retrospective cohort study found higher doses of long-term opioid therapy associated with increased risk of opioid abuse or dependence than lower doses. Compared to no opioid prescription, the adjusted odds ratios were 15 (95 percent CI 10 to 21) for 1-36 MED/day, 29 (95 percent CI 20 to 41) for 36-120 MED/day, and 122 (95 percent CI 73 to 205) for \geq 120 MED/day.
Overdose	Low	Versus 1 to 19 mg MED/day, 1 cohort study found an adjusted HR for an overdose event of 1.44 (95% CI 0.57 to 3.62) for 20 to 49 mg MED/day that increased to 11.18 (95% CI 4.80 to 26.03) at $>$ 100 mg MED/day; 1 case-control study found an adjusted OR for an opioid-related death of 1.32 (95% CI 0.94 to 1.84) for 20 to 49 mg MED/day that increased to 2.88 (95% CI 1.79 to 4.63) at \geq 200 mg MED/day
Fracture	Low	Risk of fracture increased from an adjusted HR of 1.20 (95% CI 0.92 to 1.56) at 1 to $<$ 20 mg MED/day to 2.00 (95% CI 1.24 to 3.24) at \geq 50 mg MED/day; the trend was of borderline statistical significance
Myocardial infarction	Low	Relative to a cumulative dose of 0 to 1350 mg MED over 90 days, the incidence rate ratio for myocardial infarction for 1350 to $<$ 2700 mg was 1.21 (95% CI 1.02 to 1.45), for 2700 to $<$ 8100 mg was 1.42 (95% CI 1.21 to 1.67), for 8100 to $<$ 18,000 mg was 1.89 (95% CI 1.54 to 2.33), and for $>$ 18,000 mg was 1.73 (95% CI 1.32 to 2.26)
Motor vehicle accidents	Low	No association between opioid dose and risk of motor vehicle accidents
Endocrine	Low	Relative to 0 to $<$ 20 mg MED/day, the adjusted OR for daily opioid dose of \geq 120 mg MED/day for use of medications for erectile dysfunction or testosterone replacement was 1.6 (95% CI 1.0 to 2.4)

Table 6. Summary of evidence (continued)

Key Question Outcome	Strength of Evidence Grade	Conclusion
3. Dosing strategies		
a. In patients with chronic pain, what is the comparative effectiveness of different methods for initiating and titrating opioids for outcomes related to pain, function, and quality of life; risks of overdose, addiction, abuse, or misuse; and doses of opioids used?		
Pain	Insufficient	Evidence from three trials on effects of titration with immediate-release versus sustained-release opioids reported inconsistent results on outcomes related to pain and are difficult to interpret due to additional differences between treatment arms in dosing protocols (titrated vs. fixed dosing) and doses of opioids used
Function, quality of life, outcomes related to abuse	Insufficient	No studies
b. In patients with chronic pain, what is the comparative effectiveness of short- versus long-acting opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?		
Pain, function, quality of life, outcomes related to abuse	Insufficient	No studies
c. In patients with chronic pain, what is the comparative effectiveness of different long-acting opioids on outcomes related to pain, function, and quality of life; and risk of overdose, addiction, abuse, or misuse?		
Pain and function	Low	No difference between various long-acting opioids
Assessment of risk of overdose, addiction, abuse, or misuse	Insufficient	No studies were designed to assess risk of overdose, addiction, abuse, or misuse
Overdose (as indicated by all-cause mortality)	Low	One cohort study found methadone to be associated with lower all-cause mortality risk than sustained-release morphine in a propensity adjusted analysis
Abuse and related outcomes	Insufficient	Another cohort study found some differences between long-acting opioids in rates of adverse outcomes related to abuse, but outcomes were nonspecific for opioid-related adverse events, precluding reliable conclusions
d. In patients with chronic pain, what is the comparative effectiveness of short- plus long-acting opioids vs. long-acting opioids alone on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?		
Pain, function, quality of life, outcomes related to abuse	Insufficient	No studies
e. In patients with chronic pain, what is the comparative effectiveness of scheduled, continuous versus as-needed dosing of opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?		

Table 6. Summary of evidence (continued)

Key Question Outcome	Strength of Evidence Grade	Conclusion
Pain, function, quality of life, outcomes related to abuse	Insufficient	No studies
f. In patients with chronic pain on long-term opioid therapy, what is the comparative effectiveness of dose escalation versus dose maintenance or use of dose thresholds on outcomes related to pain, function, and quality of life?		
Pain, function, withdrawal due to opioid misuse	Low	No difference between more liberal dose escalation versus maintenance of current doses in pain, function, or risk of withdrawal due to opioid misuse, but there was limited separation in opioid doses between groups (52 vs. 40 mg MED/day at the end of the trial)
g. In patients on long-term opioid therapy, what is the comparative effectiveness of opioid rotation versus maintenance of current opioid therapy on outcomes related to pain, function, and quality of life; and doses of opioids used?		
Pain, function, quality of life, outcomes related to abuse	Insufficient	No studies
h. In patients on long-term opioid therapy, what is the comparative effectiveness of different strategies for treating acute exacerbations of chronic pain on outcomes related to pain, function, and quality of life?		
Pain	Moderate	Two randomized trials found buccal fentanyl more effective than placebo for treating acute exacerbations of pain and three randomized trials found buccal fentanyl or intranasal fentanyl more effective than oral opioids for treating acute exacerbations of pain in patients on long-term opioid therapy, based on outcomes measured up to 2 hours after dosing
Abuse and related outcomes	Insufficient	No studies
i. In patients on long-term opioid therapy, what are the effects of decreasing opioid doses or of tapering off opioids versus continuation of opioids on outcomes related to pain, function, quality of life, and withdrawal?		
Pain, function	Insufficient	Abrupt cessation of morphine was associated with increased pain and decreased function compared to continuation of morphine
j. In patients on long-term opioid therapy, what is the comparative effectiveness of different tapering protocols and strategies on measures related to pain, function, quality of life, withdrawal symptoms, and likelihood of opioid cessation?		
Opioid abstinence	Insufficient	No clear differences between different methods for opioid discontinuation or tapering in likelihood of opioid abstinence after 3 to 6 months

Table 6. Summary of evidence (continued)

Key Question Outcome	Strength of Evidence Grade	Conclusion
4. Risk assessment and risk mitigation strategies		
a. In patients with chronic pain being considered for long-term opioid therapy, what is the accuracy of instruments for predicting risk of opioid overdose, addiction, abuse, or misuse?		
Diagnostic accuracy: Opioid Risk Tool	Insufficient	Based on a cutoff of >4, three studies (one poor-quality, two poor-quality) reported very inconsistent estimates of diagnostic accuracy, precluding reliable conclusions
Diagnostic accuracy: Screening and Opioid Assessment for Patients with Pain (SOAPP) version 1	Low	Based on a cutoff score of ≥8, sensitivity was 0.68 and specificity of 0.38 in 1 study, for a PLR of 1.11 and NLR of 0.83. Based on a cutoff score of >6, sensitivity was 0.73 in 1 study.
b. In patients with chronic pain, what is the effectiveness of use of risk prediction instruments on outcomes related to overdose, addiction, abuse, or misuse?		
Outcomes related to abuse	Insufficient	No study evaluated the effectiveness of risk prediction instruments for reducing outcomes related to overdose, addiction, abuse, or misuse
c. In patients with chronic pain prescribed long-term opioid therapy, what is the effectiveness of risk mitigation strategies, including 1) opioid management plans, 2) patient education, 3) urine drug screening, 4) use of prescription drug monitoring program data, 5) use of monitoring instruments, 6) more frequent monitoring intervals, 7) pill counts, and 8) use of abuse-deterring formulations on outcomes related to overdose, addiction, abuse, or misuse?		
Outcomes related to abuse	Insufficient	No studies
d. What is the comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids on outcomes related to overdose, abuse, misuse, pain, function, and quality of life?		
Outcomes related to abuse	Insufficient	No studies

Abbreviations: CI=confidence interval, HR=hazard ratio, MED=morphine equivalent dose, NLR=negative likelihood ratio,

OR=odds ratio,

PLR=positive likelihood ratio, SOAPP=Screening and Opioid Assessment for Patients with Pain.

Findings in Relationship to What is Already Known

Our findings are generally consistent with prior systematic reviews of opioid therapy for chronic pain that also found no long-term, placebo-controlled randomized trials.^{8,44} One systematic review of outcomes associated with long-term opioid therapy concluded that many patients discontinue treatment due to adverse events or insufficient pain relief, though patients who continue opioid therapy experience clinically significant pain relief.⁸ However, results of the studies included in this review are difficult to interpret because the studies had no nonopioid therapy control group, reported substantial between-study heterogeneity, and were susceptible to potential attrition and selection bias. Our findings are also consistent with a systematic review on comparative benefits and harms of various long-acting opioids and

short- versus long-acting opioids, which found no clear differences, primarily based on short-term randomized trials.¹³¹

Our review reported rates of abuse and related outcomes that are higher than a previously published systematic review of long-term opioid therapy that reported a very low rate of opioid addiction (0.27 percent).⁸ Factors that may explain this discrepancy are that the prior review included studies that did not report predefined methods for ascertaining opioid addiction, potentially resulting in underreporting, and primarily included studies that excluded high-risk patients. Like a previous systematic review, we found variability in estimates of abuse and related outcomes, with some potential differences in estimates based on clinical setting (primary care versus pain clinic) and patient characteristics (e.g., exclusion of high-risk patients).¹³²

Regarding risk mitigation strategies, our findings were similar to a previously published systematic review that found weak evidence with which to evaluate risk prediction instruments.¹³³ Unlike our review, which found no evidence on effects of risk mitigation strategies on risk of abuse, addiction, or related outcomes, a previously published review found use of opioid management plans and urine drug screens to be associated with decreased risk of misuse behaviors.¹⁴ However, this conclusion was based on four studies that did not meet inclusion criteria for our review because effects of opioid management plans and urine drug screens could not be separated from other concurrent opioid prescribing interventions,^{134, 135} use of a historical control group,^{136, 137} or before-after study design.¹³⁴

Applicability

A number of issues could impact the applicability of our findings. One challenge was difficulty in determining whether studies focused on patients with chronic pain. Although a number of large observational studies reported harms based on analyses of administrative databases, they were frequently limited in their ability to assess important clinical factors such as the duration or severity of pain. For some of these studies, we inferred the presence of chronic pain from prescribing data, such as the number of prescriptions over a defined period or the use of long-acting opioid preparations. Some potentially relevant studies were excluded because it was not possible to determine whether the sample evaluated had chronic pain or received long-term therapy.^{16, 74-78, 85}

Another issue that could impact applicability is the type of opioid used in the studies. Both long-acting and short-acting opioids are often prescribed for chronic pain. In some studies, use of short-acting opioids predominated.^{11, 18, 84} Results of studies of short-acting opioids may not generalize to patients prescribed long-acting opioids.

Selection of patients could also impact applicability. The few randomized trials that met inclusion criteria typically excluded patients at high risk of abuse or misuse and frequently used run-in periods prior to allocating treatments. The use of a run-in period preselects patients who respond to and tolerate initial exposure to the studied treatment. Therefore, benefits observed in the trials might be greater and harms lower than seen in actual clinical practice.¹³⁸

Another factor impacting applicability is that most trials were not designed or powered to assess risk of abuse, addiction, or related outcomes. For example, trials of buccal fentanyl for acute exacerbations of chronic pain focused exclusively on immediate (episode-based) outcomes and were not designed to assess long-term outcomes, including outcomes related to the potential for abuse.¹⁰⁰⁻¹⁰⁴ Long-term head-to-head trials of long-acting opioids excluded patients at high risk for these outcomes and reported no events.^{43, 96, 97}

The setting in which studies were conducted could also impact applicability. As noted in other sections of this report, rates of overdose, abuse, addiction, and related outcomes are likely to vary based on the clinical setting. Therefore, we stratified studies reporting rates of abuse according to whether they were performed in primary care or pain clinic settings. The highest-quality comparative study of methadone versus another opioid (long-acting morphine) found decreased mortality risk but was conducted in a VA setting,⁹⁸ which could limit applicability to other settings, due to factors such as how clinicians were trained in methadone use, policies on opioid prescribing, availability of resources to manage opioid prescribing, or other factors.

Implications for Clinical and Policy Decisionmaking

Our review has important implications for clinical and policy decisionmaking. Based on our review, most clinical and policy decisions regarding use of long-term opioid therapy must necessarily still be made on the basis of weak or insufficient evidence. This is in accordance with findings from a 2009 U.S. guideline on use of opioids for chronic pain, which found 21 of 25 recommendations supported by only low-quality evidence,¹⁰⁸ and a 2010 Canadian guideline,¹³⁹ which classified 3 of 24 recommendations as based on (short-term) randomized trials and 19 recommendations as based solely or partially on consensus opinion. Although randomized trials show short-term, moderate improvements in pain in highly selected, low-risk populations with chronic pain, such efficacy-based evidence is of limited usefulness for informing long-term opioid prescribing decisions in clinical practice.

Given the marked increase in numbers of overdose deaths and other serious adverse events that have occurred following the marked increase in opioid prescribing for chronic pain, recent policy efforts have focused on safer prescribing of opioids. A recent review of opioid guidelines found broad agreement regarding a number of risk mitigation strategies despite weak evidence, such as risk-assessment guided patient assessment for opioid therapy, urine drug testing, use of prescription monitoring program data, abuse-deterrent formulations, and opioid management plans.¹⁴⁰ Based on low-quality evidence regarding harms associated with long-term opioid therapy, our review provides some limited support for clinical policy efforts aimed at reducing harms. One area in which there has been less agreement across guidelines is whether dose thresholds that warrant more intense monitoring or used to define maximum ceiling doses should be implemented, and if so, what is the appropriate threshold. Some evidence is now available on dose-dependent harms associated with opioids,^{61, 84} which could help inform policies related to dose thresholds. However, research on the effects of implementing dose thresholds on clinical outcomes is limited to a single ecological study.¹¹⁵ In addition, although two observational studies were consistent in reporting a relationship between higher opioid dose and risk of overdose, estimates were highly variable at similar doses.^{61, 84} This makes it difficult to determine an optimal maximum dose threshold based on an objective parameter, such as a dose inflection point where risk rises markedly. Other studies have begun to characterize cardiovascular, endocrinological, and injury-related harms associated with long-term opioid therapy and could be used to inform clinical decisions, though using such information in balanced assessments to inform clinical and policy decision-making remains a challenge given the lack of evidence regarding long-term benefits.

Limitations of the Review Process

We excluded non-English language articles and did not search for studies published only as abstracts. We did not attempt meta-analysis or assess for publication bias using graphical or statistical methods to detect small sample effects due to the paucity of evidence. Although we

found no evidence of unpublished studies through searches on clinical trial registries and regulatory documents and solicitation of unpublished studies through SIP requests, the usefulness of such methods for identifying unpublished observational studies may be limited, as such studies are often not registered. We identified no unpublished randomized trials meeting inclusion criteria. We focused on studies that reported outcomes after at least one year of opioid therapy, though applying a shorter duration threshold for inclusion could have provided additional evidence. However, we identified no placebo-controlled trials of opioid therapy for at least 6 months.

Limitations of the Evidence Base

As noted previously, the critical limitation of our review is the lack of evidence in the target population (patients with chronic pain) and intervention (long-term opioid therapy), despite broadening of inclusion criteria to incorporate studies in which we assumed that patients were being treated for chronic pain due to the type of opioid prescribed (long-acting opioid) or number of prescriptions. We were also unable to determine how benefits and harms vary in subgroups, such as those defined by demographic characteristics, characteristics of the pain condition, and other patient characteristics (e.g., medical or psychological comorbidities). Due to the lack of evidence and methodological shortcomings in the available studies, no body of evidence (with

the exception of buccal or intranasal fentanyl for immediate pain relief) was rated higher than low, meaning that conclusions are highly uncertain.

Research Gaps

Many research gaps limit the full understanding of the effectiveness, comparative effectiveness, and harms of long-term opioid therapy, as well as of the effectiveness of different dosing methods and risk mitigation strategies, and effectiveness in special populations. Longer-term studies of patients clearly with chronic pain comparing those who are prescribed long-term opioid therapy with those receiving other pharmacological and non-pharmacological therapies are needed. Studies that include higher-risk patients, commonly treated with opioids in clinical practice, and that measure multiple important outcomes, including pain, physical and psychological functioning, as well as misuse and abuse, would be more helpful than efficacy studies focused solely on pain intensity. Greater standardization of methods for defining and identifying abuse-related outcomes in studies that report these outcomes are needed. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group recently issued recommendations on measuring abuse liability in analgesic clinical trials.¹⁴¹

Additional research is also needed to develop and validate risk prediction instruments, and to determine how using them impacts treatment decisions and, ultimately, patient outcomes. More research is needed on the comparative benefits and harms of different opioids or formulations and different prescribing methods. Studies comparing effectiveness and harms of methadone versus other long-acting opioids, to determine if findings from a study⁹⁸ conducted in a VA setting are reproducible in other settings, and to better understand factors associated with safer methadone prescribing.

Research is also needed to understand the effects of risk mitigation strategies such as urine drug screening, use of prescription drug monitoring program data, and abuse-deterrent formulations on clinical outcomes such as rates of overdose, abuse, addiction, and misuse. In one before-after study, the introduction of an abuse-deterrent opioid was followed by patients

switching to other prescription opioids or illicit opioids,¹⁴² underscoring the need for research to understand both the positive and negative clinical effects of risk mitigation strategies.

Long-term randomized trials of opioid therapy are difficult to implement due to attrition, challenges in recruitment, or ethical factors (e.g., long-term allocation of patients with pain to placebo or allocation to non-use of risk mitigation strategies recommended in clinical practice guidelines). Nonetheless, pragmatic and other non-traditional randomized trial approaches could be used to address these challenges.¹⁴³ Observational studies could also help address a number of these research questions, but should be specifically designed to evaluate patients with chronic pain prescribed long-term opioid therapy and appropriately measure and address potential confounders. Well-designed clinical registries that enroll patients with chronic pain prescribed and not prescribed chronic opioids could help address the limitations of studies based solely or primarily on administrative databases, which are often unable to fully characterize the pain condition (e.g., duration, type, and severity) or other clinical characteristics and frequently do not have information regarding outcomes related to pain, function, and quality of life. Such registry studies could be designed to extend the observations from randomized trials of opioids versus placebo or other treatments, but would differ from currently available studies by following patients who discontinue or do not start opioids, in addition to those who continue on or start opioid therapy.

Conclusions

Evidence on long-term opioid therapy for chronic pain is very limited, but suggests an increased risk of serious harms that appears to be dose-dependent. Based on our review, most clinical and policy decisions regarding use of long-term opioid therapy must necessarily still be made on the basis of weak or insufficient evidence. More research is needed to understand long-term benefits, risk of abuse and related outcomes, and effectiveness of different opioid prescribing methods and risk mitigation strategies.

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Abbreviations and Acronyms

AUROC	area under receiver operating characteristic curve
ASA	aspirin
ASI	Addiction Severity Index
APS	American Pain Society
BID	twice daily
CI	confidence interval
CIDI	Composite International Diagnostic Interview
CR	controlled release
DASS21	Depression, Anxiety, and Stress Scale-21 Items
DIRE	Diagnosis, Intractability, Risk, and Efficacy Inventory
DSM-V	Diagnostic and Statistical Manual, Fourth Edition DSM-
IV	Diagnostic and Statistical Manual, Fifth Edition
ER	extended release
GC/M	gas chromatography mass spectrometry
HR	hazard ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems Version 10 IRR
	incidence rate ratio
ITT	intent to treat
MED	morphine equivalent dose
MS	long-acting morphine sulfate
NA	not applicable
NLR	negative likelihood ratio
NR	not reported
NSAID	nonsteroidal anti-inflammatory drug
ODI	Oswestry Disability Index
OR	odds ratio
ORT	Opioid Risk Tool
PDI	Physical Disability Index
PDUQ	Prescription Drug Use Questionnaire
PLR	positive likelihood ratio
PMQ	Pain Medication Questionnaire
POTQ	Prescription Opioid Therapy Questionnaire
RCT	randomized controlled trial
SE	standard error
SDSS	Dependence Severity Scale
SOAPP	Screening and Opioid Assessment for Patients with Pain
SOAPP-R	Screening and Opioid Assessment for Patients with Pain-Revised
SOE	strength of evidence
SUQ	Self-report Substance Use Questionnaire
TDB	transdermal buprenorphine
TDF	transdermal fentanyl
U.S.	United States
UDT	urine drug test
VA	Veterans Affairs
VAS	Visual Analogue Scale

Appendix A. Search Strategies

Database: Ovid MEDLINE(R) Without Revisions

KQ 1 and 2: Comparative Effectiveness and Harms

1. exp Analgesics, Opioid/
2. opioid*.mp.
3. (alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. exp Chronic Pain/
6. (chronic adj2 pain).mp.
7. 5 or 6
8. 4 and 7
9. limit 8 to yr="2008 - 2013"
10. limit 9 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or multicenter study or randomized controlled trial)
11. 9 and random\$.mp.
12. 10 or 11

KQ 2a: Supplemental Search – Abuse and Addiction Detection

1. Analgesics, Opioid/
2. 1 and 2
3. Substance Abuse Detection/
4. Opioid-Related Disorders/ or Substance-Related Disorders/
5. 3 and (4 or 5)
6. (chronic adj3 pain).mp.
7. 1 and 7
8. 8 not 3
9. 9 and (4 or 5)
10. 6 or 10

KQ 3a-3g; 3i: Dosing Strategies

1. exp Analgesics, Opioid/
2. opioid*.mp. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or

phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.

3. or/1-3
4. Opioid-Related Disorders/
5. (opioid adj2 (abuse or addict* or misuse or diversion)).mp.
6. Drug Administration Schedule/
7. Pain Management/
8. Clinical Protocols/
9. Breakthrough Pain/
10. Dose-Response Relationship, Drug/
11. ((dose\$ or dosing) adj7 (strateg\$ or adjust\$ or titrat\$ or taper\$)).mp.
12. exp Chronic Pain/
13. (chronic adj2 pain).mp.
14. or/4-6
15. or/7-12
16. 15 and 16
17. (or/13-14) and 17
18. 18 and (random\$ or control\$ or trial or cohort or prospective or retrospective).mp.
19. limit 19 to yr="2008 - 2013"

KQ 3h: Dosing Strategies – Tapered Dosing

1. exp Analgesics, Opioid/
2. opioid*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. Opioid-Related Disorders/
6. (opioid adj2 (abuse or addict* or misuse or diversion)).mp.
7. Drug Administration Schedule/
8. Pain Management/
9. Clinical Protocols/
10. Breakthrough Pain/
11. Dose-Response Relationship, Drug/
12. ((dose\$ or dosing) adj7 (strateg\$ or adjust\$ or titrat\$ or taper\$)).mp.
13. exp Chronic Pain/
14. (chronic adj2 pain).mp.
15. or/4-6
16. or/7-12
17. 15 and 16
18. (or/13-14) and 17

19. 18 and (random\$ or control\$ or trial or cohort or prospective or retrospective).mp.
20. 19 and (taper\$ or decreas\$ or reduc\$).mp.
21. limit 20 to yr="1902 - 2007"

KQ 4a-4b: Risk Prediction

1. exp Analgesics, Opioid/
2. opioid*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. exp Chronic Pain/
6. (chronic adj2 pain).mp.
7. Opioid-Related Disorders/
8. (opioid adj2 (abuse or addict* or misuse or diversion)).mp.
9. 4 and (5 or 6)
10. 7 or 8
11. 9 or 10
12. Decision Support Techniques/
13. "Predictive Value of Tests"/
14. Prognosis/
15. Risk Assessment/
16. Risk Factors/
17. Proportional Hazards Models/
18. "Reproducibility of Results"/
19. "Sensitivity and Specificity"/
20. (sensitivity or specificity).mp.
21. (risk and (predict\$ or assess\$)).mp.
22. or/12-21
23. 11 and 22
24. limit 23 to yr="2008 - 2013"

KQ 4c: Risk Mitigation

1. exp Analgesics, Opioid/
2. opioid*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.

phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.

4. or/1-3
5. exp Chronic Pain/
6. (chronic adj2 pain).mp.
7. Opioid-Related Disorders/
8. (opioid adj2 (abuse or addict* or misuse or diversion)).mp.
9. 4 and (5 or 6)
10. 7 or 8
11. 9 or 10
12. Patient Compliance/
13. Health Services Misuse/
14. Substance Abuse Detection/
15. Drug Monitoring/
16. (urine adj7 (screen\$ or test\$ or detect\$)).mp.
17. (abus\$ or misus\$ or diversion\$ or divert\$).mp.
18. (opioid\$ adj7 (contract\$ or agree\$)).mp.
19. Contracts/
20. Patient Education as Topic/
21. Drug Overdose/
22. or/12-21
23. ((risk\$ adj7 mitigat\$) or reduc\$).mp.
24. ("risk evaluation and mitigation" or "rems").mp.
25. Risk Reduction Behavior/ or Risk/
26. or/23-25
27. 11 and 22 and 26
28. limit 27 to yr="2008 - 2013"

KQ 4d: Treatment Strategies

1. exp Analgesics, Opioid/
2. opioid*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. Opioid-Related Disorders/
6. (opioid adj2 (abuse or addict* or misuse or diversion)).mp.
7. Patient Compliance/
8. Health Services Misuse/
9. Substance Abuse Detection/
10. Drug Monitoring/

11. (urine adj7 (screen\$ or test\$ or detect\$)).mp.
12. (abus\$ or misus\$ or diversion\$ or divert\$).mp.
13. (opioid\$ adj7 (contract\$ or agree\$)).mp.
14. Contracts/
15. Patient Education as Topic/
16. Drug Overdose/
17. or/7-16
18. Substance Abuse Detection/
19. Opiate Substitution Treatment/
20. Risk Management/
21. or/18-20
22. or/4-6
23. 17 and 21 and 22
24. treatment outcome.mp. or Treatment Outcome/
25. (treatment and (strateg\$ or plan\$)).mp.
26. 23 and (24 or 25)

All KQs: Systematic Reviews

1. meta-analysis.mp. or exp Meta-Analysis/
2. (cochrane or medline).tw.
3. search\$.tw.
4. 1 or 2 or 3
5. "Review Literature as Topic"/ or systematic review.mp.
6. 4 or 5
7. exp Analgesics, Opioid/
8. opioid*.mp.
9. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or piriniramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
10. 10 (chronic and pain).mp.
11. or/7-9
12. 6 and 10 and 11
13. limit 12 to yr="2008 - 2013"

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

KQ 1 and 2: Comparative Effectiveness and Harms

1. exp Analgesics, Opioid/
2. opioid*.mp.

3. (alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. exp Chronic Pain/
6. (chronic adj2 pain).mp.
7. 5 or 6
8. 4 and 7
9. limit 8 to yr="2008 - 2013"

KQ 3a-3g, 3i: Dosing Strategies

1. exp Analgesics, Opioid/
2. opioid*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. Opioid-Related Disorders/
6. (opioid adj2 (abuse or addict* or misuse or diversion)).mp.
7. Drug Administration Schedule/
8. Pain Management/
9. Clinical Protocols/
10. Breakthrough Pain/
11. Dose-Response Relationship, Drug/
12. ((dose\$ or dosing) adj7 (strateg\$ or adjust\$ or titrat\$ or taper\$)).mp.
13. exp Chronic Pain/
14. (chronic adj2 pain).mp.
15. or/4-6
16. or/7-12
17. 15 and 16
18. (or/13-14) and 17
19. limit 18 to yr="2008 - 2013"

KQ 3h: Tapered Dosing

1. exp Analgesics, Opioid/
2. opioid*.mp.

3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. Opioid-Related Disorders/
6. (opioid adj2 (abuse or addict* or misuse or diversion)).mp.
7. Drug Administration Schedule/
8. Pain Management/
9. Clinical Protocols/
10. Breakthrough Pain/
11. Dose-Response Relationship, Drug/
12. ((dose\$ or dosing) adj7 (strateg\$ or adjust\$ or titrat\$ or taper\$)).mp.
13. exp Chronic Pain/
14. (chronic adj2 pain).mp.
15. or/4-6
16. or/7-12
17. 15 and 16
18. (or/13-14) and 17
19. 18 and (random\$ or control\$ or trial or cohort or prospective or retrospective).mp.
20. 19 and (taper\$ or decreas\$ or reduc\$).mp.
21. limit 20 to yr="1902 - 2007"

KQ 4a-b: Risk Prediction

1. exp Analgesics, Opioid/
2. opioid*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
4. or/1-3
5. exp Chronic Pain/
6. (chronic adj2 pain).mp.
7. Opioid-Related Disorders/
8. (opioid adj2 (abuse or addict* or misuse or diversion)).mp.
9. 4 and (5 or 6)
10. 7 or 8
11. 9 or 10

12. Decision Support Techniques/
13. "Predictive Value of Tests"/
14. Prognosis/
15. Risk Assessment/
16. Risk Factors/
17. Proportional Hazards Models/
18. "Reproducibility of Results"/
19. "Sensitivity and Specificity"/
20. (sensitivity or specificity).mp.
21. (risk and (predict\$ or assess\$)).mp.
22. or/12-21
23. 11 and 22
24. limit 23 to yr="2008 - 2013"

KQ 4c: Risk Mitigation

1. exp Analgesics, Opioid/
2. opioid*.mp.
3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphone or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. (20690)
4. or/1-3 (22725)
5. exp Chronic Pain/ (79)
6. (chronic adj2 pain).mp. (2585)
7. Opioid-Related Disorders/ (571)
8. (opioid adj2 (abuse or addict* or misuse or diversion)).mp. (116)
9. 4 and (5 or 6) (523)
10. 7 or 8 (630)
11. 9 or 10 (1139)
12. Patient Compliance/
13. Health Services Misuse/
14. Substance Abuse Detection/
15. Drug Monitoring/
16. (urine adj7 (screen\$ or test\$ or detect\$)).mp.
17. (abus\$ or misus\$ or diversion\$ or divert\$).mp.
18. (opioid\$ adj7 (contract\$ or agree\$)).mp.
19. Contracts/
20. Patient Education as Topic/
21. Drug Overdose/
22. or/12-21
23. ((risk\$ adj7 mitigat\$) or reduc\$).mp.
24. ("risk evaluation and mitigation" or "rems").mp.

- 25. Risk Reduction Behavior/ or Risk/
- 26. or/23-25
- 27. 11 and 22 and 26
- 28. limit 27 to yr="2008 - 2013"

KQ 4d: Treatment Strategies

- 1. exp Analgesics, Opioid/
- 2. opioid*.mp.
- 3. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
- 4. or/1-3
- 5. Opioid-Related Disorders/
- 6. (opioid adj2 (abuse or addict* or misuse or diversion)).mp.
- 7. Patient Compliance/
- 8. Health Services Misuse/
- 9. Substance Abuse Detection/
- 10. Drug Monitoring/
- 11. (urine adj7 (screen\$ or test\$ or detect\$)).mp.
- 12. (abus\$ or misus\$ or diversion\$ or divert\$).mp.
- 13. (opioid\$ adj7 (contract\$ or agree\$)).mp.
- 14. Contracts/
- 15. Patient Education as Topic/
- 16. Drug Overdose/
- 17. or/7-16
- 18. Substance Abuse Detection/
- 19. Opiate Substitution Treatment/
- 20. Risk Management/
- 21. or/18-20
- 22. or/4-6
- 23. 17 and 21 and 22
- 24. treatment outcome.mp. or Treatment Outcome/
- 25. (treatment and (strateg\$ or plan\$)).mp.
- 26. 23 and (24 or 25)

Database: PsycINFO

KQ 1 and 2: Comparative Effectiveness and Harms

- 1. opioid*.mp.
- 2. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or

dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.

3. (chronic and pain).mp.
4. (1 or 2) and 3
5. (random\$ or control\$ or trial or cohort or prospective or retrospective).mp.
6. 4 and 5
7. limit 6 to yr="2008 - 2014"
8. limit 7 to human

KQ 3a-3g, 3i: Dosing Strategies

1. opioid*.mp.
2. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
3. (chronic and pain).mp.
4. (1 or 2) and 3
5. 4 and (dose or dosing or dosage).mp.
6. limit 5 to human
7. limit 6 to yr="2008 - 2014"

KQ 3h: Tapered Dosing

1. opioid*.mp.
2. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
3. (chronic and pain).mp.
4. (1 or 2) and 3
5. 4 and (taper\$ or decreas\$).mp.
6. limit 5 to human

KQ 4a-4c: Risk Prediction and Mitigation

1. opioid*.mp.
2. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp.
3. (chronic and pain).mp.
4. (1 or 2) and 3
5. risk.mp.
6. 4 and
7. limit 6 to human
8. limit 7 to yr="2008 - 2014"

KQ 4d: Treatment Strategies

1. opioid*.mp
2. (alfentanil or alphaprodine or beta-casomorphins or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp
3. (chronic and pain).mp
4. (1 or 2) and 3
5. 4 and ((treatment and (strateg\$ or plan\$).mp
6. 5 and (overdose or abuse or misuse or pain or function or "quality of life" or "qol").mp
7. limit 6 to human

Database: EBSCO CINAHL Plus with Full Text

All Key Questions (except 3h, 4d)

1. (MH "Analgesics, Opioid") OR (MH "Narcotics") OR (MH "Alfentanil") OR "alfentanil" (MH "Alphaprodine") OR "alphaprodine" OR "beta-casomorphins" (MH "Buprenorphine") OR "buprenorphine" OR "carfentanil" (MH "Codeine") OR "codeine" OR (MH "Oxycodone") OR "deltorphin" OR (MH "Dextromethorphan") OR "dextromethorphan" OR "dezocine" OR "dihydrocodeine" OR "dihydromorphine" OR (MH "Enkephalins") OR "enkephalin" OR "ethylketocyclazocine" OR "ethylmorphine" "etorphine" OR (MH "Fentanyl") OR "fentanyl" (MH "Heroin") OR "heroin" "hydrocodone" OR (MH "Dihydromorphinone") OR "hydromorphone" OR "ketobemidone" OR "levorphanol" OR "lofentanil" OR (MH "Meperidine") OR

- "meperidine" OR "meptazinol" OR (MH "Methadone") OR "methadone" OR "methadyl acetate" OR (MH "Morphine") OR "morphine" OR (MH "Nalbuphine") OR (MH "Opium") OR "oxycodone" OR "oxymorphone" OR (MH "Pentazocine") OR "pentazocine" OR "phenazocine" OR "phenoperidine" OR "pirinitramide" OR "promedol" OR (MH "Propoxyphene") OR "propoxyphene" OR "remifentanil" OR (MH "Sufentanil") OR "sufentanil" OR "tilidine" OR (MH "Tapentadol") OR "tapentadol"
2. (MH "Chronic Pain") OR "chronic pain"
 3. 1 and 2
 4. "random*" OR "control*" OR "trial" OR "cohort" OR "prospective" OR "retrospective"
 5. 3 and 4
 6. Limit 4 to published date 20080101-20131015

KQ 3h: Tapered Dosing

1. (MH "Analgesics, Opioid") OR (MH "Narcotics") OR (MH "Alfentanil") OR "alfentanil" (MH "Alphaprodine") OR "alphaprodine" OR "beta-casomorphins" (MH "Buprenorphine") OR "buprenorphine" OR "carfentanil" (MH "Codeine") OR "codeine" OR (MH "Oxycodone") OR "deltorphin" OR (MH "Dextromethorphan") OR "dextromethorphan" OR "dezocine" OR "dihydrocodeine" OR "dihydromorphone" OR (MH "Enkephalins") OR "enkephalin" OR "ethylketocyclazocine" OR "ethylmorphine" "etorphine" OR (MH "Fentanyl") OR "fentanyl" (MH "Heroin") OR "heroin" "hydrocodone" OR (MH "Dihydromorphinone") OR "hydromorphone" OR "ketobemidone" OR "levorphanol" OR "lofentanil" OR (MH "Meperidine") OR "meperidine" OR "meptazinol" OR (MH "Methadone") OR "methadone" OR "methadyl acetate" OR (MH "Morphine") OR "morphine" OR (MH "Nalbuphine") OR (MH "Opium") OR "oxycodone" OR "oxymorphone" OR (MH "Pentazocine") OR "pentazocine" OR "phenazocine" OR "phenoperidine" OR "pirinitramide" OR "promedol" OR (MH "Propoxyphene") OR "propoxyphene" OR "remifentanil" OR (MH "Sufentanil") OR "sufentanil" OR "tilidine" OR (MH "Tapentadol") OR "tapentadol"
2. (MH "Chronic Pain") OR "chronic pain"
3. 1 and 2
4. "random*" OR "control*" OR "trial" OR "cohort" OR "prospective" OR "retrospective"
5. 3 and 4
6. "taper*" OR "decreas*"
7. 5 and 6
8. Limit 6 to published date 19920101-20071231

KQ 4d: Treatment Strategies

1. (MH "Analgesics, Opioid") OR (MH "Narcotics") OR (MH "Alfentanil") OR "alfentanil" (MH "Alphaprodine") OR "alphaprodine" OR "beta-casomorphins" (MH "Buprenorphine") OR "buprenorphine" OR "carfentanil" (MH "Codeine") OR "codeine" OR (MH "Oxycodone") OR "deltorphin" OR (MH "Dextromethorphan") OR "dextromethorphan" OR "dezocine" OR "dihydrocodeine" OR "dihydromorphone" OR (MH "Enkephalins") OR "enkephalin" OR "ethylketocyclazocine" OR "ethylmorphine" "etorphine" OR (MH "Fentanyl") OR "fentanyl" (MH "Heroin") OR "heroin" "hydrocodone" OR (MH "Dihydromorphinone") OR "hydromorphone" OR "ketobemidone" OR "levorphanol" OR "lofentanil" OR (MH "Meperidine") OR

- "meperidine" OR "meptazinol" OR (MH "Methadone") OR "methadone" OR "methadyl acetate" OR (MH "Morphine") OR "morphine" OR (MH "Nalbuphine") OR (MH "Opium") OR "oxycodone" OR "oxymorphone" OR (MH "Pentazocine") OR "pentazocine" OR "phenazocine" OR "phenoperidine" OR "pirinitramide" OR "promedol" OR (MH "Propoxyphene") OR "propoxyphene" OR "remifentanil" OR (MH "Sufentanil") OR "sufentanil" OR "tilidine" OR (MH "Tapentadol") OR "tapentadol"
2. (MH "Chronic Pain") OR "chronic pain"
 3. 1 and 2
 4. "random*" OR "control*" OR "trial" OR "cohort" OR "prospective" OR "retrospective"
 5. 3 and 4
 6. "treatment" AND ("strateg*" OR "plan*")
 7. 5 and 6
 8. Limit 7 to published date 19920101-20071231

Database: EBM Reviews – Cochrane Database of Systematic Reviews

All KQs: Systematic Reviews

1. (opioid\$ or alfentanil or alphaprodine or beta-casomorphin\$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin\$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).ti.
2. 1 and (chronic and pain).mp.
3. limit 2 to full systematic reviews

Appendix B. PICOTS

PICOT	Include	Exclude
Population and Conditions of Interest	<ul style="list-style-type: none"> For all KQs: Adults (age >18 years) with various types of chronic pain (defined as pain lasting >3 months), including patients with acute exacerbations of chronic pain (KQ Ig) For KQs 1b, 2b: Subgroups as defined by specific pain condition, patient demographics (e.g., age, race, ethnicity, sex), comorbidities (including medical comorbidities and mental health disorders, including past or current alcohol or substance abuse and related disorders, and those at high risk for addiction); For KQ 2b: Subgroups also defined by the dose of opioids used 	<ul style="list-style-type: none"> Patients with pain at end of life, acute pain, pregnant or breastfeeding, patients treated with opioids for addiction
Interventions	<ul style="list-style-type: none"> For KQs 1, 2, 3: Long- or short-acting opioids (including tapentadol) used as long-term therapy (defined as use of opioids on most days for >3months) For KQ 1d: Also include combination of opioid plus nonopioid therapy (pharmacological or nonpharmacological) For KQ 1Va, b: Risk prediction instruments For KQ 1Vc: Opioid management plans, patient education, urine drug screening, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, use of abuse deterrent formulations For KQ 1Vd: Opioid management strategies 	<ul style="list-style-type: none"> Intravenous or intramuscular administration of opioids Tramadol
Comparators	<ul style="list-style-type: none"> For KQs 1a, 1b, 2a, 2b: Opioid vs. placebo or nonopioid therapy (including usual care) For KQ 1c: Opioid vs. nonopioid therapy (pharmacological or nonpharmacological [e.g., exercise therapy, cognitive behavioral therapy, interdisciplinary rehabilitation]) For KQ 1d: Opioid plus nonopioid therapy (pharmacological or nonpharmacological) vs. opioid or nonopioid therapy alone For KQ 3a: Comparisons of different dose initiation and titration strategies For KQ 3b: Short- vs. long-acting opioids For KQ 3c: One long-acting opioid vs. another long-acting opioid For KQ 3d: Short- plus long-acting opioid vs. long-acting opioid For KQ 3e: Scheduled, continuous vs. as-needed dosing of opioid For KQ 3f: Dose escalation vs. dose maintenance or use of maximum dosing thresholds For KQ 3g: Opioid rotation vs. continuation of current opioid For KQ 3h: Comparisons of different methods for treating acute exacerbations of chronic pain For KQ 3i: Decreasing or tapering opioid doses vs. continuation of opioids For KQ 3j: Comparisons of different tapering protocols and strategies For KQ 4a: Risk prediction instruments vs. reference standard for overdose or opioid addiction, abuse or misuse For KQ 4b: Risk prediction instruments vs. nonuse of risk prediction instruments For KQ 4c: Risk mitigation strategies (see Interventions above) vs. nonuse of risk mitigation strategies For KQ 4d: Comparisons of treatment strategies for managing patients with addiction to prescription opioids 	

PICOT	Include	Exclude
Outcomes	<ul style="list-style-type: none"> For KQs 1, 3, 4: Pain (intensity, severity, bothersomeness), function (physical disability, activity limitations, activity interference, work function), and quality of life (including depression), doses of opioids used Also for KQs 2, 3, 4: Overdose, opioid use disorder, addiction, abuse, and misuse; other opioid-related harms (including gastrointestinal, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression) 	<ul style="list-style-type: none"> Intermediate outcomes (e.g., pharmacokinetics/pharmacodynamics, drug-drug interactions, dose conversions)
Timing	<ul style="list-style-type: none"> Any duration for outcomes related to overdose and injuries (falls, fractures, motor vehicle accidents), studies on treatment of acute exacerbations of chronic pain, studies on dose initiation and titration, and studies on discontinuation of opioid therapy For other outcomes: >1 year 	
Setting	<ul style="list-style-type: none"> Outpatient settings (e.g., primary care, pain clinics, other specialty clinics) 	<ul style="list-style-type: none"> Addiction treatment settings, inpatient settings
Study Design	<ul style="list-style-type: none"> For all KQs, randomized controlled trials, controlled cohort studies, and case-control studies (controlled observational studies must have performed adjustment on potential confounders) For all KQs, we excluded uncontrolled observational studies, case series, and case reports, with the exception of KQ 2a for which we included uncontrolled observational studies of patients with chronic pain prescribed long-term opioid therapy for at least one year that used predefined methods to assess rates of abuse, misuse, or addiction For KQ 4a, we included studies that evaluated the predictive ability of risk prediction instruments, and excluded studies that did not evaluate the performance of a risk prediction instrument against a reference standard. 	

KQ, key question; PICOT=populations, interventions, comparators, outcomes, timing, setting.

Appendix C. Included Studies*

- Akbik H, Butler SF, Budman SH, et al. Validation and clinical application of the screener and opioid assessment for patients with pain (SOAPP). *J Pain Symptom Manage.* 2006;32(3):287-93. PMID: 16939853.
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- Ashburn MA, Slevin KA, Messina J, et al. The efficacy and safety of fentanyl buccal tablet compared with immediate-release oxycodone for the management of breakthrough pain in opioid-tolerant patients with chronic pain. *Anesth Analg.* 2011;112(3):693-702. PMID: 21304148.
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***Appendix C is the reference list for all appendixes.**

Appendix D. Excluded Studies

No Author. Use of opioids to control arthritis pain under scrutiny. Increase in falls, fractures in older adults attributed to narcotic painkillers, such as oxycodone, Vicodin or Percocet. Duke Med Health News. 2013;19(5):7. PMID: 23802330. *Excluded: wrong study design*

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Appendix E. Data Abstraction Tables

Appendix Table E1. Uncontrolled Studies of Long-term Opioid Use and Abuse, Misuse, and Related Outcomes

Author, Year	Type of Study		Population Characteristics	Opioid Dose, Duration, and Indication	Method of Ascertaining and Defining Abuse/Misuse	Main Results	Quality
	Setting	Duration					
Banta-Green, 2009	Retrospective cohort	Patients aged 21-79 with chronic opioid prescriptions over at least 3 years (filling ≥10 opioid prescriptions in a 12-month period or filling a prescription for at least a 120-day supply and ≥6 prescriptions in a 12-month period) Exclude: patients with cancers other than benign, nonmelanoma skin cancer	n=704 Mean age: 55 years Female sex: 62% Race: 89% White	Dose: mean 50 mg/day MED Duration: NR Indication: NR	Factor scores based on DSM-IV and PDUQ criteria UDT: not specified	Opioid dependence: 13% (91/704) Opioid abuse without dependence: 8% (56/704)	Fair
Boscarino, 2010	Cross-sectional study, outpatients from nine primary care (83%) and 3 specialty clinics (17%), based on 1 year of observation	≥4 physician orders for opioid therapy in past 12 mos., identified from E.H.R.; mean prescriptions=10.7 Exclude: cancer	n=705 Age: 18-64: 79% 65+: 21% Female sex: 61% White race: 98%	Dose: NR Duration: mean of 10.7 prescriptions over 1 year Indication: noncancer, otherwise not described	Diagnostic interview: CIDI; DSM-IV criteria for opioid dependence	25.8% (95% CI: 22.0-29.9) met criteria for current opioid dependence; 35.5% (95% CI: 31.1-40.2) met criteria for lifetime dependence Factors associated with dependence: Age <65 years (OR 2.3, 95% CI 1.6 to 3.5) History of opioid abuse (OR 3.8, 95% CI 2.6 to 5.7) History of high dependence severity (OR 1.8, 95% CI 1.4 to 2.5) History of major depression (OR 1.3, 95% CI 1.0 to 1.6), Current use of psychotropic medications (OR 1.7, 95% CI 1.2 to 2.5)	Fair

Author, Year	Type of Study		Population Characteristics	Opioid Dose, Duration, and Indication	Method of Ascertaining and Defining Abuse/Misuse		Main Results	Quality
	Setting	Duration						
Carrington Reid, 2002	Retrospective cohort Two primary care centers United States	Patients who received ≥6 months of opioid prescriptions during a 1- year period for noncancer pain and were not on methadone maintenance.	n=98 (50 at VA and 48 at urban primary care clinic)	VA site vs. urban primary care site Dose: NR Duration: NR Indication: 44% low back, 10% injury-related, 8% diabetic neuropathy, 16% degenerative joint disease, 4% headache, 10% spinal stenosis vs. 25% low back pain, 13% injury-related, 10% diabetic neuropathy, 13% degenerative joint disease, 13% headache, 4% spinal stenosis	Chart review for lost or stolen opioids, documented use of other sources to obtain opioids, and requests for ≥2 early refills UDT: not specified	VA site vs. urban primary care site Opioid abuse behaviors: 24% (12/50) vs. 31% (15/48) Median time of onset of abuse behaviors: 24 months Factors associated with decreased risk of opioid abuse behaviors: No history of substance use disorder (adjusted OR 0.72, 95% CI 0.45 to 1.1) Age (adjusted OR 0.94, 95% CI 0.94 to 0.99)	VA site vs. urban primary care site Opioid abuse behaviors: 24% (12/50) vs. 31% (15/48) Median time of onset of abuse behaviors: 24 months Factors associated with decreased risk of opioid abuse behaviors: No history of substance use disorder (adjusted OR 0.72, 95% CI 0.45 to 1.1) Age (adjusted OR 0.94, 95% CI 0.94 to 0.99)	Fair
Compton, 2008	Prospective cohort VA pain clinic United States One year	Consecutive chronic nonmalignant pain patients receiving opioids Exclude: patients with diagnosed substance use disorder	n=135 Mean age: 53 years Female sex: 6% Race: NR Baseline VAS score: 6.75	Dose: NR Duration: NR Indication: 77% musculoskeletal, 19% neuropathic, 4% multicategory	Chart review for opioid discontinuation due to medication agreement violation: 28% (38/135) Discontinuation due to medication agreement violation (including for opioid misuse or abuse) UDT: not specified	Discontinuation due to medication agreement violation: 28% (38/135) Discontinuation due to specific problematic opioid misuse behaviors: 8% (11/135) Overdose deaths: none reported	Discontinuation due to medication agreement violation: 28% (38/135) Discontinuation due to specific problematic opioid misuse behaviors: 8% (11/135) Overdose deaths: none reported	Fair

Author, Year	Type of Study Setting Duration	Eligibility Criteria	Population Characteristics	Opioid Dose, Duration, and Indication	Method of Ascertaining and Defining Abuse/Misuse		Main Results	Quality
Cowan, 2003	Cross-sectional Pain clinic United Kingdom	Patients attending pain clinic and receiving controlled-release oral morphine sulfate or transdermal fentanyl	n=104 Mean age: 55.4 years Female sex: 39% Race: NR Mean duration of pain: 10.5 years	Dose: NR Duration: mean 14.1 months Indication: 34% degenerative disease, 24% failed back/neck surgery syndrome, 10% complex regional pain syndrome, 10% osteoarthritis	SUQ UDT: not specified		Self-reported addiction: 1.9% (2/104) Craving opioids: 2.9% (3/104) Has taken drugs to enhance the effect of opioids: 0.9% (1/104) Has used alcohol to enhance the effect of opioids: 0.9% (1/104)	Fair
Edlund, 2014	Retrospective HMO, PPO and point-of-service 2000-2005 database review United States	Patients age ≥18 years with a new chronic non-cancer pain diagnosis, no cancer diagnosis, and no opioid use or opioid use disorder diagnosis in prior 6 months	n=568,640 (197,269 prescribed opioids in first year; of these, 5.5% had chronic use (>90 days supply)) Mean age not reported; 11% age 18-30, 20% age 31-40, 27% age 41-50, 30% age 51-64, 12% ≥age 65 Female sex: 58% Race: NR Mean duration of pain: all patients newly diagnosed	Dose: Among those prescribed opioids in first year, median = 36 mg/day MED. Daily MED categorized as none, low (1-36 mg), medium (36-120 mg), or high (≥120 mg). Duration: Mean NR; users identified as "chronic" had ≥91 days Indication: NR; inclusion criteria required newly diagnosed chronic non-cancer pain	Diagnosis of opioid abuse or dependence (ICD-9-CM code 304.00 or 305.50) within 18 months of first chronic non-cancer pain diagnosis	Opioid abuse or dependence - No opioid prescription: 0.004% (150/371,371) Low dose, chronic: 0.72% (50/6902) Medium dose, chronic: 1.28% (47/3654) High dose, chronic: 6.1% (23/378)	Opioid abuse or dependence - No opioid prescription: 0.004% (150/371,371) Low dose, chronic: aOR* 15 (95% CI 10 to 21) Medium dose, chronic: aOR 29 (95% CI 20 to 41) High dose, chronic: aOR 122 (95% CI 73 to 206)	Fair

*Adjusted for age, sex, number of tracer pain sites, number of nonsubstance mental health disorders, previous substance abuse or dependence diagnosis, Charlson score.

Author, Year	Type of Study	Setting	Duration	Eligibility Criteria	Population Characteristics	Opioid Dose, Duration, and Indication	Method of Ascertaining and Defining Abuse/Misuse		Main Results	Quality
Fleming, 2007 See also: Saffier, 2007	Primary care practices of 235 physicians	Daily opioids over past 3 months; 96% had received opioids for 12 months	n=801	Mean age: 48.6	Female sex: 68% Race: 75.6% White; 23.1% African American; 1% other	Mean daily dose: 92 MEQ/d Duration: ≥12 mos. For 96% Osteoarthritis: 24%; low back pain, herniated disc or stenosis: 25%; migraine 8%; neuropathy 5%	In person interviews with ASI; SDSS; Aberrant Behavior 12-item List	Abuse/Misuse	Met DSM-4 criteria for opioid dependence: 3.1% Met DSM-4 criteria for opioid abuse: 0.6% Any illicit drug on UDS: 24% (mostly marijuana) Aberrant behaviors: purposely oversedated: 24% (186/785) Felt intoxicated from pain med: 33% (260/785) Requested early refills: 45% (359/785) Increased dose on own: 37% (288/785) Meds lost or stolen: 30% (236/785) Used opioid purpose other than pain: 16% (125/785) Drank alcohol to relieve pain: 20% (154/785)	Fair
Hojsted, 2010	Cross-sectional Pain clinic Denmark	Adults with chronic noncancer pain Exclude: patients suffering from cognitive dysfunction, in poor health due to other condition, or did not use any pain medication	n=253, of which 187 were receiving opioid therapy (207 total and 153 receiving opioids returned questionnaire)	Mean age: 52 years Female sex: 64% Race: NR Mean pain score: NR Receiving opioids: 74% (187/253) Indication: 93% noncancer pain, 7% cancer pain	Dose: NR Duration: mean 6.8 years (among those who completed questionnaire, n=207)	Addiction screening by physician and nurse (blinded to each other) using the ICD-10 and Portenoy's Criteria; Indication: 28% nociceptive pain, 33% neuropathic pain, 39% mixed nociceptive and neuropathic	Addiction screening by physician and nurse (blinded to each other) using the ICD-10 and Portenoy's Criteria; Indication: 28% nociceptive pain, 33% neuropathic pain, 39% mixed nociceptive and neuropathic	Addiction to opioids or hypnotics, ICD-10: 11.1% (28/253) Addiction to opioids, ICD-10: 14.4% (27/187) Addiction to opioids or hypnotics, Portenoy's Criteria: 14.6% (37/253) Addiction to opioids, Portenoy's Criteria: 19.3% (36/187) Overdose deaths: NA	Addiction to opioids or hypnotics, ICD-10: 11.1% (28/253) Addiction to opioids, ICD-10: 14.4% (27/187) Addiction to opioids or hypnotics, Portenoy's Criteria: 14.6% (37/253) Addiction to opioids, Portenoy's Criteria: 19.3% (36/187) Overdose deaths: NA	Fair

Author, Year	Type of Study		Population Characteristics	Opioid Dose, Duration, and Indication	Method of Ascertaining and Defining Abuse/Misuse		Main Results	Quality
	Setting	Duration						
Portenoy, 2007	Prospective registry study 35 pain clinics United States Three years (mean duration 23.8 months)	Adult patients who had participated in any of five previous CCTs of CR oxycodone for noncancer pain	n=227 Mean age: 56 years Female sex: 57% Race: 90% White BPI average pain score: 6.4	Dose: mean 52.5 mg/day Duration: mean 541.5 days Indication: 38% osteoarthritis, 31% diabetic neuropathy, 31% low back pain	Physician-completed brief questionnaire assessing problematic drug-related behavior with verification by an independent panel of experts UDT: not specified	Problems identified by physicians: 5.7% (13/227) Problematic drug-related behavior adjudicated by expert panel as positive and meeting DSM-IV criteria: 0 Problematic drug-related behavior adjudicated by expert panel as positive: 2.2% (5/227) Problematic drug-related behavior adjudicated by expert panel as possible: 0.4% (1/227) Problematic drug-related behavior adjudicated by expert panel as withdrawal: 0.4% (1/227) Problematic drug-related behavior adjudicated by expert panel as alleged: 2.2% (5/227) Problematic drug-related behavior adjudicated by expert panel as negative: 0.4% (1/227) Overdose deaths: 1 (phenylpropanolamine, oxycodone, and alcohol)	Fair	

Author, Year	Type of Study		Population Characteristics	Opioid Dose, Duration, and Indication	Method of Ascertaining and Defining Abuse/Misuse		Main Results	Quality
	Setting	Duration						
Schneider, 2010	Chart review Single center pain clinic United States	Patients receiving opioid therapy for ≥1 year	n=197 Mean age: 49 years Female sex: 67% Race: NR	Dose: mean 180 mg/day MED (long acting), 49 mg/day MED (short acting) Duration: mean 4.7 years Indication: 51% back pain, 10% neck pain, 9% fibromyalgia, 8% other myofascial pain	UDT: immunoassay followed by confirmatory GC/MS	Positive UDT: 8.7% (14/161) Aberrant drug-related behaviors noted in chart: 15.7% (31/197)		Fair
Wasan, 2009	Cross-sectional 5 pain clinics United States	Patients with noncancer chronic pain receiving opioid therapy	n=622 Mean age: 50.4 years Female sex: 55% Race: 80% White Mean pain score: 5.96	Dose: NR Duration: mean 6.2 years Indication: 61% low back pain	POTQ, PUDQ, and UDT	Positive scores of ≥2 on POTQ: 24% (115/480) Score ≥11 on PDUQ: 29.1% (130/447) Positive UDT: 37.1% (134/356)		Fair

Note: The references are located in Appendix C.

ASI=Addiction Severity Index; CCT=case control trial; CR=case report; CI=confidence interval; CIDI= Composite International Diagnostic Interview; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DSM-V=Diagnostic and Statistical Manual of Mental Disorders, 5th edition; GC/MS= Gas Chromatography with Mass Spectrometry confirmatory test; ICD-10=International Statistical Classification of Diseases and Related Health Problems, tenth revision; MED=morphine equivalent dose; MEQ/d=milliequivalent/hydrogen; NR=not relevant; PDUQ=Prescription Drug Use Questionnaire; POTQ=Prescription opioid therapy questionnaire; SDSS= Substance dependence severity scale; UDT=urine drug testing; VA=Veterans Administration; VAS= Visual Analog Scale

Appendix Table E2. Observational Studies of Long-Term Opioid Use and Overdose

Author, year	KQ	Type of study, setting	Eligibility criteria	Comparison groups	Population characteristics	Method for Assessing Outcomes and Confounders
Dunn, 2010	KQ2a, b	Retro-spective cohort (Group Health United States	Age > 18 years starting new episode of opioid use (no opioids in past 6 mos) from 1997 -2005; having 3 or more opioid scripts filled in first 90 days of episode; diagnosis of chronic noncancer pain in 2 wks before first opioid script.	Morphine equivalent doses: A. 1-<20 mg/day B. 20-<49 mg/day C. 50-<99 mg/day D. >=100 mg/day	Mean (SD; range) age (years): 54 (16.8; 18-99) Female sex: 59.6% Race: NR Smoking: 29.5% Depression: 26.9% Substance abuse: 6.2% Charlson Score, mean (SD; range): 0.71 (1.48;0-14) Pain diagnosis: 37.9% back; 30.3% extremity; 12.7% osteoarthritis; 12.3% injury, contusion, or fracture; 8.9% neck Opioid dose, mean (median): 13.3 mg (6.0 mg) Sedative-hypnotic use, any: 74.7% Muscle relaxant: 52.3% Benzodiazepine: 42.7% Opioid: Hydrocodone: 46.3% Oxycodone: 24.5% Codeine combination: 11.6% Long-acting morphine: 6.2% Any short acting opioid: 90.4% Any long-acting opioid: 9.6%	All patients in HMO meeting inclusion criteria

Author, year	Screened	Adjusted Variables for Statistical Analysis	Main Results	Funding Source	Quality
	Eligible				
Dunn, 2010	Screened: Not reprotoed Eligible: Not reported Enrolled: 9,940 Mean duration of follow-up (range): 42 mos (<1-119); Analyzed: All included in analysis Loss to followup: 61% had complete followup from cohort entry until end of study or event occurred; 32% left GHC during study; 7% died	Sedative-hypnotic use as time-varying covariate Age Sex Smoking Depression diagnosis Substance abuse diagnosis Index pain diagnosis Chronic disease comorbidity adjustors (RxRisk & Charlson)	51 patients with overdose events (148 per 100,000 person-years); 40 serious overdose events (116 per 100,000 person-years); 6 fatal overdose events (17 per 100,000 person-years) Rate of any overdose per 100,000 person-years (95% CI); HR (95% CI) No opioid: 36 (13-70); 0.31 (0.12-0.80); 6 overdose events A. (referent): 160 (100-233); 1.0 B. 260 (95-505); 1.44 (0.57-3.62) C. 677 (249-1317); 3.73 (1.47-9.5) D. 1791 (894-2995); 8.87 (3.99-19.72) Opioid dose, any: 256 (187-336); 5.16 (2.14-12.48); 45 overdose events HR, serious events (95% CI) No opioid: 0.19 (0.05-0.68); A. (referent): 1.0 B. 1.19 (0.4-3.6); C. 3.11 (1.01-9.51); D. 11.18 (4.8-26.03); Opioid dose, any: 8.39 (2.52-27.98)	National Institute of Drug Abuse and Wellcome Trust	Fair

Author, year	KQ	Type of study, setting	Eligibility criteria	Comparison groups	Population characteristics	Method for Assessing Outcomes and Confounders
Gomes, 2011	KQ2b	Case-Control Canada	Residents aged 15-64 with public drug coverage and an opioid for nonmalignant pain (1997-2006)	Cases: Died of an opioid-related cause (n=498 matched a control) Controls: received opioids (n=1714)	Total cohort n= 607,156 Mean age (years): 44.49 vs 44.72 Gender (not reported which one): 58.8% vs 58.0%	Controls matched on disease risk index (0.2 standard deviation caliper), age, gender, index year, and Charlson

Note: The references are located in Appendix C.

CI=confidence interval; EtOH=ethanol; GHC=Group Health Cooperative; HMO=Health Maintenance Organization; HR=hazard ratio; ICES= Institute for Clinical Evaluative Sciences; MOHLTC= Ontario Ministry of Health and Long-Term Care; NR=not relevant; RxRisk=drug index for prescription drugs

Author, year	Screened Eligible Enrolled Analyzed	Adjusted Variables for Statistical Analysis		Main Results	Funding Source	Quality
		Loss to Followup				
Gomes, 2011	Screened: 1463 Eligible: 1179 Primary- analysis: 593 with 498 matched Secondary- analysis: 873 with 781 matching	Opioid exposure categorized by Average Daily Dose: <20mg, 20- 49mg, 50-99mg, 100-199mg, 200+mg. Logistic models adjusted for: duration, income, history of EtOH abuse, interacting prescription drugs, total number of different opioids dispensed, long-acting opioid used, number of physicians prescribing opioids, number of pharmacies dispensing opioids	Risk estimates reported as adjusted OR Risk of opioid overdose death A. 1 (reference) B. 1.32 (0.94-1.84) C. 1.92 (1.30-2.85) D. 2.04 (1.28-3.24) E. 2.88 (1.79-4.63)	Secondary using 120-day exposure window risk of opioid overdose death A. 1 (reference) B. 0.93 (0.60-1.42) C. 1.31 (0.86-1.99) D. 1.47 (0.98-2.19) E. 2.24 (1.62-3.10)	MOHLTC Drug Innovation Fund and ICES, a nonprofit research institute sponsored by the Ontario MOHLTC	Good

Appendix Table E3. Observational Studies of Long-Term Opioid Use and Fractures

Author, year	KQ	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics
Li, 2013	KQ2a	Nested case control United Kingdom	Cohort: Patients with non-cancer pain with at least 1 opioid prescription between 1/1/90 and 12/31/08 in the General Practice Research Database Cases (n=21,739): First-time diagnosed fracture of the hip, humerus, or wrist during 1990-2008, age 18-80 years, >2 years of medical history before index date; excluding patients with cancer, dementia, metabolic bone disease, Cushing syndrome, hyperparathyroidism, long-term immobilization, or alcohol or drug abuse, fracture within 2 years, MVA within 90 days, osteoporosis diagnosis prior to index date Controls (n=85,326): Up to 4 controls without fracture selected for each case, matched on age, sex, index date, and general practice	A. Opioid nonuse B. Current cumulative opioid use 1 prescription C. 2-3 opioid prescriptions D. 4-5 opioid prescriptions E. 6-20 opioid prescriptions F. 21-50 opioid prescriptions G. 51-100 opioid prescriptions H. >100 opioid prescriptions 1. Opioid nonuse 2. Current use 3. Recent use 4. Past use	Mean age (years): 62 Female sex: 77% Race: NR Pain condition: NR Pain duration: NR Pain severity: NR Mean dose: NR Most commonly prescribed opioids: dihydrocodeine, codeine, propoxyphene, tramadol

Author, year	Method For Assessing Outcomes and Confounders	Screened	Eligible	Enrolled	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
		Analyzed	Loss to Followup					
Li, 2013	Used General Practice Research Database, in which drug exposures and diagnoses (including fracture) have been validated	Screened: NR Eligible: NR Enrolled: NR Analyzed: 21,739 fracture cases and 85,326 controls Number not analyzable: NR	Smoking, BMI, number of general practice visits, recorded years before index date, opioid use (new vs. prevalent), comorbidities, comedications, types of pain, recent/past opioid use (matched on age, sex, index date, and general practice)	Adjusted OR for risk of hip, humerus, or wrist fracture A. 1 (reference) B. 2.70 (95% CI 2.34-3.13) C. 1.90 (95% CI 1.67-2.17) D. 1.44 (95% CI 1.22-1.69) E. 1.17 (95% CI 1.08-1.27) F. 1.06 (95% CI 0.98-1.15) G. 1.06 (95% CI 0.96-1.16) H. 1.12 (95% CI 0.99-1.25) 1. 1 (reference) 2. 1.27 (95% CI 1.21-1.33) 3. 1.05 (95% CI 0.99-1.13) 4. 0.96 (95% CI 0.92-1.01)	None	Good		

Author, year	KQ	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics
Saunders, 2010	KQ2a, b	Cohort, Group Health Cooperative United States	Age 60+, initiating opioids (no opioid prescriptions in prior 6 months) with 3+ prescriptions in 90 days and a diagnosis of non-cancer pain 2-3 weeks prior to the index prescription. Exclusions: Cancer, <270 days enrollment in health plan in the year prior to index.	Opioid dose per day (mg/day): A: Not currently using B: 1-<20 mg/day C: 20-<50 mg/day D: ≥50 mg/day E: Any use	Mean age (years): 73 Female sex: 66% Race: NR Depression diagnosis: 22% Substance abuse diagnosis: 3.8% Dementia diagnosis: 4.8% Prior fracture: 2.6% HRT/bisphosphonate use: 34% Rxrisk score, mean (SD): 4272 (2455) Charlson Index , mean (SD): 1.32 (2.0) Pain diagnosis at index visit 42% back pain, 4.8% neck pain, 25% osteoarthritis, 2.4% headache, 34% extremity pain, 5.3% abdominal pain/hernia, 0.6% menstrual/menopausal pain, 0.2% temporomandibular disorder pain Mean morphine equivalent daily dose (mg): (s.d.) 12.8 mg (17.0) Sedative hypnotic use: 60% Antidepressant use: 57% Opioid prescribed: Hydrocodone: 42% Oxycodone: 24% Codeine combination: 14% Long-acting morphine: 8.3%

Note: The references are located in Appendix C.

CI=confidence interval; HRT=hormone replacement therapy; ICD-9=International Classification of Diseases; KQ=key question; NR=not relevant; RxRisk= drug index for prescription drugs

Author, year	Method For Assessing Outcomes and Confounders	Screened		Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
		Eligible	Enrolled				
		Loss to Followup	Analyzed				
Saunders, 2010	Fractures initially identified by ICD-9 codes (800xx-804xx; 807xx-809xx; 810xx-829xx; 2000-2006, excluded vertebral fractures) and verified by medical record review; medication data from Group Health Cooperative automated pharmacy files (over 90% of prescriptions); covariates from automated health care data	Screened: ~500,000	Eligible, enrolled, and analyzed: 2,341	Age, sex, tobacco use, depression diagnosis, substance abuse diagnosis, dementia diagnosis, index pain diagnosis, chronic disease comorbidity adjustors, sedative-hypnotic use, antidepressant use, HRT/bisphosphonate use, and prior fractures.	Fracture rate: 5.0%/year Adjusted HRs for risk of fracture A: 1 (reference) B: 1.20 (95% CI 0.92, 1.56) C: 1.34 (95% CI 0.89, 2.01) D: 2.00 (95% CI 1.24, 3.24) E: 1.28 (95% CI 0.99, 1.64)	National Institute of Drug Abuse	Fair

Appendix Table E4. Observational Studies of Long-Term Opioid Use and Cardiovascular Outcomes

Author, Year	KQ	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics
Carman, 2011	KQ2a, b	Retrospective cohort United States	Claim submitted for dispensing of opioids or COX-2 inhibitors for ≥ 180 days from July 2002 to December 2005, patients aged ≥ 18 years; controls from general populations matched on age, sex, and cohort entry date Exclude: History of MI or revascularization, cancer	A. Opioids (n=148,657) B. Rofecoxib (n=44,236) C. Celecoxib (n=64,072) D. Valdecoxib (n=20,502) E. General population not using opioids or COX-2 inhibitors (n=148,657) 1. 0 to <1350 mg MED per 90 days 2. 1350 to <2700 mg MED per 90 days 3. 2700 to <8100 mg MED per 90 days 4. 8100 to $<18,000$ mg MED per 90 days 5. $\geq 18,000$ mg MED per 90 days	A vs. B vs. C vs. D vs. E Age 18-29 years: 4.7% vs. 1.2% vs. 0.8% vs. 1.2% vs. 4.7% Age 30-39 years: 16.3% vs. 5.4% vs. 4.1% vs. 5.3% vs. 16.3% Age 40-49 years: 33.9% vs. 20.7% vs. 17.6% vs. 20.1% vs. 33.9% Age 50-64 years: 36.7% vs. 56.0% vs. 56.3% vs. 56.5% vs. 36.7% Age ≥ 65 years: 8.4% vs. 16.6% vs. 21.2% vs. 16.9% vs. 8.4% Female sex: 40.3% vs. 39.5% vs. 39.6% vs. 34.9% vs. 40.3% Diabetics: 11.7% vs. 10.2% vs. 12.4% vs. 11.1% vs. 4.1% Pain condition: NR Duration of pain: NR severity of pain: NR Opioids prescribed: NR

Appendix Table E4. Observational Studies of Long-Term Opioid Use and Cardivascular Outcomes

Author, Year	Method For Assessing Outcomes and Confounders	Screened		Adjusted Variables for Statistical Analysis	Main Results	Funding Source	Quality
		Eligible	Enrolled				
Carman, 2011	All relevant claims in database during study period	Screened: NR Eligible, enrolled, analyzed: 426,124	Incidence rates adjusted for age and sex; incidence rate ratio adjusted for age sex, CV and other other comorbidities, and use of concomitant medications	Adjusted incidence rate of MI, incidence rate ratio A: 5.93 (95% CI 5.58 to 6.30); IRR 2.66 (95% CI 2.30 to 3.08) B: 3.54 (95% CI 3.11 to 4.01); IRR 1.94 (95% CI 1.65 to 2.29) C: 3.53 (95% CI 3.15 to 3.94); IRR 1.79 (95% CI 1.53 to 2.10) D: 3.40 (95% CI 2.76 to 4.14); IRR 1.74 (95% CI 1.41 to 2.16) E: 1.58 (95% CI 1.40 to 1.78); IRR 1 (reference)	Adjusted incidence rates of MI or revascularization, incidence rate ratio A. 11.91 (95% CI 11.40 to 12.43); IRR 2.38 (95% CI 2.15 to 2.63) B. 7.98 (95% CI 7.33 to 8.67); IRR 1.93 (95% CI 1.72 to 2.15) C. 7.94 (95% CI 7.36 to 8.54); IRR 1.81 (95% CI 1.62 to 2.01) D. 7.53 (95% CI 6.56 to 8.60); IRR 1.75 (95% CI 1.50 to 2.01) E. 3.38 (95% CI 3.12 to 3.67); IRR 1 (reference)	GlaxoSmithKline	Fair

Author, Year	KQ	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics
Li, 2013	KQ2a	Case-Control UK General Practice Research Database United Kingdom	Cases (n=11,693): Age 18-80 years, 2 years of medical history data before index (onset of MI symptoms) Controls: (n=44,897): Up to 4 controls matched on age, gender, index date, and practice site using risk-set sampling Excluded: History of cancer, ischemic heart disease, heart failure, stroke, congenital heart disorders, heart transplat, arrhythmias, treated hypertension, diabetes, ETOH/Drug abuse, hepatic or renal disease before index, cardiac surgery in the 90 days prior to index.	A. Non-use B. Current (0-30 days from index) C. Recent (31-365 days out) D. Past Use (366-730 days out) Cumulative use (number of prescriptions): 1. 1-2 2. 3-10 3. 11-50 4. >50	Mean age (years): 61.8 vs. 61.6 Female sex: 31.1% vs. 31.3% Current smoker: 38.6% vs. 23.3% Low BMI (<18.5): 1.2% vs. 1.2% Normal BMI: 25.8% vs. 28.9% Overweight: 31.7% vs. 30.2% Obese: 13.8% vs. 11.3% Arthritis: 25% vs. 24.2% Rheumatoid arthritis: 3.2% vs. 1.8% Fibromyalgia: 1.1% Duration or severity of pain: NR Codeine: 16% vs. 15% Dihydrocodeine: 9.6% vs. 8.1% Propoxyphene: 13% vs. 11%

Note: The references are located in Appendix C.

BMI=body mass index; CI=confidence interval; CV= cardiovascular; IRR=incidence rate ratio; KQ=key question; MI=myocardial infarction; NR=not relevant

Author, Year	Method For Assessing Outcomes and Confounders	Screened		Adjusted Variables for Statistical Analysis	Main Results	Funding Source	Quality
		Eligible	Enrolled				
Li, 2013	Used General Practice Research Database, which has been validated on drug exposure and diagnoses (including MI)	Screened: 1,700,000 Eligible: Not reported Enrolled: 11,693 cases and 44,897 controls Analyzed: 11,693 cases and 44,897 controls	Age, gender, smoking, body mass index, number of general practice visits, years of medical history, opioid new versus prevalent use, co-morbidities, concomitant medications, abdominal and pelvic pain and other pain	Risk of MI (adjusted OR) A. 1 (reference) B. 1.28 (95% CI 1.19–1.37) C. 1.17 (95% CI 1.10–1.24) D. 1.06 (95% CI 0.98–1.14) 1. 1.10 (95% CI 1.03–1.18) 2. 1.09 (95% CI 1.02–1.17) 3. 1.38 (95% CI 1.28–1.49) 4. 1.25 (95% CI 1.11–1.40)		None disclosed	Good

Appendix Table E5. Observational Studies of Long-Term Opioid Use and Endocrine Outcomes

Author,	KQ	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method For Assessing Outcomes and Confounders
Deyo, 2013	KQ2a, b	Cross-sectional Integrated healthcare United States	Ambulatory males aged ≥18 years with diagnoses associated with low back pain Exclude: patients with evidence of systemic disease or trauma	A. Patients prescribed medication for erectile dysfunction or testosterone replacement (n=909) B. Patients not prescribed medication for erectile dysfunction or testosterone replacement (n=10,418)	A vs. B Mean age (years): 55.7 vs. 48.0 Female sex: 0% Race: 89% White, 3% Black, 3% Asian/Pacific Islander, 1% American Indian, 3.9% other (among records with race/ethnicity data available, 59% of total sample) Sedative-hypnotic use: 24.4% vs. 15.6% Diagnosis of depression: 17.3% vs. 11.3%	Review of medical and pharmacy records

Note: The references are located in Appendix C.

KQ=key question; MED=morphine equivalent dose; NIH/NCRR=National Institutes of Health/National Center for Research

Author, year	Loss to Followup	Screened	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
		Eligible				
Deyo, 2013	Screened: NR Eligible: 11,327 Enrolled: 11,327 Analyzed: 11,327	Age, comorbidity score, number of hospitalizations, sedative-hypnotic use, duration of opioid use, morphine dose at last dispensing, type of opioid (short- vs. long-acting), depression, and smoking status	No opioid use vs. short-term use vs. episodic use vs. long-term use Prescription for sildenafil, tadalafil, or vardenafil 6 months before or after index visit: 6.3% (294/4,655) vs. 6.9% (324/4,696) vs. 7.3% (12/164) vs. 11.3% (204/1,812); p<0.001 Testosterone replacement 6 months before or after index visit: 0.5% (25/2,655) vs. 0.6% (30/4,696) vs. 1.2% (2/164) vs. 2.4% (44/1,812); p<0.001 Testosterone replacement or erectile dysfunction treatment: 6.7% (312/4,655) vs. 7.4% (346/4,696) vs. 7.9% (13/164) vs. 13.1% (238/1,812); p<0.001; OR 1.5, 95% CI 1.1 to 1.9 Dosing Daily opioid dose of >120 mg MED/day associated with increased risk of use of medications for erectile dysfunction or testosterone replacement versus 0 to <20 mg MED/day (OR 1.6, 95% CI 1.0 to 2.4)	NIH/NCRR	Fair	

Appendix Table E6. Observational Studies of Long-Term Opioid Use and Motor Vehicle Accidents

Author, year	KQ	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Sampling Strategy
Gomes, 2013	KQ2b	Case-Control Canada	Residents aged 15-64 with public drug coverage and an opioid prescription (excluding methadone) (2003-2011) at least 6 months of continuous eligibility for public drug coverage before their index date and at least 1 opioid prescription with a duration that overlapped their index date. Cases and controls were excluded if they had invalid patient identifiers, had missing information about age or sex, received palliative care services in the 6 months before their index date, lived in a long-term care home at the index date, or had a prescription for a nonstudy opioid with a duration that overlapped the index date.	Cases: ED with an external cause of injury related to road trauma (codes V00 to V89 from ICD-10) (n=5,300 matched a control) Controls: (n=5300) A. 1-<20 mg/day B. 20-<50 mg/day C. 50-<100 mg/day D. 100-<200 mg/day E. ≥200 mg/day	Cases vs. Controls Mean age (years): 45.76 vs. 45.75 Female sex: 48.6% Urban resident: 83.75% vs. 83.98 Social Assistance: 22% vs. 21% Disability support: 67.9% vs. 66.6% Duration of use (years): 7.09 vs. 6.84 Charlson score No hospitalization: 61.7% vs. 62.3% 0: 23.4% vs. 22.4% 1: 6.85% vs. 6.32% ≥2: 7.96% vs. 8.49%	Incidence density sampling Cases were matched to controls by sex, age (within 3 years), index year (within 1 year), ED visit for road trauma in the past year, and disease risk index (within 0.2 SD). Cases with no matched controls were excluded from analyses.

Note: The references are located in Appendix C.

CI=confidence interval; ED=emergency department; ICD=International Classification of Diseases

Author, year	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
Gomes, 2013	Screened population: 549,878 Eligible Cases: 5300 Eligible Controls: 43,736 Controls matched 1:1	Logistic models adjusted for: age, past (3 years) hospitalization for alcoholism, past (1 year) ED visit for alcoholism, duration of opioid treatment, medication use in past 180 days (ie, selective serotonin reuptake inhibitors, other antidepressants, antipsychotics, benzodiazepines and other depressants of the central nervous system, separately), number of drugs dispensed in the past 180 days, and numbers of physician and ED visits in the past 1 year.	Risk estimates reported as adjusted OR Risk of motor vehicle crash A. 1 (reference) B. 1.09 (95% CI 0.97-1.21) C. 1.07 (95% CI 0.94-1.22) D. 1.08 (95% CI 0.93-1.24) E. 1.00 (95% CI 0.88-1.15) Dosing Relative to 1 to <20 mg MED/day, the odds of road trauma among drivers after adjustment for age, alcoholism history, concomitant medication use, total number of drugs , and number of physician and emergency department visits was 1.21 (1.02 to 1.42) for 20 to 49 mg, 1.29 (1.06 to 1.57) for 50-99 mg, 1.42 (1.15 to 1.76) for 100 to 199 mg, and 1.23 (1.02 to 1.49) for >200 mg	MOHLTC Drug Innovation Fund and ICES, a nonprofit research institute sponsored by the Ontario MOHLTC.	Good

Appendix Table E7. Trials of Different Methods for Initiating and Titrating Opioids

Author Year	Study design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened Eligible Enrolled Analyzed	Loss to Followup
Jamison, 1998	RCT 16 weeks	Single center Pain clinic United States	Chronic back pain >6 months duration, age 25 to 65 years, average pain intensify >40 on scale of 0 to 100, unsuccessful response to traditional pain treatment Exclude: Cancer, acute osteomyelitis or acute bone disease, spinal stenosis and neurogenic claudication, non-ambulatory, significant psychiatric history, pregnancy, treatment for drug or alcohol abuse, clinically unstable systemic illness, acute herniated disc within 3 months	A. Long acting morphine + short-acting oxycodone (titrated doses) + Naproxen B. Short-acting oxycodone (set dose) + Naproxen C. Naproxen A vs. B vs. C Mean dose 41.1 mg vs. NR (max 20 mg oxycodone/day) vs. NR In all groups, max 1000 mg/day of naproxen 16 weeks	Mean age (years): 43 Female sex: 57% Race: NR Indication: 39% failed back syndrome, 25% myofascial pain syndrome, 19% degenerative spine disease, 14% radiculopathy, 3% discogenic back pain Prior opioid use: NR Mean pain duration: 79 months	Screened: 48 Eligible: NR Enrolled: 36 Analyzed: 36	
Salzman, 1999	RCT 10 days	Multicenter Rheumatology clinics and others United States	18 years or older, chronic stable moderate to severe back pain despite analgesic therapy with or without opioids Exclude: Contraindication to opioid history of substance abuse, unable to discontinue nonstudy narcotic, or current oxycodone dose >80 mg/day Titration to 80 mg without achieving pain control	A: Sustained-release Oxycodone (titrated) B: Immediate-release Oxycodone (titrated) Titration comparison Mean dose A: 104 mg/day Mean dose B: 113 mg/day 10 days	Mean age (years): 56 Female sex: 54% Race: 87% White, 13% Hispanic Indication: Intervertebral disc disease, nerve root entrapment, spondylolisthesis, osteoarthritis, and other non-malignant conditions 84% (48/57) Pain duration: NR	Screened: NR Eligible: NR Enrolled: 57 Analyzed: 57	

Note: The references are located in Appendix C.

NR=not reported; RCT=randomized control trial; SF=short form

Author	Outcomes Assessed	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Year					
Jamison, 1998	Pain Intensity: timing not specified, Comprehensive Pain Evaluation Questionnaire Functional status: baseline and at end of treatment (SF-36) Symptom checklist: baseline and at end of treatment (Symptom Checklist-90) Weekly activity record at baseline and once a month Medication diary weekly Overall helpfulness during titration and at end of study (categorical scale, 0= no help, 10=extremely helpful)	A vs. B vs. C Average pain (means, 0-100 VAS): 54.9 vs. 59.8 vs. 65.5 Current pain (means, 0-100 VAS): 51.3 vs. 55.3 vs. 62.7 Highest pain (means, 0-100 VAS): 71.4 vs. 75.5 vs. 78.9 Anxiety (means): 11.2 vs. 15.0 vs. 31.6 Depression (means): 10.8 vs. 16.4 vs. 26.9 Irritability (means): 17.7 vs. 20.5 vs. 33.7 Level of activity (means, 0-100 scale): 49.3 vs. 49.3 vs. 51.5 Hours of sleep (means): 5.9 vs. 5.9 vs. 6.1	A vs. B Somnolence: 27% (8/30) vs. 37% (10/27) Nausea: 50% (15/30) vs. 33% (9/27) Vomiting: 20% (6/30) vs. 4% (1/27) Postural hypotension: 0% vs. 0% Constipation: 30% (9/30) vs. 37% (10/27) Pruritus: 30% (9/30) vs. 26% (7/27) Confusion: 3% (1/30) vs. 0% Dry mouth: 0% vs. 11% (3/27) Dizziness: 30% (9/30) vs. 22% (6/27) Nervousness: 0% vs. 7% (2/27) Asthenia: 7% (2/30) vs. 11% (3/27) Headache: 13% (4/30) vs. 26% (7/27) Withdrawal due to adverse events: 20% (6/30) vs. 7% (2/27)	Roxane Laboratories (maker of long-acting morphine and short-acting oxycodone). Not clear if authors employed by Roxane	Fair
Salzman, 1999	Pain Intensity: daily diary, categorical scale (0-3, none-severe) Study Medication Use: daily diary, amount used Rescue Drug Use: daily diary, amount used Achievement of Stable Pain Control: Stable pain control considered achieved if pain intensity rated as 1.5 or less for 48 hours with no more than 2 doses of rescue medication Time to Stable Pain Control: Days	A vs. B Mean decrease in pain intensity (0 to 3 scale): 1.1 vs. 1.3 (NS) Proportion achieving stable analgesia: 87% (26/30) vs. 96% (26/27) (p = 0.36) Time to stable pain control: 2.7 vs. 3.0 days (p = 0.90). Mean number of dose adjustments: 1.1 vs. 1.7 adjustments (p = 0.58)	A vs. B vs. C Withdrawal due to adverse events: 54% (29/54) vs. 34% (20/59) vs. 130% (6/54) (p=0.008 for A or C vs. B) Withdrawal due to nausea and/or vomiting: 46% (25/54) vs. 22% (13/59) vs. 22% (12/54) Any adverse event: 76% vs. 70% vs. 61% Dizziness: 7% vs. 7% vs. 7% Headache: 18% vs. 15% vs. 13% Dry mouth: 0% vs. 2% vs. 6% Constipation: 7% vs. 3% vs. 11% Diarrhea: 7% vs. 5% vs. 2% Vomiting: 18% vs. 12% vs. 7% Nausea: 54% vs. 42% vs. 33% Somnolence: 9% vs. 7% vs. 0% Pruritus: 4% vs. 2% vs. 7%	Purdue Pharma sponsored study 2 authors employees of Purdue Role not otherwise reported.	Fair

Appendix Table E8a. Head-to-Head Trials of Different Long-Acting Opioids

Author Year	Study design Duration	Setting Country	Eligibility criteria	Interventions	Sample Characteristics	Screened		Outcomes Assessed
						Eligible	Enrolled	
Allan, 2005	RCT 13 months	Europe Multicenter (number of sites not clear)	Adults with chronic low back pain requiring regular strong opioids Exclude: Receipt of more than 4 doses of strong opioids in a week in the 4 weeks before the study, high risk of ventilatory depression or intolerance to study drugs, prior alcohol or substance abuse, presence of other chronic pain disorders, or life-limiting illness	A: Transdermal fentanyl (titrated from 25 mcg/hr) (Mean dose 57 mcg/h) B: Sustained-release morphine (titrated from 30 mg q 12 hrs (Mean dose: 140 mg)	Avg. 54.0 years, 61% female Race: not reported, Prior opioid use not reported 35% nociceptive, 4% neuropathic, 46% nociceptive and neuropathic, 3% psychologic factors, 4% neuropathic with psychologic factors, 83% mechanical low back pain, 8% inflammatory 39% trauma/surgery, 1% metabolic, 3% other Pain duration average 124.7 months	Number approached and eligible not reported 683 randomized (338 to transdermal fentanyl and 342 to sustained-release morphine, 3 group assignment not reported)	Pain score (mean, 0-100 VAS) Severe pain at rest Severe pain on movement Severe pain during the day Severe pain at night Rescue strong opioids use Quality of life (SF-36) Loss of working days Withdrawal due to lack of efficacy	
Mitra, 2013	RCT 12 months	One site in Townsville, Australia	Inclusion: Patients > 18, reporting persistent pain for greater part of day and night for at least 1 year, opioid-naïve, appropriate for treatment with transdermal patches after medical assessment, with no comorbid psychiatric history.	A: TDB initial dose=5 mcg/h, n=22; B: TDF initial dose=12.5 mcg/h, n=24; Both titrated to optimal doses over 4 weeks; increased doses beyond that given as clinically indicated	None reported by treatment group: Age, mean (range): 49 (22- 80); Male: 48%; Back pain: 61%; Other types of pain: 39%; Duration of pain, mean (range): 11.7 yrs (6 mos to 50 yrs); Duration of follow-up: 3 mos (35%), 6 mos (13%), 12 mos (52%)	Considered for trial: 82; Enrolled: 46; Completed and analyzed at 12 mos: 30 (TDB-14 pts and TDF-16 pts)	SPAASMS: Activity & mobility: Rescue pain meds: GP/ED visits: Sleep quality: Side effects: Mood: Pain VAS: DASS21: PDI:	

Author	Year	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Allan, 2005		<p>Transdermal fentanyl (A) vs. sustained-release morphine (B): Pain score (mean, 0-100 VAS) at 56 weeks (N=608): 56.0 (A) vs. 55.8 (B)</p> <p>Severe pain at rest (per protocol analyses, N=248 and 162): 22/248 (9%) (A) vs. 20/162 (12%) (B), p=0.030 (no significant differences in ITT analysis, but data not provided)</p> <p>Severe pain on movement (per protocol): 70/248 (28%) (A) vs. 43/162 (27%) (B), p=0.61</p> <p>Severe pain during the day (per protocol): 48/248 (19%) (A) vs. 40/162 (25%) (B), p=0.385</p> <p>Severe pain at night (per protocol): 25/248 (10%) (A) vs. 26/162 (16%) (B), p=0.003 (no significant differences in ITT analysis, but data not provided)</p> <p>Rescue strong opioids use: 154/296 (52%) (A) vs. 154/291 (53%) (B).</p> <p>Quality of life (SF-36): No differences between interventions</p> <p>Loss of working days: No differences between interventions</p> <p>Withdrawal due to lack of efficacy: 18/335 (5%) vs. 15/342 (4%)</p>	<p>Transdermal fentanyl (N=338) vs. sustained-release oral morphine (N=342)</p> <p>Any adverse event: 87% vs. 91%</p> <p>Constipation (ITT): 176/338 (52%) vs. 220/338 (65%) (p<0.05)</p> <p>Nausea: 54% vs. 50%</p> <p>Vomiting: 29% vs. 26%</p> <p>Somnolence: 17% vs. 30%</p> <p>Dizziness: 25% vs. 24%</p> <p>Fatigue: 17% vs. 14%</p> <p>Pruritus: 15% vs. 20%</p> <p>Application site reactions: 9% in transdermal fentanyl group.</p> <p>Deaths: None;</p> <p>Addiction: None reported.</p> <p>Use of laxatives: 177/336 (53%) vs. 221/336 (66%) (p<0.001)</p> <p>Use of antiemetics/anticholinergics: 38% vs. 36%</p> <p>Use of antihistamines: 21% vs. 12% (p=0.002)</p> <p>Withdrawal (Overall): 52% (177/338) vs. 47% (162/342).</p> <p>Withdrawal (adverse events): 125/335 (37%) vs. 104/337 (31%) (p=0.098)</p>	Janssen Pharma- ceutica	Fair
Mitra, 2013		<p>12 month results:</p> <p>16 of 46 patients continued for 12 mos and gained effective relief;</p> <p>SPAAMS: Score=13/28 possible in both groups at 12 mos (reading from Figure 5d)</p> <p>Activity & mobility: no numbers provided, groups look similar at 12 mos;</p> <p>Rescue pain meds: initially higher in TDF group; higher in TDB group near study end (no numbers provided);</p> <p>GP/ED visits: increase in visit frequency in TDB group near study end (no numbers provided);</p> <p>Sleep quality: No significant difference between groups (no numbers provided)</p> <p>Side effects: see Adverse event column</p> <p>Mood: TDB had relatively better score at 12 mos (no numbers provided);</p> <p>Pain VAS: 3-point (scale 1-10) reduction in pain in 11% in each treatment group (raw numbers not reported);</p> <p>DASS21: TDB had relatively better score at 12 mos (no numbers provided);</p> <p>PDI: looks similar in Figure 5b (no numbers provided)</p>	<p>Discontinued due to AEs or unsatisfactory relief (not separated by AEs only):</p> <p>A: TDB: 8/22 (41%);</p> <p>number patients with side effects at 12 mos≤1 (reading from Figure 4a);</p> <p>number patients with local skin reaction at 12 mos=1 (reading from Figure 4b);</p> <p>B: TDF: 8/24 (37.5%)</p> <p>number patients with side effects at 12 mos≤1 (reading from Figure 4a);</p> <p>number patients with local skin reaction at 12 mos=0 (reading from Figure 4b)</p>	Private Practice Research Fund of Townsville	Poor

Author Year	Study design Duration	Setting Country	Eligibility criteria	Interventions	Sample Characteristics	Screened	Eligible	Enrolled	Analyzed	Loss to Followup	Outcomes Assessed
Wild 2010	RCT 12 months	53 sites in North America; 36 sites in Europe	Inclusion: Men/ nonpregnant, nonlactating women ≥18 yrs, with diagnosis of moderate/ severe knee or hip osteo, or LBP of noncancer origin; ≥ 3 mo history pain prior to screening, dissatisfied with current analgesic; NRS score ≥4 (of 11) at baseline, after 3-7 day washout from previous anagesics. Exclusion: lifelong seizures; mild/moderate TBI, stroke, TIA, brain neoplasm within one year; severe TBI within 15 years; malignancy within 2 years; history of etoh/drug abuse; history of Hep B/C; HIV; allergy to oxycodone/ acetaminophen; participation in previous tapentadol studies; patients with reference joint or back surgery within 3 months or during study; hepatic or renal dysfunction, uncontrolled hypertension, significant pain with conditions other than osteo or LBP.	A. Tapentadol ER 100-250 mg BID (adjustable) (n=894; 413 completed 6 mos; 227 completed 12 mos) B. Oxycodone CR 20- 50 mg BID (adjustable) (n=223; 78 completed 6 mos; 44 completed 12 mos)	A vs B Age, mean (SD): 56.8 (12.5) vs 58.1 (11.8); Age category: <65 72.6% vs 70%; Male: 42.4% vs 43.9%; Race: White:88.6% vs Black: 6.7% vs 5.8%, Hispanic: 2.9% vs 1.8%, Other: 1.8% vs 1.3%; BMI: 31.7 vs 31.8; Pain intensity, Mean (SD): 7.6 (1.5) vs 7.6 (1.62); Pain intensity category: Moderate: 10% vs 13%, Severe: 90% vs 87%; Prior opioids: No 47.1% vs 49.8%	Screened: 1123 Randomized: 1121 Received drug: 1117 Discontinued-A: 53.8%; 22.7% to AEs; Discontinued-B: 65.0; 36% to AEs%	AEs; vital signs; physical exams; labs; ECGs; PROs: PAC-SYM; COWS; SOWS; TEAEs				

Note: The references are located in Appendix C.

AE=adverse event; ASA=aspirin; ECG=electrocardiogram; BID=twice daily; COWS=Clinical opiate withdrawal scale; DASS2= Depression Anxiety Stress Scale; GmbH=German liability company; GP/ED=general practitioner/emergency department; Hep B/C=Hepatitis B and/or C; HIV=human immunodeficiency virus; LBP=low blood pressure; NSAIDS=non-steroidal anti-inflammatory drug; PDI=physical disability index; ITT=intent to treat; PROs=patient reported outcomes; PAC-SYM=patient assessment of constipation syndrome; RCT=randomized controlled trial; SD=standard deviation; SE=standard error; SOWS=Subjective Opiate Withdrawal Scale; SPAASMS= score, physical, activity level, additional pain medication, additional physician/ER visits, sleep quality, mood, medication side-effects; TBI=traumatic brain injury; TDB=transdermal buprenorphine; TDF=transdermal fentanyl; VAS=visual analog scale; TEAC=treatment emergent adverse criteria; TEAEs=Treatment-Emergent Adverse Event; TIA=transient ischemic attack

Author	Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Year				
Wild 2010	<p>Mean (SE) pain intensity score: decreased 4.4 (0.09) vs 4.5 (0.17); Global assessment, score of (very) much improved: 48.1% (394/819) vs 41.2% (73/177); Median duration of treatment (days): A: 268 (range 1-385) B: 59 (range 1-384); Mean (SD) total daily dose for study completers: A: 380.5 (102.43) mg B: 71.0 (22.89) mg Concomitant nonopioid analgesics (NSAIDS, ASA, acetaminophen): A: 19.9% (178/894) B: 17% (38/223)</p>	<p>Discontinued due to AEs: A: 22.7% B: 36.8%; At least one TEAC: A: 85.7% (766/894) B: 90.6% (202/223); A vs B: Constipation: 22.6% vs 38.6%; Nausea: 18.1% vs 33.2% Vomiting: 7.0% vs 13.5%; Pruritis: 5.4% vs 10.3%; Dizziness: 14.8% vs 19.3%; Serious TEACs: 5.5% vs 4.0%; No relevant AEs on labs, vitals, ECGs; No deaths; Mean change (SE) PAC-SYM: 0.3 (0.05) vs 0.5 (0.14); COWS, 5 days post treatment, no withdrawal: 88% (145/166) vs 84% (42/50); Mean SOWS at 2-5 days post treatment - consistent with COWS</p>	J & J; grunenthal GmbH	Fair

Appendix Table E8b. Observational Studies of Different Long-Acting Opioids

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method For Assessing Outcomes and Confounders
Hartung, 2007	Retrospective cohort Medicaid claims United States	Patients prescribed at least one ≥28-day supply of methadone, ER oxycodone, ER morphine, or transdermal fentanyl	A. Transdermal fentanyl (n=1,546) B. Methadone (n=974) C. ER oxycodone (n=1,866) D. ER morphine (n=1,298)	A vs. B vs. C vs. D Mean age: 70.6 vs. 51.1 vs. 57.4 vs. 58.5 years Female sex: 74% vs. 63% vs. 65% vs. 65% Race: 6.1% vs. 10.5% vs. 7.7% vs. 9.6% non-White Mean MED dose: 96 vs. 247 vs. 67 vs. 74 mg Cancer: 19.9% vs. 18.3% vs. 25.2% vs. 26.1% Osteoarthritis: 13.7% vs. 22.6% vs. 19.3% vs. 18.0% Back pain: 17.5% vs. 41.8% vs. 35.0% vs. 27.3%	Review of claims using ICD-9 codes

Author, Year	Screened Eligible Enrolled Analyzed Loss to Followup	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
Hartung, 2007	Screened: NR Eligible: NR Enrolled: 5,684 Analyzed: 5,684	Age, sex, race, long-term care residence, number of unique prescribers, disease severity, concomitant prescriptions known to interact with opioids , type of presumed pain diagnosis, history of abuse or dependence, enrollment in a substance abuse treatment program	A vs. B vs. C (reference: D) Mortality: adjusted HR 0.71 (95% CI 0.46 to 1.08) vs. HR 0.71 (95% CI 0.54 to 0.94) vs. 0.80 (95% CI 0.63 to 1.02) ED encounter or hospitalization involving an opioid-related adverse event (HR 0.45, 95% CI 0.26 to 0.77) Among patients with noncancer pain: Fentanyl associated with higher risk of ED encounters than sustained-release morphine (HR 1.27, 95% CI 1.02 to 1.59) Methadone associated with greater risk of overdose symptoms than sustained-release morphine (HR 1.57, 95% CI 1.03 to 2.40) No significant differences between methadone and long-acting morphine in risk of death (adjusted HR 0.71, 95% CI 0.46 to 1.08) or overdose symptoms	NR	Fair

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method For Assessing Outcomes and Confounders
Krebs, 2011	Retrospective cohort VA United States	New prescription for >= 28 days' supply of PO methadone or LA morphine tabs/caps from a VA outpatient pharmacy between 1/1/2000 and 12/31/2007. Preceded by 30 day window free of LA opioid prescriptions. Excluded: Liquid/IV forms of methadone/morphine; metastatic cancer, palliative care, receiving methadone for addiction; methadone 40 mg diskettes; < 17 or > 100 years of age; missing gender data.	A: Methadone (n=28,554) B: Long-acting morphine sulfate (MS) (n=79,938)	Mean (SD) daily LA MS dose: 67.5 mg (77.4); median (IQR) 46.7 (45); Mean (SD) daily methadone dose: 25.4 mg (25.8); median (IQR): 20 (20); 99th %ile MS: 360-7200 mg; 99th %ile methadone: 124-560 mg; A vs B: Age: mean (SD): 56 (12) vs 59 (13); Race: white: 40% vs 41%; nonwhite: 52% vs 49%; unknown: 8% vs 9%; MI: 9% vs 11%; CHF: 15% vs 19%; PWD: 17% vs 20%; CVD: 15% vs 17%; COPD: 35% vs 38%; Diabetes: 31% vs 33%; Malignancy: 15% vs 26%; Depression: 62% vs 54%; Bipolar: 10% vs 8%; Anxiety: 32% vs 27%; EtOH: 25% vs 22%; Drug disorderz: 25% vs 18%; Tobacco: 47% vs 42%; Back pain: 85% vs 76%; Joint/limb pain: 86% vs 82%; Headache: 25% vs 21%; Neuropathic pain: 35% vs 29%	All patients meeting eligibility criteria

Note: The references are located in Appendix C.

CHF=congestive heart failure; CI=confidence interval; COPD=chronic obstructive pulmonary disease; CVD=cardiovascular disease; ER=extended release; EtOH=Ethyl alcohol; HR=hazard ratio; ICD-9=International Classification of Diseases; IQR=interquartile range; LA=long acting; MI=myocardial infarction; MS=morphine sulfate; PO=oral route; PVD=peripheral vascular disease SD=standard deviation; VA=Veterans Affairs; VISN=Veterans integrated service networks

Author, Year	Screened	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
	Eligible				
Krebs, 2011	Screened: Not applicable; Eligible: 133,969; Enrolled: 108,492; Analyzed: 98,068; Loss to followup: 3,347 (died); 94,721 (censored)	Propensity score for receiving methadone was estimated with logistic regression model that included age, gender, race, geographic area (VISN), depression, anxiety, bipolar dx, schizophrenia, etoh, drug, tobacco disorders, back pain, joint/limb pain, headache, neuropathic pain; Medical comorbidities included via Romano adaptation of Charlson Comorbidity Score; Quintiles calculated and then used in Cox model; Interaction term consisting of propensity quintile and opioid group	All-cause mortality: Unadjusted: 3,347 (3.4%) patients died; highest mortality within 1st 30 days (1.2% in methadone and 3.7% in MS); raw death rates form MS higher than methadone for all 30-day intervals; Death rate: Quintile #1 (0.042 vs 0.133); Quintile #2 (0.034 vs 0.078); Quintile #3 (0.025 vs 0.053); Quintile #4 (0.022 vs 0.034); Quintile #5 (0.017 vs 0.020); Propensity adjusted mortality (HR): Overall risk of mortality lower with methadone than morphine (adjusted HR 0.56, 95% CI 0.51 to 0.62) Quintile #1: 0.36 (95% CI: 0.26, 0.49); Quintile #2: 0.46 (0.37, 0.56); Quintile #3: 0.50 (0.41, 0.61); Quintile #4: 0.66 (0.54, 0.81); Quintile #5: 0.92 (0.74, 1.16); Results robust in validation dataset	VA	Fair

Appendix Table E9. Trials of Opioid Dose Escalation Versus Dose Maintenance or Use of Maximum Dose Ceilings

Author Year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened		Outcomes Assessed
						Eligible	Enrolled	
Naliboff 2011	RCT 12 months	VA pain clinic U.S.	Patients referred to chronic pain clinic; nonmalignant chronic pain for at least 6 months; clinician determination that patient was eligible for long-term opioids. Excluded: anticipated surgery, post-op pain, pulmonary disease or CHF, current or history of substance abuse disorder, hospitalization for psych disorder in past 2 years	A. Escalating opioid dose; mean morphine equivalent 52 mg (n=67) B. Stable opioid dose; mean morphine equivalent 40 mg (n=73)	A vs B Mean age 53 vs 52 years 89% vs 99% male Race not reported Pain: -78% vs 77% musculoskeletal -19% vs 19% neuropathic -3% vs 4% complex Initial morphine equivalent 29.2 (SD 19.6) vs 32.3 (SD 23.1) mg Mean usual VAS 7.0 (SD 1.9) vs 6.7 (SD 1.8) Mean worst VAS 8.4 (SD 1.2) vs 8.0 (SD 1.7) Mean ABC score 1.5 (SD 2.0) vs 1.6 (SD 2.1) Mean ODI 48.6 (SD 12.6) vs 47.8 (SD 14.0)	Screened: not reported Eligible: 140 Enrolled: 140 Analyzed: 134 Loss to followup: 10/140 (7%)	Pain Functional disability Use of nonopioid medications	

Note: The references are located in Appendix C.

CI=confidence interval, NSAID=nonsteroidal anti-inflammatory drug, ODI=Oswestry Disability Index, RCT=randomized controlled trial, SD=standard deviation, US=United States, VA=Veterans Affairs, VAS=Visual Analog Scale

Author		Results	Adverse Events and Withdrawals Due To Adverse Events	Sponsor	Quality
Year					
Naliboff 2011	A vs B	Mean VAS usual pain at 12 months: 5.6 (SD 1.5) vs 6.2 (SD 1.5); p=0.11* Usual pain VAS decrease ≥1.5 points: 19/67 (28%) vs 15/73 (20%); RR 1.38; 95% CI 0.76 to 2.49 Mean VAS pain relief at 12 months: 6.0 (SD 1.7) vs 5.3 (SD 1.8); p=0.11* Increase in pain relief ≥1.5 points: 19/67 (29%) vs 11/73 (15%); RR 1.88; 95% CI 0.97 to 3.66 Worst pain VAS decrease ≥1.5 points: 9/67 (14%) vs 4/73 (6%); RR 2.45; 95% CI 0.79 to 7.59 Mean ODI at 12 months: 45.8 (SD 14.8) vs 45.0 (SD 19.4); p=0.85* ODI decrease ≥10 points: 19/67 (29%) vs 20/73 (23%); RR 1.04; 95% CI 0.61 to 1.76 Use of nonopioid treatments (A: n=64; B: n=70): -NSAID: 35/64 (55%) vs 42/70 (60%); RR 0.92; 95% CI 0.68 to 1.22 -Muscle relaxant: 10/64 (15%) vs 14/70 (20%); RR 0.78; 95% CI 0.37 to 1.63 -Anti-seizure: 40/64 (63%) vs 46/70 (66%); RR 0.95; 95% CI 0.74 to 1.23 -Anti-anxiety: 19/64 (29%) vs 24/70 (34%); RR 0.87; 95% CI 0.53 to 1.42 -Antidepressants: 45/64 (71%) vs 48/70 (69%); 1.03; 95% CI 0.82 to 1.28 -Topical: 11/64 (17%) vs 11/70 (16%); RR 1.06; 95% CI 0.49 to 2.28 -Injectable: 17/64 (26%) vs 25/70 (36%); RR 0.74; 95% CI 0.44 to 1.24 -Physical therapy: 31/64 (48%) vs 44/70 (63%); RR 0.77; 95% CI 0.57 to 1.05	A vs B All-cause withdrawals: 33/67 (49%) vs 41/73 (56%); RR 0.88; 95% CI 0.64 to 1.20 Withdrawal due to opioid misuse: 16/67 (24%) vs 22/73 (30%); RR 0.79; 95% CI 0.46 to 1.38	Department of Veterans Affairs	Fair

*p-value calculated based on completers (A: n=34; B: n=32)

Appendix Table E10. Trials of Different Strategies for Treating Acute Exacerbations of Chronic Pain in Patients on Long-term Opioid Therapy

Author year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics
Ashburn, 2011	RCT (crossover) Duration: up to 42 days total (two treatment periods of 10 breakthrough pain episodes each within 21 days)	46 centers United States	Patients aged 18 to 80 years with ≥ 3 months of chronic pain associated with diabetic neuropathy, postherpetic neuralgia, traumatic injury, complex regional pain syndrome, back pain, neck pain, fibromyalgia, chronic pancreatitis, osteoarthritis, or cancer; receiving ≥ 60 mg/day MED, with 1-4 episodes of breakthrough pain per day	A. Fentanyl buccal tablet (n=183) B. Oxycodone (n=183)	Mean age: 48.8 years Female sex: 62% Race: 92% White, 5% Black, 3% other Pain intensity in 24 hours prior to enrollment: 5.1 Indication (most common): 57% back pain, 11% osteoarthritis, 8% neck pain, 9% fibromyalgia, 4% traumatic injury, 4% complex regional pain syndrome
Davies, 2011	RCT (crossover) 3-21 days	35 cancer centers Europe and India	Patients with histologically confirmed cancer, receiving a fixed-schedule opioid regimen at a total daily dose equivalent ≥ 60 mg MED, with 1-4 episodes of breakthrough pain per day	A. Fentanyl pectin nasal spray (n=106 for safety and n=84 for efficacy) B. Immediate-release morphine sulfate (n=106 for safety and n=84 for efficacy)	Mean age: 55.9 years Female sex: NR Race: NR

Author year	Screened, Eligible, Enrolled, Analyzed Loss to Followup	Outcomes Assessed	Results	Adverse Events and Withdrawals Due To Adverse Events		Sponsor	Quality
Ashburn, 2011	Screened: 486 Eligible: 360 Enrolled: 323 (titration phase) Analyzed: 320 (safety), 183 (efficacy)	Pain intensity, pain relief, and total pain relief	A vs. B Pain intensity difference at 15 minutes: 0.82 vs. 0.60 (p<0.001) Pain relief at 15 minutes: 0.69 vs. 0.53 (p<0.05) Meaningful pain relief within 15 minutes: 16% vs. 12% of episodes (p<0.05)	A vs. B Any adverse event: 38% (106/281) vs. 31% (88/284); RR 1.22 (95% CI 0.97 to 1.53)		Cephalon, Inc.	Good
Davies, 2011	Screened: NR Eligible: NR Enrolled: 110 (titration phase) Analyzed: 106 (safety population), 84 (randomized after titration phase)	Pain intensity, pain relief, and total pain relief	A vs. B ≥2-point reduction in pain intensity at 10 minutes: 52.4% vs. 45.4% (p<0.05) ≥2 pain relief at 15 minutes: 60.2% vs. 53.4% (p<0.05) Total pain relief ≥33% at 15 minutes: 52.3% vs. 43.5% (p<0.01)	A vs. B Treatment-emergent adverse events resulting in discontinuation: 6 vs. 2		No financial support provided	Fair

Author year	Study Design		Setting Country	Eligibility Criteria	Interventions	Sample Characteristics
	Duration					
Portenoy, 2007	RCT 3 weeks	Multicenter Clinic setting not described United States		18 to 80 years, chronic low back pain associated with osteoarthritis, degenerative disc disease, or spondylolisthesis resulting in functional disability for at least 3 months, receiving morphine average pain intensity scale in 24 hours prior to entry, duration of breakthrough pain less than 4 hours, use of an opioid to treat breakthrough pain described as at least somewhat effective Exclude: Uncontrolled or rapidly escalating pain, allergies or contraindications to study drug, cardiopulmonary disease that might affect safety, psychiatric or medical disease that might affect data collection, alcohol or substance abuse during the past 5 years, lactating, participated in an earlier fentanyl buccal tablet trial, or expected to have surgery during study	A: Buccal fentanyl 100 to 800 mcg for an episode of breakthrough pain B: Placebo <input type="checkbox"/> Dose of buccal fentanyl: 800 mcg 56%; 600 mcg 24%; 400 mcg 15%; 200 mcg 5%	Not reported for randomization groups Mean age: 47 years Female gender: 55% Non-white race: 12% Baseline pain intensity: 5.1 (10 point scale) Primary etiology of low back pain degenerative disc disease: 68%

Author year	Screened, Eligible, Enrolled, Analyzed Loss to Followup	Outcomes Assessed	Results	Adverse Events and Withdrawals Due To Adverse Events		Sponsor	Quality
Portenoy, 2007	Screened: 124 Eligible: NR Enrolled: 105 (in open-label dose titration), 77 (in randomized phase; randomized to one of 3 treatment sequences consisting of 6 fentanyl buccal tablets and 3 placebo tablets in different orders)	Pain intensity: 0 to 10 scale Pain relief: 5-point scale (0 = none to 4 - complete) Onset time of "meaningful" pain relief	A vs. B Sum of the pain intensity differences from 5 through 60 minutes: 8.3 vs. 3.6 Proportion of breakthrough pain episodes with "meaningful" pain reduction: 70% (289/413) vs. 30% (63/207) ($p < 0.0001$) Proportion of breakthrough pain episodes with $\geq 33\%$ reduction in pain intensity after 30 minutes: 42% (172/413) vs. 18% (18/207) ($p \leq 0.0001$) Proportion of breakthrough pain episodes with $\geq 50\%$ reduction in pain intensity after 30 minutes: 30% (122/413) vs. 13% (27/207) ($p \leq 0.0001$) Proportion of breakthrough pain episodes with $\geq 33\%$ reduction in pain intensity after 120 minutes: 65% (269/413) vs. 28% (57/207) ($p \leq 0.0001$) Proportion of breakthrough pain episodes with $\geq 50\%$ reduction in pain intensity after 120 minutes: 48% (198/413) vs. 16% (33/207) ($p \leq 0.0001$)	All data reported only for buccal fentanyl Withdrawn due to adverse event: 1% (1/77) Serious adverse events: 3% (2/77) Nausea: 1% Dizziness: 4% Somnolence: 0% Dysgeusia: 8% Vomiting: 0% Dry mouth: 4%	Cephalon, Inc.	Good	

Author year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics
Simpson, 2007	RCT (crossover) 3 weeks	Multicenter Clinic setting not described United States	18 to 80 years old, ≥3 months history of chronic neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, traumatic injury, or complex regional pain syndrome, on chronic opioids (at least 60 mg/day or morphine or equivalent), pain intensity <7 on a 0 to 10 scale, 1 to 4 daily episodes of breakthrough pain, use of opioid therapy for breakthrough pain described as at least partially effective; had to identify effective dose during dose-titration phase to be entered into randomized portion of trial Exclude: Unstable, uncontrolled, or rapidly escalating pain; allergies or other contraindications to study drug; alcohol or substance abuse in past 5 years; significant cardiopulmonary disease; significant medical or psychiatric disease; pregnancy or lactating	A: Buccal fentanyl 100 to 800 mcg for an episode of breakthrough pain B: Placebo Dose of buccal fentanyl: 800 mcg 54%; 600 mcg 19%; 400 mcg 18%; 200 mcg 5%, 100 mcg 5%	NR for randomization groups
Webster, 2013	RCT (crossover) Duration: up to 42 days total (two treatment periods of 10 breakthrough pain episodes each within 21 days)	42 sites Setting not described United States	Patients aged 18 to 80 years with >3 months of chronic pain associated with diabetic neuropathy, postherpetic neuralgia, traumatic injury, complex regional pain syndrome, back pain, neck pain, fibromyalgia, chronic pancreatitis, osteoarthritis, or cancer; receiving >60 mg/day MED, with an average pain intensity ≤6 and 1-4 episodes of breakthrough pain per day Exclude: recent history of substance abuse, positive UDT	A. Fentanyl buccal tablet (n=137) B. Oxycodone (n=137)	Mean age: 50.8 years Female sex: 58% Race: 91% White, 7% Black, 2% other Pain intensity in 24 hours prior to enrollment: 5.1

Note: The references are located in Appendix C.

CI=confidence interval; MED=morphine equivalent dose; NR=not relevant ; RCT=randomized controlled trial

Author year	Screened, Eligible, Enrolled, Analyzed Loss to Followup	Outcomes Assessed	Results	Adverse Events and Withdrawals Due To Adverse Events		Sponsor	Quality
Simpson, 2007	<p>Screened: 129 Eligible: NR Enrolled: 103 (in open-label dose titration), 79 (in randomized phase; randomized to one of 3 crossover treatment sequences consisting of 6 fentanyl buccal tablets and 3 placebo tablets)</p> <p>Discontinued early: 2.5% (2/79)</p>	<p>Pain Intensity: 0 to 10 scale Sum of Pain Intensity differences from 5 through 60 minutes differences from 5 through 60 minutes after administration of study drug</p>	<p>A vs. B Sum of the pain intensity differences from 5 through 60 minutes: 9.63 vs. 5.73 ($p<0.001$) Proportion of breakthrough pain episodes with 'meaningful' pain reduction: 69% vs. 36% ($p<0.0001$) Proportion of breakthrough pain episodes with $\geq 50\%$ reduction in pain intensity after 15 minutes: 12% vs. 5% ($p\leq 0.0001$), $p<0.0001$ for each subsequent time point from 30 to 120 minutes Use of supplemental medication: 14% (59/432) vs. 36% (77/213) (OR=0.28, 95% CI 0.18 to 0.42)</p>	<p>All data reported only for buccal fentanyl: Withdrawn due to adverse event: 2.5% (2/79); 12% (12/103) withdrawn due to adverse events during open-label dose titration Nausea: 0% Dizziness: 1% Somnolence: 1% Vomiting: 0%</p> <p>Application site adverse event: 8% (8/103) during open-label dose titration</p>		Cephalon, Inc.	Good
Webster, 2013	<p>Screened: 307 Eligible: NR Enrolled: 213 (titration phase) Analyzed: 211 (safety), 137 (efficacy)</p>	<p>Pain intensity, pain relief, and total pain relief</p>	<p>A vs. B Pain intensity difference at 15 minutes: 0.88 vs. 0.76 ($p<0.001$) Pain relief at 15 minutes: 38% vs. 34% ($p<0.05$) Meaningful pain relief within 15 minutes: 17% vs. 16% ($p=NS$) Meaningful pain relief within 30 minutes: 46% vs. 38% ($p<0.01$)</p>	<p>A vs. B Any adverse event: 18% (25/138) vs. 14% (20/142); RR 1.29 (95% CI 0.75 to 2.20)</p>		Teva Pharmaceuticals (formerly Cephalon, Inc.)	Good

Appendix Table E11. Trials of Decreasing Opioid Doses or of Tapering Off Opioids Versus Continuation of Opioids

Author year	Study design Duration	Setting Country	Eligibility criteria	Interventions	Sample Characteristics	Screened
						Eligible
Cowan, 2005	RCT (crossover) 60 hours	Single center Pain clinic United Kingdom	>18 years, chronic noncancer pain on sustained-release oral morphine for ≥ 30 days, willing to abstain from morphine, able to give regular blood samples Exclude: Pain not adequately controlled by immobilization and alternative medication, patient may require a sudden change in opioid dose, pregnant or lactating	A: Continued sustained-release morphine for 60 hours B: Abrupt cessation of morphine for 60 hours	Mean age: 56 years Female gender: 40% Non-white race: Not reported Pain >5 years: 90% Duration of morphine use: mean 2.2 years Dose ≤ 60 mg/day: 90%	Screened: 33 Eligible: 11 Enrolled: 10 Analyzed: 10

Note: The references are located in Appendix C.

RCT=randomized controlled trial

Author year	Outcomes Assessed	Results	Adverse Events and Withdrawals		Sponsor	Quality
			Due To Adverse Events			
Cowan, 2005	Effects of cessation of opioids: Unvalidated 19-item questionnaire Brief Pain Inventory Evaluation of physiologic parameters (heart rate, blood pressure, temperature, respiration, pupil size)	Continued sustained-release morphine vs. abrupt cessation Brief Pain Inventory, average pain in last 24 hours (0 to 10): 3.2 vs. 5.3 ($p<0.026$) Pain interference with general activity in last 24 hours (0 to 10): 0.2 vs. 4.3 ($p<0.027$) Physiologic parameters: No differences	Adverse events during cessation of opioids: 3/10 (30%) "Do you have any drug craving?": 0/10 after abrupt cessation of therapy		Janssen-Cilag Ltd., Napp Pharmaceuticals	Poor

Appendix Table E12. Nonrandomized Trials of Different Opioid Tapering Protocols and Strategies

Author Year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics
Ralphs, 1994	Non-randomized trial 6 months	Inpatient, single center United Kingdom	<p>Patients referred to inpatient pain management, on opioids, chronic non-cancer pain, with any two of following: widespread disruption in activity due to pain, habitual over-activity leading to increased pain, regular use of analgesics and/or sedatives for >6 months, high affective distress, use of unnecessary aids, high levels of reported or observed pain behaviors, work reduced, impaired, or ceased owing to pain</p> <p>Exclude: Cannot use English, cannot climb stairs, current major psychiatric illness, unavailable for 4-week program, suitable for further physical treatments after medical examinations, pain of less than 1 year's duration, under 18 years old, currently using opioids for treatment of drug dependency</p>	<p>A: Patient-controlled reduction (patient discussed desired rate of reduction, aiming for abstinence by discharge, allowed to take longer if they wished, patients kept pills in room, plans adjusted as appropriate)</p> <p>B: Cocktail method (opioid mixed into a cocktail with dose gradually reduced, patient unaware of reduction schedule)</p>	<p>Mean age: 47 vs. 50 years Female gender: 49% vs. 71% Non-white race: Not reported Pain duration: 124 vs. 101 months Pain distress (0 to 100): 66 vs. 73 Mean opiate dose: 35.8 mg/day</p>
Tennant, 1982	Non-randomized clinical trial 3 to 18 months	Single center Outpatient clinic United States	<p>Patients on opioids who volunteered for outpatient treatment for withdrawing opioids</p>	<p>A: Detoxification/counseling: Detoxification over 3 weeks with methadone, propoxyphene, clonidine, diphenoxylate, or sedative-hypnotics, followed by weekly psychotherapeutic counseling</p> <p>B: Detoxification/maintenance: Detoxification as above, with maintenance on opioid if detoxification unsuccessful</p>	<p>Mean age: 33 vs. 44 years Female gender: 48% vs. 52% Nonwhite race: 19% vs. 14% Duration of opioid use: 7.2 vs. 9.2 years Proportion with chronic pain: 62% vs. 71% Back/spine disorder: 24% vs. 19% Use of codeine: 67% vs. 48%</p>

Note: The references are located in Appendix C.

NR=not reported

Author Year	Loss to Followup	Outcomes Assessed	Results	Adverse Events and Withdrawals Due To Adverse Events		Sponsor	Quality
Ralphs, 1994	<p>Screened: 132 Eligible: NR Enrolled: 108 (63 to patient-controlled method and 45 to cocktail method) Analyzed: 108 Attrition: 24% (26/108)</p>	<p>Abstinent at discharge Abstinent at 6 month after discharge Use of other drugs, pain, or psychological variables at 6 months</p>	<p>Patient-controlled reduction versus cocktail method Abstinent at discharge: 68% vs. 89% ($p<0.05$) Abstinent 6 months after discharge: 54% (27/50) vs. 56% (18/32) Use of other drugs, pain, or psychological variables at 6 months: No differences between groups</p>	NR		King Edwards Hospital Fund for London, Special Trustees of St. Thomas Hospital, and the South East Thames Regional Health Authority	Poor
Tennant, 1982	<p>Screened: NR Eligible: NR Enrolled: 42 (21 to detoxification/ counseling and 21 to detoxification/ maintenance) Analyzed: 42</p>	<p>Proportion remaining in treatment past 3 weeks Proportion abstinent from opioids (as judged by history, negative urine test, and no further requests for opioids)</p>	<p>Detoxification/counseling vs. detoxification/maintenance Proportion remaining in treatment past 3 weeks: 24% (5/21) vs. 95% (20/21) Abstinent after 90 days: 10% (2/21) vs. 19% (4/21)</p>	NR	NR		Poor

Appendix Table E13. Prospective Studies on Use of Screening Instruments To Predict the Risk of Aberrant Drug-Related Behaviors

Author, Year	Study Design	Eligibility Criteria	Population Characteristics	N	Instrument	Method of Administration	Reference Standard	True Positives (n)
Akbik 2006	Prospective cohort	Chronic pain patients attending one of two pain clinics	Mean age 43 years (SD 9.6) 33% female 86% White, other races not reported Pain: 39% back	n=155 (with reference standard, of 397 enrolled)	SOAPP	Self-report	Positive urine screening	SOAPP score ≥8: 30
Jones 2012 (Study 2)	Retrospective cohort	Consecutive pain clinic patients being evaluated for risk of opioid addiction prior to opioid initiation	Mean age 48 years (SD 13) 56% female 96% White, other races not reported Pain: 45% low back pain, 21% arthritis or fibromyalgia, 14% joint pain, 10% pelvic or abdominal pain, 7% neck or upper back pain	n=263	ORT PMQ SOAPP-R Clinician assessment	Self-report; clinician interview	Subsequent opioid discontinuation due to abuse	ORT score >4: 8 PMQ score >30: 13 SOAPP-R score >17: 20 Clinician assessment of high-risk: 27
Moore 2009	Retrospective cohort	New adult patients at a pain clinic	Mean age 44 years (SD 11) 60% female Race not reported Pain not reported	n=48	SOAPP DIRE ORT Clinician assessment	Self-report (SOAPP, DIRE, ORT); clinician interview	Subsequent opioid discontinuation due to abuse	SOAPP: 35 DIRE: 8 ORT: 21 Clinical interview: 37

Author, Year	False Positives	True Negatives	False Negatives	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio	AUROC	Quality
	(n)	(n)	(n)						
Akbik 2006	SOAPP score ≥8: 59	SOAPP score ≥8: 37	SOAPP score ≥8: 14	SOAPP score ≥8: 0.68 (95% CI 0.52 to 0.81)	SOAPP score ≥8: 0.39 (95% CI 0.29 to 0.49)	SOAPP score ≥8: 1.11 (95% CI 0.86 to 1.43)	SOAPP score ≥8: 0.83 (95% CI 0.52 to 1.31)	Not reported	Fair
Jones 2012 (Study 2)	ORT score >4: 19 PMQ score >30: 41 SOAPP-R score >17: 65 Clinician assessment of high-risk: 57	ORT score >4: 142 PMQ score >30: 134 SOAPP-R score >17: 17 Clinician assessment of high-risk: 84	ORT score >4: 33 PMQ score >30: 25 SOAPP-R score >17: 17 Clinician assessment of high-risk: 11	ORT score >4: 0.20 (95% CI 0.15 to 0.27) PMQ score >30: 0.34 (95% CI 0.20 to 0.51) SOAPP-R score >17: 0.39 (95% CI 0.26 to 0.54) Clinician assessment of high-risk: 0.71 (95% CI 0.54 to 0.84)	ORT score >4: 0.88 (95% CI 0.82 to 0.93) PMQ score >30: 0.77 (95% CI 0.69 to 0.80) SOAPP-R score >17: 0.69 (95% CI 0.63 to 0.75) Clinician assessment of high-risk: 0.60 (95% CI 0.51 to 0.68)	ORT score >4: 1.65 (95% CI 0.78 to 3.51) PMQ score >30: 1.46 (95% CI 0.87 to 2.45) SOAPP-R score >17: 1.27 (95% CI 0.86 to 1.90) Clinician assessment of high-risk: 1.76 (95% CI 1.32 to 2.34)	ORT score >4: 0.91 (95% CI 0.78 to 1.06) PMQ score >30: 0.86 (95% CI 0.68 to 1.08) SOAPP-R score >17: 0.88 (95% CI 0.70 to 1.10) Clinician assessment of high-risk: 0.49 (95% CI 0.29 to 0.81)	ORT 0.53 PMQ 0.57 SOAPP-R 0.54	Poor
Moore 2009	Not calculable	Not calculable	SOAPP: 13 DIRE: 40 ORT: 27 Clinical interview: 11	SOAPP score ≥6: 0.73 DIRE score <14: 0.17 ORT score >4: 0.45 Clinical interview assessment medium or high risk: 0.77	Not reported	Not reported	Not reported	Not reported	Poor

Author, Year	Study Design	Eligibility Criteria	Population Characteristics	N	Instrument	Method of Administration	Reference Standard	True Positives (n)
Webster 2005	Prospective cohort	New chronic pain patients at a pain clinic	Mean age 44 years (SD 13) 58% female Race not reported Pain: 45% back; 18% head; 16% neuropathic; 16% musculoskeletal; 5% visceral	n=185	ORT	Self-report	Documentation of aberrant behavior during followup	ORT score 1-3 (low risk): 1 ORT score 4-7 (moderate risk): 35 ORT score ≥8 (high risk): 40

Note: The references are located in Appendix C.

AUROC=area under receiver operating characteristic curve; CI=confidence interval; DIRE= Diagnosis, Intractability, Risk and Efficacy Inventory; ORT=Opioid Risk Tool; PMQ=Pain Medication Questionnaire; SOAPP-R= Revised Screener and Opioid Assessment for Patients with Pain

Author, Year	False Positives		True Negatives		False Negatives (n)		Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio	AUROC	Quality
	(n)	(n)										
Webster 2005	ORT score 1-3 (low risk): 17	ORT score 1-3 (low risk): 92	ORT score 1-3 (low risk): 75	ORT score ≥4: 0.99 (95% CI 0.92 to 0.999)	ORT score ≥4: 0.16 (95% CI 0.10 to 0.24)	ORT score ≥4: 1.17 (95% CI 1.07 to 1.27)	ORT score ≥4: 0.08 (95% CI 0.01 to 0.65)	ORT score 1-3 (low risk): 0.08	ORT score 4-7 (moderate risk): 0.57 (95% CI 0.44 to 0.74)	ORT score ≥8 (high risk): 14.34 (95% CI 5.35 to 38)	Not reported	Fair
	ORT score 4-7 (moderate risk): 88	ORT score 4-7 (moderate risk): 21	ORT score 4-7 (moderate risk): 41									
	ORT score high (≥8): 4	ORT score high (≥8): 105	ORT score high (≥8): 36									

Appendix F. Quality Assessment Tables

Appendix Table F1. Quality Assessment of Cohort Studies

Author, Year	KQ	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria (inception cohort)?		Were the groups comparable at baseline on key prognostic factors (e.g., by restriction)		Did the study maintain comparable groups through the study period?		Did the study use accurate methods for ascertaining exposures and potential confounders?		Were outcome assessors and/or data analysts blinded to the exposure being studied?		Did the article report attrition?	Is there important differential loss to followup or overall high loss to followup?	Did the study perform appropriate statistical analyses on potential confounders?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Quality
		or matching)?	study period?	potential confounders?	being studied?											
Carman, 2011	KQ2a, b myocardial infarction	Yes	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Yes	Yes	Yes	Fair		
Dunn, 2010	KQ2a, b overdose	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair		
Edlund, 2014	KQ2a, b abuse	Yes	Unclear	Yes	Yes	Unclear	No	No	Yes	Yes	Yes	Yes	Yes	Fair		
Hartung, 2007	KQ3c	Yes	No	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Yes	Yes	Yes	Fair		
Krebs, 2011	KQ3c	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Fair		
Saunders, 2010	KQ2a, b fractures	Yes	Unclear	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Yes	Yes	Yes	Fair		

Note: The references are available in Appendix C.

Based on United States Preventive Services Task Force Quality Assessment Criteria (see Methods section for details).

KQ=key question

Appendix Table F2. Quality Assessment of Cross-Sectional Studies

Author, Year	KQ	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were outcome assessors blinded to patient characteristics?	Did the article report attrition?	Is there overall high loss to followup?	Were prespecified outcomes assessed in all patients?	Quality
Banta-Green, 2009	KQ2a abuse	Yes	Unclear	NA	NA	Yes	Fair
Boscarino, 2010	KQ2a abuse	Yes; random	No	NA	NA	No (high proportion of nonrespondents)	Fair
Carrington Reid, 2002	KQ2a abuse	Yes	No	NA	NA	Yes	Fair
Compton, 2008	KQ2a abuse	Yes; consecutive	No	No	Unclear	Yes	Fair
Cowan, 2003	KQ2a abuse	Yes	Unclear	NA	NA	Yes	Fair
Deyo, 2013	KQ2a , b endocrine	Yes	Unclear	NA	NA	Yes	Fair
Fleming, 2007 See also: Saffier, 2007	KQ2a abuse	Yes; all	No	NA	NA	Yes	Fair
Hojsted, 2010	KQ2a abuse	Unclear	No	NA	NA	Yes	Fair
Portenoy, 2007	KQ2a abuse	No (28% of eligible patients enrolled, not clear why most did not enroll)	No	Yes	Yes (Table 3)	Yes	Fair
Schneider, 2010	KQ2a abuse	Yes	No	NA	NA	No; UDT only in 82% of patients	Fair
Wasan, 2009	KQ2a abuse	Unclear	Yes	NA	NA	No	Fair

Note: The references are located in Appendix C.

Based on United States Preventive Services Task Force Quality Assessment Criteria (see Methods section for details).

KQ=key question; NA=not applicable; UDT=urine drug test

Appendix Table F3. Quality Assessment of Case Control Studies

Author, Year	KQ	Did the study attempt to enroll all or random sample of cases using predefined criteria?		Were the groups comparable at baseline on key prognostic factors?	Were enrollment rates similar in cases and controls invited to participate?	Did the study use accurate methods for identifying outcomes?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Did the study perform appropriate statistical analyses on potential confounders?	Quality
		Were the controls derived from the same population as the cases?							
Gomes, 2011	KQ2b overdose	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Good
Gomes, 2013	KQ2b, motor vehicle accident	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Good
Li, 2013a	KQ2a fractures	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Good
Li, 2013b	KQ2a myocardial infarction	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Good

Note: The references are available in Appendix C.

Based on United States Preventive Services Task Force Quality Assessment Criteria (see Methods section for details).

KQ=key question

Appendix Table F4. Quality Assessment of Trials

Author, year	KQ	Randomization	Concealed treatment allocation	Baseline group similarity	Patient blinded	Care provider blinded	Outcome assessor blinded	Counter-ven-tions avoided or similar	Compli-ance accept-able in all groups		Attrition reported	Attrition accept-able	Timing of outcome assess-ment in all groups		Intention to treat analysis	Avoid-ance of selective outcomes reporting	Quality
Allan, 2005	KQ3c	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Fair
Ashburn, 2011	KQ3h	Yes	Yes	Yes	Yes	Yes	Yes	Unclear; probably yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Cowan, 2005	KQ3i	Yes	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	No	Unclear	Yes	Yes	Yes	Unclear	Poor	
Davies, 2011	KQ3h	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Jamison, 1998	KQ3a	Unclear	Unclear	Unclear	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Fair	
Mitra, 2013	KQ3c	Yes	No	Unclear	Unclear	No	Yes	Yes	No	Yes	No	No	Yes	No	No	Poor	
Naliboff 2011	KQ3f	Yes	Yes	Yes	Yes	Yes	No	Unclear	Yes (similar in both groups)	Unclear	Yes	No	Yes	Yes	Yes	Fair	
Portenoy, 2007	KQ3h	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Good
Ralphs, 1994	KQ3j	No	No	No	No	No	No	No	yes	unclear	No	Unclear	yes	yes	unclear	Poor	
Salzman, 1999	KQ3a	Unclear	Unclear	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Fair	
Simpson, 2007	KQ3h	Yes	Unclear	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	
Tennant, 1982	KQ3j	No	No	No	No	No	No	No	Unclear	Unclear	No	Unclear	Yes	Yes	Unclear	Poor	
Webster, 2013	KQ3h	Yes	Yes	Yes	Yes	Yes	Yes	Unclear; probably yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good	
Wild 2010	KQ3c	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Fair	

Note: The references are available in Appendix C.

Based on Cochrane Back Review Group Quality Assessment Methods (see Methods section for details).

KQ=key question

Appendix Table F5. Quality Assessment of Screening Instrument Studies

Author, year	Evaluates population other than the one used to derive the instrument		Consecutive series of patients or a random subset		Describes severity of symptoms, opioid dose/duration and underlying conditions		Appropriate criteria included in screening instrument		Adequate description of methods for identifying aberrant drug-related behaviors	Appropriate criteria used to identify aberrant drug related behaviors	Aberrant drug-related behaviors assessed in all enrollees	Blinded assessment of aberrant drug-related behaviors	Quality
	Avoided case-control design					Adequate description of screening instrument	Included in screening instrument						
Akbik, 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Unclear	Fair	
Jones, 2012	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	No	Unclear	Poor	
Moore, 2009	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	No	Unclear	Poor	
Webster, 2005	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Unclear	Unclear	Unclear	Fair	

Note: The references are available in Appendix C.

Based on various methods sources (see Methods section for details).

Appendix G. Strength of Evidence Table

Key Question Outcome	Study Design						Reporting Bias	Strength of Evidence Grade
	Number of Studies (N)	Study Limitations	Consistency	Directness	Precision			
1. Effectiveness and comparative effectiveness								
a. In patients with chronic pain, what is the effectiveness of long-term opioid therapy versus placebo or no opioid therapy for long-term (>1 year) outcomes related to pain, function, and quality of life?	Pain, function, quality of life	No studies	-	-	-	-	-	Insufficient
b. How does effectiveness vary depending on: 1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including low back pain], fibromyalgia, sickle cell disease, inflammatory pain, and headache disorders); 2) patient demographics (e.g., age, race, ethnicity, gender); 3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities and high risk for addiction)?	Pain, function, quality of life	No studies	-	-	-	-	-	Insufficient
c. In patients with chronic pain, what is the comparative effectiveness of opioids versus nonopioid therapies (pharmacological or nonpharmacological) on outcomes related to pain, function, and quality of life?	Pain, function, quality of life	No studies	-	-	-	-	-	Insufficient
d. In patients with chronic pain, what is the comparative effectiveness of opioids plus nonopioid interventions (pharmacological or nonpharmacological) versus opioids or nonopioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used?	Pain, function, quality of life	No studies	-	-	-	-	-	Insufficient
	Pain, function, quality of life	No studies	-	-	-	-	-	Insufficient

Key Question Outcome	Study Design						Reporting Bias	Strength of Evidence Grade
	Number of Studies (N)	Study Limitations	Consistency	Directness	Precision			
2. Harms and adverse events								
a. In patients with chronic pain, what are the risks of opioids versus placebo or no opioid on: 1) opioid abuse, addiction, and related outcomes; 2) overdose; and 3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?								
Abuse, addiction	1 cohort study (n=568,640)	Moderate	Unknown (1 study)	Direct	Precise	Undetected	Low	
Abuse, addiction	10 uncontrolled studies (n=3,780)	High	Inconsistent	Direct	Precise	Undetected	Insufficient	
Overdose	1 cohort study (n=9,940)	Moderate	Unknown (1 study)	Direct	Imprecise	Undetected	Low	
Fractures	1 cohort study (n=2,341) and 1 case-control study (21,739 cases)	Moderate	Consistent	Direct	Precise	Undetected	Low	
Myocardial infarction	1 cohort study (n=426,124) and 1 case-control study (11,693 cases)	Low	Consistent	Direct	Precise	Undetected	Low	
Endocrine	1 cross-section study (n=11,327)	Moderate	Unknown (1 study)	Direct	Precise	Undetected	Low	
Gastrointestinal harms, motor vehicle accidents, infections, psychological harms, cognitive harms	No studies	-	-	-	-	-	-	Insufficient
b. How do harms vary depending on: 1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including back pain], fibromyalgia, sickle cell disease, inflammatory pain, headache disorders); 2) patient demographics; 3) patient comorbidities (including past or current substance use disorder or at high risk for addiction)?								
Various harms	No studies	-	-	-	-	-	-	Insufficient

Key Question Outcome	Study Design						Reporting Bias	Strength of Evidence Grade
	Number of Studies (N)	Study Limitations	Consistency	Directness	Precision			
b. How do harms vary depending on the dose of opioids used?								
Abuse, addiction	1 cohort study (n=568,640)	Moderate	Unknown (1 study)	Direct	Precise	Undetected	Low	
Overdose	1 cohort study (n=9,940) and 1 case-control study (593 cases in primary analysis)	Moderate	Consistent	Direct	Precise	Undetected	Low	
Fracture	1 cohort study (n=2,341)	Moderate	Unknown (1 study)	Direct	Imprecise	Undetected	Low	
Myocardial infarction	1 cohort study (n=426,124)	Moderate	Unknown (1 study)	Direct	Precise	Undetected	Low	
Motor vehicle accidents	1 case-control study (5,300 cases)	Low	Unknown (1 study)	Direct	Precise	Undetected	Low	
Endocrine	1 cross-sectional study (n=11,327)	Moderate	Unknown (1 study)	Direct	Precise	Undetected	Low	
3. Dosing strategies								
a. In patients with chronic pain, what is the comparative effectiveness of different methods for initiating and titrating opioids for outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?								
Pain	2 randomized trials (n=93)	Moderate	Inconsistent	Direct	Imprecise	Undetected	Insufficient	
Function, quality of life, outcomes related to abuse	No studies	-	-	-	-	-	Insufficient	
b. In patients with chronic pain, what is the comparative effectiveness of short- versus long-acting opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?								
Pain, function, quality of life, outcomes related to abuse	No studies	-	-	-	-	-	Insufficient	

Key Question Outcome	Study Design						Reporting Bias	Strength of Evidence Grade
	Number of Studies (N)	Study Limitations	Consistency	Directness	Precision			
c. In patients with chronic pain, what is the comparative effectiveness of different long-acting opioids on outcomes related to pain, function, and quality of life; and risk of overdose, addiction, abuse, or misuse?								
Pain and function	3 randomized trials (n=1,850)	Moderate	Consistent	Direct	Precise	Undetected	-	Low
Assessment of risk of overdose, addiction, abuse, or misuse	No studies	-	-	-	-	-	-	Insufficient
Overdose (as indicated by all-cause mortality)	1 cohort study (n=108,492)	Moderate	Unknown (1 study)	Direct	Precise	Undetected	-	Low
Abuse and related outcomes	1 cohort study (n=5,684)	Moderate	Unknown (1 study)	Direct	Imprecise	Undetected	-	Insufficient
d. In patients with chronic pain, what is the comparative effectiveness of short- plus long-acting opioids vs. long-acting opioids alone on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?								
Pain, function, quality of life, outcomes related to abuse	No studies	-	-	-	-	-	-	Insufficient
e. In patients with chronic pain, what is the comparative effectiveness of scheduled, continuous versus as-needed dosing of opioids on outcomes related to pain, function, and quality of life; risk of overdose, addiction, abuse, or misuse; and doses of opioids used?								
Pain, function, quality of life, outcomes related to abuse	No studies	-	-	-	-	-	-	Insufficient
f. In patients with chronic pain on long-term opioid therapy, what is the comparative effectiveness of dose escalation versus dose maintenance or use of maximum dose ceilings on outcomes related to pain, function, and quality of life?								
Pain, function, withdrawal due to opioid misuse	1 randomized trial (n=140)	Moderate	Unknown (1 study)	Direct	Imprecise	Undetected	-	Low

Key Question Outcome	Study Design		Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
	Number of Studies (N)							
g. In patients on long-term opioid therapy, what is the comparative effectiveness of opioid rotation versus maintenance of current opioid therapy on outcomes related to pain, function, and quality of life; and doses of opioids used?			-	-	-	-	-	
Pain, function, quality of life, outcomes related to abuse	No studies							Insufficient
h. In patients on long-term opioid therapy, what is the comparative effectiveness of different strategies for treating acute exacerbations of chronic pain on outcomes related to pain, function, and quality of life?			-	-	-	-	-	
Pain	5 randomized trials (n=802)	Moderate	Consistent	Direct	Precise	Undetected	Moderate	
Function, quality of life, abuse and related outcomes	No studies	-	-	-	-	-	-	Insufficient
i. In patients on long-term opioid therapy, what are the effects of decreasing opioid doses or of tapering off opioids versus continuation of opioids on outcomes related to pain, function, quality of life, and withdrawal symptoms?								
Pain, function	1 randomized trial (n=10)	High	Unknown (1 study)	Direct	Imprecise	Undetected	Insufficient	
j. In patients on long-term opioid therapy, what is the comparative effectiveness of different tapering protocols and strategies on measures related to pain, function, quality of life, withdrawal symptoms, and likelihood of opioid cessation?								
Opioid abstinence	2 nonrandomized trials (n=150)	High	Consistent	Direct	Imprecise	Undetected	Insufficient	

Key Question	Outcome	Study Design		Study Limitations	Consistency	Directness	Precision	Reporting Bias	Strength of Evidence Grade
		Number of Studies	(N)						
4. Risk assessment and risk mitigation strategies									
a. In patients with chronic pain being considered for long-term opioid therapy, what is the accuracy of instruments for predicting risk of opioid overdose, addiction, abuse, or misuse?									
Diagnostic accuracy: Opioid Risk Tool		3 studies of diagnostic accuracy (n=496)		Moderate	Inconsistent	Direct	Imprecise	Undetected	Insufficient
Diagnostic accuracy: Screening and Opioid Assessment for Patients with Pain version 1		2 studies of diagnostic accuracy (n=203)		High	Consistent	Direct	Imprecise	Undetected	Low
; with chronic pain, what is the effectiveness of use of risk instruments on outcomes related to overdose, addiction, abuse, or									
Outcomes related to abuse		No studies		-	-	-	-	-	Insufficient
c. In patients with chronic pain prescribed long-term opioid therapy, what is the effectiveness of risk mitigation strategies, including 1) opioid management plans, 2) patient education, 3) urine drug screening, 4) use of prescription drug monitoring program data, 5) use of monitoring instruments, 6) more frequent monitoring intervals, 7) pill counts, and 8) use of abuse- deterrent formulations on outcomes related to overdose, addiction, abuse, or misuse?									
Outcomes related to abuse		No studies		-	-	-	-	-	Insufficient
d. What is the comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids on outcomes related to overdose, abuse, misuse, pain, function, and quality of life?									
Outcomes related to abuse		No studies		-	-	-	-	-	Insufficient

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Perspective

Reducing the Risks of Relief — The CDC Opioid-Prescribing Guideline

Thomas R. Frieden, M.D., M.P.H., and Debra Houry, M.D., M.P.H.
N Engl J Med 2016; 374:1501-1504 | April 21, 2016 | DOI: 10.1056/NEJMmp1515917

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Deaths from prescription-opioid overdose have increased dramatically in the United States, quadrupling in the past 15 years. Efforts to improve pain management resulted in quadrupled rates of opioid prescribing, which propelled a tightly correlated epidemic of addiction, overdose, and death from prescription opioids that is now further evolving to include increasing use and overdoses of heroin and illicitly produced fentanyl.

The pendulum of opioid use in pain management has swung back and forth several times over the past 100 years. Beginning in the 1990s, efforts to improve treatment of pain failed to adequately take into account opioids' addictiveness, low therapeutic ratio, and lack of documented effectiveness in the treatment of chronic pain. Increased prescribing was also fueled by aggressive and sometimes misleading marketing of long-acting opioids to physicians.¹ It has become increasingly clear that opioids carry substantial risks and uncertain benefits, especially as compared with other treatments for chronic pain.

On March 15, 2016, the Centers for Disease Control and Prevention (CDC) released a "Guideline for Prescribing Opioids for Chronic Pain" to chart a safer, more effective course.² The guideline is designed to support clinicians caring for patients outside the context of active cancer treatment or palliative or end-of-life care. More research is needed to fill in critical evidence gaps regarding the effectiveness, safety, and economic efficiency of long-term opioid therapy. However, given what we know about the risks associated with long-term opioid therapy and the availability of effective nonpharmacologic and nonopioid pharmacologic treatment options, the guideline uses the best available scientific data to provide information and recommendations to support patients and clinicians in balancing the risks of addiction and overdose with the limited evidence of benefits of opioids for the treatment of chronic pain.

Most placebo-controlled, randomized trials of opioids have lasted 6 weeks or less, and we are aware of no study that has compared opioid therapy with other treatments in terms of long-term (more than 1 year) outcomes related to pain, function, or quality of life.² The few randomized trials to evaluate opioid efficacy for longer than 6 weeks had consistently poor results. In fact, several studies have shown that use of opioids for chronic pain may actually worsen pain and functioning, possibly by potentiating pain perception. A 3-year prospective observational study of more than 69,000 postmenopausal women with recurrent pain conditions showed that patients who had received opioid therapy were less likely to have improvement in pain (odds ratio, 0.42; 95% confidence interval [CI], 0.36 to 0.49) and had worsened function (odds ratio, 1.25; 95% CI, 1.04 to 1.51).³ An observational case-control study of patients undergoing orthopedic surgery showed that those receiving long-term opioid therapy had significantly higher levels of preoperative hyperalgesia.⁴ After surgery, patients who had received long-term opioid therapy reported higher



Interview with Dr. Debra Houry on a new opioid-prescribing guideline from the Centers for Disease Control and Prevention. (7:42)

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pain intensity (a rating of 7.6 vs. 5.5 out of 10) in the recovery room than patients who had not been taking opioids.

Whereas the benefits of opioids for chronic pain remain uncertain, the risks of addiction and overdose are clear. Although partial agonists such as buprenorphine may carry a lower risk of dependence, prescription opioids that are full mu-opioid-receptor agonists — nearly all the products on the market — are no less addictive than heroin. Although abuse-deterrent formulations may reduce the likelihood that patients will inject melted pills, these formulations are no less addictive and do not prevent opioid abuse or fatal overdose through oral intake.

The prevalence of opioid dependence may be as high as 26% among patients in primary care receiving opioids for chronic non–cancer-related pain.² Risk-stratification tools do not allow clinicians to predict accurately whether a patient will become addicted to opioids, although persons with a history of mental illness or addiction are at higher risk.² Overdose risk increases in a dose-response manner, at least doubling at 50 to 99 morphine milligram equivalents (MME) per day and increasing by a factor of up to 9 at 100 or more MME per day, as compared with doses of less than 20 MME per day.² Overall, 1 of every 550 patients started on opioid therapy died of opioid-related causes a median of 2.6 years after the first opioid prescription; the proportion was as high as 1 in 32 among patients receiving doses of 200 MME or higher.⁵ We know of no other medication routinely used for a nonfatal condition that kills patients so frequently.

The new CDC guideline emphasizes both patient care and safety. We developed the guideline using a rigorous process that included a systematic review of the scientific evidence and input from hundreds of leading experts and practitioners, other federal agencies, more than 150 professional and advocacy organizations, a wide range of key patient and provider groups, a federal advisory committee, peer reviewers, and more than 4000 public comments.

Three key principles underlie the guideline's 12 recommendations (see The CDC Opioid-Prescribing Guideline). First, nonopioid therapy is preferred for chronic pain outside the context of active cancer, palliative, or end-of-life care. Opioids should be added to other treatments for chronic pain only when their expected benefits for both pain and function are likely to outweigh the substantial risks inherent in this class of medication.

Nonpharmacologic therapies can ameliorate chronic pain while posing substantially less risk to patients. In some instances, other therapies result in better outcomes than opioids. These therapies include exercise therapy, weight loss, psychological therapies such as cognitive behavioral therapy, interventions to improve sleep, and certain procedures. The evidence review conducted in developing the guideline revealed that exercise therapy helped improve, and sustain improvements in, pain and function in patients with osteoarthritis. It did not find evidence that opioids were more effective for pain reduction than nonopiod treatments such as nonsteroidal antiinflammatory drugs for low back pain or antidepressants for neuropathic pain, but it did find that nonopiod treatments could be better tolerated and superior for improving physical function while conferring little or no risk of addiction and substantially lower risks of overdose and death.²

Second, when opioids are used, the lowest possible effective dose should be prescribed to reduce the risks of opioid use disorder and overdose. Clinicians should carefully reassess individual benefits and risks when increasing a dose to 50 MME or more per day. Doses of 90 MME or more should be avoided, or the decision to titrate above this level should be carefully considered and justified. When prescribing opioids, the rule of thumb is to “start low and go slow.”

Third, clinicians should exercise caution when prescribing opioids and should monitor all patients closely. Prescribers should mitigate risk by, for example, avoiding concurrent use of benzodiazepines if possible, reviewing data from a prescription-drug monitoring program when deciding whether to start or continue opioid therapy, offering naloxone at least to patients who are at greater risk for overdose, having a clear “off-ramp” plan to taper and discontinue therapy, reevaluating the dosage and necessity of opioid treatment regularly, and obtaining urine toxicology screening at the initiation of treatment and, for some patients, periodically thereafter. For patients who become addicted to opioids, treatment with methadone, buprenorphine, or naltrexone improves outcomes.

Initiation of treatment with opioids is a momentous decision and should be undertaken only with full understanding by both the physician and the patient of the substantial risks involved. Clinicians need to recognize the risk associated with any treatment with opioids and should prescribe only the shortest course needed. Although the guideline addresses chronic pain, many patients become addicted to opioids after being treated for acute pain. Three days of treatment or less will often be sufficient; more than 7 days will rarely be required. Some trauma and surgery may require longer courses; treatment of postsurgical pain is beyond the scope of this guideline. Furthermore, it is important to discuss storage of opioids in a secure location to prevent diversion, as well as to counsel patients regarding the overdose risk posed to household members and other persons.

Management of chronic pain is an art and a science. The science of opioids for chronic pain is clear: for the vast majority of patients, the known, serious, and too-often-fatal risks far outweigh the

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THE CDC OPIOID-PRESCRIBING GUIDELINE.

1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.
2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
3. Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and provider responsibilities for managing therapy.
4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.
5. When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥ 50 morphine milligram equivalents (MME) per day, and should avoid increasing dosage to ≥ 90 MME per day or carefully justify a decision to titrate dosage to ≥ 90 MME per day.
6. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than 7 days will rarely be needed.
7. Clinicians should evaluate benefits and harms with patients within 1–4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids.
8. Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥ 50 MME/day), or concurrent benzodiazepine use are present.
9. Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months.
10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.
11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.
12. Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid-use disorder.

[Disclosure forms](#) provided by the authors are available with the full text of this article at NEJM.org.

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SOURCE INFORMATION

Reducing the Risks of Opioids: The CDC's Opioid Prescribing Guideline – NEJM
From the Centers for Disease Control and Prevention, Atlanta.

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REVIEW ARTICLE

Dan L. Longo, M.D., Editor

Opioid Abuse in Chronic Pain — Misconceptions and Mitigation Strategies

Nora D. Volkow, M.D., and A. Thomas McLellan, Ph.D.
N Engl J Med 2016; 374:1253-1263 | March 31, 2016 | DOI: 10.1056/NEJMra1507771

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Chronic pain not caused by cancer is among the most prevalent and debilitating medical conditions but also among the most controversial and complex to manage. The urgency of patients' needs, the demonstrated effectiveness of opioid analgesics for the management of acute pain, and the limited therapeutic alternatives for chronic pain have combined to produce an overreliance on opioid medications in the United States, with associated alarming increases in diversion, overdose, and addiction. Given the lack of clinical consensus and research-supported guidance, physicians understandably have questions about whether, when, and how to prescribe opioid analgesics for chronic pain without increasing public health risks. Here, we draw on recent research to address common misconceptions regarding the abuse-related risks of opioid analgesics and highlight strategies to minimize those risks.

SOURCE OF THE OPIOID EPIDEMIC

More than 30% of Americans have some form of acute or chronic pain.^{1,2} Among older adults, the prevalence of chronic pain is more than 40%.² Given the prevalence of chronic pain and its often disabling effects, it is not surprising that opioid analgesics are now the most commonly prescribed class of medications in the United States.³ In 2014 alone, U.S. retail pharmacies dispensed 245 million prescriptions for opioid pain relievers.^{4,5} Of these prescriptions, 65% were for short-term therapy (<3 weeks),⁶ but 3 to 4% of the adult population (9.6 million to 11.5 million persons) were prescribed longer-term opioid therapy.⁷ Although opioid analgesics rapidly relieve many types of acute pain and improve function, the benefits of opioids when prescribed for chronic pain are much more questionable.⁸

However, two major facts can no longer be questioned. First, opioid analgesics are widely diverted and improperly used, and the widespread use of the drugs has resulted in a national epidemic of opioid overdose deaths and addictions. More than a third (37%) of the 44,000 drug-overdose deaths that were reported in 2013 (the most recent year for which estimates are available) were attributable to pharmaceutical opioids; heroin accounted for an additional 19%. At the same time, there has been a parallel increase in the rate of opioid addiction, affecting approximately 2.5 million adults in 2014.⁹ Second, the major source of diverted opioids is physician prescriptions.^{10,11} For these reasons, physicians and medical associations have begun questioning prescribing practices for opioids, particularly as they relate to the management of chronic pain. Moreover, many physicians admit that they are not confident about how to prescribe opioids safely,¹² how to detect abuse or emerging addiction, or even how to discuss these issues with their patients.¹³

This review is not intended as clinical instruction in chronic pain management; for that, we suggest recent clinical guidelines.¹⁴⁻¹⁷ Instead, this review focuses on the pharmacologic properties of opioids that underlie both their therapeutic effects and their abuse-producing effects and on the ways in which these properties should inform us in correcting common clinical misconceptions that interfere with the proper prescription and monitoring of opioids in the management of chronic pain (Table 1).

WHY OPIOID MEDICATIONS ARE DIVERTED AND ABUSED

Opioid medications exert their analgesic effects predominantly by binding to mu-opioid receptors. Mu-opioid receptors are densely concentrated in brain

TABLE 1

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regions that regulate pain perception (periaqueductal gray, thalamus, cingulate cortex, and insula), including pain-induced emotional responses (amygdala), and in brain reward regions (ventral tegmental area and nucleus accumbens) that underlie the perception of pleasure and well-being. This explains why opioid medications can produce both analgesia and euphoria. Mu-opioid receptors in other brain regions and in peripheral organs account for other common opioid effects. In particular, mu-opioid receptors in the brain stem are mainly responsible for the respiratory depression associated with opioid-overdose incidents and deaths^{21,22} (Figure 1).

Opioids not only directly activate these brain analgesia and reward regions but also concurrently mediate a learned association between receipt of the drug and the physiological and perceptual effects of the drug — a type of Pavlovian conditioning.²³ Repeated receipt of opioids strengthens these learned associations and over time becomes part of the desire (craving) for the drug's effects — analgesic or pleasurable.²⁴ For a patient in chronic pain, even mild levels of pain can trigger the learned associations between pain and drug relief, which are manifested as an urge for relief. Such a conditioned urge for relief from even mild pain can lead to the early, inappropriate use of an opioid outside prescribed scheduling.

Opioid medications vary with respect to their affinity and selectivity for the mu-opioid receptor, since some also bind to kappa- or delta-opioid receptors or to other neurotransmitter receptors and transporters. There is also considerable variation among the drugs with respect to their pharmacokinetics and bioavailability. When combined, these pharmacologic properties affect the rapidity of onset, potency, and duration of both the analgesic and pleasurable effects of opioids.

The effects of opioids — particularly their rewarding effects — are accentuated most when the drugs are delivered rapidly into the brain.²⁵ This is why diverted opioids that are taken for their rewarding effects are frequently injected. This also explains why the Food and Drug Administration has encouraged and approved abuse-deterrent formulations that are designed to prevent the injection of pharmaceutical opioids²⁶ (Table 2).

OPIOID-INDUCED TOLERANCE AND PHYSICAL DEPENDENCE

There is lingering misunderstanding among some physicians about the important differences between physical dependence and addiction. The repeated administration of any opioid almost inevitably results in the development of tolerance and physical dependence. These predictable phenomena reflect counter-adaptations in opioid receptors and their intracellular signaling cascades.²⁹ These short-term results of repeated opioid administration resolve rapidly after discontinuation of the opioid (i.e., in a few days to a few weeks, depending on the duration of exposure, type of opioid, and dose). In contrast, addiction will occur in only a small percentage of patients exposed to opioids. Addiction develops slowly, usually only after months of exposure, but once addiction develops, it is a separate, often chronic medical illness that will typically not remit simply with opioid discontinuation and will carry a high risk of relapse for years without proper treatment. The molecular processes responsible for addiction are also distinct from those underlying tolerance and physical dependence, and so are the clinical consequences.

Tolerance leads to a decrease in opioid potency with repeated administration. Thus, prescribing opioids long-term for their analgesic effects will typically require increasingly higher doses in order to maintain the initial level of analgesia — up to 10 times the original dose.³⁰ Similarly, tolerance with respect to the rewarding effects of opioids leads to the characteristic dose escalation seen in opioid addiction, which can result in daily doses of up to 800 morphine milligram equivalents (MME, the conversion factor used to facilitate comparison of potency among opioids).³¹

Some opioid effects show tolerance after a single dose,³² whereas for others, tolerance occurs more slowly.²⁹ In particular, tolerance to the analgesic and euphoric effects of opioids develops quickly, whereas tolerance to respiratory depression develops more slowly,^{33,34} which explains why increases in dose by the prescriber or patient to maintain analgesia (or reward) can markedly increase the risk of overdose.

Physical dependence underlies the physiological adaptations that are responsible for the emergence of withdrawal symptoms on the abrupt discontinuation of opioids. Withdrawal symptoms (e.g., piloerection, chills, insomnia, diarrhea, nausea, vomiting, and muscle aches) vary appreciably in severity (from not noticeable to quite uncomfortable) and duration (1 to 14 days) on the basis of the type, dose, and duration of opioid prescribed.^{35,36}

In the context of chronic pain management, the discontinuation of opioids requires dose tapering in order to prevent the emergence of such withdrawal symptoms. In some patients, the repeated use of opioids can also lead to hyperalgesia, which is a state of heightened pain sensitivity.^{37,38} In the



Misconceptions
Regarding Opioids
and Addiction.

FIGURE 1



Location of Mu-Opioid
Receptors.

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clinical context, hyperalgesia can lead to inappropriate increases in opioid doses, which further exacerbate rather than ameliorate pain.³⁹ In the case of hyperalgesia, dose tapering or tapering to discontinuation is a better pain-relief strategy.⁴⁰

Unlike tolerance and physical dependence, addiction is not a predictable result of opioid prescribing. Addiction occurs in only a small percentage of persons who are exposed to opioids — even among those with preexisting vulnerabilities (**Table 3**). Older medical texts and several versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) either overemphasized the role of tolerance and physical dependence in the definition of addiction or equated these processes (DSM-III and DSM-IV). However, more recent studies have shown that the molecular mechanisms underlying addiction are distinct from those responsible for tolerance and physical dependence, in that they evolve much more slowly, last much longer, and disrupt multiple brain processes.⁵⁷

Risk factor	Description
Genetic risk	Family history of substance abuse, particularly if it is early onset, hereditary risk factors, genetic variants associated with drug metabolism, and genetic variants associated with drug reward.
Environmental risk	Exposure to substances during pregnancy, peer pressure, social environment, and mental health conditions.
Neurobiological risk	Brain imaging studies showing differences in brain structure and function, particularly in the prefrontal cortex and limbic system.

Cardinal features of addiction include a pronounced craving for the drug, obsessive thinking about the drug, erosion of inhibitory control over efforts to refrain from drug use, and compulsive drug taking (DSM-5). These behavioral changes in turn are associated with structural and functional changes in the reward, inhibitory, and emotional circuits of the brain.^{58,59} Clinical studies have also shown that the ability of opioids to produce addiction is genetically modulated, with heritability rates similar to those of diabetes, asthma, and hypertension.^{60,61} For these reasons, we do not know the total dose or the duration of opioid administration that will reliably produce addiction. However, we do know that the risk of opioid addiction varies substantially among persons, that genetic vulnerability accounts for at least 35 to 40% of the risk associated with addiction,⁶²⁻⁶⁴ and that adolescents are at increased risk because of the enhanced neuroplasticity of their brains and their underdeveloped frontal cortex, which is necessary for self-control.^{52,62} Hence, in adolescents, the risks and benefits of prescribing opioids for pain management need to be even more carefully weighed than in adults.

Factors Associated with the Risk of Opioid Overdose or Addiction.

In a person with an opioid addiction, discontinuation of the opioid will rapidly reverse the tolerance and physical dependence within days or a couple of weeks. In contrast, the underlying changes that are associated with addiction will persist for months and even years after the discontinuation of opioids.⁶⁵ This finding is clinically relevant, because after abstinence from opioids, addicted patients are particularly vulnerable to overdosing: their intense drive to take the drug persists, but the tolerance that previously protected them from overdosing is no longer present. These effects explain the high risk of overdosing among persons with an opioid addiction after they have been released from prison or from a detoxification program.^{66,67}

MITIGATION STRATEGIES

The rewarding effects of opioids play a major role in the risks of opioid diversion, overdose, and addiction. However, the likelihood and severity of these risks are largely independent and governed by different factors. All these risks are present to some degree with all opioids and with all pain diagnoses. This means that no single or simple change in prescribing behavior can be expected to alleviate all risks while properly managing pain. For example, these risks cannot be mitigated simply by restricting prescribing to a particular type of opioid or by avoiding the prescription of opioids to a particular type of patient. However, there are common strategies that can help mitigate all risks, including limiting the prescribed opioid to the lowest effective dose for the shortest effective duration (for both acute and chronic pain) without compromising effective analgesia. Regular monitoring and reassessment provide opportunities to minimize the risks associated with long-term opioid use by allowing for the tapering and discontinuing of opioids among patients who are not receiving a clear benefit or among those who are engaging in practices that increase the risk of overdose (e.g., consumption of high doses of alcohol, concurrent use of benzodiazepines, and poor adherence to opiate medications).⁶⁸

Preventing Drug Diversion

The most common form of diversion is the transfer of opioid analgesics by patients who have received legitimately prescribed opioids to family members or friends who are usually trying to self-medicate a generic pain.⁶⁹ This type of diversion applies to prescriptions given for the management of either chronic or acute pain and would be best managed by educating patients on the dangers of sharing their medications and on the importance of safe storage and disposal.⁷⁰

Approximately 7 to 10% of diversion occurs among patients who feign pain to acquire prescribed opioids,⁷¹ usually with the goal of maintaining their addiction, and who will often attempt to acquire opioids from multiple physicians (doctor shopping).⁷¹⁻⁷³ Physicians have attempted to identify dissembling or addicted patients through screening instruments or through detection of so-called aberrant behaviors that are thought to be indicative of addiction (**Table 4**).⁷⁷ However, the most recent review of patient screening efforts showed no evidence that any scale or procedure was effective.⁸ Risks of diversion through doctor shopping are best mitigated by the full participation of all prescribers in Prescription Drug Monitoring Programs (PDMPs). PDMPs are statewide electronic databases that collect information on prescription and

TABLE 3

Factors Associated with the Risk of Opioid Overdose or Addiction

TABLE 4

dispensing of controlled prescription drugs (including opioid drugs) and were designed to monitor information pertaining to suspected abuse or diversion.⁷⁸ Although these data have been shown to help health care professionals reduce doctor shopping and overdoses,⁷⁹⁻⁸¹ their use by health care providers is inconsistent.⁸²⁻⁸⁴ This in part reflects the fact that PDMPs are voluntary programs in many states. Although 25 states and the District of Columbia update their databases daily, as of this writing, only Oklahoma provides real-time reporting.⁸⁵ In addition, only 22 of 49 PDMPs share information across states.⁸⁶ Another obstacle is that access to PDMP data requires a computer that is separate from that used to access electronic health records. However, implementation and consistent use will be facilitated by rapid changes in laws to require mandatory consultation of a PDMP before prescribing, advances in electronic technologies to deliver PDMP information in real time, better integration of PDMPs with electronic health records, and access of PDMP data across state lines.⁸⁷

Table 1. Mitigation Strategies against Opioid Misuse and Abuse.	
Source: Adapted from the National Institute on Drug Abuse. For more information, visit www.drugabuse.gov .	
Programs * These include the Prescription Drug Monitoring Program (PDMP), which tracks controlled substances dispensed by a prescription or over-the-counter (OTC) route. It also tracks controlled substances dispensed by a physician or pharmacist at a medical facility or a hospital. Some states have expanded their PDMP to include non-controlled substances. Some states have expanded their PDMP to include non-controlled substances. Some states have expanded their PDMP to include non-controlled substances.	
Use of data from the Prescription Drug Monitoring Program. Such data can be used to identify patients who may be at risk for opioid misuse or abuse. Use of data from the Prescription Drug Monitoring Program. Such data can be used to identify patients who may be at risk for opioid misuse or abuse.	
Use of urine drug screening. Such screening, which can be performed before prescription of opioids and periodically as part of regular follow-up, can help detect misuse or abuse of prescription opioids. Use of urine drug screening. Such screening, which can be performed before prescription of opioids and periodically as part of regular follow-up, can help detect misuse or abuse of prescription opioids.	
Screening for depression. Such personal concern can lead to increased detection in monitoring a patient's adherence to prescribed opioid therapy. However, it is worth noting that the evidence showed that only limited data are available regarding the efficacy of urine drug screening.	

Mitigation Strategies against Opioid Diversion and Misuse.

Reducing Risk of Overdose

The rate of death from opioid overdose has quadrupled during the past 15 years in the United States.⁸⁸ Researchers at the Centers for Disease Control and Prevention have estimated that 28,647 drug overdose deaths (61%) in 2014 in the United States involved some type of opioid, including heroin.⁸⁹ Even more prevalent are nonfatal opioid overdoses that require medical care in a hospital or emergency department. Such events have increased by a factor of six in the past 15 years.⁹⁰

The contributing factors associated with overdose can be divided into those associated with the opioid itself (type, dose, potency, and duration of action) and those associated with critical features of the patient (Table 3). Although the use of any opioid can lead to overdose, research suggests that exposure to higher doses of all opioids increases the risk of overdose. Opioid doses of more than 100 MME^{91,92} are disproportionately associated with overdose-related hospital admissions and deaths⁴⁵ (Table S1 in the *Supplementary Appendix*, available with the full text of this article at NEJM.org). The use of long-acting opioids, such as methadone and oxycodone, has also been associated with an increased risk of overdose.⁴⁵

Several identifiable characteristics among patients have been reliably associated with an elevated risk of opioid overdose (Table 3). Included among these factors are a history of overdose,^{51,93} a history of addiction to any substance (but particularly alcohol, benzodiazepines, or opioids),⁹³ and health problems associated with respiratory depression or concurrent prescription of any medication that has a depressive effect on the respiratory system, such as benzodiazepines and sedative hypnotics.⁸⁸ The presence of renal or hepatic dysfunction also increases the risk of overdose, since in patients with either of these conditions, the clearance of many opioid drugs is impaired, which leads to higher and longer-lasting drug levels in blood.^{54,55} Finally, because some cases of overdose may be purposeful suicide attempts,^{94,95} a history of suicidal thoughts or attempts and a diagnosis of major depression are also markers for an elevated risk of overdose.

Recommended mitigation strategies include an overdose risk assessment (Table 3) and urine drug screening before prescription or represcription of opioids (to verify absence of drugs of abuse). The identification of these risks does not automatically rule out opioids as part of effective pain management. However, these risks do indicate the needs for much greater education of the patient (and the patient's family) about overdose risks, the use of an opioid treatment agreement,⁹⁶ increased caution in prescribing high opioid doses or long-acting opioids, more frequent clinical follow-up, and, potentially, a prescription for and instruction in the use of naloxone, an opioid antagonist that can reverse an opioid-induced overdose. Indeed, expanding access to naloxone has been shown to significantly reduce the rate of death from opioid overdoses.⁹⁷

Minimizing the Risk of Addiction

For many years, it was believed that pain protected against the development of addiction to opioid medications. However, epidemiologic studies of opioid addiction among patients in pain, as well as preclinical studies of addiction in animal models of chronic pain,^{24,98,99} have disproved this belief. Although published estimates of iatrogenic addiction vary substantially from less than 1% to more than 26% of cases,¹⁰⁰ part of this variability is due to confusion in definition. Rates of carefully diagnosed addiction have averaged less than 8% in published studies, whereas rates of misuse, abuse, and addiction-related aberrant behaviors have ranged from 15 to 26%.¹⁰¹⁻¹⁰³ A small (estimated at 4%) but growing percentage of persons who are addicted to prescription opioids transition to heroin,¹ mainly because heroin is typically cheaper and in some instances easier to obtain than opioids.

Clinical efforts to prevent the emergence of addiction can be initiated in primary care settings. Assessment of addiction risks before opiates are prescribed is recommended as a mitigation strategy (Table 3). Emerging signs of addiction can be identified and managed through regular monitoring, including urine drug testing before every prescription is written, to assess for the presence of other opioids or drugs of abuse. Responsible physicians should be prepared to make a referral for specialty addiction treatment when indicated. Although addiction is a serious chronic

condition, recovery is a predictable result of comprehensive, continuing care and monitoring.¹⁰⁴ In particular, the use of medication-assisted therapy in managing opioid addiction among patients with co-occurring pain significantly improves outcomes.¹⁰⁵

On the basis of research and clinical evidence, the Department of Health and Human Services recently launched an initiative to reduce opioid overdoses and addiction that focuses on improving opioid prescribing practices to reduce opioid-use disorders and overdoses, expanding the use of naloxone to prevent overdoses, and extending the use of medication-assisted treatment to reduce opioid-use disorders and overdoses.¹⁰⁶

CONCLUSIONS

It is no longer possible to simply continue previous practices with respect to the management of chronic pain. The associated risks of opioid diversion, overdose, and addiction demand change. Although there are no simple solutions, we recommend three practice and policy changes that can reduce abuse-related risks and improve the treatment of chronic pain.

Increased Use of Science-Supported Prescribing and Management Practices

The extended prescription of opioids (>8 weeks) for the treatment of chronic pain has questionable benefits for individual patients and presents substantial public health risks.⁸ The risks of overdose and addiction from this prescribing practice — both among patients with chronic pain and the public at large — increase with higher doses (>100 MME), longer duration of prescribing, and perhaps the use of long-acting opioids. Despite these facts, a Medicaid study showed that more than 50% of opioid prescriptions were for doses higher than 90 MME and for periods of more than 6 months.¹⁰⁷ Better results can be obtained by using the most contemporary guidelines for pain management.¹⁴

Increased Medical School Training on Pain and Addiction

Very few medical schools offer adequate training in pain management, and still fewer offer even one course in addiction. The result is that even experienced clinicians are unsure about how to deal with fundamental and omnipresent clinical issues in their practices. Many motivated, well-intentioned physicians do not know whether to prescribe opioids for pain management and, if so, which ones and for how long. Still fewer understand the pharmacologic or clinical relationships among tolerance, physical dependence, and addiction.¹⁰⁸ This education is particularly critical for primary care practitioners, who prescribe more than 70% of opioid analgesics.

Increased Research on Pain

At a recent workshop at the National Institutes of Health on the role of opioids in the treatment of chronic pain, attendants recommended several areas of research that are needed for improved clinical practice guidelines. These areas included how to differentiate the unique properties of acute and chronic pain and how to describe the process by which acute pain transitions into chronic pain.⁸ Discovery-oriented research was also recommended to identify new, potent nonopioid analgesics and other pain-treatment strategies (Table 5). Access to biomarkers of pain and analgesia that take advantage of neuroimaging technologies or genetic analyses would accelerate the development of new medications and allow for more personalized clinical interventions for pain management.

TABLE 5

Alternative Treatments for Chronic Pain.

[Disclosure forms](#) provided by the authors are available with the full text of this article at NEJM.org.

Dr. McLellan reports receiving fees for serving on the board of directors of Indivior Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

SOURCE INFORMATION

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EXHIBIT 31

Pain | Opioid Facts

OPIOID DICTIONARY

Let's clear up the meaning of some important words, such as addiction, tolerance, and dependence. They are sometimes used incorrectly because they are not well understood.

- **ADDICTION** - A craving that drives a person to take an opioid even though it causes harm. This is a problem that needs immediate treatment. This happens to some patients who use opioids.

Sometimes people behave as if they are addicted, when they are really in need of more medication. This can be treated with higher doses of medicine.

- **MISUSE** - Any use of a prescription drug that is different from accepted medical practice.
- **PHYSICAL DEPENDENCE** - Withdrawal symptoms occur when regular doses of an opioid are stopped too quickly. These symptoms include restlessness, muscle and bone pain, or insomnia. Physical dependence is a normal result of taking opioids and does not result from misuse. These symptoms usually go away after a short period of time.
- **TOLERANCE** - The need for higher doses of a drug to give the same pain relief. This sometimes happens when the body gets used to an opioid. This does not mean misuse or addiction.

Opioids, the most effective pain relievers available, have been used to treat pain for thousands of years. Today, doctors prescribe opioids to treat:

- severe, short-term pain
- chronic pain (caused by a variety of conditions)
- osteoarthritis
- neuropathic pain (caused by problems with the nerves)
- cancer pain

The goal of opioid therapy is to control pain and improve your function.

WHAT ARE "OPIOIDS"?

Opioids are related to opium, a natural pain-killing substance taken from poppy plants. These drugs are also sometimes called narcotics. Opioids come from plants other than poppies and are also man-made. The most commonly prescribed opioids are morphine, codeine, and oxycodone. Others include methadone, fentanyl, oxymorphone, hydrocodone, and hydromorphone.

There are two basic types of opioids:

- **short-acting** – taken for a short period of time to treat severe or sudden pain that occurs after surgery, fractures, infections, or during labor and childbirth
- **long-acting** – taken for a long period of time for “around-the-clock” relief of ongoing pain that lasts more than a few weeks or months

HOW DO OPIOIDS WORK?

When your body is injured, your nerves send a “pain” message to your brain. Your brain tells you that you are experiencing pain. Opioids are chemicals that block your body’s ability to communicate the pain. Although you still have pain, opioids keep your brain from sending your body the message.

HOW ARE OPIOIDS TAKEN?

Patients can take opioids in several ways. The most common is by mouth. Your doctor may prescribe an opioid delivered in one of the following ways:

- **intravenously (IV)** – injected into a vein
- **subcutaneously** – an injection under the skin, into a muscle, or in the space around your spinal cord
- **transdermally** – a patch placed on the skin
- **transmucosally** – a lozenge or lollipop, placed between the cheek and gums
- **rectally** – a suppository inserted in the rectum
- **orally** – a liquid or pill taken by mouth

For greater pain relief, some opioids are combined with non-opioid drugs like aspirin or acetaminophen.



Conducted as a part of the National Initiative on Pain Control®(NIPC®), sponsored by Professional Postgraduate Services®, Secaucus, NJ.

Supported by an unrestricted educational grant from Endo Pharmaceuticals, Inc.

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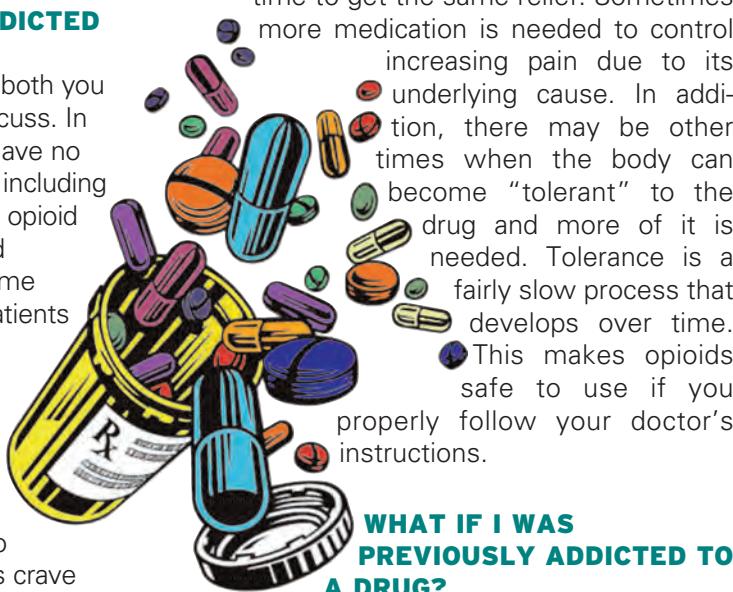
WHAT ARE THE SIDE EFFECTS?

Opioids can make you feel drowsy or unusually happy, or they may cause other common symptoms. The most common side effect is constipation. If this happens, your doctor may tell you to take a stool softener or laxative, add more fiber to your diet, and drink plenty of liquids. Other common side effects include:

- nausea and vomiting
- dizziness
- itching
- dry mouth
- sweating
- confusion

WILL I BECOME ADDICTED TO OPIOIDS?

This is a key issue for both you and your doctor to discuss. In general, people who have no history of drug abuse, including tobacco, and use their opioid medication as directed will probably not become addicted. However, patients who misuse or abuse opioids can become addicted to them, so openly discussing your concerns with your doctor is important. People who are addicted to opioids crave the "unusually happy" effect the drug has on them (a "buzz" or "high") and will continue to use the drug even though it harms them.



pain, or insomnia. However, physical dependence is normal and expected, and does not mean that you are addicted to that substance.

In the case of opioids, when it's time to stop taking the medication, your doctor can help manage or reduce withdrawal symptoms by gradually lowering the dose over a period of time.

A person who takes opioids for pain control may need a higher dose over time to get the same relief. Sometimes more medication is needed to control increasing pain due to its underlying cause. In addition, there may be other times when the body can become "tolerant" to the drug and more of it is needed. Tolerance is a fairly slow process that develops over time. This makes opioids safe to use if you properly follow your doctor's instructions.

WILL I BECOME DEPENDENT ON OPIOIDS?

Physical dependence occurs when the body becomes used to a substance in its system. If the substance is stopped abruptly or greatly reduced, withdrawal symptoms may occur. These symptoms include restlessness, muscle and bone

A history of addiction would not rule out the use of opioid pain relievers. However, your doctor will perform a thorough assessment before opioids are prescribed and carefully monitor your treatment for any evidence of overuse or misuse. People who have abused opioids, other prescription medications, or alcohol in the past may have a greater risk of developing an addiction to opioids, so these issues must also be discussed with your doctor.

FOR MORE INFORMATION:

TALK TO YOUR PHYSICIAN OR VISIT PAINKNOWLEDGE.ORG

TIPS FOR TAKING OPIOIDS

- Follow your doctor's instructions exactly on how to take your medicine
- Tell your doctor about all other medications you use
- Take your medicine on a regular schedule
- Do not skip doses of your medicine
- Do not drink alcohol while taking an opioid
- Tell your doctor immediately about any side effects you feel
- If your pain continues while taking the opioid, contact your doctor to adjust the dose
- Ask for a refill in plenty of time so that you do not run out
- Use the same pharmacy for all prescriptions to make sure they are always available
- Do not let others use your opioid medication
- Do not use other people's medications

WRITE OR CALL THE FOLLOWING ORGANIZATIONS FOR MORE INFORMATION:

American Pain Society

4700 W. Lake Avenue
Glenview, IL 60025
Phone: 1 (847) 375-4715
Web Address:
<http://www.ampainsoc.org>

American Academy of Pain Management

13947 Mono Way #A
Sonora, CA 95370
Phone: 1 (209) 533-9744
Web Address:
www.aapainmanage.org

American Pain Foundation

201 North Charles Street
Suite 710
Baltimore, MD 21201
Phone: 1 (888) 615-PAIN (7246)
Web Address:
<http://www.painfoundation.org>

EXHIBIT 32

A Policymaker's Guide to Understanding Pain & Its Management



American Pain Foundation
A United Voice of Hope and Power over Pain



Pain is a complex experience that differs enormously from one person to another, even among those with seemingly identical injuries or illnesses.

ABOUT THE AMERICAN PAIN FOUNDATION

Founded in 1997, the American Pain Foundation (APF) is an independent, nonprofit 501(c)3 and the largest national advocacy organization serving people affected by pain. APF speaks out with people living with pain, caregivers, health care providers and allied organizations, working together to dismantle the barriers that impede access to quality pain care for all.

OUR MISSION

The American Pain Foundation educates, supports and advocates for people affected by pain.

A Policymaker's Guide

to Understanding Pain & Its Management

PURPOSE OF THIS GUIDE

Policymakers within the federal or state government and regulatory agencies must keep in mind that they represent Americans who live with pain, many of whom have pain every day of their life.

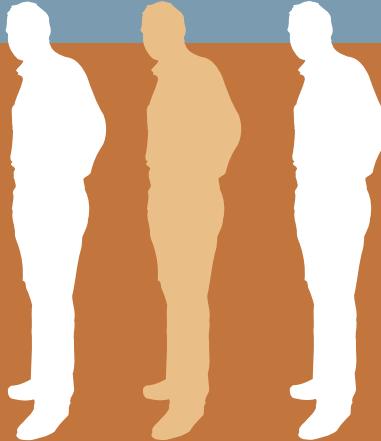
Because pain can and should be treated as a legitimate medical condition just like diabetes, hypertension, obesity and cancer, the American Pain Foundation (APF) has developed this guide as a primer on pain and its management to help meet the informational needs of busy policymakers and their staff members. We know pain is a complex topic, and hope you will find this to be a useful resource in your work to help shape positive, balanced pain policies.

INSIDE YOU WILL FIND:

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PAIN AFFECTS EVERYONE

Chronic pain affects
1 in 3
Americans, according to
the Institute of Medicine.



Consider the following...

- Most Americans — eight in 10 — will suffer from back pain at some point in their lives.
- As we age, arthritis hinders the normally smooth sliding motion of our joints and connective tissues, resulting in stiffness and discomfort. Arthritis is the leading cause of disability in people over the age of 55.
- Pain associated with pediatric immunizations is a significant source of anxiety for children receiving immunizations, and evidence suggests that the way children and parents cope can set the stage for future pain responses.
- Damage to or dysfunction of the central nervous system due to stroke, multiple sclerosis and brain or spinal cord injuries also stimulates pain pathways. Undertreated or poorly treated acute pain can manifest as chronic pain for the same reasons.
- An estimated 30 to 50 percent of individuals undergoing active treatment for cancer and 70 percent of those with advanced stages of the disease experience significant levels of pain and may be reluctant to discuss their pain with their health care providers.
- Pain continues to rank among the top medical complaints of active duty military personnel and veterans. An estimated nine out of 10 Iraq and Afghanistan veterans reportedly return home with some type of pain.

Sources: The American Academy of Physical Medicine and Rehabilitation, Arthritis Foundation, Mayday Fund, National Institute of Neurological Disorders and Stroke, National Cancer Institute.

Introduction

Everyone has experienced pain — whether it is a pounding headache at the end of a long day, a throbbing toothache warning of a cavity or infection, a cut or sprained ankle from a fall, or a stinging burn from touching a hot pan. There are also hundreds of pain syndromes, and pain is often a chief complaint with most chronic medical conditions, including cancer, diabetes, arthritis, fibromyalgia and a host of neurological disorders.

While acute pain serves as nature's biological red flag that something is wrong, pain that persists beyond the expected point of healing has no physiological value — in a sense, the nervous system has broken. For many Americans, pain is a constant and unwanted companion and it's only when someone is in the grips of pain that they truly know how agonizing and life-limiting it can be.

If untreated, pain can significantly infringe on a person's quality of life and productivity. Aside from the human suffering, untreated pain exacts a tremendous financial toll on individuals and society at large.

COMMON TYPES OF PAIN

Acute Pain — usually has a clear cause and signals a problem

- Postoperative pain
- Dysmenorrhea (severe menstrual pain)
- Chest pain signaling a heart attack
- Post-traumatic pain: Cuts, scrapes, bruises, fractures
- Mild stress or sinus headache
- Epigastric pain from cardiac problems, gastroesophageal reflux disease (GERD) or other digestive disorder
- Sudden, severe headache signaling stroke or brain aneurysm

Chronic — continues beyond the expected point of recovery

- Persistent back or neck pain from an injury
- Migraine
- Arthritis
- Phantom limb pain
- Shingles/postherpetic neuralgia
- Neuropathic pain due to damage to the central nervous system from diabetes, cardiovascular disease, cancer treatment (surgery, chemotherapy, radiation therapy), spinal cord injury, stroke, blast injury

BURDEN OF PAIN IN AMERICA: AN EVOLVING PUBLIC HEALTH CRISIS

Pain is a serious and costly public health issue. Chronic pain affects 116 million American adults — that's one out of every three — yet it remains misunderstood. It afflicts more people than diabetes, heart disease and cancer combined, and is a leading cause of disability in the United States. Even though pain is one of the most common reasons patients consult a health care provider, it is often inadequately assessed and treated, resulting in needless suffering and poor patient outcomes.

Untreated or poorly managed pain can compromise every aspect of life including a person's:

- physical and mental health,
- social and intimate relations,
- ability to sleep and perform everyday tasks,
- work productivity, and
- financial well-being.

Chronic pain is not only emotionally and physically debilitating for the individual, it also places a tremendous burden on family members and caregivers, and contributes to excessive health care costs. Pain costs the U.S. an estimated \$635 billion in health care expenses and lost productivity each year.¹

Health care providers and policymakers will soon see a substantial increase in the number of people needing treatment for chronic pain when the 75 million baby boomers move into their late 60s and 70s in the coming years. This uptick will not only affect providers, but it is also expected to increase the cost of chronic pain in the U.S.



Treating and managing pain is an integral part of clinical care in primary care settings and across all specialties. Pain management matters; **it guards against needless suffering, improves quality of life and productivity and can cut health care costs.**

Even though pain is one of the most common reasons patients consult a health care provider, it is often inadequately assessed and treated, resulting in needless suffering and poor patient outcomes. It also costs the nation \$635 billion in medical treatment and lost productivity every year.

¹ Institute of Medicine of the National Academies. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education and Research*. June 2011 brief report. Available at www.iom.edu/relievingpain.

SOME COMMON MISCONCEPTIONS ABOUT PAIN

Pain is “all in your head.” Although our brains process the perception of pain, this does not mean that pain is imaginary when the source of pain is not well understood. Pain is all too real to the person who lives with it on a daily basis.

Pain is inevitable; you must learn to tolerate it and suffer in silence. Pain traditionally has been viewed as an inevitable consequence of a disease or condition. The fact is most pain can be relieved with proper pain management.

Pain is a natural part of growing older. While pain is more common as we age, because conditions that cause pain (e.g., arthritis, degenerative joint diseases, cancer, shingles, osteoporosis) are more frequent in older adults, it should not be something people have to endure untreated.

All pain is the same. Many studies failed to find that similar pain stimuli will produce the same pain level intensity. There is an individual difference when sensation is first recognized as painful (pain threshold). There is a difference with pain intensity that each person is able to accept (pain tolerance). Identical injuries can be described differently by sensation and intensity.

The best judge of pain is the physician or nurse. There is little relationship between what a physician or nurse might “guess” about a person’s pain and their actual pain experience. The person with pain is the authority on the existence and severity of his/her pain. His or her self-report is the most reliable indicator.

Seeking medical care for pain is a sign of weakness. Pain carries a stigma, and many people are hesitant to talk about their pain and how it affects their daily life; they also don’t want to be considered a “bad” or high-maintenance patient.

Use of strong pain medication leads to addiction. Many people living with pain, and even some health care practitioners, falsely believe that opioid pain medicines are universally addictive. As with any medication, there are risks, but these risks can be managed when these medicines are properly prescribed and taken as directed. For more information about safety issues related to opioids and other pain therapies, visit www.painsafe.org.

Pain is complex and frequently misunderstood by the public, policymakers, and even health care providers. The issue of pain is riddled with myths and misconceptions, which makes the task of informing and educating people about pain and its management that much more challenging.

Unfortunately, too many Americans are not getting the pain care they need and deserve.

Some common reasons for difficulty in obtaining adequate care include:

- Lack of access to care because of too few trained professionals and problems with insurance coverage.
- Limited or no professional training in pain management, which leaves health care providers ill-equipped to respond effectively to their patients' reports of pain.
- Cultural norms and the stigma associated with admitting pain.
- Restrictive or ambiguous state laws governing health care practice relating to pain care.
- Misconceptions about opioid addiction.
- Concerns among providers about prescribing pain medications for chronic pain, and fears of scrutiny by regulators or law enforcement.
- Persisting disparities leaving certain populations vulnerable to denials of appropriate pain treatment (e.g., infants and children, women, minorities and certain ethnic groups, the elderly, the institutionalized including those in the prison system).

While pain is a symptom of many chronic diseases and is expected after many surgical procedures, persistent pain should not be viewed simply as a symptom. Ongoing pain is a sign that something is wrong in the body.

POLICY AFFECTS PAIN MANAGEMENT PRACTICE

Regulation and legislation can have a significant effect on the practice of pain management and access to care, much like it does for other health conditions such as HIV/AIDS and breast cancer. Policymakers and health care regulators play an active role in the development of laws governing pain treatment; however, a number of factors can influence the content and messages of such policies, affecting public access to pain care treatment options. For example, availability of prescription opioid analgesic medications especially may be hindered by restrictive state policies, and therapeutic switching and/or step therapies imposed by insurance companies may limit pain treatment options.

KEY CHALLENGES TO CONSIDER WHEN WORKING TO IMPROVE PAIN-RELATED POLICY

- Persisting social stigma of pain management and the medical use of opioid pain medications, especially among legal and government regulatory bodies.
- Lack of awareness of current state policy content.
- Predominant focus on abuse and diversion of opioid analgesics. While abuse and diversion of prescription pain medication is certainly a problem that can have tragic consequences, so too are policies that hinder access to safe and effective pain care for those with legitimate medical need. The little attention paid to access to care for those with addictive disease or mental health disorders compound this issue.
 - As a group, lawmakers, educators, health care providers, the pharmaceutical industry, and caregivers could address the dual public health crises of the undertreatment of pain and rising prescription drug abuse together.²
- Outdated terminology that confuses physical dependence with addiction and has the potential to stigmatize people with pain as addicts and restrict prescribing practices.
- Lack of sufficient treatment resources and no clear definition of what constitutes a pain expert.
- Lack of reimbursement or support for pharmacological and nonpharmacological treatments for pain. Yet, there is increasing evidence that a multimodal treatment approach leads to better outcomes, gets people back to work sooner and costs less over the long run.
- Poor communication and/or implementation of policy that may unintentionally harm patients or limit access to pain therapies. Even if the substance of a policy upholds pain treatment as integral to the provision of quality medical care, sometimes the implementation of a policy can negatively affect the clinical practice of pain care. Intractable pain treatment acts are one example (see APF's *Pain Care Policy Topic Brief* for more information).

² American Pain Foundation. Provider Prescribing Patterns and Perceptions: Identifying Solutions to Build Consensus on Opioid Use in Pain Management — A Roundtable Discussion. April 2008. Available at www.painfoundation.org.

A Primer on Pain and Its Management

BURDEN OF PAIN IN AMERICA: AN EVOLVING PUBLIC HEALTH CRISIS

Pain is a serious and costly public health issue. It affects more American adults than diabetes, heart disease and cancer combined, and is a leading cause of disability in the United States. Even though pain is one of the most common reasons people consult a health care provider, it is often inadequately assessed and treated, resulting in needless suffering, poor outcomes and reduced quality of life and productivity.

Pain is a complex perception that differs enormously from one person to another, even those with seemingly identical injuries or illnesses.

Untreated or undertreated or inappropriately treated pain can compromise every aspect of life, including a person's physical and mental health, social and intimate relations, ability to sleep and perform everyday tasks, work productivity and financial well-being.

Persistent pain is not only emotionally and physically debilitating for patients, it also places a tremendous burden on families and caregivers, and contributes to excessive health care costs. Chronic pain costs the nation an estimated \$635 billion in medical treatment and lost productivity each year. As the 75 million baby boomers move toward retirement, the epidemic of untreated or undertreated pain is expected to rise.

Chronic pain affects 1 out of 3 Americans — or an estimated 116 million adults, according to the Institute of Medicine.

*A Primer on Pain and Its Management***PAIN BASICS**

The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. In 1968, Margo McCaffery, RN, a pioneer in the field of pain management nursing, stated pain is “whatever the experiencing person says it is, existing whenever and wherever the person says it does.”

COMMON PAIN CONDITIONS

In a National Center of Health Statistics survey, the following are common types of pain:

- low back pain (27 percent)
- severe headache or migraine pain (15 percent)
- neck pain (15 percent)
- facial ache or pain (4 percent)

See:

[http://www.painfoundation.org/
media/resources/pain-facts-
figures.html](http://www.painfoundation.org/media/resources/pain-facts-figures.html).

At its best, acute pain is the body's natural alarm system, alerting us to injury (or further injury if already injured). It prompts us to stop a harmful behavior or seek medical attention. For example, lifting too much weight might result in a piercing pain in a person's back. Within moments of touching a hot surface, the fiery sensation of a burn warns us to quickly pull away.

Worsening abdominal pain may be a sign of appendicitis or other serious infection. The experience of pain also beckons the injured person to rest, promoting healing.

At its worst, persistent pain robs people of their livelihood and well-being. When pain persists, it is often a sign that the body's alert system has broken down. In other words, pain signals remain active. Over time, this heightened response may:

- Harm the nerves, blood vessels and organs
- Suppress immune function
- Result in excessive inflammation
- Delay healing

Since the brain remembers pain, pain may be imprinted into the nerve tissue and continue to send pain sensations even in the absence of painful stimuli. This change in the nervous system means that pain has now evolved into disease state with no physiological meaning or value.

Chronic Pain-Brain Connection

New research is unraveling how chronic activation of the biological pathways transmitting pain is associated with structural and chemical changes in the brain. A recent study suggests that constant pain signals can result in mental rewiring that affects the frontal cortex — the area of the brain mainly associated with emotion and attention. According to researchers, this provides the first objective proof of brain disturbances in people with chronic pain that is unrelated to the sensation of physical pain. Functional magnetic resonance imaging reveals changes in brain activity and sensitization in people with pain.

*A Primer on Pain and Its Management***TYPES OF PAIN**

	Acute	Chronic
Cause	Generally known	May be known, but often unknown
Duration	Short, well described	Prolonged beyond healing \geq 3 months
Onset	Usually sudden	Sudden or gradual development
Treatment	Resolve underlying cause; self-limiting	Focus on underlying cause, if known, and pain disorder: pain reduction, function improvement, minimize side effects
Prognosis	Total relief typically possible	Total relief often impossible

Acute pain occurs suddenly due to illness, inflammation, injury or surgery. It has a short duration that subsides when the injured tissue heals. The cause of the pain can usually be diagnosed and treated.

Persistent (chronic) pain is pain that lasts long enough (after normal healing or for at least three months), or is intense enough, to affect a person's normal activities and well-being. Failure to treat acute pain promptly and appropriately at the time of injury, during initial medical and surgical care or at the time of transition to community-based care, contributes to the development of chronic pain syndromes. Every time someone undergoes surgery in which nerves and tissue are cut, he or she is at risk for ongoing pain if their initial pain is not addressed or their pain processing is altered during healing.

With chronic pain, pain signals may remain active in the nervous system for weeks, months or even years. Unlike acute pain, chronic pain has no value or benefit; it is a disease in its own right. It can also be especially challenging to treat.

A Primer on Pain and Its Management

PAIN ASSESSMENT



Timely access to quality pain management is the best way to minimize the suffering and disability often associated with undertreated pain and to avoid additional problems down the road.

Most hospitals, nursing homes and other health care facilities are now required to assess and treat pain. To correctly diagnose pain, a health care professional will:

- Perform a thorough physical exam
- Complete a pain assessment
- Ask detailed questions about the individual's medical history and lifestyle
- Order blood work, X-rays, electrical tests to detect nerve damage, or other diagnostic and laboratory tests

Pain is a subjective experience, and it is critical for health care providers to have a complete picture of the patient's pain history. He/she may ask about seven characteristics of pain to help LOCATE the pain and make the correct diagnosis.

- L** the exact Location of the pain and whether it travels to other body parts
- O** Other associated symptoms such as nausea, numbness or weakness
- C** The Character of the pain, whether it's throbbing, sharp, dull or burning
- A** Aggravating or Alleviating factors. What makes the pain better or worse?
- T** the Timing of the pain, how long it lasts, is it constant or intermittent?
- E** the Environment where the pain occurs, for example, while working or at home

The type of pain someone is experiencing is often a clue to its cause; for example, persistent pain that is burning or tingling is often the result of nerve disease (neuropathy).

EFFECTS OF UNRELIEVED PAIN ON PHYSICAL AND MENTAL HEALTH

If untreated, pain can have serious physiological, psychological and social consequences. It can:

- Limit the ability to work, sleep, exercise or perform everyday tasks (for example, dressing, going to the grocery store, lifting a child)
- Reduce mobility
- Impair strength
- Diminish appetite
- Make it difficult to recover from an injury or fight infection by weakening the immune system
- Aggravate other health problems
- Lead to depression and/or anxiety, which often worsen pain sensations
- Make it difficult to concentrate or reason
- Place added strain on relationships and interfere with intimacy
- Result in a loss of self-esteem and independence

A Primer on Pain and Its Management

Pain intensity scales are additional tools available to help individuals with pain describe only one feature of their pain, its intensity. These assessment tools help health care providers better understand the level of pain experienced at rest, during activities and how it varies throughout the day. These include numeric, verbal or visual scales.

With **numerical scales**, patients use numbers from 0 to 10 (0 being no pain and 10 being the worst pain ever) to rate the intensity of the pain.

Verbal scales contain commonly used words such as “mild,” “moderate” and “severe” to help patients’ describe the severity of the pain.

Visual scales use aids like pictures of facial expressions, colors or gaming objects, such as poker chips, to help explain the severity of pain. One type, the Wong Baker Faces Pain Rating Scale, shows six different facial expressions from happy (no hurt) to agony (hurts the worst) to help show health care providers how much pain a patient feels. Body diagrams may also be used to help pinpoint where the pain occurs.



From Hockenberry MJ, Wilson D, Winkelstein ML: *Wong's Essentials of Pediatric Nursing*, ed. 7, St. Louis, 2005, p. 1259. Used with permission. Copyright, Mosby.

Multidimensional pain assessment tools, such as the McGill Pain Questionnaire (MPQ) and the Brief Pain Inventory (BPI), have been developed to quantify different aspects of pain, including location and quality of pain and its effect on mood and function. However, these take longer to administer than the simpler scales and some patients who are cognitively impaired or poorly educated may find them difficult to complete. They are generally used in pain research, and have been adapted for clinical use in many settings.

The processing of pain is complex. A basic explanation is that the pain signals of acute pain are initiated when receptors on the skin, within an organ, tissue or nerve are triggered by injury or disease, known or unknown. A series of events follow: an electrical impulse, or pain message, is generated that is then carried on nerve fibers to the spinal cord. The spinal cord transmits the pain signal to various levels of the brain for interpretation and response. At any time during the transport of pain messaging, these noxious signals can be blocked, enhanced or modified. Signaling associated with chronic pain is much more complicated than acute pain as science is beginning to show.

A Primer on Pain and Its Management

TREATING PAIN

Successful pain management aims to:

- 1) lessen the pain,
- 2) improve functioning and
- 3) enhance quality of life.

Pain treatment should be:

- patient-centered — tailored to the individual
- multimodal — use a variety of pain treatment options
- multidisciplinary — involve a team of health care providers working directly with the person with pain, caregivers and family members as needed

Not one treatment strategy will work for everyone — a “cookie cutter” approach to pain care is ineffective.

Treatment options may include:

- Medication (anti-inflammatory medicines, opioids or other classes of medications called adjuvants)
- Psychosocial interventions (cognitive-behavioral counseling, guided imagery)
- Rehabilitative approaches (exercise, application of heat/cold, myofascial release, occupational therapy, if needed)
- Complementary alternative medicine (massage, acupuncture, hypnosis)
- Injection or infusion therapies

- Implantable devices and surgical procedures

Research shows that pain can affect one's emotions and behavior and interfere with the ability to concentrate, manage everyday tasks and cope with stress. Likewise, stress and emotional pressures can make pain worse, provoking “flare ups” and contributing to alterations in the immune system response. These relationships are not always easily recognized or readily fixed by medical procedures or medications alone.

New treatments under investigation are aimed at the physical, psychological and environmental components of chronic pain. Research is also examining the role of genetic predisposition and the immune system in mitigating pain signals.

For a detailed description of the different treatment modalities for managing pain, please refer to the America Pain Foundation's *Treatment Options: A Guide for People Living with Pain*.

PainSAFE (Pain Safety & Access for Everyone), www.painsafe.org, includes information and tips for consumers and clinicians on the safe and appropriate use of pain therapies.

MEDICATIONS & PAIN MANAGEMENT

Medications play an important role in the treatment of pain. There are three major classes of medications for pain control:

Non-opioids: nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen

Opioids: morphine, oxycodone, methadone, codeine and fentanyl are examples

Adjuvant analgesics: a loose term referring to the many medications originally used to treat conditions other than pain, but now are used to help relieve specific pain problems; examples include some antidepressants and anticonvulsants. Some of these medications have been shown to work well for specific types of pain.

Medications that have no direct pain-relieving properties may also be prescribed as part of a pain management plan. These include medications to treat insomnia, anxiety, depression and muscle spasms, and can help a great deal in the overall management of pain in some individuals.

Publication date: November 2008
Updated September 2011

Topic Brief

THE FDA, REMS AND THE POTENTIAL IMPACT ON ACCESS TO PAIN TREATMENTS



The U.S. Food and Drug Administration (FDA) regulates new drug approvals, product labeling for both prescription and over-the-counter (OTC) medications and the manufacturing process. When reviewing new drug applications, the agency carefully weighs the benefits and risks of each medication.

New laws also give the FDA authority to regulate these products after they have been approved. Such expanded jurisdiction over prescription and OTC medications is well-intended to help ensure additional oversight of medications after they come to market and provide extra safeguards for medication safety.

Because of its role in regulating controlled substances, including ingredients in pain medication, the Drug Enforcement Agency (DEA) is also influential in shaping federal pain policy and regulations. The non-medical use and abuse of prescription drugs has become a serious public health issue. Both FDA and DEA are involved with pain medication regulation in an attempt to curb the misuse and diversion of these medications, while at the same time ensuring access for people with legitimate medical need. The challenge — and concern — is that new policies to curb the non-medical use of various prescription medications could end up interfering with legitimate access to treatments for certain patient populations, most notably people living with persistent pain.

POST-APPROVAL DRUG REGULATION

In 2007, the Food and Drug Administration Amendments Act (FDAAA) gave the FDA authority to regulate drugs after they are approved.

As part of this charge, the FDA has been working with the pharmaceutical industry and consumer stakeholders to develop Risk Evaluation and Mitigation Strategies, or REMS, for a number of classes of medications, including opioid analgesics. Opioids are often a necessary part of a comprehensive pain management plan for certain patients with moderate to severe pain to help alleviate pain, restore functioning and improve quality of life. See APF's *Chronic Pain and Opioid Therapy Topic Brief* for more information.

In February 2009, the FDA sent letters to the manufacturers of 24 short- and long-acting opioid medications announcing they will be required to institute REMS to ensure the benefits of the

medications outweigh the risks, such as those related to misuse, abuse and overdose. New opioid medications will require REMS; some of the long-acting and rapid-onset opioids that are currently available by prescription already have REMS.

As of March 2010, more than 100 medications have REMS in place. Strategies for reducing risk of harm or misuse can range from providing basic patient and prescriber information and education packets or mandating continuing education for pharmacists and prescribers to restricting channels of distribution for certain medications and requiring patients to sign on to a registry.

It is well documented and widely understood that pain is undertreated or poorly treated for millions of people. FDAAA states that REMS should not place undue burden on access to care for those with legitimate need. The REMS process is well-intended and is meant to ensure

the safe use of medications in part by helping to ensure proper patient selection (an opioid tolerant individual who has low risk for misuse or becoming addicted) and requiring patient education on how to safely store and dispose of these medicines so they don't fall into the wrong hands. However, the American Pain Foundation (APF) — along with other leading consumer and provider organizations in the pain community — is concerned that the REMS process, while well-intentioned, will erect new barriers to timely and appropriate pain care.

REMS MAY UNINTENTIONALLY THREATEN ACCESS TO CARE FOR PEOPLE WITH PAIN

While well-intentioned, REMS have the potential to further limit access to opioid pain medication. There is not clear evidence that the proposed strategies will reduce abuse or misuse of prescription medication. Such strategies may cause people living with pain to

Topic Brief The FDA, REMS and the Potential Impact on Access to Pain Treatments

not receive the medications that are most appropriate for their needs.

Currently, REMS recommended by the FDA would only be required for long-acting opioids – not short-acting. This can affect prescribing choices. By making it more difficult for a health care provider to prescribe one class of medication and easier to prescribe another, prescribers may gravitate toward less stringently-regulated products. In some cases where a long-acting opioid could greatly improve the life of a person with pain, they may be prescribed a short-acting opioid because it is “easier” for the prescriber, yet more burdensome and less efficacious for their patient. This is not optimal pain care and may diminish the quality of life for the person in pain. It also does not address the underlying problem of prescription drug abuse, as those with substance use disorder or participants in criminal diversion will simply move to products that have fewer restrictions and are easier to obtain.

Additionally, from the clinician perspective many may choose not to treat people with pain who require opioid therapy amid such onerous requirements. These protocols serve to reinforce the fear that their medical license and livelihood are at risk each and every time they write a prescription. Regulations can be so restrictive that they deter health care professionals from the practice of pain care altogether.

A CALL FOR BALANCE

Prescription drug abuse is a serious public health issue — one that may make it more difficult for people with pain to access medication that can make their lives worth living; ideally, REMS

can be a part of the solution in terms of making abuse and misuse of pain medication more difficult. However, regulations designed to reduce prescription drug abuse should not come at the expense of people with a legitimate medical need.

As such, REMS must protect and not interfere with patient access to these important medicines. Negative stereotypes about individuals with pain and fear of ramifications of opioid prescribing can prevent early and effective treatment. Any strategies that further interfere with the ability of prescribers and other appropriate health care practitioners to responsibly develop, provide and adjust pain management regimens for their patients, including regimens that use opioid medication, will prove detrimental to patient care and are financially burdensome.

The cost of pain not only includes direct costs associated with health care provider visits, diagnostics and medication, but indirect costs such as lost wages and productivity of people with pain, as well as family members and caregivers. Aside from stealing livelihoods, untreated pain has been shown to shorten the lives of those who suffer. Some, who no longer consider their lives worth living, see suicide as their only option. These lives and livelihoods lost to pain are worth no less than lives and livelihoods lost to prescription drug misuse or abuse.

RATIONAL AND OUTCOME-BASED SOLUTIONS DESPERATELY NEEDED

Access to appropriate medicines should not be disrupted. As REMS evolve, the elements or strategies included should be proven to reduce the risk of abuse, misuse or diversion.

APF endorses recommendations made to the FDA to provide a balanced solution that will measurably curb the non-medical use and diversion of opioids, while ensuring and protecting patient access to opioid pain medications for those who medically need them. Recommendations include:

- 1) REMS should not interfere with the ability of prescribers and other appropriate health care practitioners to responsibly develop, provide and adjust pain management regimens for their patients.
- 2) REMS elements should be designed so they can be measured to determine their effectiveness in reducing risk of abuse, misuse and overdose.
- 3) Appropriate metrics are needed to determine successful outcomes for patient care as well as abuse, misuse, and diversion. Success thresholds should be predefined, reasonable and achievable. The following questions should be answered:
 - a. Is there convincing data to show a direct link between the non-medical use and abuse of prescription drugs to the prescribing behaviors of responsible health care professionals and use by people with pain who legitimately require opioids as part of their pain treatment plan?
 - b. Does the increase in prescriptions for legitimate medical use provide a surplus of prescription opioid analgesics in medicine cabinets and mailboxes for others to divert?

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For example:

- To differentiate accidental overdose by those who are prescribed opioids and overdoses caused as a result of non-medical use, abuse or diversion, REMS metrics should capture more detail about prescribers and patients (similar to cancer, stroke, or trauma registries) so there is insight on who is prescribing (family practice, rural, urban, etc), at what doses, and to what types of patients.
- Improved metrics are needed to better understand the national prevalence data that separates out incidents of accidental overdose due to inadequate knowledge (of the prescriber and their patients), misuse, abuse and diversion by the patient population as compared to the non-medical use by the public at large.
- More information is needed to identify sources for non-medical access to prescription medications, as it relates to unintentional and intentional overdose, misuse, abuse and diversion.
- Impact on access to pain care from REMS requires data collection and analysis to monitor for unintentional harm to people living with pain who require opioid therapy as one of their pain treatment options.

- 4) Short-acting opioids should also be subject to the class-wide REMS to eliminate any inclination to substitute short-acting for long-acting opioids.
- 5) New patient registries should not be a part of REMS for opioids. Restrictive, punitive systems such as patient "registries" further stigmatize people with pain and create additional hardships and new barriers to effective pain care.
- 6) Prescriber and dispenser risk mitigation education should be conducted as effectively as possible, and tied to DEA registration requirements or otherwise incentivized to encourage responsible prescribing and ensure compliance. Educational efforts directed to the prescriber, the dispenser and the intended end user need to focus on the safe use, safe storage and safe disposal of medicines to prevent prescription opioid medication from entering illicit channels of distribution.
- 7) Patient education materials can be developed for individual products to help prescribers and dispensers provide patients with appropriate use, storage, and disposal information, as well as any specific precautions relating to individual products.

Conclusions/Next Steps

Regulators, health care providers and people with pain all face a difficult challenge in the current environment. Balancing policies in such a way that they effectively address two concurrent and sometimes conflicting public health crises is extraordinarily difficult. REMS is not the sole solution to this dilemma, but it can be one incremental step in the direction of resolving it. For this to happen, it is necessary for policymakers to continually remind themselves that there are two groups of people at risk of morbidity and even mortality in this situation, and to continually ask if policy proposals will serve the needs of both groups.

In part, this challenge is so difficult because we have never addressed a pair of problems so diametrically opposed and have never thoroughly evaluated the outcomes to determine the extent to which the solutions were, in fact, solutions. It is imperative that such outcome studies be conducted with any REMS for opioids, so that we implement policies that protect both the millions of people with chronic pain and the millions of people with substance use disorders. Failure to conduct such an evaluation could leave us spending huge amounts of time and effort — not to mention money — implementing policies that are, in fact, harmful rather than helpful. Intervening in the manner evidence indicates is best is not just necessary in the practice of medicine, but also in the practice of public policy.

As FDA implements the new REMS for long-acting opioids and evaluates its effect, it is important to recognize that the lives and livelihoods lost to uncontrolled pain are worth no less than those who misuse or abuse prescription medications.

For more information, visit www.painfoundation.org.

Topic Brief

STATE-BASED PAIN CARE POLICY

A Snapshot of State-Based Policies Affecting Pain Care

Untreated pain is a silent epidemic in America. Chronic pain significantly and negatively affects the lives of an estimated one out of every three Americans, and costs the nation as much as \$635 billion in added health care expenses and lost productivity each year, according to the Institute of Medicine. This figure does not begin to cover the physical, emotional and economic strain of pain on the individual and caregivers.

As with efforts to advance the prevention, diagnosis and treatment of other diseases — for example HIV/AIDS and cancer — legislative and regulatory policies can strengthen or hinder efforts to improve pain care — a fundamental tenet in medicine.

In June 2011, the Institute of Medicine (IOM) released a seminal consensus report, “Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research,” and called for a comprehensive, population-level strategy to address pain as a complex disease, not just a symptom of injury or illness.

Included among the IOM’s recommendations to improve pain management are:

- **Developing a comprehensive plan by the U.S. Department of Health and Human Services** with specific goals, actions and timeframes by the end of 2012;
- **Reducing barriers** to access — whether legal, regulatory, reimbursement or cultural;
- **Educating the public** on prevention, treatment and self-management;
- **Improving professional education** across the spectrum of disciplines, and throughout the continuum of undergraduate, graduate and continuing health professions training; and
- **Focusing pain research efforts at the National Institutes of Health (NIH)**, and coordinating that research with other government agencies and the private sector to speed the development of **new therapies**, foster **interdisciplinary approaches**, increase **longitudinal research** of people in pain, and **increase the number of pain researchers**.

For more information, see IOM (Institute of Medicine) 2011. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education and Research*, Washington, DC; The National Academies Press. Available at <http://iom.edu/Reports/2011/Relieving-Pain-in-America-A-Blueprint-for-Transforming-Prevention-Care-Education-Research.aspx>.

Of course, federal and state elected officials, along with members of regulatory and licensing bodies, play a role in many of these areas and help shape the practice of pain management throughout the United States through the passing of federal and state policy.

At the same time, the non-medical use and diversion of prescription medications — including opioid analgesics — is also an important public health and safety issue that has influenced many policies in this area. For this reason, most of the policies discussed in this topic brief relate to the medical use of opioids, and the restrictions affecting the safe and appropriate provision of opioids for the treatment of moderate to severe pain. This in no way diminishes the importance of a multidisciplinary, multimodal therapeutic approach to pain management; opioids are only one tool within a broad range of treatment options. Indeed, many policies governing opioid therapy recognize the benefits of a multidisciplinary clinical approach. Moreover, policy responses to prevent the non-medical use of any therapy should not only protect the public from harm, but also maintain access to treatment for those with legitimate medical needs.

Topic Brief State-Based Pain Care Policy

State-based Legislation and Regulatory Policy

State governments have the authority to adopt policies that provide the legal basis for health care practice, including professional practice relating to pain management and the medical use of opioids. Legislatures create statutes that are broad and general, and then depend on the relevant regulatory agency to interpret and implement the statutes through regulations. In the field of medicine, for example, the state legislature grants authority to the state medical board to define and implement its laws through regulations that are consistent with legislative provisions.

Although these laws can establish requirements and prohibitions affecting treatment decisions about pain care, including chronic non-cancer pain, regulations are designed to be revised periodically to keep pace with changing practice standards. Conversely, legislation has been slow to change

in reaction to updated professional standards. Please refer to the section below titled *Challenges to Policies Promoting Safe and Effective Use*, which provides examples of pain-related statutes or regulations relating to opioid prescribing that contain potentially restrictive or ambiguous language.

Well-crafted pain policy promotes acceptable medical treatment, including pain management and the appropriate use of pain medications, and assures that the non-medical use of medications is clinically monitored and addressed effectively. However, overly restrictive prescribing requirements or prohibitions may create barriers to adequate pain treatment. Policies relating to the access of pain medications, therefore, must balance the public's health with protecting public safety through appropriate and effective drug control. Minimizing drug abuse and diversion must not interfere with the availability of medications for legitimate medical and scientific purposes.

Policies that promote the safe and effective use of pain medications are adopted and implemented within the context of two public health issues: (1) the under-treatment of pain and (2) the abuse of prescription pain medications. The story most commonly communicated to the public is too often focused on fears of substance abuse and diversion of opioids.

When the perception of undue risk outweighs therapeutic benefit, detrimental clinical consequences will occur. People with pain will be unable to access pain treatment options that enable them to be more functional and have an optimal quality of life. On the other hand, the abuse and diversion of opioids constitute a serious public health problem, and policies must be developed to reduce the resultant morbidity and mortality.

For more information, read the American Pain Foundation (APF) *Chronic Pain and Opioid Therapy* topic brief.

POLICIES CAN AND DO INFLUENCE PAIN CARE

Policies of any kind may either directly or unintentionally stigmatize individuals and/or make it harder for them to get appropriate pain care, which is already difficult to obtain for clinical or systemic reasons. In addition, health care professionals generally are hesitant to engage in policy change activities because of a lack of guidance about how best to approach and interact with policymakers around these issues.

Furthermore, good policy does not necessarily equal good practice. Once good policy is in place, a number of actions must follow to translate it into practice. Policymakers, health care professionals and people with pain must understand what constitutes good pain management and what certain policies allow. Any policy responses must be thoughtfully approached and uphold access to humane care that prevents needless suffering and improves quality of life.

A Snapshot of State Pain Laws and Policies that Influence Pain Management

The ability to effectively and responsibly manage pain is influenced by federal laws, state statutes, regulations, regulatory guidelines and policy statements.

The following provides a snapshot of some of the existing policies that can affect pain care at the state level.

Some state-based laws and policies that can influence the provision of pain care:

- Prescription Monitoring Programs
- Professional Licensing Board Regulatory Policies
- Mandated Continuing Education in Pain/Palliative Care
- Intractable Pain Treatment Acts
- Controlling Pharmaceutical Costs in Medicaid Programs
- Workers' Compensation
- Step Therapy (Fail First) and Therapeutic Switching Insurance Policies

• Prescription Monitoring Programs (PMPs, also called prescription drug monitoring programs [PDMPs])

PDMPs are state-based programs that aim to reduce the abuse and diversion of prescription medications. These programs track controlled substances prescribed by authorized practitioners and dispensed at pharmacies. PDMPs can help identify individuals who obtain similar medications from multiple prescribers or pharmacies (also called "doctor shopping" or "pharmacy hopping"). Not only can PDMPs provide early warnings of drug abuse hot spots (especially when considered with other data) and help investigators uncover diversion and insurance fraud, they also can be a useful clinical practice tool to improve patient care.

By mid-2011, 36 states had operational PDMPs; another eight states have adopted laws authorizing the creation of these programs.

In its recent report, "Epidemic: Responding to America's Prescription Drug Abuse Crisis," the White House supports the expansion of state-based PDMPs to all 50 states as a "promising approach" to help curtail prescription drug diversion and abuse (See http://www.whitehousedrugpolicy.gov/publications/pdf/rx_abuse_plan.pdf), but also recognizes the need for improvements, stating that "more work is needed to determine how to maximize their effectiveness." In particular, PDMPs currently are limited by their inability to:

- Share inter-state data to determine whether an individual has obtained medications from other states (although this may soon change);
- Authorize electronic access to prescribers; or
- Provide "real-time" data to prescribers and dispensers.

There also is a need to effectively promote the appropriate use of PDMPs when they become available so that prescribers can better utilize the PDMP data to inform their treatment decisions when prescribing opioids. For information about the current status of PDMPs, visit <http://www.aapainmanage.org/aboutus/Advocacy.php>.

APF outlines key considerations for policymakers when drafting or reviewing PDMP legislation, and calls for research to study the effect of PDMPs on physician prescribing practices, pain management and drug diversion and misuse. To read APF's statement, visit <http://www.painfoundation.org/about/position-statements/pmp.html>.

• Professional Licensing Board Regulatory Policies

Most states have avoided enacting pain legislation. Instead, states promote health care regulatory board regulations, guidelines or policy statements.

These policies typically promote the message that pain management and the safe and effective use of controlled substances is an accepted part of professional practice. Another goal of such policies is to reassure clinicians that they have nothing to fear from their licensing agency if reasonable professional practices are followed when using controlled substances for patient care.

Much of this recent policy activity was prompted in 2004 by the Federation of State Medical Boards' creation of the model policy to promote consistency in state medical board policy (see http://www.fsbm.org/pdf/2004_grpol_Controlled_Substances.pdf). Now, 45 states have some type of medical board policy to address pain relief.

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Other states have joint statements on pain management, palliative care or end-of-life care adopted by health care boards. Examples are:

- Minnesota:
<http://www.phcybrd.state.mn.us/forms/jspm.pdf>;
- Kansas:
http://www.state.mn.us/mn/externalDocs/BMP/BMP_Joint_Policy_Statement_091404112418_Joint%20Statement%20on%20Pain%20Management.htm;
- Oregon:
<http://www.painpolicy.wisc.edu/domestic/states/OR/joint.pdf>;
- South Carolina:
<http://www.painpolicy.wisc.edu/domestic/states/SC/scjoint.pdf>

• Mandated Continuing Education in Pain/Palliative Care

Some legislatures and regulatory boards either mandate or strongly encourage that continuing education (CE) for health care professionals to renew their license include pain and palliative care education. Such policies have been deemed necessary based on evidence that many health care professionals lack knowledge about pain management and receive little training in medical school.

These mandates should incorporate outcomes research to demonstrate the value of CE, including data to show whether and to what extent the curriculum and teaching methods improved pain treatment. Such research also may suggest how CE programs could be modified to increase their effectiveness.

• Intractable Pain Treatment Acts (IPTAs)

IPTAs are a class of statutes intended to provide immunity to health care professionals who prescribe opioids to treat intractable pain. Although the intent of IPTAs is commendable, the statutes historically have contained restrictions or ambiguities that may limit clinical decision-making practices. For example, these laws may require people living with pain to have a consultation with one or more health care professionals before their pain can be treated when the goal should be to make it easier for clinicians to treat pain.

Additional problematic language includes implying that opioids are outside legitimate professional practice; providing immunity only for individuals living with persistent pain that does not respond to other treatment options; prohibiting prescribing to people with substance use disorder; and confusing addiction with physical dependence. IPTAs also tend to omit clear statements supporting enhanced pain management and access to care.

In recognizing these issues, several states have repealed such requirements and ambiguities — including the term and definition of “intractable pain,” in effect extending the immunity of this law to treating all types of pain.

• Controlling Pharmaceutical Costs in Medicaid Programs

Medicaid programs control which medications are on a drug formulary by establishing preferred drug lists (PDLs) to accomplish cost containment. Medications not included on the PDL remain available only with prior approval, which can delay access to the medically recommended medication. Pharmaceutical companies are often required by Medicaid to provide supplemental rebates to have their product included in the formulary.

Ideally, states should make decisions based on safety, clinical efficacy, and cost, rather than solely on the cost as the primary criteria in determining which medications are included in a PDL.

“The struggle for pain relief can ill-afford any more unnecessary obstacles, even those masquerading as fiscal responsibility. It is never responsible to exchange pain and suffering for a per-pill cost ledger. Without also taking efficacy, expediency, and safety into account along with overall cost, this committee will also need to be accountable for unnecessary pain and suffering among the most vulnerable citizens in Maryland, a toll for which each member can justly feel responsible.”

— 2005 Maryland P & T Committee Testimony by F. Michael Gloth, III, MD.

Another mechanism that can be used by Medicaid to both control costs and enhance patient safety is a “lock-in” program, in which an individual may be assigned a single practitioner and single pharmacy from which to obtain pain medication.

The premise behind lock-in programs is that heightened tracking helps ensure Medicaid recipients receive appropriate treatment, while controlling costs by reducing visits to hospitals, clinics, physician offices and emergency rooms, as well as duplicative or unnecessary prescriptions. North Carolina enacted a lock-in program specific to opioid pain medication in 2010. Other states, like Wisconsin, monitor controlled substances, including benzodiazepines and stimulants as well as opioids. Lock-in requests can be made by pharmacists when the prescription recipient is suspected of non-medical use.

- **Workers' Compensation**

Workers' compensation, like Medicaid, is a very expensive area for government health care funding. Some states have established extensive guidelines for workers' compensation-related pain treatment, as a means of controlling both costs and the risk of non-medical use of medications and diversion. Unfortunately, some of these guidelines are extremely restrictive and run the risk of impeding effective and appropriate pain treatment.

For example, in Washington state, the Health Technology Clinical Committee has denied coverage of several pain care devices and treatments for those enrolled in state-paid medical

plans: Medicaid, workers' compensation and Uniform Medical. As of May 2011, coverage denials include the use of intrathecal pumps, transcutaneous electrical nerve stimulator (TENS) units and spinal cord stimulators. The decisions to deny reimbursement for these three chronic pain devices affects approximately 330,000 public employees and retirees, 70,000 individuals in the Basic Health Program, 900,000 in the Medicaid program, and 2.5 million workers with approximately 130,000 claims (Labor & Industries, Workers' compensation).

This is a complex area of work — one that deserves more focused attention from the pain community and policymakers alike. Third-party payer policies and practices that usurp the “doctor-patient” relationship, deny pain care access to vulnerable groups, or are developed primarily for cost savings supersede the best interest of patient care. These actions serve as an inappropriate and unacceptable form of health care rationing.

For more information, read APF's Access to Care Position Statement.

- **Step Therapy (Fail First) and Therapeutic Switching — Insurance Policies**

Step or fail first therapy requires alternate medications, which in some cases includes over-the-counter medication, or other therapies to be used before the health care provider-recommended medication is approved for reimbursement. These patients can be required to “fail” numerous other

treatment options before the insurer will grant reimbursement access to the treatment option that was originally prescribed by the clinician. This protocol is used as a cost-saving measure for the insurer.

Step therapy often sets the stage for forced “off-label” use of medications that may no longer be appropriate nor provide optimal efficacy for an individual’s medical condition. This policy can actually increase costs for the insurer because the delay in recommended care may decrease the person’s response to treatment or cause other health complications.

Therapeutic switching (or “therapeutic substitution”) is when the *insurer* substitutes less expensive medications or alternate medications. These are not the medications prescribed by the health care professional and the individual is not usually aware of the change until he or she arrives at the pharmacy to pick up their medication. These medications may have more side effects or be less effective for the person with pain. Pharmacists and clinicians are put in the unfortunate predicament of confronting insurers to defend the medication therapy that they prescribed. This is different than “therapeutic interchange,” where exchanges are in accordance with previously established and *medical* staff-approved written guidelines or protocols, within a drug formulary system.

It is understandable that insurance companies try to cut costs and avoid unnecessary medical interventions; however, the clinical judgment of the direct care provider to an individual’s health care must not be undermined. Legislative and

regulatory ruling must help correct this by placing prescribing power back in the hands of health care professionals in charge of their patient's care. APF supports the American Medical Association's official statement on this issue:

...[T]he AMA accepts the concept of therapeutic *interchange*; i.e., the authorized

exchange of therapeutic alternates in accordance with previously established and medical staff-approved written guidelines or protocols, within a drug formulary system.

...[T]he AMA clearly differentiates therapeutic interchange from therapeutic *substitution*; i.e. the act of dispensing a therapeutic

alternate for the drug product prescribed without prior authorization of the prescriber, and reaffirms its strong opposition to therapeutic substitution in any patient care setting.

For more information, read APF's position statements on therapeutic switching and step therapies.

Challenges to Policies Promoting Safe and Effective Use

Pain generally is poorly understood by the public, policymakers, and even many health care professionals. An integral part of pain care policy is educating people — and in some cases reeducating people — about how pain affects lives, its cost to society and the tremendous toll it can exact on families, the workplace and the community. Such efforts to improve the awareness and understanding of pain treatment issues, however, may be undermined by policies included in the previous section and also by requirements and language found in other policies.

Addiction terminology

One of the most common problematic provisions remaining in state policy today is archaic terminology that confuses physical dependence with addiction. As of mid-2011, 41 states have adopted language clarifying the distinction between these clinical phenomena. Such up-to-date terminology is typically contained in health care regulatory guidelines or policy statements; however, the statutes of 14 states and the health care regulations in two states continue to classify physical dependence as synonymous with addiction. As a result, these states have conflicting standards about what constitutes addiction, which may create ambiguity and has significant clinical implications.

When such archaic standards are applied in practice, they have the potential to stigmatize people with pain as "addicts" and restrict prescribing practices, leading to inadequate pain management for those who need opioid pain medication for management of their pain condition.

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ADDITIONAL RESOURCES FOR APPROPRIATE DEFINITIONS

American Pain Foundation issued an At-a-glance page defining each of these terms in its *Chronic Pain and Opioid Therapy* topic brief.

The American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine released a consensus document about this issue. These professional organizations recognize the following definitions and recommend their use. See <http://www.ampainsoc.org/library/bulletin/mar99/president.htm> for additional information.

- **Addiction**

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

- **Physical Dependence**

Physical dependence is a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

- **Tolerance**

Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.

For additional resources, see the Federation of State Medical Boards' influential Model Policy for the Use of Controlled Substances for the Treatment of Pain. Responsible Opioid Prescribing: A Physician's Guide at www.fsmb.org/pain-model-policy.html.

Reporting People Who are Prescribed Opioids

The laws in some states contain problematic language relating to the reporting of people being treated with opioids. For example:

- In Pennsylvania, pharmacies must report the identity of every person being treated with schedule II controlled substances to the state attorney general (28 Pennsylvania Code § 25.131).
- A law in North Carolina requires all health care practitioners who treat “drug dependent persons” to report their patients to the state Department of Health and Human Services. This law may

classify individuals as “drug dependent” if they are taking opioids for a legitimate medical purpose and are physically dependent on the medication. It seems, therefore, that practitioners prescribing opioids to treat people with pain could be subject to this requirement (North Carolina General Statutes § 90-109.1(c)).

- Finally, the California Department of Justice can assign a physician to examine any person taking a schedule I, II, or III medication, or who has an addiction to a controlled substance. The person must submit to the examination, or

could be found guilty of a misdemeanor (California Health & Safety Code § 11453).

Excessive Prescribing

A frequent dictate on health care practice is the creation of ambiguous practice standards, such as defining unprofessional conduct to include “excessive prescribing” without operationalizing the term or defining how it would be determined. Such vague standards need to be clarified in or removed from state laws.

Pain Management and the Legal System

Prescribers frequently cite fear of prosecution and loss of license as reasons they fear treating people with pain. If legal or regulatory sanction is perceived as a significant risk, it presents a barrier to proper pain management. All health care professionals need to know how to assess and treat pain knowledgeably. Prescribers must know how and when to add opioid-based medications to

the pain treatment plan. They must be aware of federal and state laws governing the prescribing and handling of controlled-substance pain medications to avoid contributing to abuse and diversion. At the same time, legislators and regulatory officials should successfully address prescription drug abuse and diversion without limiting the availability of any pain treatment option, including opioid analgesics that are warranted for legitimate medical use.



HOW POLICIES MAY HAVE UNINTENDED CONSEQUENCES

In Washington state, three policies have been problematic for people living with pain and their health care professionals:

- ESHB 2876 — a new opioid prescribing law that went into effect in June 2011, adds barriers to prescribing opioids to people living with pain by adding burden and cost to practitioners and patients.
- HTA—Washington state's Health Technology Assessment Committee denied coverage of three technologies (spinal cord stimulation, intrathecal drug delivery systems and TENS units) for people with pain in the public payer system and voted to cover four out of five spinal injections in early 2011.
- HB1311—proposes the creation of a committee that may decide to limit options for pain care, contributing to this disturbing climate in Washington state. In each of these instances, well-intentioned laws can have consequences not only for people with pain and those with a substance use disorder, but also for anyone receiving a controlled substance to treat a medical condition.

Ironically, this policy activity was promoted as an effective response to the abuse and overdose deaths related to prescription pain medications, without evidence that such public health issues result from inappropriate prescribing by health care professionals. Of course, initiatives to safely and successfully reduce the non-medical use of prescription opioids are essential, but only to the extent that they avoid undermining clinical decision-making practices and legitimate patient care. Unfortunately, such policy activity encourages similar policy adoption in other states before its impact either on non-medical use and overdose deaths or on the treatment of patients with legitimate medical conditions is known.

Non-Governmental Regulations Promoting Good Pain Management

Not all policy affecting pain management comes from government agencies. The Joint Commission, a voluntary, independent, not-for-profit organization, provides accreditation services to more than 18,000 health care facilities and programs in the United States. Joint Commission accreditation is, in many ways, the “gold standard” of achievement for health care organizations, and recognizes the adherence to high standards in many aspects of patient care.

In 2001, thanks largely to the efforts of Dr. June Dahl and her colleagues from the University of Wisconsin, the Joint Commission issued its first set of standards focused specifically on a symptom or disorder: pain. The standards for pain assessment and treatment required organizations to

- regularly assess and document the presence, severity, and qualities of pain;
- provide appropriate treatment for pain when it is present;
- educate patients, their caregivers, and practitioners about pain treatment; and
- engage in performance improvement efforts related to pain management, among other standards.

These standards resulted in many institutions adopting “pain as a fifth vital sign” policies.

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Evaluating State Policies

Pain advisory committees (also known as pain commissions or pain task forces) play a role in evaluating state pain care policies. These state-level workgroups are used to improve pain management practices by evaluating state laws and regulations that could interfere with access to adequate pain care and to develop recommendations for corrective action.

To be most effective, pain advisory committees should comprise a multidisciplinary team of individuals representing state agencies and health care organizations, health care professionals with pain expertise, people with pain, caregivers and public citizens. They should also serve an advisory and educational function, surveying the status of pain policy and practice in the state and recommending changes to policymakers about achieving better balance in policy and improved practice of pain management. As a result, successful collaborations between committee members and policymakers can influence a state's legislative or regulatory agenda to diminish or avoid establishing barriers to pain management, as well as reduce the non-medical use and diversion of prescription pain medications. One successful model to consider is the pain management commission for the state of Oregon, established in 1999 (see <http://www.oregon.gov/OHA/OHPR/PMC/index.shtml/>).

In addition, the University of Wisconsin Pain & Policy Studies Group (PPSG) created a criteria-based evaluation related to opioid analgesics to quantify and assign grades representing the quality of each state's pain policies aimed at

preventing drug abuse, regulating professional practice, and improving patient care. These criteria can then be used to compare all states and track policy changes over time. Five evaluations over an eight-year period by PPSG show continuous improvement in state policies governing the medical use of opioid medications. See: http://www.painpolicy.wisc.edu/Achieving_Balance/PRC2008.pdf

Grades range from A to F, including mid-point grades (e.g., B+, C+, D+). Higher grades are associated with state policies that are more balanced and consistent with modern medicine. A lower grade means that a state's policies contain potential barriers to patient

pain relief (i.e., language that creates ambiguous practice standards or contradicts current medical knowledge, policies that are not consistent with the policy guidance recommendations from authoritative sources and fail to communicate the appropriate messages about pain management to professionals, patients and the public). See the table below for a list of states' most recent grades related to the content of statutes, regulations, and health care regulatory board guidelines/policy statements involving opioids.

State Grades for 2008

State	2008 Grade	State	2008 Grade
Alabama	B+	Montana	C+
Alaska	C+	Nebraska	B+
Arizona	B+	Nevada	C
Arkansas	B	New Hampshire	B
California	B	New Jersey	C+
Colorado	B	New Mexico	B+
Connecticut	B	New York	C
Delaware	C+	North Carolina	B
District of Columbia	C+	North Dakota	B
Florida	B	Ohio	B
Georgia	B	Oklahoma	C+
Hawaii	B	Oregon	A
Idaho	B	Pennsylvania	C+
Illinois	C	Rhode Island	B+
Indiana	C+	South Carolina	C+
Iowa	B	South Dakota	B
Kansas	A	Tennessee	C
Kentucky	B	Texas	C
Louisiana	C	Utah	B+
Maine	B+	Vermont	B+
Maryland	B	Virginia	A
Massachusetts	B+	Washington	B+
Michigan	A	West Virginia	B
Minnesota	B+	Wisconsin	A
Mississippi	C+	Wyoming	C+
Missouri	C+		

PPSG provides a database of state statutes, regulations and other government policies affecting pain management. Visit www.painpolicy.wisc.edu/matrix.htm to find pain management policies in your state.

What's Next to Improve Policy Content Related to Pain Care

We all must thoughtfully consider existing and proposed legislation and regulatory policies to find requirements that might unduly impede access to pain management, while also maintaining the potential to protect against harm from the inappropriate use of any treatment modality. To guide efforts within a state to create new or modify existing policies that both promote the safe and effective treatment of pain and minimize the public health consequences of the non-medical use of prescription opioids, we encourage policymakers to:

- Identify the policy needs/issues in your state by engaging with the constituencies governed/affected by such policy
- Ask questions of pain experts and people affected by pain
- Focus on removing archaic or ambiguous language/requirements
- Avoid legislation that establishes standards that are slow to change in reaction to professional developments
- Anticipate how policies, even if not directly related to pain management, could influence pain care
- Support efforts to evaluate outcomes of policy change to determine if the intended goals were met, if unintended consequences need to be addressed, and if there is a way to modify policy to achieve more intended and fewer unintended consequences.
- Use available resources to guide policy changes/recommendations, such as the American Pain Foundation (www.painfoundation.org) or the Pain & Policies Study Group state policy evaluation findings (http://www.painpolicy.wisc.edu/Achieving_Balance/EG2008.pdf). These resources could provide an idea about what other states may have done to address similar issues, or could point to the existence of policy templates that are available.

STATE POLICY WATCH

State policies influencing pain management continue to evolve. Policymakers, health care professionals and the public need to be mindful about unintended consequences that could introduce hardships for prescribers, dissuade well-meaning health professionals from providing pain and palliative care, and hinder access to quality and timely pain care. Experts expect the following to be ongoing policy topics in the years to come:

- Expanding and improving consistency of prescription monitoring programs, especially efforts to link these programs across state lines and evaluate outcomes to make them more effective.
- Shutting down “pill mills,” which contribute to prescription drug trafficking, endanger individuals receiving medications from these illegal clinics and threaten the communities where they are located, through dedicated legislation.
- Increasing the number of community-based take back programs to ensure proper disposal of expired and unused prescription medications and, in turn, prevent diversion and non-medical use.
- Developing regulatory policies aimed at health care professionals to promote the safe and effective treatment of pain.
- Creating policies aimed to curb morbidity and mortality from prescription medication abuse that might impede efforts to protect access to quality pain management.

Topic Brief State-Based Pain Care Policy

LEGISLATORS CAN USE THE FOLLOWING TIPS AND QUESTIONS, DEVELOPED BY PPSG, TO HELP IMPROVE PAIN MANAGEMENT IN THEIR STATES.

What can state legislatures do to improve pain management?

First, study the problem. Create a multidisciplinary task force, commission or committee with public hearings to study carefully the barriers to pain management for all types of pain in the state (cancer, chronic non-cancer, post-surgical, sickle cell, AIDS, etc.); review relevant state policies outlined below; make and implement recommendations in legislation, leadership, public information, education, training, program development, etc.

1. Drug, pharmacy, controlled substances policy

- Does the state controlled substances act recognize the essential medical uses of controlled substances as in federal law and as recommended by the National Conference of Commissioners on Uniform State Laws?
- Does state law or regulations unduly restrict prescribing of controlled substances, e.g., government-required prescription forms; exclusion of addicts even if they have pain; require second opinion, consultation or informed consent; legal terminology confusing addicts with pain patients/addict reporting, limit number of dosage units of controlled substances (e.g., opioids) that can be prescribed at one time, or limit unrealistically the period of validity of a prescription for a scheduled substance?
- Does state policy allow physicians and pharmacists to take full advantage of the flexibility in federal controlled substances regulation regarding faxing and partial dispensing of controlled substances prescriptions?

2. Medical policy

- Does the medical practice act or regulations contain any policies with regard to prescribing controlled substances which are unduly restrictive or confusing when applied to the prescribing of controlled substances for the treatment of pain? (i.e., no prescribing to addicts, even if they have pain?)
- Does the medical board have a policy statement or guidelines which clarifies that the board recognizes that the use of controlled substances for the treatment of chronic pain is accepted

medical practice and clarifies the principles which a physician can follow to confidently avoid the risk of discipline or arrest by any agency in the state?

3. Facility regulation (hospice, nursing home, home care, etc.)

- What is the attitude of the state facility regulators: is pain a priority or is the priority only reducing the use of controlled drugs?
- Do certification and inspection criteria include assessment and treatment of pain and training of patient care staff; is technical assistance on pain and symptom management available?

4. State health policy

- Does the state cancer control program include a funded emphasis on pain management and palliative care for cancer patients in the state?
- Is there a state pain initiative and does it have adequate support?
- Does the public have access to information about pain and symptom management including chronic non-cancer pain, and where to go for help?
- Do toll free numbers for other chronic conditions, like cancer or diabetes, include information about pain management?
- Do managed care organizations have adequate policies: pain assessment, treatment, reimbursement, appropriate access to specialists?
- Does state Medicaid policy reimburse the controlled medications used in pain and symptom management?
- Does workers' compensation adequately address the needs of people with chronic severe pain?

5. Drug enforcement policy

- Do the agencies in the state which are involved in drug law enforcement and monitoring of controlled substances prescribing, dispensing and patient use have adequate safeguards against the inappropriate scrutiny of practitioners who prescribe and dispense legitimate controlled substances?

Topic Brief

CHRONIC PAIN AND OPIOID THERAPY

Effective management of chronic pain often requires a step-wise, coordinated and integrated trial of different treatment options, a team of health care providers and social support from family and friends. Health care providers may start with behavioral and non-pharmacological interventions (e.g., hot/cold therapy, physical therapy, relaxation techniques) when devising pain treatment plans. Strong prescription pain relievers like opioid analgesics may be recommended as one of the treatment options to help reduce moderate to severe pain so that function and quality of life can be improved. According to the American Pain Society, the American Academy of Pain Management and the American Geriatrics Society, individuals with severe or functionally limiting pain that is not sufficiently relieved by other means should be considered for a trial of opioid therapy.

Key Issues

- An estimated 116 million Americans suffer with chronic pain.¹ The consequences of unmanaged persistent pain are devastating for individuals and their families. Sadly, many people with chronic, debilitating pain are made to feel as though the pain is "just in their head."
- For some people, opioids are a necessary and integral part of a comprehensive pain management plan to help relieve pain, restore functioning and improve quality of life.^{2,3}
- Unfortunately, access to these medications may be hindered by unduly restrictive state policies, persisting social stigma surrounding their use, as well as therapeutic switching and/or step therapies imposed by insurance companies. For more information about policies that directly or unintentionally affect access to pain care, read the *State-Based Pain Care Policies Topic Brief*.
- Unless a person with pain has a past or current personal or family history of substance abuse, the likelihood of addiction is low when opioids are appropriately prescribed, taken as directed and monitored by a responsible and knowledgeable health care provider. Although more well-controlled studies are needed, current evidence indicates that addiction prevalence in pain patients may be no different from prevalence of addiction in the general U.S. population.^{4,5}
- Rising rates of non-medical use of prescription medications and emergency room admissions related to prescription drug abuse, as well as an increase in the theft and illegal resale of prescription drugs, indicate that drug diversion is a growing problem nationwide.⁶ The main source of drug diversion is from theft by family members, friends and workers in the home or from the sharing and selling of medications though often with good intentions.⁷
- Diverse players (e.g., lawmakers, educators, health care providers, the pharmaceutical industry, caregivers) must come together to address the dual public health crises of the undertreatment of pain and rising prescription drug abuse.⁸
- Alleviating pain remains a medical imperative — one that must be balanced with measures to address rising non-medical use of prescription drugs and to protect the public health.⁸

Opioids 101

Opioids include morphine, oxycodone, oxymorphone, hydrocodone, hydromorphone, methadone, codeine and fentanyl. Opioids are classified in several ways, most commonly based on their origin and duration of effects.⁹

Common classifications for opioids^{9,10}

SOURCE	Natural or semisynthetic: Contained in or slightly modified (semisynthetic) from chemicals found in poppy resin	Synthetic: Synthesized in the laboratory
DURATION OF RESPONSE	Short-acting: Provide quick-acting pain relief and are used primarily as "rescue medication," as in acute pain	Long-acting: Provide longer duration of pain relief and are most often used for stable, chronic pain

One of the advantages of opioids is that they can be given in so many different ways. For example, they can be administered by mouth, oral mucosal or sublingual delivery systems, rectal suppository, intravenous injection (IV), subcutaneously (under the skin), transdermally (in the form of a patch) or into a region around the spinal cord. Patches, IV injections and infusions are very important for patients who cannot swallow, or whose GI tracts are not working normally.¹¹

Opioids are believed to work by binding to specific proteins (opioid receptors), which are found in specialized pain-controlling regions of the brain and spinal cord. When these compounds attach to certain opioid receptors, the electrical and chemical signals in these regions are altered, ultimately reducing pain.⁹

Because of their long history of use, the clinical profile of opioids has been very well characterized. Multiple clinical studies have shown that long-acting opioids, in particular, are effective in improving:

- Daily function
- Psychological health
- Overall health-related quality of life for people with chronic pain¹²

However, some types of pain, such as pain caused by nerve compression or destruction, do not appear to be relieved by opioids.¹⁰

Adverse Effects

Side effects of opioids result primarily from activation of opioid receptors outside and within the nervous system. Activation of opioid receptors in the gut, for example, may cause constipation,

nausea and vomiting, and other gastrointestinal effects. Tolerance to nausea and vomiting usually develops within the first few days or weeks of therapy, but some people are intolerant to opioids and experience severe adverse side effects.¹⁰ Other side effects include drowsiness, mental clouding and, in some people, euphoria.⁹ Recent research shows that genetic variations may influence opioid metabolism.

Depending on the amount taken, opioids can depress breathing. However, this effect usually is not present after someone has taken opioids over time. The risk of sedation and respiratory depression is heightened when opioids are taken with other sedating medications (e.g., antihistamines, benzodiazepines), reinforcing the need to carefully monitor individuals who are taking such combinations..

Careful Monitoring and Open Communication

People taking opioids must be carefully selected and monitored by a knowledgeable and responsible prescriber. People with pain should speak openly with their health care provider about noticeable improvements in functioning, as well as side effects and other concerns (e.g., constipation, fears of addiction).

The American Pain Foundation's *Targeting Chronic Pain* materials help facilitate open dialogue between people who live with pain and their health care team, and give prescribers tools for selecting, monitoring and following their patients. To access these resources, visit www.painfoundation.org and click on Publications under the Learn about Pain tab.

The Four “A’s”

The Four “A’s” of pain management are used by clinicians to measure key treatment outcomes — pain relief, psychosocial functioning, side effects and addiction-related outcomes.

Analgesia – Is the pain relief clinically significant? Is there a reduction in the pain score (0-10)?

Activity levels – What is the patient’s level of physical and psychosocial functioning? Has treatment made an improvement?

Adverse effects – Is the patient experiencing side effects from pain relievers? If so, are they tolerable?

Aberrant behaviors – Are there any behaviors of concern such as early refills or lost medication? Does the patient show signs of misuse, abuse or addiction? What is the plan of action?

Source: Passik & Weinreb, 1998; Passik & Portenoy, 1998

Dual Public Health Crises: Balancing Medical Imperative to Relieve Suffering and Protect Public Safety

Pain affects more Americans than diabetes, heart disease and cancer combined, and it is one of the leading causes of disability in the United States. Recognition of pain as a growing public health crisis has led to the establishment of specialized pain clinics, treatment guidelines for certain types of pain, as well as greater use of treatment strategies to effectively alleviate pain and improve functioning, including prescription pain medicines.

As the therapeutic use of opioids has increased to appropriately address pain, there has been a simultaneous and dramatic rise in non-medical use of prescription drugs.¹³ When misused — that is, taken by someone other than the person for whom the medication was prescribed, or taken in a manner or dosage other than what was prescribed — prescription medications can produce serious adverse health effects and can lead to addiction, overdose and even death.

People who abuse opioids typically do so for the euphoric effects (e.g., the “high”); however, most abusers are **not** patients who take opioids to manage pain.¹⁴ Rather, they are often people within the social network of the person who possesses a lawful prescription. In fact, 71 percent of people abusing prescription pain relievers received them from a friend or family member without a prescription.⁷ Prescription pain relievers are frequently illegally stolen from medicine cabinets, purchased or shared in schools, or simply given away.

Picture of Prescription Drug Abuse in America

- In 2009, 16 million Americans 12 years of age and older had taken a prescription pain reliever, tranquilizer, stimulant or sedative for non-medical purposes at least once in the previous year.¹⁴
- The rate of non-medical use of medications has risen among teenagers. In fact, prescription drugs are now the second most abused category of drugs behind marijuana.¹⁵
- In 2007, 93 percent of unintentional poisoning deaths in the U.S. were caused by drugs. Opioid pain medications, such as methadone, hydrocodone, or oxycodone, were most commonly involved, followed by cocaine and heroin.¹⁶
- Most people who use prescription drugs nonmedically (7 out of 10) get them from friends or family; very few obtain them from drug dealers or the Internet.¹⁴

Nonmedical use includes misuse, abuse or otherwise not taking a drug as prescribed.

The growing prevalence of prescription drug abuse not only threatens the lives of abusers; concerns about misuse, abuse and diversion may also jeopardize effective pain management by impeding appropriate access to opioids for legitimate medical need. Concern about scrutiny by regulators or law enforcement, and specific action by some agencies, has had a “chilling effect” on the willingness of some doctors, nurse practitioners and physician assistants to prescribe opioids.^{8,17}

Moreover, high profile reports of drug abuse, diversion and addiction, or of legal actions taken against prescribers have helped perpetuate a negative — and

often false — picture of chronic pain management.⁸ Over time, these reports overshadow the stories of people with pain — those whose lives have been shattered by unrelenting pain — who get needed pain relief from these medications. Understanding the difference between tolerance, physical dependence, abuse and addiction is also critical to telling the story. According to medical experts, use of the term “narcotic” in news reports may further reinforce the myths and misconceptions of this class of drugs, given the negative connotation.⁸

“Clinicians continue to approach opioid prescribing with a spectrum of highly diverse practices, from complete avoidance to alacrity. Both extremes ignore either patient-specific indications and context for opioid therapy or the risks associated with such therapy. Idiosyncratic approaches need to give way to principles-based practices, focusing on well-established therapeutic goals and clinical indications, risk stratification and matched structuring of care, titration and stabilization, ongoing monitoring and outcomes (safe and effective use).”

— Perry Fine, MD, Topics in Pain Management

Strategies to Address Twin Public Health Crises

Systematic and targeted approaches are essential to address the growing prevalence and complexity of the non-medical use of prescription drugs, while simultaneously ensuring that people with legitimate medical needs receive effective treatment.

These approaches can generally be categorized as follows:

- Legislative strategies to create balanced and consistent laws and improve state-based prescription drug monitoring programs.
- Educational efforts to raise awareness about prescription drug abuse and its dangers among schools, families, health care providers, patients and potential abusers.
- Greater public awareness and acceptance of pain and the need to be able to access appropriate treatment with medical oversight.
- Medical strategies to help identify and monitor people with pain who require opioid management, incorporating risk

management into the treatment plan (e.g., informed consent, appropriate pain assessment, diagnostic testing and monitoring, transition planning, collaborative practice with addiction medicine and behavioral health specialists as indicated).

- Pharmaceutical industry strategies to help prevent misuse, abuse and diversion by developing new tamper resistant packaging and/or formulations (e.g., tamper-resistant bottles, electromagnetic chips to track medication, new formulations that could resist or deter common methods of opioid abuse).

For additional recommendations, see the American Pain Foundation's report outlining critical barriers to appropriate opioid prescribing for pain management, *Provider Prescribing Patterns and Perceptions: Identifying Solutions to Build Consensus on Opioid Use in Pain Management*. This 16-page report calls for a more balanced perspective of the risks and benefits of these medications in practice and policy and summarizes key challenges and actionable solutions discussed by leading pain experts at a roundtable meeting hosted by APF.

Making the Grade: Evaluation of State Policies

The Pain & Policy Studies Group (PPSG) report "Achieving Balance in State Pain Policy: A Progress Report" graded states on quality of its policies affecting pain treatment and centered on the balance between preventing abuse, trafficking and diversion of controlled substances and simultaneously ensuring the availability of these medications for legitimate medical purposes. PPSG researchers evaluated whether state pain policies and regulations enhance or impede pain management and assigned each state a grade from 'A' to 'F.'

State Grades for 2008			
State	2008 Grade	State	2008 Grade
Alabama	B+	Montana	C+
Alaska	C+	Nebraska	B+
Arizona	B+	Nevada	C
Arkansas	B	New Hampshire	B
California	B	New Jersey	C+
Colorado	B	New Mexico	B+
Connecticut	B	New York	C
Delaware	C+	North Carolina	B
District of Columbia	C+	North Dakota	B
Florida	B	Ohio	B
Georgia	B	Oklahoma	C+
Hawaii	B	Oregon	A
Idaho	B	Pennsylvania	C+
Illinois	C	Rhode Island	B+
Indiana	C+	South Carolina	C+
Iowa	B	South Dakota	B
Kansas	A	Tennessee	C
Kentucky	B	Texas	C
Louisiana	C	Utah	B+
Maine	B+	Vermont	B+
Maryland	B	Virginia	A
Massachusetts	B+	Washington	B+
Michigan	A	West Virginia	B
Minnesota	B+	Wisconsin	A
Mississippi	C+	Wyoming	C+
Missouri	C+		

Source: The Pain & Policy Studies Group, http://www.painpolicy.wisc.edu/Achieving_Balance/PRC2008.pdf.

At a Glance: Differentiating physical dependence, tolerance, abuse and addiction

Unfortunately, confusion between normal physiological responses to opioids (physical dependence and analgesic tolerance) and pathological phenomena such as addiction or substance abuse persist. Such misunderstandings not only reinforce the stigma surrounding medical use of these medicines, they also fuel fears of addiction and, in turn, may impinge on access to these medications for legitimate medical need. Although opioids have an abuse liability, clinical studies have shown that the potential for addiction is low for the vast majority of individuals using opioids for the long-term management of chronic pain.¹⁹ As with any medication, there are risks, but these risks can be managed.

Physical dependence is characterized by biological changes that lead to withdrawal symptoms (e.g., sweating, rapid heart rate, nausea, diarrhea, goosebumps, anxiety) when a medication is discontinued. Physical dependence differs from psychological dependence, or the cravings for the euphoria caused by opioid abuse. Symptoms of physical dependence can often be ameliorated by gradually decreasing the dose of medication during discontinuation.⁹

Analgesic tolerance is a biological process in which a patient requires increasing amounts of a medication to achieve the same amount of pain relief. Dose escalations of opioid therapies are sometimes necessary and reflect a biological adaptation to the medication. Although the exact mechanisms are unclear, current research indicates that tolerance to opioid therapy develops from changes in opioid receptors on the surface of cells.⁹ Thus, the need for higher doses of medication is not necessarily indicative of addiction.³

“Universal agreement on definitions of addiction, physical dependence and tolerance is critical to the optimization of pain treatment and the management of addictive disorders.”

— Consensus document from the American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine

Addiction is a disease characterized by preoccupation with and compulsive use of a substance, despite physical or psychological harm to the person or others.³ Behaviors suggestive of addiction may include: taking multiple doses together, frequent reports of lost or stolen prescriptions, and/or altering oral formulations of opioids.

Abuse is the intentional self-administration of a medication for a non-medical purpose, such as to obtain a high.³ Both the intended patient and others have the potential to abuse prescription drugs; in fact, the majority of people who abuse opioids do not suffer from chronic pain.¹⁴

Pseudo-addiction describes patient behaviors that may occur when pain is undertreated. Patients with unrelieved pain may become focused on obtaining medications and may otherwise seem inappropriately “drug seeking,” which may be misidentified as addiction by the patient’s physician. Pseudo-addiction can be distinguished from true addiction in that this behavior ceases when pain is effectively treated.³

MISUSE VS. ABUSE

- **Medication Misuse:** Legitimate use of a valid personal prescription but using differently from provider's instruction, such as taking more frequently or higher than the recommended doses. Use may be unintentional and considered an educational issue.
- **Medication Abuse:** Using a valid personal prescription for reasons other than its intent, such as to alleviate emotional stress, sleep restoration/prevention, performance improvement, etc. Use may be unintentional and considered an educational issue.
- **Prescription Drug Misuse:** Intentional use of someone else's prescription medication for the purpose of alleviating symptoms that may be related to a health problem. The use may be appropriate to treat the problem but access to obtain this drug may be difficult/untimely or may have been provided from a well-intentioned family member or friend.
- **Prescription Drug Abuse:** Intentional use of a scheduled prescription medication to experiment, to get high or to create an altered state. Access to the source may be diversion from family, friends or obtained on the street. Inappropriate or alteration of drug delivery system, used in combination with other drugs or used to prevent withdrawal from other substances that are being abused are included in this definition.

Source: Carol J. Boyd PhD, MSN, RN; Director: Institute for Research on Women and Gender, Substance Abuse Research Center, University of Michigan

Risk factors for opioid addiction include, but are not limited to:^{2,3}

- Personal or family history of prescription drug or alcohol abuse
- Cigarette smoking
- History of motor vehicle accidents
- Substance use disorder
- Major psychiatric disorder (e.g., bipolar disorder, major depression, personality disorder)
- Poor family support
- History of preadolescent sexual abuse

NOTE: Unless an individual has a past or current history of substance abuse, the potential for addiction is low when opioid medications are appropriately prescribed by a licensed health care provider and taken as directed. Those with chronic pain and addictive disease deserve the same quality of pain treatment as others and will require greater structure and resources in their care.

WEB RESOURCES

PainSAFE
www.painsafe.org

Opioid RX
http://pain-topics.org/opioid_rx/

Tufts Health Care Institute Program on Opioid Risk Management
<http://www.thci.org/opioid/>

Emerging Solutions
http://www.emergingsolutionsinpain.com/index.php?option=com_continued&cat=37&Itemid=303

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Topic Brief

PAIN MANAGEMENT & DISPARITIES

The undertreatment of pain in America is a growing public health crisis, especially among underserved populations, including ethnic minorities, women, older Americans and those who are socioeconomically disadvantaged.

Despite an overall improvement in health for most Americans, certain segments of the population continue to experience poor health status.¹ There is compelling evidence that minorities are less likely to have access to routine, coordinated medical care or health insurance than whites. They are also more likely to receive inappropriate or insufficient care, resulting in poorer health outcomes.

As the U.S. population becomes increasingly diverse, there is an urgent need to eliminate health disparities. Patients have a right to appropriate assessment and treatment of their pain without regard to race, ethnicity or other factors.

“Of all the forms of inequality, injustice in health is the most shocking and the most inhumane.”

—Martin Luther King, Jr.

Health Disparities Defined

According to the National Institutes of Health, health disparities are defined as “differences in the incidence, prevalence, mortality, and burden of diseases and other adverse health conditions that exist among specific population groups in the United States.”

Disparities in health care are complex and multifaceted resulting from:

- Patient/personal factors (e.g., low socioeconomic status, communication barriers)
- Health care provider factors (e.g., bias, cultural insensitivity)
- Systematic/health system factors (e.g., health insurance status, access to care)



Snapshot of U.S. Population, An Older and More Diverse Nation

According to projections by the U.S. Census Bureau:

- Minorities now comprise roughly one-third of the U.S. population.
- By 2023, more than half of all children will be from minority groups.
- Minorities are expected to become the majority in 2042.
- In 2050, the nation is projected to be 54 percent minority.
- The Latino population, already the nation's largest minority group, will triple in size between 2005 and 2050.
- The nation's population of elders will more than double in size from 2005 through 2050 as the baby boom generation enters traditional retirement years.

Source: U.S. Census Bureau, 2008,
<http://www.census.gov/PressRelease/www/releases/archives/population/012496.html>; Pew Hispanic Center.

Disparities in Pain Care

Pain is widely recognized as an undertreated health problem in the general population.² However, a growing body of research reveals even more extensive gaps in pain assessment and treatment among racial and ethnic populations, with minorities receiving less care for pain than non-Hispanic whites.^{3,4,5,6}

Differences in pain care occur across all types of pain (e.g., acute, chronic, cancer-related) and medical settings (e.g., emergency departments and primary care).^{3,4,5,6,7} Even when income, insurance status and access to health care are accounted for, minorities are still less likely than whites to receive necessary pain treatments.^{3,4,8}

Minorities are less likely to:

- Have access to pain management services and treatments
- Have their pain documented by health care providers
- Receive pain medications

And more likely to:

- Use the emergency department for pain care, but less likely to receive adequate care
- Experience greater severity of pain
- Experience and report physical disability
- Experience poorer health and quality of life related to pain

There are clear variations in the way pain is assessed and managed among all minority populations. Significant gaps exist in the provision of effective quality pain care due to the lack of research and medical training focused on pain care disparities.^{3,4,9}

Research also shows gender differences in the experience and

RESEARCH ON DISPARITIES IN PAIN CARE HAVE SHOWN:

- Blacks were less likely than whites to receive pain medication and had a 66 percent greater risk of receiving no pain medication at all.^{5,6,7,9}
- Hispanics were twice as likely as non-Hispanic whites to receive no pain medication in the emergency department (55 percent of Hispanics received no pain medication vs. 26 percent of non-Hispanic whites).^{7,10}
- Minority patients were less likely to have pain recorded relative to whites, which is critical to providing quality patient care.¹¹
- Only 25 percent of pharmacies in predominantly nonwhite neighborhoods had opioid supplies that were sufficient to treat patients in severe pain, as compared with 72 percent of pharmacies in white neighborhoods.¹²
- In a study of minority outpatients with recurrent or metastatic cancer, 65 percent did not receive guideline-recommended analgesic prescriptions compared with 50 percent of nonminority patients ($P < 0.001$). Hispanic patients in particular reported less pain relief and had less adequate analgesia.¹³

treatment of pain. Most chronic pain conditions are more prevalent among women; however, women's pain complaints tend to be poorly assessed and undertreated.³

Additionally, gender differences have been identified in patient responsiveness to analgesics and pain stimuli. While estrogen and progesterone play a role in how pain signals are received in men and women, psychology and culture may also account for some of the difference. For example, children may learn how to respond to pain later in life depending on how their pain complaints were treated in their formative years (e.g., receiving comfort and validation versus being encouraged to tough it out or dismiss the pain).¹⁴ For more information, see the *Special Considerations: Pain in Specific Populations Topic Brief*.

In response to the overwhelming discrepancies in pain treatment among minority groups, the Joint Commission issued a statement recognizing the rights of all patients to receive appropriate assessment and management of pain, and the World Health

Organization has declared that pain relief is a human right.

Patient and provider factors drive pain disparities

Multiple factors contribute to racial and ethnic disparities in pain care, including beliefs about pain, preconceived bias and cultural insensitivity and poor patient-provider communication.

Positive physician-patient interaction and communication is critical in accurate pain assessment.² Some research has shown that patients take a more active role in their own pain treatment when their health care providers are of similar ethnic backgrounds.^{3,4}

“Pain is a complex, subjective response with several quantifiable features, including intensity, time course, quality, impact, and personal meaning. The reporting of pain is a social transaction between caregiver and patient.”¹⁵

Patient sources of racial and ethnic disparities:³

- Low socioeconomic status
- Patients' attitudes or beliefs regarding pain and patient-level decision making and preferences
 - Stoicism and the belief that pain is an inevitable part of disease
- Minority patients more likely to:
 - Refuse recommended pain therapies
 - Poorly adhere to treatment regimens
 - Delay seeking medical care
- Mistrust of physicians or previous negative experiences with health care system
- Limited health literacy
- Language barriers that hinder communication with providers

Physician sources of racial and ethnic disparities:³

- Perceptions of race and ethnicity
- Racism or bias
- Poor cross cultural communication skills/cultural insensitivity
- Underrepresentation of physicians from racially/ethnically diverse backgrounds/lack of cultural sensitivity

HOT TOPICS

Disparities & Pain: HOT TOPICS

- Aging and increasingly diverse U.S. population could lead to greater disease burden if pain remains untreated
- Undertreatment of minorities in emergency departments
- Minority pain complaints receive less attention than others
- Impact of pain on productivity and quality of life among minority patients
- Pain relief as a human right

Minorities lack access to effective pain care

Limited access to pain care services is a key contributor to poorer pain treatment among minorities.

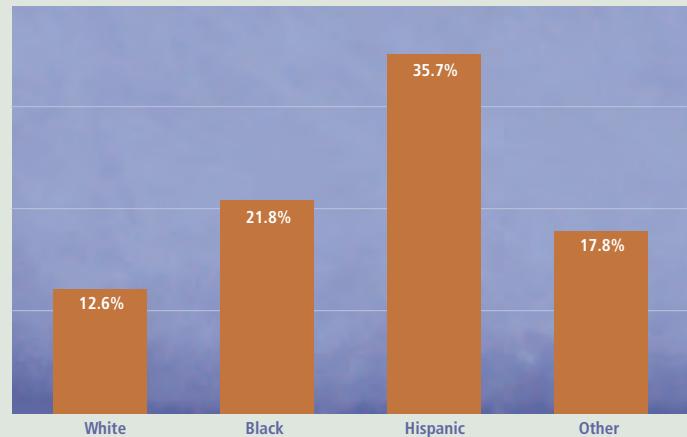
- Overall, minorities tend to be financially poorer than non-Hispanic whites.
- Socioeconomic factors can impede access to health insurance and primary health care services, and minorities are less likely to have access to pain treatment services than the general population.^{3,4,7,16,17}
- Racial and ethnic minorities are at increased risk of having their pain complaints ignored by health care providers, thereby limiting their options for accessing appropriate pain treatment.^{3,4,6,7}

According to the Robert Wood Johnson Foundation, 46 million

Americans, including 9 million children, are living without health care coverage. More than eight out of 10 are from working families. The consequences of being uninsured are widely recognized and include: lack of access to health care, poor quality care, lost economic productivity, as well as financial burdens on individuals and society overall. As the minority population in the U.S. continues to grow, it becomes increasingly important to address the numbers of uninsured and underinsured among racial and ethnic groups.

Barriers also exist in patient access to pain medications. Research shows that physicians may be less likely to prescribe pain medications for minority populations^{6,7,16,18} and pharmacies in neighborhoods with large minority populations often do not carry opioid medications.^{3,4,12}

PERCENTAGE UNINSURED AMONG THE NONELDERLY POPULATION BY RACE AND ETHNIC ORIGIN, 2006



Sources: Employee Benefit Research Institute estimates from the March Current Population Survey, 2007 Supplement. Cover the Uninsured, www.covertheuninsured.org.

“Inequities in access can contribute to and exacerbate existing disparities in health and quality of life, creating barriers to a strong and productive life.”

— The Commonwealth Fund

More extensive research needed to close disparities gap

While national attention has become increasingly focused on health disparities, less attention has been given specifically to inequities in pain care.^{19,20} However, the growing interest in health disparities in general provides pain treatment providers, researchers and advocates with an opportunity to raise awareness about disparities in pain management and the need for additional pain disparities research. Currently, the social impact of pain on patients, their families and communities is largely absent in most federal research plans.^{3,4}

Additional studies and a comprehensive pain research agenda are needed to:

- Understand the role of stereotypes and bias in doctor-patient interactions
- Improve training for health care providers
- Plan educational interventions for patients
- Understand the differences in patient behaviors that may contribute to pain care disparities
- Develop culturally sensitive pain assessment tools
- Raise consciousness about disparities in pain management and barriers to effective health care overall

WEB RESOURCES

CDC Office of Minority Health and Health Disparities

<http://www.cdc.gov/omhd/>

Cover the Uninsured: a Project of the Robert Wood Johnson Foundation

<http://covertheuninsured.org/>

American Pain Society: Racial and Ethnic Identifiers in Pain Management: The Importance to Research, Clinical Practice, and Public Health Policy

<http://www.ampainsoc.org/advocacy/ethnoracial.htm>

Agency for Health care Research and Quality: Addressing Racial and Ethnic Disparities in Health Care

<http://www.ahrq.gov/research/disparit.htm>
<http://www.ahrq.gov/qual/nhdr03/nhdrsum03.htm>

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Topic Brief

SPECIAL CONSIDERATIONS: PAIN IN SPECIFIC POPULATIONS

Although pain is a significant problem among all Americans, certain populations are more susceptible to and at greater risk for undertreatment, including children, minorities and those with advanced, life-limiting medical illness. Studies conducted in emergency departments suggest that women receive less attention in response to reports of severe pain than men. Also, due to military training and culture which teaches service members to be tough, and the complex nature of pain and post-traumatic stress, active duty military personnel and veterans tend to experience greater challenges achieving optimal pain relief than the civilian population.

In order to provide the most effective pain care possible and minimize pain-related morbidity, characteristics of vulnerable populations must be taken into consideration when performing pain assessment and implementing treatment plans. Health care professionals must also become aware of their own biases and understand that, regardless of demographic or social position, every individual with pain requires evaluation and treatment tailored to his or her specific clinical circumstances.

Children and Pain

Every child will experience pain at one time or another, whether it's from everyday bumps and bruises, or more chronic conditions such as headaches, gastrointestinal problems or diabetes. In fact, chronic pain affects up to 38 percent of children.¹

Pediatric pain stems from a wide range of chronic conditions.

For example:

- Each year, 1.5 million children have surgery, and many receive inadequate pain relief. In 20 percent of cases, the pain becomes chronic.²
- Of children aged 5 to 17 years, 20 percent suffer headaches.²
- More than one-third of children complain of abdominal pain lasting two weeks or longer.³
- Juvenile arthritis, which causes joint inflammation and aches, affects nearly 250,000 people under the age of 16 years.⁴
- About one in 1,000 U.S. children are cancer survivors and may have to deal with late and long-term effects of treatment (e.g., chronic fatigue and pain syndromes, nerve damage).²
- Recent evidence reveals reduced pain sensitivity is a common feature of children with autism

and Asperger's syndrome.²

- Musculoskeletal pain can result from "growing pains," a normal occurrence in about 25 to 40 percent of children.⁵

COMMON CAUSES OF PAIN IN CHILDREN

- Abdominal pain (e.g., irritable bowel syndrome, ulcerative colitis)
- Headaches
- Scrapes and bruises
- Needlestic pain from immunizations (most children receive up to 24 immunizations by their 2nd birthday)
- Sports injuries (e.g., sprains, concussion, fractures)
- Chronic illnesses (e.g., sickle cell disease, type I diabetes)

According to the American Medical Association, children and infants are at increased risk of inadequate pain management, with age-related factors playing a major role. Physical and psychological changes that occur during childhood development can make understanding and managing pain in children significantly more complicated than treating pain in adults.

Many things affect the way a child experiences, communicates

and responds to pain, including their:

- age
- beliefs and understanding of what is causing the pain
- ability to cope
- activity and anxiety levels
- previous experiences with pain and how they learned to respond
- support from parents and siblings
- parental pain, stress and family functioning may also play a role in pediatric pain
- preliminary data suggest that a mother's anxiety may be transmitted more strongly to her daughters than her sons, resulting in increased anxiety and pain in girls, but not boys.⁶

If pain is not addressed and treated early on, it can greatly impact a child's quality of life by interfering with mood, sleep, appetite, school attendance, academic performance, and participation in sports and other extracurricular activities. Furthermore, if unrelieved, childhood pain can pave the way to more pain later in life.⁷ It is essential that health care providers

Topic Brief Special Considerations: Pain in Specific Populations

MYTHS AND TRUTHS ABOUT PAIN IN CHILDREN	
MYTH: Children who are playing or sleeping must not be in pain.	Children who are playing or sleeping must not be in pain. Children cope with pain by distracting themselves, often through play. Sleep may also be a coping mechanism, and/or because they are exhausted.
MYTH: Young infants do not feel pain because their nervous systems are immature and unable to perceive and experience pain the way adults do.	Young infants do not feel pain because their nervous systems are immature and unable to perceive and experience pain the way adults do.
TRUTH: Decades ago it was believed that a newborn couldn't feel pain, and surgery was routinely performed on infants without anesthetic. Today, we know that the central nervous system of a 26-week-old fetus has the capability of experiencing pain. There is strong evidence that children experience increasing anxiety and perception of pain with multiple procedures or painful stimuli. ⁸	Decades ago it was believed that a newborn couldn't feel pain, and surgery was routinely performed on infants without anesthetic. Today, we know that the central nervous system of a 26-week-old fetus has the capability of experiencing pain. There is strong evidence that children experience increasing anxiety and perception of pain with multiple procedures or painful stimuli. ⁸
MYTH: Children can easily become addicted to pain medications.	Children can easily become addicted to pain medications.
TRUTH: Less than 1 percent of children treated with opioids become addicted. ⁹	Less than 1 percent of children treated with opioids become addicted. ⁹
MYTH: Children will tell adults when they are having pain.	Children will tell adults when they are having pain.
TRUTH: Children may not have the words to express pain (e.g., hurt, "ouch") or know to point to where it hurts. They may also be afraid of the consequences (e.g., extra visits to the pediatrician, shots, medicine). There are many tools available to assess pain in children. Adults need to recognize how children of different ages express pain in both behaviors and words.	Children may not have the words to express pain (e.g., hurt, "ouch") or know to point to where it hurts. They may also be afraid of the consequences (e.g., extra visits to the pediatrician, shots, medicine). There are many tools available to assess pain in children. Adults need to recognize how children of different ages express pain in both behaviors and words.

Potential barriers to the effective treatment of pain in children¹⁰

- The myth that children, especially infants, do not feel pain the way adults do;
- Lack of routine assessment for the presence of pain in children;
- The idea that treating pediatric pain takes too much time and effort;
- Fears of adverse effects of analgesic medications, including respiratory depression and addiction;
- Differing personal values and beliefs of health care professionals about the meaning and value of pain in the development of the child (e.g., the belief that pain builds character).

WEB RESOURCES

American Pain Society
www.ampainsoc.org

International Association for the Study of Pain
Pain in Children
<http://childpain.org>

UCLA Pediatric Pain Program
www.mattel.ucla.edu/pedspain/home.php

American Academy of Pediatrics
www.aap.org

Whole Child Foundation
www.wholechildla.org

Topic Brief Special Considerations: Pain in Specific Populations

Gender and Pain

Although it has long been thought that women and men have similar pain experiences, recent research reveals significant differences in the way male and female brains process pain,¹ as well as in women's expression of pain and their responsiveness to analgesics and pain stimulus.^{2,3}

Historically, women have been categorized as being emotional and overly sensitive; often influencing the way physicians assessed and managed their pain.⁴ Even though research now shows that chronic pain conditions are generally more prevalent among women, they continue to be treated less aggressively for their pain than men.^{5,6} And while women are more likely than men to seek treatment for their pain, they are less likely to receive it.⁷

Women report pain more often than men do and in more body regions, and they also tend to have more severe, recurrent and persistent pain, as well as a reduced pain threshold when compared with men.³ However, despite their increased pain burden, women reportedly cope with pain better than men, possibly due to the fact that they experience pain more often throughout the course of their lives (e.g., menstruation, pregnancy and child birth, and other health issues specific to women).³

Female hormones are also likely to play a role in pain perception. Some pain conditions like migraine tend to vary with a woman's menstrual cycle, and many of the observed gender differences in pain appear to diminish following the reproductive years.⁸

Hormones May Influence Pain Experience

- Estrogen administration in women and in men can increase the incidence of chronic pain conditions.^{9,10}
- Variations in women's estrogen levels, like those that occur during the menstrual cycle or during pregnancy, may regulate the brain's natural ability to suppress pain.¹¹
- Some pain conditions such as migraine and fibromyalgia tend to fluctuate with a woman's menstrual cycle.
- Observed gender differences in pain appear to diminish following menopause.

Additionally, cultural conditioning may impact the expression of pain among women and men. As children, girls are more likely to be permitted to express pain and show emotion than boys, and attitudes about the social acceptability of gender and pain often carry into adulthood.³

PAIN DISORDERS WITH HIGHER PREVALENCE IN WOMEN

- Migraine
- Irritable bowel syndrome
- Fibromyalgia
- Chronic pelvic pain
- Interstitial cystitis
- Temporomandibular joint disorder (TMJ)

- Breast pain (mastalgia)
- Autoimmune disorders (e.g., lupus and chronic fatigue syndrome)
- Rheumatoid arthritis
- Osteoarthritis

Potential Sources of Gender Differences in Pain

Biological factors including:

- sex hormones
- genetics
- anatomical differences

Psychosocial influences including:

- emotion (e.g., anxiety, depression)
- coping strategies
- gender roles
- cultural conditioning
- health behaviors
- use of health care services

As advances in brain imaging technology provide further insights into gender variations in the experience of pain, it is becoming evident that different pain experiences among men and women will call for different approaches to pain management.

Ongoing research is essential to achieve:

- A better understanding of the biological and psychosocial factors that influence gender differences in pain
- A greater appreciation of the different health needs of men and women
- More effective and targeted pain treatments for women

WEB RESOURCES

International Association for the Study of Pain: Real Women, Real Pain
www.iasp-pain.org

National Institutes of Health: Gender & Pain
<http://painconsortium.nih.gov/genderandpain/summary.htm>

HealthyWomen.org
www.healthywomen.org/

Society for Neuroscience: Gender & Pain
www.sfn.org/index.cfm?pagename=brainBriefings_gender_and_pain

Topic Brief Special Considerations: Pain in Specific Populations

Older Adults and Pain

As we age, pain becomes a more common problem due to the high prevalence of chronic and progressive pain-producing conditions associated with aging. It is estimated that up to 50 percent of older persons living in the community have pain that interferes with normal function, and 59 to 80 percent of nursing home residents experience persistent pain.^{1,2} Alarmingly, being older than 70 is the leading risk

factor for inadequate pain management.³

Diagnosing and treating pain in older adults can be challenging. Those 65 and older often present with multiple medical and nutritional problems, take multiple medications and have many potential sources of pain. Older persons with dementia or communication problems are at even greater risk of undertreatment of pain due to difficulties

communicating their pain.⁴ Use of certain medications in older persons becomes problematic because of physiological changes.⁵

The most common cause of persistent pain in older adults is musculoskeletal in nature, typically from osteoarthritis or other bone, joint and spine disorders. According to the Arthritis Foundation, arthritis affects up to 80 percent of older adults, who report being fearful of recurring pain and disability. But the predilection for painful conditions does not mean that older adults need to live with uncontrolled pain. Quite the opposite; older adults can be effectively treated, and in so doing, pain-related morbidity — and even premature mortality — can and should be obviated.

COMMON PAIN CONDITIONS IN OLDER ADULTS

- Arthritis
- Lower back and neck pain; vertebral compression fractures from osteoporosis
- Abdominal pain (e.g., gallstones, bowel obstruction, peptic ulcer disease, abdominal aortic aneurysm)
- Cancer-related pain (symptom of disease or effect of nerve damage from treatments)
- Neuropathic pain due to diabetes, herpes zoster ("shingles"), kidney disease or other medical problems
- Muscle cramps, restless leg pain, itchy skin and sores due to circulatory problems or vitamin D deficiency
- Fibromyalgia
- Complex regional pain syndrome (CRPS), a neuropathic pain condition which can develop after an illness or injury and often affects the extremities
- Injuries, especially from falls



WEB RESOURCES

Handbook of Pain Relief in Older Adults — An Evidence-Based Approach

By Gloth III, F. Michael

http://www.amazon.com/Handbook-Pain-Relief-Older-Adults/dp/1607616173#reader_1607616173

**American Medical Association
Assessing and Treating Pain in Older Adults**

http://www.ama-cmeonline.com/pain_mgmt/module05/index.htm

**American Geriatrics Society Foundation
The Management of Persistent Pain:
Resources for Older Adults and Caregivers**

http://www.healthinaging.org/public_education/pain

Topic Brief Special Considerations: Pain in Specific Populations

End-of-life and Pain

Pain control is one of the most challenging aspects of end-of-life care.¹ Terminal illness is often accompanied by severe pain, and a significant number of people suffer needlessly at the end-of-life. While the goal of end-of-life care should be making the terminally ill more comfortable, the health care system has been designed to take a curative approach to disease, rather than focusing on symptom relief.² Hospital research reveals that health care providers continue to inadequately treat pain, and tend to under-medicate terminal pain.

Individuals at end-of-life may have their pain undertreated for variety of reasons, including a lack of knowledgeable and experienced physicians and myths about addiction to pain medication, leading unnecessarily to patient and family suffering.³

Despite advances in research on end-of-life pain treatment, health care providers remain influenced by social and legal concerns, as well as misconceptions about medications including addiction, overdose, lasting side effects and diminished physical capacity.⁵ The terminally ill and their families may also hesitate to begin using pain medications as they often associate such treatment with imminent death, thereby allowing patient suffering to worsen and continue.⁴

However, thorough and ongoing pain assessment, paired with well-

designed and aggressive medication plans, as well as counseling for patients and their families can have a significant impact on pain relief and side effects among dying patients.^{4,5}

END-OF-LIFE PAIN MAY BE EXACERBATED BY MANY OTHER SYMPTOMS INCLUDING:

- Dry mouth
- Nausea
- Water retention and swelling
- Lack of appetite
- Shortness of breath
- Mental distress and anxiety caused by fear or denial of impending death

Effective pain management at the end-of-life requires addressing the total pain experience, including physical causes, as well as interpersonal and spiritual pain.^{3,4}

Pain associated with terminal illness often requires special treatment that can be best provided by hospice and palliative care programs available in many medical facilities. Hospice focuses on relieving symptoms and supporting patients who are nearing the end of their life, while palliative care is designed to provide comfort and pain relief at any time during a person's illness.⁷ The goal of both programs is to alleviate physical, emotional, spiritual pain and suffering while respecting the dignity of the individual with a life-limiting illness.

“Suicidal wishes in patients with advanced disease are closely linked to unrelieved pain and to mood alterations such as depression and anxiety, which like pain, frequently respond to clinician treatment if the clinician identifies and addresses them.”^{2,6}

Essential Components of End-of-life Care⁸

- Continual assessment and management of pain and other physical symptoms
- Assessment and management of psychological and spiritual needs
- Helping the individual identify personal goals for pain treatment and end-of-life care
- Assessment of the person's support system

WEB RESOURCES

American Academy of Family Physicians: Challenges in Pain Management at the End of Life

www.aafp.org/afp/20011001/1227.html

American Pain Society: Treatment of Pain at the End of Life

www.ampainsoc.org/advocacy/treatment.htm

Discovery Health Center: End of Life Q&A with Dr. Scott Fishman

<http://health.discovery.com/centers/pain/endoflife/endoflife.html>

National Hospice and Palliative Care Organization

www.nhpco.org/i4a/pages/index.cfm?pageid=3254

“When someone is dying, time is a luxury and wait-and-see is not an option. What matters most in the final days is that patients are free of crippling pain and unbearable suffering so that they can finish their lives in ways that bring comfort, peace, and completion. Concerns about lasting side effects or diminished physical capacity from months of using a drug become „secondary to making a patient comfortable. No one has to die in pain.”

— Dr. Scott Fishman

Topic Brief Special Considerations: Pain in Specific Populations

Military/Veterans and Pain¹

Pain is a major issue among military personnel and veterans, who are at heightened risk for injury and combat wounds. Although modern body armor and rapid evacuation to medical care is saving lives, there are more maimed and shattered limbs than ever before, with instances of amputation nearly doubling since before the Vietnam War. Hundreds of thousands of returning veterans will seek medical care and claim disability compensation for a wide variety of injuries and health problems they sustained during their tours of duty. It is estimated that the U.S. will be paying the cost of related medical care and disability claims for the next 40 years.

Veterans are more likely to experience psychological distress and other medical conditions, including post-traumatic stress disorder, depression, amputations, traumatic brain injuries, substance abuse and other injuries, which further complicate effective pain management.

COMMON PAIN CONDITIONS AMONG MILITARY MEMBERS

Post-traumatic stress disorder (PTSD) commonly affects soldiers returning from war, and is triggered by exposure to a situation or event that is or could be perceived as highly threatening to a person's life or those around him/her. PTSD may not emerge for years after the initial trauma.

It is a normal reaction to an abnormal situation. Not every service member will be diagnosed with a disorder, but most will experience some level of post-traumatic stress which can exacerbate pain conditions.

Chronic pain symptoms and PTSD frequently co-occur and may intensify an individual's experience of both conditions. Together, they result in fear, avoidance behaviors, anxiety and feelings of isolation.

Amputations have long been a tragic, unavoidable consequence of combat — "one of the most visible and enduring reminders of the cost of war," according to the Amputee Coalition of America. While there have been major advances in medicine, prosthetics and technologies that allow amputees to lead more independent lives, most of these patients continue to need specialized long-term or lifelong support. Managing wound, post-operative, phantom and stump pain is important to reduce suffering and improve quality of life.

A **traumatic brain injury (TBI)** is a blow or jolt to the head or a penetrating head injury that disrupts the function of the brain and is a major cause of lifelong disability and death. Managing pain in veterans with TBIs may be complicated by memory lapses affecting medication management, difficulty organizing and following complicated and sometimes even simple pain management regimens, and difficulty learning new coping skills. Rehabilitation should incorporate efforts to relieve associated pain.

Veterans have significantly worse pain than the general public, and while military medical care is among the best in the world, there are still long-term problems and challenges with managing disability and chronic pain.

Military culture may also present a significant barrier to appropriate pain care. The persisting stigma around pain and pain treatment is particularly pronounced in the military, and pain is often perceived as a sign of weakness leading many individuals to choose to suffer in silence. Seeking mental health care for PTSD and depression, which so often accompany pain is important; pain is best managed when depression and PTSD are treated simultaneously.

A recent analysis found that the Veterans Health Administration (VHA) is already overwhelmed by the sheer number of returning veterans and the seriousness of their health care needs. Without increased staffing and funding for veterans medical care, it will not be able to provide quality care in a timely fashion.

Topic Brief Special Considerations: Pain in Specific Populations

However, after the 2009 passage of the military and veterans pain care laws, the Department of Defense and the Veterans Health Administration have begun to work together to improve pain care for service members. They jointly developed a pain management task force and issued a report: *Providing a Standardized DoD and VHA Vision and Approach to Pain Management to Optimize the Care for Warriors and their Families* outlining more than 100 recommendations to improve pain care within these health care systems. To find out more, visit http://www.health.mil/Libraries/HA_Policies_and_Guidelines/11-003.pdf.

Barriers to optimal pain management among veterans and military personnel may include fears about:

- No longer being physically capable of fulfilling their duties
- Being discharged and no longer having a sense of purpose
- Letting down or losing the respect of their peers
- Becoming addicted to pain medications
- Experiencing personality changes or problems with sexual relations due to pain medications
- Losing their benefits/pension if they acknowledge a pain condition

The U.S. Veterans Health Administration is instructing physicians and nurses who treat veterans to regard pain as a “fifth vital sign,” to be routinely assessed along with blood pressure, pulse, temperature and respiration.

WEB RESOURCES

American Pain Foundation:

Military/Veterans and Pain

www.painfoundation.org

www.exitwoundsforveterans.org

Amputee Coalition of America

www.amputee-coalition.org

Defense and Veterans Brain Injury Center

www.dvbic.org

Disabled American Veterans (DAV)

www.dav.org

U.S. Department of Veterans Affairs

www.va.gov

HOT TOPICS**Children & Pain**

- Maternal anxiety influencing daughters' experience of pain
- Some neonatologists still do not treat pain in pre-term low birth weight babies because they "won't remember it"
- Investigations into "chronic daily headaches" in children
- Unraveling pediatric pain conditions and their impact into adulthood (e.g., whether complex regional pain syndrome in children leads to adult CRPS, whether irritable bowel syndrome in adolescents is this the same as IBS in adults)
- Complementary and alternative medicine: how and what is safe to use in children with chronic pain?
- Factors leading to pain-related disability in children (e.g., missing school, not sleeping, avoiding physical and social activities, not eating)

Gender & Pain

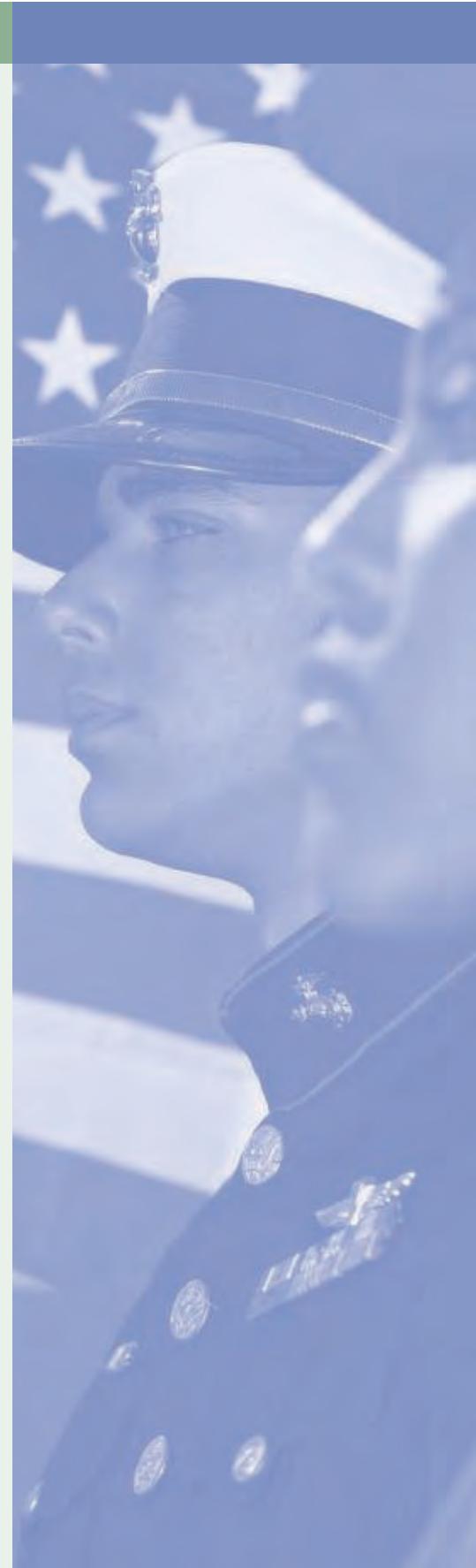
- Prevalent pain conditions in women (e.g., fibromyalgia, chronic pelvic pain)
- Interface of hormones and the pain experience
- Brain imaging, uncovering routes of pain transmission and tolerance
- Differential effects of medicines across genders
- Impact of chronic pain on sexuality and self-image

HOT TOPICS**Older Adults and End-of-life Care & Pain**

- False belief that pain is an inevitable part of aging
- Vitamin deficiencies and musculoskeletal pain
- Limited consumer awareness of the options that exist other than traditional "acute care" approaches (e.g., doctor's office visits, ER visits, hospitalizations)
- Insufficient numbers of adequately trained and skilled health care professionals to manage the myriad issues confronting patients/families with advanced medical illness; limited number of providers with specialty in geriatrics
- Variability in delivery of hospice and palliative care services across the country
- Lack of clinical research data on pain care among elders

Military/Veterans & Pain

- DOD/VA responds to the Military and Veterans Pain Care Acts of 2009
- Emerging Options: Interdisciplinary approaches to pain care
- Acupuncture now being incorporated into treatment plans at Walter Reed Army Medical Center
- Competitive athletics as a form of therapy



Topic Brief Special Considerations: Pain in Specific Populations

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Children and Pain

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EXHIBIT 33



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Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects

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See the reply "[Fundamental problem with opioid trials for chronic pain](#)" in volume 176 on page 1308.

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Abstract

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Background

Chronic noncancer pain (CNCP) is a major health problem, for which opioids provide one treatment option. However, evidence is needed about side effects, efficacy, and risk of misuse or addiction.

Methods

This meta-analysis was carried out with these objectives: to compare the efficacy of opioids for CNCP with other drugs and placebo; to identify types of CNCP that respond better to opioids; and to determine the most common side effects of opioids. We searched MEDLINE, EMBASE, CENTRAL (up to May 2005) and reference lists for randomized controlled trials of any opioid administered by oral or transdermal routes or rectal suppositories for CNCP (defined as pain for longer than 6 mo). Extracted outcomes included pain, function or side effects. Methodological quality was assessed with the Jadad instrument; analyses were conducted with Revman 4.2.7.

Results

Included were 41 randomized trials involving 6019 patients: 80% of the patients had nociceptive pain (osteoarthritis, rheumatoid arthritis or back pain); 12%, neuropathic pain (postherpetic neuralgia, diabetic neuropathy or phantom limb pain); 7%, fibromyalgia; and 1%, mixed pain. The methodological quality of 87% of the studies was high. The opioids studied were classified as weak (tramadol, propoxyphene, codeine) or strong (morphine, oxycodone). Average duration of treatment was 5 (range 1–16) weeks. Dropout rates averaged 33% in the opioid groups and 38% in the placebo groups. Opioids were more effective than placebo for both pain and functional outcomes in patients with nociceptive or neuropathic pain or fibromyalgia. Strong, but not weak, opioids were significantly superior to naproxen and nortriptyline, and only for pain relief. Among the side effects of opioids, only constipation and nausea were clinically and statistically significant.

Interpretation

Weak and strong opioids outperformed placebo for pain and function in all types of CNCP. Other drugs produced better functional outcomes than opioids, whereas for pain relief they were outperformed only by strong opioids. Despite the relative shortness of the trials, more than one-third of the participants abandoned treatment.

Chronic non–cancer-related pain (CNCP) includes chronic pain of a nociceptive or neuropathic nature with variable influence by psychological and socioenvironmental factors. Opioids are the most potent analgesics available and are well established for the treatment of severe acute,¹ surgical² and cancer pain.³ However, their use to ameliorate CNCP is still controversial because of the side effects of opioids, the physical tolerance they build up (with the related withdrawal reactions and possibility of addiction) and anxiety over disapproval by regulatory bodies.⁴

The prevalence of CNCP varies according to the type of pain and the population studied. A study conducted in the United Kingdom in a community in the greater London area to quantify the prevalence of chronic pain found that 46.5% of the general population reported chronic pain; low-back problems and arthritis were the leading causes.⁵ A recent epidemiological study in Denmark⁶ found that nearly 130 000 adults, corresponding to 3% of the Danish population, regularly used opioids. CNCP had a prevalence of 19%, and 12% of those who had CNCP used opioid medications.

The objectives of this review were 4-fold: to determine the efficacy of opioids for CNCP compared with placebo; to compare the effectiveness of opioids for CNCP with that of other drugs; to identify categories of CNCP with better response to opioids; and to determine the most common side effects and complications of opioid therapy for CNCP, including incidences of opioid addiction and sexual dysfunction.

Methods

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We followed the QUOROM guidelines for reporting meta-analyses of randomized controlled trials.⁷

We searched the literature up to May 2005 through the OVID interface: MEDLINE (from 1960), EMBASE (from 1988), the Cochrane Database of Systematic Reviews, the Cochrane Controlled Trials Register (CENTRAL), the ACP Journal Club and DARE. We also reviewed the reference lists in the articles, reviews and textbooks retrieved. Our search strategies for MEDLINE and EM BASE are available online as Appendix 1 and Appendix 2, respectively (all appendices for this article are available at www.cmaj.ca/cgi/content/full/174/11/1589/DC1). A single reviewer (J.A.S.) ran the electronic searches and entered the data into Reference Manager 10, removing all duplicates.

Each of 2 independent reviewers (A.D.F., J.A.S.) screened all titles and abstracts for studies that might meet the following inclusion criteria.

- Study characteristics: randomized controlled trials published in English, French or Spanish (the languages that could be read by the members of our team). Studies published only as abstracts were excluded.
- Study populations: people with CNCP, defined as pain for longer than 6 months, including neuropathic pain, osteoarthritis, rheumatoid arthritis, fibromyalgia, and back and musculoskeletal pain. Migraines, dental pain, abdominal pains (from chronic pancreatitis, kidney stones, etc.) and ischemic pain from vascular disease were excluded because they are usually not classified as CNCP.
- Interventions: any opioid administered via an oral, transdermal or rectal route for 7 days or more. We excluded comparisons of different opioids. We included tramadol, a centrally acting, synthetic opioid analgesic with 2 complementary mechanisms of action: binding of parent and M1 metabolite to μ -opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.^{8,9} In our review we

classified the opioids studied as weak (propoxyphene, codeine, tramadol) or strong (oxycodone, morphine).¹⁰

- Outcomes: the data extracted were those quantifying pain (intensity or relief), function and side effects.

Hard copies of potential studies were retrieved and the same 2 independent reviewers met to reach consensus on the studies to be included. When in doubt, the study authors were contacted; if this was not possible, a third reviewer (A.M.G.) was consulted.

Methodological quality was assessed by the same 2 independent reviewers (unmasked to authors, journals or results), who met to reach consensus. In cases of disagreement, a third reviewer was consulted. We scored the studies from 0 to 5 with the instrument developed by Jadad and colleagues,¹¹ which has 3 questions about a study's methods of randomization and double-blinding, and numbers of withdrawals. Studies scoring 3, 4 or 5 were considered to be of high quality; 0, 1 or 2, of low quality. The sensitivity analysis was repeated, but with the upper limit for low quality changed to 3, to see if this changed the main conclusion.

Meta-analyses were conducted with Revman 4.2.7 software, with standardized mean differences (SMDs) for pain relief and functional outcomes. For side effects, absolute risk differences (RDs) were calculated. Statistical heterogeneity was tested by Q test (χ^2) and reported with the I^2 statistic (in which higher values indicate higher heterogeneity). All meta-analyses were carried out with use of a random effects model. Sensitivity analyses were calculated within subgroups of studies (decided a priori) to assess the robustness of the main conclusions. Cumulative meta-analysis was conducted with STATA. The clinical significance of side effects was considered when the incidence was 10% or higher in the opioid or reference group.

Results

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Data was abstracted from 41 randomized trials that met the inclusion criteria (Appendix 3). The characteristics of all the trials included for meta-analysis are summarized in Appendix 4 (www.cmaj.ca/cgi/content/full/174/11/1589/DC1). We found that 90% were either funded by or had 1 or more coauthors affiliated with the pharmaceuticals industry.

Although all trials included were described as randomized, patient assignment was judged adequate to be called random in only 17. The remainder did not report the randomization method, and its adequacy could not be gauged. Thirty-nine trials were described as double-blinded (the exceptions were Jamison¹² and Gobel¹³ and their respective coinvestigators); the majority of these (30 trials) were judged as having adequate methods of double-blinding, for example the double-dummy technique, the capsule-in-capsule technique, or just identical appearance of active and control medications. The average dropout rate in the opioid groups was 33%: 15% left because pain relief was inadequate and 21% withdrew because of side effects (some patients dropped out for both reasons). In the control groups, the average dropout rate was 38%: 30% because pain relief was inadequate and 10% because of side effects.

A total of 6019 patients with CNCP were included in this systematic review: 80% classified as having nociceptive pain (osteoarthritis, rheumatoid arthritis and back pain without radiculopathy); 12%, neuropathic pain (including diabetic neuropathy, postherpetic neuralgia, phantom limb pain and regional cervicobrachial pain syndrome); 7%, fibromyalgia; and 1%, mixed nociceptive and neuropathic pain. The average age of the people involved was 58.1 (range 40–71) years; 63% of participants were female and 85%, white.

[Table 1](#) shows the 5 different opioids prescribed in these 41 trials: codeine, morphine, oxycodone, tramadol and propoxyphene. All were administered orally; the range of doses used were reported in all 41 studies; the average dose, only in 28. Trials with parallel groups were longer than those of crossover design (5.6 v. 3.8 weeks, on average). Treatment duration also varied according to type of pain ([Table 2](#)): Durations of opioid therapy during the studies of fibromyalgia and mixed types of pain (mean lengths 8.8 and 8.5 weeks, respectively) were about twice as long as those involving patients with nociceptive and neuropathic pain (4.8 and 4.3 weeks, respectively).

Measurement	Table 3			Number of observations, n	Type of analysis	Total R-squared
	Yield	Root length	Root length			
Control	120	4	4 (4%)	1-15	Regression	0.10%
Ammonium sulphate	120	1	1 (1%)	1-15	Regression	0.00%
Biofertilizer	120	1	1 (1%)	1-15	Regression	0.00%
Biofertilizer + ammonium sulphate	120	1	1 (1%)	1-15	Regression	0.00%
Ammonium	714	10	10 (1%)	2-114	Regression	0.00%
Ammonium + biofertilizer	714	10	10 (1%)	2-114	Regression	0.00%
Ammonium sulphate	40	1	1 (1%)	1-5	Regression	0.00%
Ammonium sulphate + biofertilizer	40	1	1 (1%)	1-5	Regression	0.00%
Ammonium + ammonium sulphate	40	1	1 (1%)	1-5	Regression	0.00%
Root length	210	10	10 (1%)	2-114	Regression	0.00%
Root length + ammonium sulphate	210	10	10 (1%)	2-114	Regression	0.00%
Root length + biofertilizer	210	10	10 (1%)	2-114	Regression	0.00%
Root length + ammonium + ammonium sulphate	210	10	10 (1%)	2-114	Regression	0.00%
Root length + ammonium + biofertilizer	210	10	10 (1%)	2-114	Regression	0.00%
Root length + ammonium + ammonium sulphate + biofertilizer	210	10	10 (1%)	2-114	Regression	0.00%
Total	210	10	10 (1%)	2-114	Regression	0.00%

Table 1

Table 2				
Table 2: Duration of opioid therapy				
Diagnosis	No. of studies	Duration of therapy		
		Average	Minimum	Max
Noiciceptive pain	25	4.8	1	
Neuropathic pain	12	4.4	1	
Mixed pain	2	8.5	1	
Fibromyalgia	2	8.8	6	

Table 2

Efficacy of opioids compared with placebo

Although we found 30 placebo-controlled trials of opioids for pain relief, only 28 reported data that could be meta-analyzed. Meta-analysis of these 28 studies showed results in favour of opioids (SMD –0.60, 95% confidence interval [CI] –0.69 to –0.50; Appendix 5); the 2 trials not included in the meta-analyses^{14,15} also had findings in favour of opioids. The sensitivity analysis (Appendix 6) showed no change in the conclusions with the type of opioid, methodological quality of the study (with cut-off points of either 2 or 3 points) or study design. Only for the patient category of “mixed pain” was the difference between opioids and placebo statistically nonsignificant, and this was a single trial with a small patient sample. Cumulative meta-analysis of these 28 trials (Appendix 7) revealed that the efficacy of opioids compared with placebo reached a stable effect size in 2002; in other words, the additional 8 trials published in 2003 and 2004 did not change the conclusions.

Similarly, the meta-analysis of the 20 trials that had data on functional outcomes showed results in favour of opioids (SMD -0.31 , 95% CI -0.41 to -0.22 ; Appendix 8). The sensitivity analysis (Appendix 6) showed that in all cases the benefit of opioids compared with placebo for functional outcomes was statistically significant except for long-acting morphine, patients with “mixed pain” and “low quality” studies (defined as having 2 or fewer points in the Jadad scale). In these 3 cases, the overall effect was in favour of opioids, but the confidence interval included the null effect. Our cumulative meta-analysis of these 20 trials (Appendix 9, www.cmaj.ca/cgi/content/full/174/11/1589/DC1) corroborated the results of the cumulative meta-analysis of pain-relief outcomes.

Effectiveness of opioids compared with other drugs

Meta-analysis of the 8 trials with suitable data available that compared opioids and other analgesics for pain relief (which are summarized in Appendix 4D) showed that the difference between was statistically nonsignificant (SMD -0.05, 95% CI -0.32 to 0.21; Appendix 10). Sensitivity analysis (Appendix 11) showed that this conclusion did not change with the type of comparison group (nonsteroidal anti-inflammatory drugs [NSAIDs] or tricyclic antidepressants [TCAs]) or with the study's methodological quality (high or low). However, when sensitivity analysis was conducted based on the type of opioids, the strong opioids (oxycodone, morphine) were significantly more effective than other drugs for pain relief (SMD -0.34, 95% CI -0.67 to -0.01). One trial¹⁶ not included in the meta-analysis showed that the addition of codeine to a regimen of acetaminophen was superior to acetaminophen alone at 7 days of follow-up, but not afterward.

For functional outcomes, the other analgesics were significantly more effective than were opioids (SMD 0.16, 95% CI 0.03 to 0.30; Appendix 12, www.cmaj.ca/cgi/content/full/174/11/1589/DC1). This is primarily explained by the findings of 1 study¹⁷ that accounted for 74% of our meta-analysis, in which the authors compared dextropropoxyphene (a weak opioid) with diclofenac. In the other 2 comparisons of tramadol versus diclofenac¹⁸ and controlled-release morphine versus nortriptyline¹⁹, the differences were not statistically significant.

Side effects and other problematic outcomes

There were 6 side effects that occurred significantly more often among those taking opioids than those in the placebo groups: constipation (RD 16%, 95% CI 10%–22%); nausea (RD 15% (11%–19%); dizziness or vertigo (RD 8% (5%–12%); somnolence or drowsiness (RD 9% (5%–13%); vomiting (RD 5% (2%–7%); and dry skin, itching or pruritus (RD 4% (1%–6%). Risk differences for the other side effects noted (diarrhea, appetite loss, abdominal pain, dry mouth, headache, fatigue, blurred vision or accommodation disturbance, sleeplessness or insomnia, confusion, and sweating) were all statistically nonsignificant.

Compared with other drugs, only 3 side effects occurred significantly more frequently with opioids: the RD for nausea was 14% (95% CI 4%–25%); constipation, 9% (1%–17%); and somnolence or drowsiness, 6% (0–11%). One side effect, diarrhea (RD –2%, 95% CI –3% to 0), occurred less often with opioids than with other drugs. Risk differences for the other 12 side effects (vomiting, dizziness, dry skin, loss of appetite, abdominal pain, dry mouth, headache, fatigue, vision disturbance, insomnia, confusion and sweating) were not statistically significant.

Patients with history of addiction (alcohol or drugs) were excluded from 25 trials.^{12,14,18–40} In the others, this information was unreported. With regard to the incidence of opioid addiction developed during the trials, only 3^{13,33,41} asked participants about symptoms and signs of addiction. Of these, 2 used indirect questioning; the other³³ inquired if the patients experienced “drug craving,” and reported that 8.7% in the morphine and 4.3% in the placebo group developed drug craving.

Only 4 studies^{29,32,33,42} inquired about sexual activity by using the Pain Disability Index (PDI). This index consists of 7 self-reported disability subscales, one of which refers to sexual activity; each scale is graded from 0 to 10, where 0 = no disability and 10 = total disability. Only 2 studies give a specific score on sexual activity. In the first,³² with 46 patients randomly assigned to receive controlled-release codeine or placebo, the score was 4.1 and 6.3, respectively. In the other,²⁹ which involved 45 patients, the score was 3.4 for controlled-release oxycodone and 4.5 for placebo. Both studies, therefore, suggested that patients taking opioid medications self-reported better sexual function than those taking placebo.

Interpretation

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This systematic review demonstrated that, based on the available trials analyzed:

- Opioids were effective in the treatment of CNCP overall; they reduced pain and improved functional outcomes better than placebo.
- Opioids were more effective than placebo for both nociceptive and neuropathic pain syndromes.
- Tramadol reduced pain and improved functional outcomes in patients with fibromyalgia.
- Strong opioids (oxycodone and morphine) were significantly superior, statistically, to naproxen and nortriptyline (respectively) for pain relief but not for functional outcomes.

- Weak opioids (propoxyphene, tramadol and codeine) did not significantly outperform NSAIDs or TCAs for either pain relief or functional outcomes.
- Clinically (> 10%) and statistically, only constipation and nausea were significantly more common with opioids.
- Although recent studies^{43,44} have indicated that endocrinological abnormalities and erectile dysfunction can be experienced by patients taking opioid medication for chronic conditions, most researchers did not ask participants about sexual dysfunction. The few studies in our review that collected such data were relatively short for the observation of any endocrinological abnormalities. The only 2 studies^{29,32} that reported data on sexual function showed that patients taking opioids actually perceived themselves as doing better in terms of sexual behaviour compared with those in the control groups. Improvement of well-being secondary to better pain control may account for this result: the PDI is a patient-rated global rating of function and does not measure variables such as libido, sexual dysfunction or gonadal function, and cannot be used to estimate the risk of hypogonadism.
- Addiction or opioid abuse in patients with chronic pain cannot be assumed not to exist (despite popular statements), because the existing randomized trials are not designed to evaluate it; the duration of the trials was too short to allow for the development or detection of aberrant drug use, even if appropriate screening tools for addiction had been used. An adequate measure of “diagnosis of addiction” is also lacking in every study. For example, it is hazardous to equate reported “drug craving” or “reported symptoms and signs of addiction” with addiction. At best, this analysis suggests that only in a minority of comparative trials have investigators even attempted to approach this question. Furthermore, none of the studies have been methodologically sound enough to allow for conclusions about opioid addiction or abuse.

In regard to the contentious issue of whether opioids for pain patients can improve function, this meta-analysis depends on standardized measures of function that were adopted in the respective studies. Such instruments are often self-reported measures, such as the Pain Disability Index. The specific functional change is measured narrowly in terms of the functional measure used. For example, one cannot assume that functional improvement should be interpreted to mean improvement in any and all functions.

Most trials that compare opioids with other drugs were not adequately designed as equivalence or noninferiority trials.^{45,46} We therefore have some reservations about declaring any equivalence between opioids and these other drugs. There is a need for well-designed equivalence trials to compare opioids and other drugs.

Chronic pain is a long-term disorder. The studies included in this meta-analysis had various follow-up periods; most trials were not long enough to estimate the duration of efficacy of opioids in chronic pain, the potential for opioid tolerance, or long-range adverse effects such as hypogonadism or opioid abuse.

The majority of the studies included in this review were funded by the pharmaceutical industry. However, there is insufficient information to determine whether or not pharmaceutical-industry funding might introduce publication bias by not publishing small or unfavourable studies.

The results of our review were similar to those of others recently conducted. In 2004, Kalso and colleagues⁴⁷ systematically reviewed studies of World Health Organization step 3 opioids for CNCP and found the mean decrease with opioids in pain intensity in most studies to be at least 30%, with comparable effects on neuropathic and musculoskeletal pain. Their review did not include evidence from studies of weak opioids (tramadol or codeine), nor did it assess the effectiveness of opioids compared with other analgesics. A Cochrane systematic review by Duhmke and associates⁴⁸ published

in 2004 showed that tramadol is an effective treatment for neuropathic pain. Eisenberg and coworkers' 2005 systematic review⁴⁹ of 8 randomized controlled trials of opioid agonists (excluding tramadol) for neuropathic pain demonstrated opioid efficacy for spontaneous neuropathic pain with intermediate-term follow-up. Moore and McQuay⁵⁰ recently published a systematic review of the side effects of opioids for chronic nonmalignant pain; they found the most common adverse effects to be dry mouth (25%), nausea (21%) and constipation (15%).

Our cumulative meta-analyses for placebo-controlled trials of orally administered opioids in regard to pain relief and functional outcomes showed that additional placebo-controlled trials of these outcomes are desirable only for other-than-oral routes of administration. For example, we found no reports of placebo-controlled trials of transdermal or rectal routes of administration of opioids, nor infusion programs for chronic pain. More refined experimental strategies will be required to assess other outcomes such as opioid abuse or addiction, sexual dysfunction and hypogonadism. Solid conclusions about the relative effectiveness and risk or benefit of opioids compared with other nonopioid drugs are still to be determined in adequately designed equivalence trials. Future trials of opioids for CNCP should consistently have well-defined methods and follow-up periods adequate in length to assess long-term complications such as sexual dysfunction or addiction. More attention should be paid to factors affecting methodological rigour, such as success of blinding, avoidance of dropouts, and adequate intention-to-treat analysis.

Supplementary Material

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[Online Appendices]

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Acknowledgments

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Footnotes

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This article has been peer reviewed.

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EXHIBIT 34

Health & Science

Patient advocacy group funded by success of painkiller drugs, probe finds

By Charles Ornstein and Tracy Weber December 23, 2011

The news about narcotic painkillers is increasingly dire: Overdoses now kill nearly 15,000 people a year — more than heroin and cocaine combined. In some states, the painkiller death toll exceeds that of car crashes.

The head of the Centers for Disease Control and Prevention has declared the overdoses from opioid drugs like OxyContin an “epidemic.” And a growing group of experts doubts that they work for long-term pain.

But the pills continue to have an influential champion in the American Pain Foundation, which describes itself as the nation’s largest advocacy group for pain patients. Its message: The risk of addiction is overblown, and the drugs are underused.

What the nonprofit organization doesn’t highlight is the money behind that message.

The foundation collected nearly 90 percent of its \$5 million in funding last year from the drug and medical-device industry — and closely mirrors its positions, an examination by ProPublica found.

Although the foundation maintains it is sticking up for the needs of millions of suffering patients, records and interviews show that it favors those who want to preserve access to the drugs over those who worry about their risks.

Some of the foundation’s board members have extensive financial ties to drugmakers, ProPublica found, and the group has lobbied against federal and state proposals to limit opioid use. Painkiller sales have increased fourfold since 1999, but the foundation argues that pain remains widely undertreated.

The group says industry money has had no effect on its advocacy.

“I’m convinced with every shred of my body that our interest is improving the lives of people affected by pain,” said Will Rowe, the foundation’s chief executive, “and we want to do that the best way we can.”

The problem isn't opioids, Rowe and other group leaders say. It's poorly trained doctors who prescribe them too easily or in excess.

Yet, critics say the Baltimore-based foundation is making it harder to address a major public-health problem.

"If you were a drug company, wouldn't it be smart to make it look like you had a patient-oriented group?" said Gary Franklin, a Washington state official who tussled with the foundation over new restrictions on high-dose painkillers.

Its funding makes the group "one and the same" with the pain industry, Franklin said.

ProPublica's review found that the foundation's guides for patients, journalists and policymakers play down the risks associated with opioids and exaggerate their benefits. Opioids, derived from the poppy plant, reduce the perception of pain by attaching to opioid receptors in the brain, spinal cord and elsewhere in the body.

Some of the foundation's materials on the drugs include statements that are misleading or based on scant or disputed research.

The group's board includes some patients but also doctors who are paid to speak and consult for drug companies, a researcher whose clinic has relied on their funding for survival and a public-relations executive whose firm represents them.

Last year, one board member was the lead author of a study about a Cephalon drug. Cephalon sponsored the study, and its employees were co-authors. The study found that the drug, Fentora, was "generally safe and well-tolerated" in non-cancer patients even though it is only approved for severe cancer pain.

Andrew Kolodny, a New York psychiatrist who heads Physicians for Responsible Opioid Prescribing, said the foundation has built credibility with politicians and regulators who might not be aware of the extensive industry ties.

"I don't think they realize that in many ways the American Pain Foundation is a front for opioid manufacturers," Kolodny said.

Rowe, however, said that with scant options to treat chronic pain, opioids have made the difference between days and nights of agony and a return to productive life for millions of patients. Critics, he said, have a hard time understanding that these patients are willing to risk serious side effects to gain relief.

"Policymakers can go to bed at night and say, 'Well, I protected society' " by restricting access to a risky painkiller, Rowe said. "The person with pain or the person with cancer could say: 'You know, I'm sorry. I'm living with this, and I want to take this chance.' "

Sales skyrocketed

In the late 1980s and early '90s, physicians who cared for pain patients excitedly embraced opioids as a low-risk treatment for suffering.

Many doctors, especially those providing primary care, had long ignored pain as a condition that warranted its own treatment.

But in recent years, pain doctors split. Some began decrying the increasingly widespread use of opioids and questioned whether the drugs worked. Others, like the foundation's leaders, said the drugs were being unfairly maligned, making pain patients feel like criminals and discouraging doctors from prescribing them.

Despite the debate, sales of the drugs have skyrocketed.

Last year, \$8.5 billion worth of narcotic painkillers were sold in the United States, according to the prescription-tracking company IMS Health. Enough of the drugs were prescribed last year to "medicate every American adult around the clock for a month," the CDC said.

Some of the pills have become household names: Vicodin, Percocet, OxyContin. On its own, OxyContin, an extended-release painkiller, accounted for \$3.1 billion in sales last year, up from \$752 million in 2006, according to IMS Health.

"Right now, the system is awash in opioids, dangerous drugs that got people hooked and keep them hooked," CDC Director Thomas Frieden said in a recent news briefing.

Today, the American Pain Foundation's Web site offers publications for patients, policymakers and even journalists. Each depicts the benefits of opioids, and each is underwritten by the makers of those drugs.

Its patient guide, paid for by four companies, discusses several treatments for pain. It says such pain relievers as aspirin, ibuprofen and naproxen commonly cause gastrointestinal bleeding or ulcers, delay blood clotting, decrease kidney function and could increase the risk of stroke or heart attack. And it warns patients to use these pain pills at the lowest dose and stop them unless clearly needed.

The side effects of opioids, on the other hand, are minor, and most go away "after a few days," the foundation's guide says. Patients, it says, shouldn't worry if they need more of a drug. They are not developing an addiction.

"Many times when a person needs a larger dose of a drug," the guide says, "it's because their pain is worse or the problem causing their pain has changed."

Another guide, written for journalists and supported by Alpharma Pharmaceuticals, likewise is reassuring. It notes in at least five places that the risk of opioid addiction is low, and it references a 1996 article in Scientific American, saying fewer than 1 percent of children treated with opioids become addicted.

But the cited article does not include this statistic or deal with addiction in children. “I would much prefer that they would put in there something that could be substantiated by a real reference,” said Leonard Paulozzi, a CDC medical epidemiologist specializing in drug overdoses.

A recent report by the National Institute on Drug Abuse said estimates of addiction among chronic pain patients using opioids range from 3 percent to as high as 40 percent.

Rowe, the foundation’s chief executive, acknowledged that some of its publications need updating. He pointed to additional materials on the group’s new PainSAFE Web site, which includes a broader description of the risks. But the foundation continues to post outdated guides and even refers to them in newer materials.

Arguing in court

The foundation doesn’t just offer advice about opioids; it takes its arguments into court.

In 2005, it filed a friend-of-the-court brief in the U.S. Court of Appeals for the 4th Circuit in support of William Hurwitz, a pain doctor in Virginia who had been convicted on 50 counts of drug trafficking.

The doctor had been accused of prescribing a single patient as many as 1,600 Roxicodone pain pills in one day. Hurwitz allegedly had prescribed that patient alone more than 500,000 pills between July 1999 and October 2002.

The pain foundation and its allies argued that the jury instructions in the case didn’t distinguish between criminal behavior and mistakes by a well-intentioned physician. “It is not drug dealing to prescribe opioids to patients that might be ‘suspected’ addicts or substance abusers,” the foundation and two other groups wrote in a brief.

Rowe said the foundation intervened in the case on principle, fearing the drugs would be “demonized.” The appeals court threw out the conviction, but Hurwitz was retried and convicted on 16 counts of trafficking.

Years earlier, the foundation opposed several pain patients who had sued Purdue Pharma in an Ohio county court for obscuring the risks of OxyContin.

The foundation filed a friend-of-the-court brief backing Purdue, arguing that the health of all pain patients would be harmed if the class-action lawsuit went forward because doctors would be fearful of prescribing opioids.

Ohio was plagued by “opiophobia” according to a brief written by the foundation and two smaller pain nonprofits.

The Ohio Supreme Court decided in 2004 not to allow a class action.

In a separate federal case in 2007, Purdue pleaded guilty to misbranding OxyContin “in an effort to mislead and defraud physicians and consumers” and agreed to pay \$600 million in penalties, according to a statement from prosecutors. Three top

officials also pleaded guilty to misdemeanors and agreed to pay \$34.5 million.

Two months after the conviction, however, then-foundation Chairman James Campbell praised Purdue in a statement to a U.S. Senate committee.

"I believe Purdue and its management deserve recognition for their contribution to the welfare of these many patients," Campbell wrote. Prosecuting the executives, he wrote, sent a "chilling message to those who dare to develop high-risk drugs for important diseases."

The foundation routinely weighs in on state and federal debates over how to regulate painkillers. But although its officials blame poorly educated physicians for the growing problems with opioids, it fought against a 2009 suggestion by the Food and Drug Administration that doctors be certified to ensure they understood the drugs' risks.

The FDA backed off. Such education remains voluntary.

Questions about benefits

Missing from the American Pain Foundation literature is any suggestion that the drugs don't work for many chronic pain sufferers.

Recent editorials in medical journals and scientific reviews cite little evidence of long-term benefit.

Most of the clinical trials for opioids to treat chronic pain "were small, lasted less than 16 weeks and excluded patients with a history of substance abuse, psychiatric illness and depression, who are at increased risk for opioid misuse and abuse," three physicians wrote in an editorial this year in the Archives of Internal Medicine.

"How can a therapy be considered if there's no evidence that it works and there's evidence of lots of side effects?" Mitchell Katz, one of the authors and director of the Los Angeles County Department of Health Services, said in an interview.

Rowe said he knows plenty of patients for whom the drugs work, "and their lives are together because they use them."

The foundation board's chairman and president, Scott Fishman, is stepping down at the end of the month. In a statement to ProPublica, he said that his views have evolved and that he now believes opioids are overused and addictive. But he defended the group.

"I have not always agreed with APF positions and have had disagreements with some APF leaders and patient advocates about many issues in pain management, including the appropriate place of chronic opioid therapy," wrote Fishman, chief of pain medicine at the University of California at Davis.

“Nonetheless, I have always believed that patients in pain in the United States need strong patient advocacy, which APF has offered.”

Weber and Ornstein report for ProPublica, a nonprofit investigative newsroom in New York City. A longer version of this article is available at www.propublica.org.

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EXHIBIT 35



ELSEVIER

Opioid Treatment Guidelines

Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain

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Abstract: Use of chronic opioid therapy for chronic noncancer pain has increased substantially. The American Pain Society and the American Academy of Pain Medicine commissioned a systematic review of the evidence on chronic opioid therapy for chronic noncancer pain and convened a multidisciplinary expert panel to review the evidence and formulate recommendations. Although evidence is limited, the expert panel concluded that chronic opioid therapy can be an effective therapy for

This article is based on research conducted at the Oregon Evidence-based Practice Center with funding from the American Pain Society (APS). The authors are solely responsible for the content of this article and the decision to submit for publication.

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carefully selected and monitored patients with chronic noncancer pain. However, opioids are also associated with potentially serious harms, including opioid-related adverse effects and outcomes related to the abuse potential of opioids. The recommendations presented in this document provide guidance on patient selection and risk stratification; informed consent and opioid management plans; initiation and titration of chronic opioid therapy; use of methadone; monitoring of patients on chronic opioid therapy; dose escalations, high-dose opioid therapy, opioid rotation, and indications for discontinuation of therapy; prevention and management of opioid-related adverse effects; driving and work safety; identifying a medical home and when to obtain consultation; management of breakthrough pain; chronic opioid therapy in pregnancy; and opioid-related policies.

Perspective: Safe and effective chronic opioid therapy for chronic noncancer pain requires clinical skills and knowledge in both the principles of opioid prescribing and on the assessment and management of risks associated with opioid abuse, addiction, and diversion. Although evidence is limited in many areas related to use of opioids for chronic noncancer pain, this guideline provides recommendations developed by a multidisciplinary expert panel after a systematic review of the evidence.

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Key words: Clinical practice guideline, opioids, opioid analgesics, risk assessment, monitoring, chronic pain.

Editor's Note: The American Pain Society and the American Academy of Pain Medicine present this first of 3 articles in this 3-part report as a guideline for opioid treatment of noncancer pain.

Opioid analgesics are widely accepted for the treatment of severe acute pain and chronic pain related to active cancer or at the end of life. In contrast, the use of chronic opioid therapy (COT, see Appendix B, Glossary) to treat other types of chronic pain remains controversial. Chronic pain is defined by the International Association for the Study of Pain as "pain that persists beyond normal tissue healing time, which is assumed to be three months."⁵⁹ Chronic pain may occur in the context of numerous diseases and syndromes.^{51,134} For the purposes of this guideline, all chronic pain disorders outside of cancer pain or pain at end of life are collectively labeled "chronic noncancer pain" (CNCP). CNCP conditions, including common conditions such as back pain, osteoarthritis, fibromyalgia, and headache, are extremely prevalent and account for very large costs. For back pain alone, total health care expenditures in 2004 and 2005 were estimated at \$85 to \$100 billion.⁷⁵ CNCP is a leading cause of disability^{16,128} and can have deleterious effects on ability to work, functional status and other quality of life domains.

There are numerous treatments for CNCP and a comprehensive assessment is needed in every case to guide therapeutic decision making. Some patients with CNCP are appropriate for focused therapy with a small number of modalities. Patients with more complex cases, including those with disabling CNCP, tend to experience better outcomes if they are managed using a comprehensive approach that integrates strategies to improve pain with those that address the functional impairment and psychosocial factors that are often associated with CNCP.⁸⁸ Whether the plan of care is limited or is designed to be more comprehensive, opioid therapy may be a useful component of the management plan.^{30,132} However, the selection of patients for an opioid trial, and decisions

about chronic opioid therapy (COT), must weigh potential benefits of opioids against the risk of significant harms, including a wide range of adverse effects as well as adverse outcomes associated with abuse (refer to Appendix B, Glossary for definition) potential.

Opioid prescriptions have increased substantially over the last 20 years,^{14,90} in part due to a growing consensus that opioid therapy is appropriate for some patients with CNCP.¹³² An increase in prescription opioid misuse (see Glossary) and mortality associated with opioid use has also been observed, affecting adolescent and adults of all ages.⁹ Clinicians and regulators must jointly seek a balanced approach to opioid use, acknowledging the legitimate medical need for opioids in some patients with CNCP, while concurrently recognizing the serious public health problem of abuse (see Appendix B, Glossary), addiction (see Appendix B, Glossary) and diversion (see Appendix B, Glossary), and implement procedures to reduce these risks.

The American Pain Society (APS), in partnership with the American Academy of Pain Medicine (AAPM), commissioned a multidisciplinary panel to develop evidence-based guidelines on COT for adults with CNCP. These recommendations are based on a systematic evidence review also commissioned by the APS and AAPM.¹⁹

Methods

Panel Composition

The APS and AAPM convened a multidisciplinary panel of 21 experts to review the evidence and formulate recommendations (see Appendix 1 for list of panel members). Two co-chairs (P.F. and G.F.) were selected by the APS and AAPM to lead the panel, which also included the Chair of the APS Clinical Practice Guidelines Committee (C.M.) and the APS Director of Clinical Guidelines Development (R.C.).

Target Audience and Scope

The intent of the guideline is to provide evidence-based recommendations for use of COT for CNCP in

both primary care and specialty settings. The target audience is all clinicians who provide care for adults with CNCP, including cancer survivors with chronic pain due to their cancer or its treatment. Management of cancer pain, pain at end of life, acute pain, postsurgical pain, labor pain, or CNCP in children and adolescents is outside the scope of this guideline. Separate APS guidelines address management of sickle cell pain⁵ and cancer pain.⁸³

Funding and Conflicts of Interest

Funding for the guideline was provided by the APS. The guideline was approved by the APS and AAPM, but the content of the guideline is the sole responsibility of the authors and panel members. All panelists were required to disclose conflicts of interest within the preceding 5 years at all face-to-face meetings and before submission of the guideline for publication, and recused themselves from votes if a conflict was present. Conflicts of interest of the authors and panel members are listed in Appendix 1.

Evidence Review

This guideline is informed by an evidence review conducted at the Oregon Evidence-based Practice Center and commissioned by APS and AAPM.¹⁹ The panel developed the key questions, scope, and inclusion criteria used to guide the evidence review. Literature searches were conducted through November 2007. Investigators reviewed 8,034 abstracts from searches for systematic reviews and primary studies from multiple electronic databases, reference lists of relevant articles, and suggestions from expert reviewers. A total of 14 systematic reviews and 57 primary studies (not included in previously published systematic reviews) were included in the evidence report.¹⁹

Grading of the Evidence and Recommendations

The panel used methods adapted from the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group to rate the recommendations included in this guideline.⁵² Each recommendation received a separate grade for the strength of the recommendation (strong or weak) and for the quality of evidence (high, moderate, or poor) (Appendix 2). In general, a strong recommendation is based on the panel's assessment that potential benefits of following the recommendation clearly outweigh potential harms and burdens. Given the available evidence, most clinicians and patients would choose to follow a strong recommendation. A weak rating is based on more closely balanced benefits to harms or burdens, or weaker evidence. Decisions to follow a weak recommendation could vary depending on specific clinical circumstances or patient preferences and values. For grading the quality of a body of evidence that supports a recommendation, we considered the type, number, size, and quality of studies; strength of associations or effects; and consistency of results among studies.⁵²

Guideline Development Process

The guideline panel met in person on three occasions between September 2006 and January 2008. At the first meeting, the panel developed the scope and key questions used to guide the systematic evidence review. At the second meeting, the panel reviewed the results of the evidence review and drafted initial potential recommendation statements. In between the second and third meetings, panelists participated in a multi-stage Delphi process, in which the draft recommendations were ranked and revised. At each stage of the Delphi process, the lowest-ranked recommendations were eliminated. At the third meeting, the final set of recommendations and recommendation grades were finalized and approved. Although a two-thirds majority was required for a recommendation to be approved, unanimous agreement was achieved on all but two recommendations (5.2 and 5.3 each had 2 panelists voting against). After the third meeting, the guideline was written by various panel members and drafts distributed to the panel for feedback and revisions. Over twenty external peer reviewers were solicited for additional comments. After another round of revisions and panel approval, the guideline was submitted to the APS and AAPM Executive Committees for approval.

The APS intends to update its clinical practice guidelines regularly. This guideline and the evidence report used to develop it will be reviewed and updated by 2012, or earlier if critical new evidence becomes available.

Recommendations

1. Patient Selection and Risk Stratification

Recommendations

- 1.1 Before initiating COT, clinicians should conduct a history, physical examination and appropriate testing, including an assessment of risk of substance abuse, misuse, or addiction (strong recommendation, low-quality evidence).
- 1.2 Clinicians may consider a trial of COT as an option if CNCP is moderate or severe, pain is having an adverse impact on function or quality of life, and potential therapeutic benefits outweigh or are likely to outweigh potential harms (strong recommendation, low-quality evidence).
- 1.3 A benefit-to-harm evaluation including a history, physical examination, and appropriate diagnostic testing, should be performed and documented before and on an ongoing basis during COT (strong recommendation, low-quality evidence).

Proper patient selection is critical and requires a comprehensive benefit-to-harm evaluation that weighs the potential positive effects of opioids on pain and function against potential risks. Thorough risk assessment and stratification is appropriate in every case. This approach is justified by estimates of aberrant drug-related behaviors (see Appendix B, Glossary), drug abuse, or misuse

in patients with CNCP, which range from 0% to 50%, depending on the population evaluated and methods used to define and identify these outcomes.⁵⁷ Risk stratification pertaining to outcomes associated with the abuse liability of opioids—misuse, abuse, addiction and diversion—is a vital but relatively undeveloped skill for many clinicians.⁹⁶ However, all clinicians prescribing opioids should be knowledgeable about risk factors for opioid abuse and methods for assessing risk. Assessment of risks for opioid-associated adverse effects also should be performed, given their high prevalence.⁸⁶

A thorough history and physical examination, including an assessment of psychosocial factors and family history, is essential for adequate risk stratification. Implicit in the recommendation to conduct a comprehensive benefit-to-harm analysis is the recognition that an opioid trial may not be appropriate. Clinicians should obtain appropriate diagnostic tests to evaluate the underlying pain condition, and should consider whether the pain condition may be treated more effectively with nonopioid therapy rather than with COT. For example, COT generally would not be appropriate before a trial of an anticonvulsant for trigeminal neuralgia,⁷ a disease-modifying antirheumatic drug for rheumatoid arthritis,²⁷ a corticosteroid for polymyalgia rheumatica,¹¹⁸ or various abortive and prophylactic therapies for migraine headache.

Reliable evidence on methods to accurately assess the potential benefits of COT is limited. However, randomized trials that demonstrate the benefits of COT are most applicable to patients with moderate or more severe pain who have not responded to nonopioid therapies.^{42,63} Presence of poorly-defined pain conditions, a likely somatoform disorder, or unresolved compensation or legal issues may predict poorer response to all therapies, including COT.^{103,114} Although neuropathic and non-neuropathic pain conditions appear in general to respond similarly to COT,^{42,63,86} evidence that demonstrates the efficacy of COT for conditions with strong psychosocial contributors such as some types of chronic low back pain,⁷⁴ daily headache,¹¹⁹ and fibromyalgia⁴⁸ is sparse. There is insufficient evidence to recommend use of an intravenous opioid trial to predict likelihood of benefit from COT.⁶³

The factor that appears to be most strongly predictive of drug abuse, misuse, or other aberrant drug-related behaviors after initiation of COT is a personal or family history of alcohol or drug abuse.^{28,35,60,72,85,111} Younger age and presence of psychiatric conditions are also associated with aberrant drug-related behaviors in some studies.^{28,35,60,84,111} Preexisting constipation, nausea, pulmonary disease, and cognitive impairment probably predict risk for opioid-related adverse effects, though no studies have adequately evaluated the utility of these factors for use in risk stratification.

Clinicians should consider a trial of COT for CNCP when potential benefits are likely to outweigh risks, and there is no alternative therapy that is likely to pose as favorable a balance of benefits to harms. For example, a patient who is 60 years old, has chronic disabling osteoarthritis pain despite nonopioid therapies, and whose history reveals no significant psychiatric comorbidities, major med-

ical comorbidities, or personal or family history of drug abuse or addiction would be assessed as having high potential benefits from COT relative to potential risks. COT could be prescribed to this patient in most clinical settings with routine monitoring (see Section 5). In contrast, a patient who is 30 years old with fibromyalgia and recent intravenous drug abuse would have high potential risks relative to benefits. COT in this context requires intensive structure, monitoring, and management by professionals with expertise in both addiction medicine and pain medicine and should be undertaken only if risks can be adequately managed (see Section 6). The selection of patients between these two extremes requires careful assessment and characterization of patient risk and structuring of care to match risk (see Section 5). In patients with a history of substance abuse or a psychiatric comorbidity, this may require assistance from persons with expertise in managing pain, addiction or other mental health concerns (see Section 6), and in some cases opioids may not be appropriate or should be deferred until the comorbidity has been adequately addressed.

Screening tools that assess the potential risks associated with COT based on patient characteristics are likely to be helpful for risk stratification, though more validation and prospective outcome studies are needed to understand how their use predicts and affects clinical outcomes. Tools that appear to have good content, face, and construct validity include the Screener and Opioid Assessment for Patients with Pain (SOAPP) Version 1 (Appendix 3),¹⁰ the revised SOAPP (SOAPP-R),¹² the Opioid Risk Tool (ORT) (Appendix 4),¹³⁸ and the Diagnosis, Intractability, Risk, Efficacy (DIRE) instrument (Appendix 5).⁴ DIRE is clinician-administered and is designed to assess potential efficacy as well as harms. The SOAPP Version 1, SOAPP-R and ORT are patient self-report questionnaires that assess risk of aberrant drug-related behaviors.

2. Informed Consent and Opioid Management Plans

Recommendations

- 2.1 When starting COT, informed consent should be obtained. A continuing discussion with the patient regarding COT should include goals, expectations, potential risks, and alternatives to COT (strong recommendation, low-quality evidence).
- 2.2 Clinicians may consider using a written COT management plan to document patient and clinician responsibilities and expectations and assist in patient education (weak recommendation, low-quality evidence).

Clinicians should inform patients about the risks and benefits associated with COT before initiating a trial of therapy.³⁰ In patients already on COT, clinicians should periodically review risks and benefits of therapy. Patients should be counseled about the potential for common opioid-related adverse effects (eg, constipation, nausea, sedation) as well as other serious risks (eg, abuse, addiction, overdose). Potential risks of long-term or high-dose

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COT (eg, hyperalgesia (see Appendix B, Glossary), endocrinologic or sexual dysfunction) should also be discussed, though more evidence is needed to better understand and quantify these risks.^{24,25,73,82} The goal of the consent process is to assist patients to make appropriate medical decisions that are consistent with their preferences and values. In some states, clinicians are required to document this discussion, though specific requirements vary.⁹⁵ A sample informed consent form is shown in Appendix 6.

It is important for clinicians to discuss a COT management plan before initiating a course of treatment and on an ongoing basis while patients are on therapy.³⁰ The COT management plan includes goals of therapy, how opioids will be prescribed and taken, expectations for clinic follow-up and monitoring (see Section 5), alternatives to COT, expectations regarding use of concomitant therapies, and potential indications for tapering or discontinuing COT, which may include failure to make progress toward therapeutic goals, intolerable adverse effects, or repeated or serious aberrant drug-related behaviors.² Patients should be counseled that opioids may be just one part of a multimodal treatment plan (see Section 9) to reduce pain intensity and improve quality of life, especially functional capacity. To avoid unrealistic patient expectations regarding likely benefits, patients should be counseled that total pain relief with COT is rare. Indeed, trials suggest that improvement averages less than 2 to 3 points on a 0 to 10 scale.^{42,63}

Although evidence is lacking about the most effective methods to convey the COT management plan, written documentation can help clarify the plan with the patient, the patient's family, and other clinicians who may become involved in the patient's care. For patients at higher risk for misuse of opioid analgesics, use of clear written guidelines may be particularly helpful to reinforce expectations about the appropriate and safe use of opioids. Though the content of written COT management plans vary,³⁴ provisions may include: Obtaining opioids from one prescriber, filling opioids prescriptions at one designated pharmacy, random urine drug screens, office visits at a specified minimum interval, use of pill counts, limited prescriptions (in weekly or biweekly instead of monthly amounts) and enumeration of behaviors that may lead to discontinuation of opioids. However, there is insufficient evidence to guide specific recommendations on which provisions to include. A sample COT management plan is shown in Appendix 7.

There is increasing awareness that theft from medicine cabinets is a major source of diverted opioids. All patients should be encouraged to lock their medications (eg, using a medicine safe). Guidance is available on best methods for disposing of opioids.⁸⁹

3. Initiation and titration of COT

Recommendations

3.1 Clinicians and patients should regard initial treatment with opioids as a therapeutic trial to

determine whether COT is appropriate (strong recommendation, low-quality evidence).

3.2 Opioid selection, initial dosing, and titration should be individualized according to the patient's health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms (strong recommendation, low-quality evidence). There is insufficient evidence to recommend short-acting versus long-acting opioids, or as-needed versus around-the-clock dosing of opioids.

An initial course of treatment with opioids for CNCP should be viewed as a short-term, therapeutic trial lasting from several weeks to several months. The decision to proceed with COT should be intentional and based on careful consideration of outcomes during the trial. Outcomes to consider include progress toward meeting therapeutic goals, presence of opioid-related adverse effects, changes in the underlying pain condition, changes in psychiatric or medical comorbidities, and the identification of aberrant drug-related behaviors, addiction, or diversion (see Section 5 on monitoring). In most cases, the therapeutic trial includes individualization of the dose through incremental dose escalations, as long as no serious harms are present. In patients who experience mild or moderate opioid-related adverse effects, a longer trial may be indicated because some adverse effects decrease with longer exposure. Some adverse effects can be managed with additional therapies (see Section 8). Suspected aberrant drug-related behaviors require further evaluation and action (see Section 6).

In patients who are opioid-naïve, or have modest previous opioid exposure, opioids should be started at a low dose and titrated slowly, to decrease risk of opioid-related adverse effects. However, there is insufficient evidence to recommend specific optimal starting doses and methods of dose titration. In general, opioid doses should be individualized based on risk for adverse outcomes and responses to therapy. Some patients, such as frail older persons or those with comorbidities, may benefit from more cautious initiation and titration of therapy. Short-acting opioids are probably safer for initial therapy since they have a shorter half-life and may be associated with a lower risk of inadvertent overdose. However, there is no direct evidence from randomized trials that demonstrates that any one opioid is superior to any other for initial therapy (see Section 4 for issues regarding methadone).¹⁷ There is also insufficient evidence to guide recommendations for use of short-acting versus long-acting opioids,¹⁷ or as-needed versus around-the-clock dosing. Proposed benefits of transitioning to long-acting opioids with around-the-clock dosing include more consistent control of pain, improved adherence and lower risk of addiction or abuse, though well-conducted studies have not examined these benefits.

4. Methadone

Recommendation

4.1 Methadone is characterized by complicated and variable pharmacokinetics and pharmacodynamics

and should be initiated and titrated cautiously, by clinicians familiar with its use and risks (strong recommendation, moderate-quality evidence).

Use of methadone for CNCP has increased dramatically.¹⁵ However, few trials have evaluated benefits and harms of methadone for CNCP.¹⁷ In addition, a number of epidemiologic studies suggest an increased rate of methadone-associated deaths in the United States.^{15,44,76,91} QTc prolongation and cardiac arrhythmias may occur in patients on methadone, particularly at higher doses, or with concomitant use of drugs that interact with methadone or that themselves prolong QTc.^{21,23,68}

Clinicians who prescribe methadone should be familiar with its clinical pharmacology and associated risks. Methadone has a very long and highly variable half-life, which necessitates careful titration to avoid delayed adverse events, such as overdose. Although the half-life of methadone is usually estimated at 15 to 60 hours, in some reports the half-life is as high as 120 hours.⁷¹ In a patient for whom the methadone half-life is 60 hours, it would take almost 12 days on a stable dose of methadone to approach a steady state (5 half-lives). Methadone should therefore be started at low doses and titrated slowly. Based on panel consensus, a safe starting dose in most opioid-naïve patients is 2.5 mg every 8 hours, with dose increases occurring no more frequently than weekly. In older patients or those with renal or hepatic comorbidities, less frequent dosing and more cautious dose titration are recommended.

In opioid-tolerant patients, conversion to methadone should be performed cautiously. Equianalgesic dose ratios for methadone relative to other opioids are variable and can range from 0.1% to 10% morphine equivalents (lower at higher doses). In patients on lower doses of other opioids, safe starting doses of methadone may be similar to those used for opioid-naïve patients. Starting methadone doses should generally not exceed 30 to 40 mg a day even in patients on high doses of other opioids. Several algorithms are available for converting from other opioids to methadone, though there is insufficient evidence to recommend a particular method, and much of the evidence is derived from studies of patients with cancer.^{49,69,112} Because of its long half-life and variable pharmacokinetics, the panel recommends that methadone not be used to treat breakthrough pain or as an as-needed medication.

5. Monitoring

Recommendations

- 5.1 Clinicians should reassess patients on COT periodically and as warranted by changing circumstances. Monitoring should include documentation of pain intensity and level of functioning, assessments of progress toward achieving therapeutic goals, presence of adverse events, and adherence to prescribed therapies (strong recommendation, low-quality evidence).
- 5.2 In patients on COT who are at high risk or who have engaged in aberrant drug-related behaviors,

clinicians should periodically obtain urine drug screens or other information to confirm adherence to the COT plan of care (strong recommendation, low-quality evidence).

- 5.3 In patients on COT not at high risk and not known to have engaged in aberrant drug-related behaviors, clinicians should consider periodically obtaining urine drug screens or other information to confirm adherence to the COT plan of care (weak recommendation, low-quality evidence).

Clinicians should periodically reassess all patients on COT. Regular monitoring of patients once COT is initiated is critical because therapeutic risks and benefits do not remain static and can be affected by changes in the underlying pain condition, presence of coexisting disease, or changes in psychological or social circumstances. Monitoring is essential to identify patients who are benefiting from COT, those who might benefit more with restructuring of treatment or receiving additional services such as treatment for addiction, and those whose benefits from treatment are outweighed by harms. Insufficient evidence exists to guide precise recommendations on appropriate monitoring intervals. However, risk stratification (see Section 1) is useful for guiding the approach to monitoring. In patients at low risk for adverse outcomes and on stable doses of opioids, monitoring at least once every three to six months may be sufficient. Patients who may need more frequent or intense monitoring, at least for a period of time after initiation of therapy or changes in opioid doses, include those with a prior history of an addictive disorder, those in an occupation demanding mental acuity, older adults, patients with an unstable or dysfunctional social environment, and those with comorbid psychiatric or medical conditions. For patients at very high risk for adverse outcomes, monitoring on a weekly basis may be a reasonable strategy.

Monitoring that involves regular, repeated evaluations and addresses a variety of domains is likely to be more informative than infrequent, narrowly focused evaluations. Although there is insufficient evidence for specific recommendations about how to monitor patients on COT, there is general agreement that monitoring should routinely include assessment and documentation of pain severity and functional ability, progress toward achieving therapeutic goals, and presence of adverse effects.⁹⁸ In addition, clinicians should routinely carry out a thorough clinical assessment for presence of aberrant drug-related behaviors, substance use, and psychological issues. Because patient self-report may be unreliable for determining amount of opioid use, functionality, or aberrant drug-related behaviors,^{31,67,110} pill counts, urine drug screening, family member or caregiver interviews, and use of prescription monitoring program data can be useful supplements. Although evidence is lacking on the accuracy and effects on clinical outcomes of formal screening instruments for identification of aberrant drug-related behaviors, use of tools with strong content, face and construct validity, such as the PADT (Appendix 8)^{97,98} and COMM (Appendix 9)¹¹ are

recommended as an efficient method of assessment and documentation.

Periodic urine drug screening can be a helpful tool to monitor patients on COT.⁶⁵ Urine drug screening is likely to result in a higher yield in patients with risk factors for drug abuse or diversion. However, targeted (nonuniversal) urine drug screening will miss some proportion of patients who engage in aberrant drug-related behaviors, as predictors of such behaviors are relatively weak.¹⁸ Random urine drug screens may be more informative than scheduled or routine testing, as patients may change behaviors when they expect to be tested, though there are no studies comparing these approaches. Although evidence on accuracy of urine drug screening to identify aberrant drug-related behaviors or diversion is lacking, and no evidence exists that demonstrates that screening improves clinical outcomes, absence of prescribed opioids or presence of unprescribed opioids or illicit drugs can be a marker for problematic issues that would not be apparent without urine drug screening.⁶⁷ Interpretation of urine drug screen results is a challenge, and requires an understanding of opioid drug metabolism, pharmacokinetics and limits of laboratory testing methods.⁸ In fact, urine drug screen results usually do not suggest a definitive course of action, but rather should be interpreted in the context of individual patient circumstances.⁵⁵ Clinicians should consider a differential diagnosis for abnormal urine drug screen results, including drug abuse or addiction, self-treatment of poorly controlled pain, psychological issues, or diversion (which may be suggested by absence of prescribed opioids).

6. High-Risk Patients

Recommendations

- 6.1 Clinicians may consider COT for patients with CNCP and history of drug abuse, psychiatric issues, or serious aberrant drug-related behaviors only if they are able to implement more frequent and stringent monitoring parameters. In such situations, clinicians should strongly consider consultation with a mental health or addiction specialist (strong recommendation, low-quality evidence).
- 6.2 Clinicians should evaluate patients engaging in aberrant drug-related behaviors for appropriateness of COT or need for restructuring of therapy, referral for assistance in management, or discontinuation of COT (strong recommendation, low-quality evidence).

CNCP is common in patients with suspected aberrant drug-related behaviors, psychosocial comorbidities, and history of substance abuse.^{115,129} Use of COT is challenging in these patients because they are more vulnerable to drug misuse, abuse, and addiction. In some patients, such as those actively using illicit drugs, potential benefits are outweighed by potential risks, and COT should not be prescribed outside of highly controlled and specialized settings (such as an opioid treatment program with directly observed therapy). In other patients, potential

benefits of COT may outweigh potential risks. Although evidence is lacking on best methods for managing such patients, potential risks may be minimized by more frequent and intense monitoring compared with lower risk patients (see Section 5), authorization of limited prescription quantities, and consultation or co-management with persons who have expertise in addiction or mental health issues. In settings where local access to specialists is limited, clinicians may need to consider alternative methods (such as telemedicine or web-based resources) for obtaining consultative services, though there is no evidence evaluating risks and benefits compared with traditional face-to-face consultation. Clinicians should also be aware of and use prescription monitoring programs if they are available in their area of practice, as they can help identify patients who obtain drugs from multiple sources.⁶²

The occurrence of aberrant drug-related behavior always suggests the need for re-evaluation, and perhaps a change in therapy. However, aberrant drug-related behaviors vary in seriousness. Clinicians should formulate a differential diagnosis when evaluating suspected aberrant drug-related behaviors (see Section 5).⁴¹ The response to aberrant drug-related behavior reflects a clinical judgment about its seriousness, its cause or causes, the likelihood that behaviors of this type will recur, and the clinical context. Although evidence to guide optimal management strategies is lacking, anecdotal experience of panel members suggests that patients who are not assessed as being at high risk and engage in a relatively nonserious aberrant behavior, such as one or two episodes of unauthorized opioid escalations, can often be managed with patient education and enhanced monitoring. Patients who are repeatedly nonadherent and patients who engage in more serious aberrant behaviors (such as use of cocaine, use of unprescribed opioids, or obtaining opioids from multiple outside sources) may require consultation or referral (if not already done), major restructuring of therapy, and in many cases discontinuation of COT (see Section 7). In one study, four or more previous aberrant drug-related behaviors were a strong predictor of a current substance use disorder.³⁵ Patients who report a subjective sense of losing control regarding opioid use may also require restructuring of therapy, as this may predict future aberrant drug-related behaviors.¹³⁹ Patients who meet criteria for a substance use disorder should be referred for treatment of this serious comorbidity.

Restructuring of therapy may include more frequent or intense monitoring strategies, temporary or permanent tapering of opioid doses, or the addition of psychological therapies or other nonopioid treatments. In patients with opioid addiction who require ongoing pain treatment and do not respond to nonopioid analgesic interventions, structured opioid agonist treatment with methadone or buprenorphine by a licensed program may be an appropriate option. COT must be discontinued in patients who are known to be diverting opioids or in those engaging in seriously aberrant behaviors (such as injecting an oral formulation). Patients whose COT is to be discontinued may require referral or

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consultation for assistance with opioid detoxification and management of withdrawal (see Section 7).

7. Dose Escalations, High-Dose Opioid Therapy, Opioid Rotation, and Indications for Discontinuation of Therapy

Recommendations

- 7.1 When repeated dose escalations occur in patients on COT, clinicians should evaluate potential causes and reassess benefits relative to harms (strong recommendation, low-quality evidence).
- 7.2 In patients who require relatively high doses of COT, clinicians should evaluate for unique opioid-related adverse effects, changes in health status, and adherence to the COT treatment plan on an ongoing basis, and consider more frequent follow-up visits (strong recommendation, low-quality evidence).
- 7.3 Clinicians should consider opioid rotation when patients on COT experience intolerable adverse effects or inadequate benefit despite dose increases (weak recommendation, low-quality evidence).
- 7.4 Clinicians should taper or wean patients off of COT who engage in repeated aberrant drug-related behaviors or drug abuse/diversion, experience no progress toward meeting therapeutic goals, or experience intolerable adverse effects (strong recommendation, low-quality evidence).

Management of treatment-refractory patients on high doses of COT is challenging. Although progressively higher opioid doses may improve symptom control in some patients, repeated dose escalations can also be a marker for a substance use disorder or diversion. In some patients, repeated dose escalations may have limited utility because of adverse effects, the lack of incremental benefit with higher doses, or other factors. Theoretically, opioids have no maximum or ceiling dose, but there is little evidence to guide safe and effective prescribing at higher doses and there is no standardized definition for what constitutes a "high" dose. By panel consensus, a reasonable definition for high dose opioid therapy is >200 mg daily of oral morphine (or equivalent), based on maximum opioid doses studied in randomized trials^{42,63} and average opioid doses observed in observational studies.¹⁰⁵ Some studies suggest that hyperalgesia,^{1,20} neuroendocrinologic dysfunction,^{25,70} and possibly immunosuppression^{113,116} may be more likely at higher opioid doses, though more evidence is needed to define these risks, their relationship to dose, and their relationship to clinical outcomes.

Clinicians should carefully reassess (see Section 5) all patients on COT who have repeated dose escalations. When opioid doses reach 200 mg daily of morphine (or equivalent), more frequent and intense monitoring is often appropriate, to sufficiently inform the decision to continue therapy or consider additional dose escalations. Opioid treatment may require restructuring (including weaning or discontinuation of COT) if assessments indi-

cate reduced analgesia, function, or quality of life; aberrant drug-related behaviors; or the presence of intolerable adverse effects.

Opioid rotation (switching from one opioid to another opioid) is a potential strategy for patients on COT who experience intolerable adverse effects or inadequate benefit despite dose increases. The theory behind opioid rotation is based on concepts of incomplete cross-tolerance to the analgesic and nonanalgesic effects across opioids and a high degree of individual variation in response to different opioids. This could potentially lead to a better balance of benefits to harms when one opioid is changed to another.^{80,108} However, well-designed studies that evaluate the benefits and harms of opioid rotation are lacking, and available studies in patients with CNCP show inconsistent results.³⁸⁻⁴⁰ There is also insufficient evidence to guide specific recommendations for performing opioid rotation. Dose conversion tables and rotation protocols are available¹⁰² and generally suggest that a switch to a new drug should be accompanied by a moderate (usually 25% to 50%) reduction in the calculated equianalgesic dose. However, this method does not apply to cases in which patients are being rotated to methadone (see Section 4).

Patients should be tapered or weaned off COT when they engage in serious or repeated aberrant drug-related behaviors or diversion, experience intolerable adverse effects, or make no progress toward meeting therapeutic goals. Although there is insufficient evidence to guide specific recommendations on optimal strategies, a taper or wean can often be achieved in the outpatient setting in patients without severe medical or psychiatric comorbidities. When available, opioid detoxification in a rehabilitation setting (outpatient or inpatient) can be helpful, especially for patients unable to reduce their opioid dose in a less structured setting. When aberrant drug-related behaviors are a continuing issue, the clinician may need to enforce weaning efforts. If the aberrant behaviors are thought to be due to addiction, addiction treatment resources should be made available and continued follow-up arranged to provide both support for nonopioid pain management and to motivate the patient to seek treatment for addiction.

Symptoms of opioid withdrawal can be very unpleasant, but are generally not life threatening. Approaches to weaning range from a slow 10% dose reduction per week to a more rapid 25% to 50% reduction every few days. Evidence to guide specific recommendations on the rate of reduction is lacking, though a slower rate may help reduce the unpleasant symptoms of opioid withdrawal.^{22,109,131} Factors that may influence the rate of reduction include the reason driving the decision to discontinue COT, presence of medical and psychiatric comorbidities, the starting dose, and the occurrence of withdrawal symptoms as the process is initiated. Anecdotal clinical experience of panel members suggests that at high doses (eg, over 200 mg/d of morphine or equivalent), the initial wean can be more rapid. The rate of dose reduction often must be slowed when relatively low daily doses, such as 60 to 80 mg daily of morphine (or equivalent), are reached, due to occurrence

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of more withdrawal symptoms. Patients weaned from COT because of lack of effectiveness may report improvements in well-being and function without any worsening in pain,³ though other patients may experience pain hypersensitivity during opioid withdrawal.¹ Clinicians should continue to treat patients who are withdrawn from COT for their painful condition as well as for substance use or psychiatric disorders.

8. Opioid-Related Adverse Effects

Recommendation

- 8.1 Clinicians should anticipate, identify, and treat common opioid-associated adverse effects (strong recommendation, moderate-quality evidence).

An important goal of any COT management plan is to maintain a favorable balance of benefits relative to harms. Anticipation and treatment of opioid-associated adverse effects reduce the likelihood that patients will discontinue COT due to intolerable adverse effects, and may allow use of higher opioid doses if needed for uncontrolled pain.

Constipation is one of the most common opioid-related adverse effects.⁸⁶ Most patients develop some degree of constipation after opioid initiation or dose increases, and resolution of constipating effects of opioids often does not occur with continued exposure. In older adults or other patients with additional reasons to develop constipation, we recommend routinely considering initiation of a bowel regimen before the development of constipation. Though most evidence is anecdotal, bowel regimens including increased fluid and fiber intake, stool softeners, and laxatives are often effective. There is insufficient evidence to recommend oral opioid antagonists to prevent or treat opioid-induced bowel dysfunction in persons with CNCP, though randomized trials suggest some potential benefits over placebo.^{100,137}

Nausea or vomiting is another common opioid-associated adverse effect that tends to diminish over days or weeks of continued opioid exposure. A number of antiemetic therapies, in both oral and rectal forms, are available to treat nausea or vomiting.

Sedation or clouded mentation after opioid initiation also tends to wane over time. When initiating or changing doses of opioids, patients should be counseled about driving and work and home safety (see Section 10). In addition, patients should be counseled on effects and risks of concomitant exposure to other drugs and substances with sedating effects. There is insufficient evidence to recommend specific pharmacologic therapies for persistent opioid-related sedation.

Chronic use of sustained-release oral opioids for CNCP was associated with hypogonadism and decreased levels of dehydroepiandrosterone sulfate in several cross-sectional studies.²⁴⁻²⁶ Patients should be tested for such hormonal deficiencies if they report symptoms consistent with their presence, such as decreased libido, sexual dysfunction, or fatigue. Insufficient evidence exists to recommend routine monitoring of asymptomatic patients

on COT for CNCP for hormonal deficiencies, or to guide specific treatment approaches if a deficiency is identified.

Other common opioid-related adverse effects include pruritus and myoclonus. Effective treatment strategies for either condition are largely anecdotal. Respiratory depression may occur when initial opioid doses are too high, opioids are titrated too rapidly, or opioids are combined with other drugs that are associated with respiratory depression or that may potentiate opioid-induced respiratory depression (such as benzodiazepines). Patients with sleep apnea or other underlying pulmonary conditions may be at higher risk for respiratory depression and opioids should be initiated and titrated carefully.

9. Use of Psychotherapeutic Cointerventions

Recommendation

- 9.1 As CNCP is often a complex biopsychosocial condition, clinicians who prescribe COT should routinely integrate psychotherapeutic interventions, functional restoration, interdisciplinary therapy, and other adjunctive nonopioid therapies (strong recommendation, moderate-quality evidence).

CNCP is often a complex condition that may involve biological, psychological, and environmental factors.⁸⁸ When pain is accompanied by comorbidities, impaired function, or psychological disturbances, COT is likely to be most effective as part of multimodality treatment that addresses all of these domains. Clinicians should routinely integrate therapies that target the psychosocial and functional factors that contribute to or are affected by CNCP.

Cognitive-behavioral therapy is the best-studied psychological therapy and is consistently shown to be effective for CNCP.^{56,78,87,92,133} It often focuses on helping patients cope with chronic pain to improve function. Other potentially beneficial psychological therapies include progressive relaxation, biofeedback, and other techniques.¹³³ Functional restoration with specific behavioral interventions, pain education, and simulated or actual physical tasks in a supervised environment may enhance function and improve strength, endurance, flexibility, and cardiovascular fitness.¹²¹ Interdisciplinary or multidisciplinary pain management approaches coordinate physical, vocational, or psychological components and are provided by at least two health care professionals with different clinical backgrounds, and may be the best method for providing multimodality therapy for the highly disabled CNCP patient.^{36,53,64} The intensity and content of interdisciplinary therapy varies widely, but most involve an exercise program and some type of psychological therapy. More intensive interdisciplinary programs tend to be more effective than less intensive programs.⁵³ Barriers to obtaining interdisciplinary therapy include high costs, limited availability in the United States, and frequent lack of insurance coverage. In addition, patients are more likely to benefit if highly

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motivated to participate, because interdisciplinary rehabilitation generally requires a high degree of engagement and commitment of time and effort.

10. Driving and Work Safety

Recommendation

10.1 Clinicians should counsel patients on COT about transient or lasting cognitive impairment that may affect driving and work safety. Patients should be counseled not to drive or engage in potentially dangerous activities when impaired or if they describe or demonstrate signs of impairment (strong recommendation, low-quality evidence).

Opioids may cause somnolence, clouded mentation, decreased concentration, and slower reflexes or incoordination, especially when initiating therapy, increasing doses, or when opioids are taken with other drugs or substances that affect the central nervous system.^{86,101,126}

These effects could impair patients' abilities to drive or work safely. However, epidemiologic studies suggest that motor vehicle accidents, fatalities, and citations for impaired driving are not disproportionately associated with opioid use.^{32,33} Other studies indicate that patients who initiate opioids or are on COT perform similarly to patients not on COT on standardized driving tests.^{13,43,45,79,117} Shortcomings of the evidence include a reliance on cross-study comparisons (eg, rates of opioid use in persons involved in motor vehicle accidents compared with estimates of opioid use in the general population), use of simulated and other controlled driving tests that may not completely mirror real-world driving conditions, and probable selection bias, as patients experiencing central nervous system opioid-related adverse effects are probably less likely to drive or to participate in studies that evaluate driving ability. No studies have evaluated the effects of COT on work safety.

As a public health measure and for the individual patient's safety, clinicians should counsel all patients initially prescribed COT not to drive or engage in potentially dangerous work or other activities when impaired. Patients should be educated about the greater risk of impairment when starting opioid therapy, when increasing doses, and when taking other drugs or substances that may have central nervous effects, including alcohol. Clinicians should counsel patients not to drive or engage in potentially dangerous activities if they describe or demonstrate signs of impairment, and should refer to state laws regarding physician-reporting requirements to local authorities in these situations. In the absence of signs or symptoms of impairment, no evidence exists to suggest that patients maintained on COT should be restricted from driving or engaging in most work activities. Some studies suggest that COT may improve cognitive functioning due to better control of pain.^{61,130} However, clinicians should be aware that certain professions (such as bus drivers and pilots) may be subject to additional regulations and laws regarding use of opioids.

11. Identifying a Medical Home and When to Obtain Consultation

Recommendations

11.1 Patients on COT should identify a clinician who accepts primary responsibility for their overall medical care. This clinician may or may not prescribe COT, but should coordinate consultation and communication among all clinicians involved in the patient's care (strong recommendation, low-quality evidence).

11.2 Clinicians should pursue consultation, including interdisciplinary pain management, when patients with CNCP may benefit from additional skills or resources that they cannot provide (strong recommendation, moderate-quality evidence).

Studies show that patients do better when they have continuous access to a clinician who provides comprehensive care for the large majority of their health care needs and who coordinates care when the services of other health care professionals are needed.¹²⁷ Having a clinician who accepts primary responsibility for their overall medical care is likely to be particularly important for patients with CNCP, as they use health care services more frequently¹²² and have more comorbidities¹³⁶ than those without CNCP. US adults with a primary care clinician, rather than a specialist, as their main health care provider had 33% lower costs of care and were 19% less likely to die at a given age compared with a matched cohort, after adjusting for demographic and health characteristics.³⁷ Having a primary care clinician is a powerful predictor of longevity.¹²⁴

The attributes of effective primary care were described recently in a model known as the patient-centered primary care medical home.⁹⁹ With their multiple and complex health care needs, patients with CNCP require the coordinated and comprehensive services offered through a medical home. The medical home model does not necessarily require the primary care clinician to prescribe and monitor COT. In fact, patients with CNCP may need additional or special services that may not be available in their medical home. In such cases, consultation with other professionals is essential. In particular, pain centers that provide access to an array of pain therapies and specialists trained to assess, prescribe, and monitor COT can be highly valuable. Nonetheless, the primary care clinician should continue to coordinate consultation and communication among all clinicians involved in the patient's treatment.

12. Breakthrough Pain

Recommendation

12.1 In patients on around-the-clock COT with breakthrough pain, clinicians may consider as-needed opioids based upon an initial and ongoing analysis of therapeutic benefit versus risk (weak recommendation, low-quality evidence).

Patients prescribed stable doses of around-the-clock COT for CNCP frequently experience periods of increased

pain (ie, breakthrough pain).^{6,106} Breakthrough pain (see Appendix B, Glossary) should be assessed separately from the baseline pain, and can be related to progression of the underlying condition, or a new or unrelated pain condition. Appropriate evaluation of breakthrough pain may require additional diagnostic testing, follow-up visits, or consultation in order to identify the etiology of the pain or the factors precipitating it. Management of breakthrough pain should include consideration of specific therapies directed at the cause of the pain or the precipitating factors, or nonspecific symptomatic therapies intended to lessen the impact of breakthrough pain when it occurs.

There is insufficient evidence to guide recommendations regarding optimal treatment strategies for breakthrough pain in patients with CNCP. Limited evidence from short-term trials suggest that short-acting or rapid onset, as-needed opioids may be effective in this setting, but more studies are needed to evaluate the long-term benefits and harms of this strategy, and to compare effects of different short-acting or rapid onset opioids.^{104,125} Clinicians should weigh carefully the potential benefits versus risks when considering the addition of an as-needed opioid for treatment of breakthrough pain, and consider both nonopioid drug therapies and nonpharmacologic treatments as other options. Although there is no evidence on the risk of aberrant drug-related behavior in relation to the availability of medication prescribed for breakthrough pain, it is reasonable to assume that access to a short-acting drug may increase the risk of such behavior in those already engaging in them or at high risk to do so. In patients at low risk for aberrant drug-related behaviors, a trial of an as-needed opioid with routine follow-up and monitoring may be a reasonable strategy. In patients at higher risk for aberrant drug-related behaviors, a trial of an as-needed opioid should only occur in conjunction with more frequent monitoring and follow-up. In all cases, clinicians should carefully assess for aberrant drug-related behaviors and progress toward meeting therapeutic goals, and periodically reassess relative benefits to risks of the as-needed opioid to make appropriate decisions regarding continuation of this therapy.

13. Opioids in Pregnancy

Recommendation

13.1 Clinicians should counsel women of childbearing potential about the risks and benefits of COT during pregnancy and after delivery. Clinicians should encourage minimal or no use of COT during pregnancy, unless potential benefits outweigh risks. If COT is used during pregnancy, clinicians should be prepared to anticipate and manage risks to the patient and newborn (strong recommendation, low-quality evidence).

Managing CNCP in pregnant women is challenging. COT in this setting affects at least two patients, one of whom (the fetus) is unable to consent to treatment. In addition, due to the paucity of research that has been done, or is likely to be done for ethical reasons, it is diffi-

cult to evaluate benefits and risks of COT in pregnancy. Most of the literature on pregnancy and opioids has focused on women in methadone maintenance treatment, or women who used opioids for analgesia during labor, rather than COT for CNCP.

Although there are survey data that associate the use of COT during pregnancy with adverse newborn outcomes including low birth weight, premature birth, hypoxic-ischemic brain injury, and neonatal death,⁵⁴ it is difficult to separate effects of opioid use from other maternal factors that may contribute to these adverse newborn outcomes.²⁹ Other neonatal complications associated with maternal opioid use include prolonged QT syndrome and opioid withdrawal syndrome. The risks of adverse neonatal outcomes may be lower when women are on methadone for chronic pain management rather than for opioid dependence treatment.¹²³ Higher doses of antenatal methadone in tolerant mothers do not seem to increase complication rates.⁷⁷

Given potential risks of opioids during pregnancy, clinicians should counsel women about risks and benefits of COT and recommend minimal or no use of opioids unless potential benefits outweigh risks (eg, severe disabling pain only controllable with opioids). Clinicians who care for pregnant women on COT must be prepared to address the additional risks. While antenatal harms may be difficult to predict and prevent, opioid withdrawal can be expected in up to half of newborns of opioid-dependent mothers. If the mother is receiving COT at or near the time of delivery, a professional who is experienced in the management of neonatal withdrawal should be available.

14. Opioid Policies

Recommendation

14.1 Clinicians should be aware of current federal and state laws, regulatory guidelines, and policy statements that govern the medical use of COT for CNCP (strong recommendation, low-quality evidence).

Surveys show that clinicians have a poor or limited understanding of the laws, regulations, and other policies that govern the prescribing, dispensing, or administration of controlled substances, including opioid analgesics.^{46,107} Little research has been conducted to determine the extent that clinicians' knowledge of policies impacts healthcare practice and patient care.⁴⁷ However, clinicians are more vulnerable to regulatory investigation or discipline if they fail to comply with practice standards or regulations. Clinicians who prescribe COT for CNCP should be aware of the substantial policy changes that have occurred in recent years, and take steps to understand their responsibilities under federal and state laws, regulations, and other governmental policies that govern such practice. Resources are available to provide clinicians with information regarding opioid-prescribing policies in all 50 states and the District of Columbia.⁹³⁻⁹⁵

Conclusions

Use of COT for CNCP has been steadily increasing for 2 decades. Guidelines based on the best available

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evidence and developed by multidisciplinary panels of experts are critical for promoting the effective and safe use of COT for CNCP. Although evidence is limited, an expert panel convened by APS and AAPM concludes that COT can be an effective therapy for carefully selected and monitored patients with CNCP. However, opioids are also associated with potentially serious harms, including opioid-related adverse effects and outcomes related to the abuse potential of opioids. The guidelines presented in this document are based on the underlying assumption that safe and effective therapy requires clinical skills and knowledge in both the principles of opioid prescribing and on the assessment and management of risks associated with opioid abuse, addiction, and diversion.

Although these guidelines are based on a systematic review of the evidence on COT for CNCP, the panel identified numerous research gaps. In fact, the panel did not rate any of its 25 recommendations as supported by high quality evidence. Only 4 recommendations were viewed as supported by even moderate quality evidence. Nonetheless, the panel came to unanimous consensus on almost all of its recommendations. Optimally balancing benefits and risks of COT for CNCP is dependent on careful patient evaluation and structuring of opioid therapy to accommodate identified risk, appropriate initiation and titration of COT, regular and comprehensive monitoring while on COT, and anticipation and management of opioid-related adverse effects. Other areas of strong consensus include recommendations to use therapies targeting psychosocial fac-

tors and to identify a medical home for all chronic pain patients. Critical research gaps are present in methods for providing informed consent, effective components of opioid management plans, balancing risks and benefits of high-dose opioid therapy, utility of opioid rotation, and treatment of breakthrough pain. More research is also needed on how policies that govern prescribing and use of COT affect clinical outcomes.

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Note: Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. As part of a shared decision making approach, it may be appropriate for the clinician to inform a patient that a particular recommendation may not be applicable, after considering all circumstances pertinent to that individual.

Supplementary Data

Supplementary data accompanying this article is available online at www.jpain.org, www.sciencedirect.com, and at doi:[10.1016/j.jpain.2008.10.008](https://doi.org/10.1016/j.jpain.2008.10.008). The supplementary data include Appendices 1–9.

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Appendix A

American Pain Society and American Academy of Pain Medicine Opioids Guidelines Panel Members; Discipline and Affiliation

Director, APS Clinical Guidelines Project, Roger Chou, MD – Internal Medicine, Oregon Health and Sciences University – Oregon Evidence-based Practice Center.

Co-chairs: Gilbert J. Fanciullo, MD, MS – Anesthesiology/Pain Medicine, Dartmouth-Hitchcock Medical Center, Department of Anesthesiology, Pain Management Center.

Perry G. Fine, MD, Anesthesiology/Pain Medicine and Palliative Care, University of Utah, Pain Research Center.

Chair, APS Clinical Practice Guidelines Committee: Christine Miaskowski, RN, PhD, FAAN, Registered Nurse/Pain Medicine, University of San Francisco, Department of Physiological Nursing.

Panel: Jeremy A. Adler, MS, PA-C, Physician Assistant, Pacific Pain Medicine Consultants.

Jane C. Ballantyne, MD, Anesthesiology/Pain Medicine, Massachusetts General Hospital, Department of Anesthesia and Critical Care.

Pamela Davies, MS, ARNP, Nurse Practitioner/Pain Medicine, Seattle Cancer Care Alliance (Formerly Internal medicine, Veterans Affairs Medical Center, Seattle).

Marilee I. Donovan, PhD, RN, Registered Nurse/Pain Medicine, Kaiser Permanente Northwest, Pain Management Clinic.

David A. Fishbain, MD, FAPA, Psychiatry/Pain Medicine, University of Miami, School of Medicine, Neurological Surgery and Anesthesiology.

Kathy M. Foley, MD, Neurology/Pain Medicine and Palliative Care, Memorial Sloan-Kettering Cancer Center, Pain and Palliative Care Service, Department of Neurology.

Jeffrey Fudin, BS, PharmD, DAAPM, Clinical Pharmacy, Samuel S. Stratton Department of Veterans Affairs Medical Center, and Albany College of Pharmacy & Health Sciences.

Aaron M. Gilson, PhD, Health Policy, University of Wisconsin Paul P. Carbone Comprehensive Cancer Center, Pain and Policy Studies Group.

Alexander Kelter, MD, Public Health, California Department of Health Services, Epidemiology and Prevention for Injury Control (EPIC) Branch (retired 2005).

Alexander Mauskop, MD, FAAN, Neurology, New York Headache Center, State University of New York, Downstate Medical Center.

Patrick G. O'Connor, MD, MPH, Internal Medicine, Yale University School of Medicine and Yale-New Haven Hospital, Section of General Internal Medicine.

Steven D. Passik, PhD, MA, Psychology/Addiction, Memorial Sloan-Kettering Cancer Center, Department of Psychiatry and Behavioral Sciences.

Gavril W. Pasternak, MD, PhD, Neuropharmacology, Memorial Sloan-Kettering Cancer Center, Laboratory of Molecular Neuropharmacology.

Russell K. Portenoy, MD, Neurology/Pain Medicine and Palliative Care, Beth Israel Medical Center, Department of Pain Medicine and Palliative Care.

Ben A. Rich, JD, PhD, Law/Ethics, University of California, Davis, School of Medicine, Division of Bioethics.

Richard G. Roberts, MD, JD, FAAFP, FCLM, Family Practice, University of Wisconsin, School of Medicine and Public Health.

Knox H. Todd, MD, MPH, FACEP, Emergency Medicine, Beth Israel Medical Center - Pain and Emergency Medicine Institute.

Appendix B. Glossary

TERM	DEFINITION
Aberrant drug-related behavior	A behavior outside the boundaries of the agreed on treatment plan which is established as early as possible in the doctor-patient relationship. ⁵⁰
Abuse	Any use of an illegal drug, or the intentional self-administration of a medication for a nonmedical purpose such as altering one's state of consciousness, for example, getting high. ⁶⁶
Addiction	A primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. ¹²⁰
Breakthrough pain	Transient or episodic exacerbation of pain that occurs in patients with pain that is otherwise considered stable but persistent ⁸¹
Chronic opioid therapy	Daily or near-daily use of opioids for at least 90 days, often indefinitely (adapted from Von Korff et al). ¹³⁵
Diversion	The intentional transfer of a controlled substance from legitimate distribution and dispensing channels. ⁶⁶
Hyperalgesia	An increased response to a stimulus which is normally painful. ⁵⁸
Misuse	Use of a medication (for a medical purpose) other than as directed or as indicated, whether willful or unintentional, and whether harm results or not. ⁶⁶
Physical dependence	A state of adaptation manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. ¹²⁰
Tolerance	A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more opioid effects over time. ¹²⁰

Appendix 1. List of Panel Members and Conflict of Interest Statements**Director, APS Clinical Guidelines Project****Roger Chou, MD***Oregon Health & Sciences University - Oregon Evidence-based Practice Center*

- No conflicts to report

Co-chairs**Gilbert J. Fanciullo, MD, MS***Dartmouth-Hitchcock Medical Center - Department of Anesthesiology, Pain Management Center*

Fee Income:

- Medtronic: Research grant; Speaker, Consultant
- Janssen: Research support
- Teva Pharmaceuticals: Expert Witness
- Pfizer: Educational support for Fellows in Dartmouth Fellowship Program

Perry G. Fine, MD*University of Utah - Pain Research Center*

Fee Income:

- Combined honoraria income (exceeding \$10,000) from serving on advisory boards related to opioid analgesics for Alpharma, Cephalon, Endo Pharmaceuticals, GlaxoSmithKline, Lilly, Merck, NIH, Ortho-McNeil (J & J), Purdue Pharma, and Wyeth
- Total income of above sources over last three years estimated at \$30,000

Ownership interests:

- 17,500 shares in ZARS Pharma, a privately owned company that develops opioid delivery systems

Chair, APS Guidelines**Christine Miaskowski, PhD, RN, FAAN***University of San Francisco - Department of Physiological Nursing*

Fee Income:

- Consultant/Speaker' Bureaus for Anesta, Cephalon, Endo,GlaxoSmithKline, Merck, and Pricara

Panel**Jeremy A. Adler, MS, PA-C***Pacific Pain Medicine Consultants*

Fee Income:

- Advisory Board member: Alpharma
- Speaker's Bureau: Alpharma, Elan, Endo, Pfizer, and Victory pharmaceutical companies

Jane C. Ballantyne, MD*Massachusetts General Hospital - Department of Anesthesia and Critical Care*

Fee Income:

- Harvard International Outreach in Geneva & Bern, Switzerland – 4 weeks sponsored by Novartis, August 2005
- Evidence Base of Acute Pain Management Panel of Experts – results published in *Anesthesia & Analgesia*, sponsored by Orthopedic Review, November 2005
- Hydromorphone Expert Panel/Advisory – sponsored by Endo Pharmaceuticals, May 2006
- Harvard Medical School received \$1,500, 000 from Purdue Pharma used to sponsor research and education programs at Massachusetts General Hospital Pain Unit

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Appendix 1. Continued

Pamela Davies, MS, ARNP

Seattle Cancer Care Alliance

Fee Income:

- Received honorarium payments from Alpharma and Endo Pharmaceuticals for work as Clinical Advisor
- Received honorarium from Endo Pharmaceuticals for work at University of Washington, School of Nursing Continuing Education
- Total of all honoraria in last 3 years: approximately \$5,000

Marilee I. Donovan, PhD, RN

Kaiser Permanente Northwest - Pain Management Clinic

Employment:

- Manager of Kaiser-Permanente Northwest region Pain Management Clinic
- Application for ROI to develop predictors of addiction
- Department accepts test equipment from vendors who then sell department equipment and supplies for interventional pain management procedures
- Consultant to JCAHO re: pain standards
- Clinical lead for outcomes process for Kaiser-Permanente Chronic Pain Guidelines

David A. Fishbain, MD, FAPA

University of Miami - School of Medicine, Neurological Surgery and Anesthesiology

- No conflicts to report

Kathy M. Foley, MD

Memorial Sloan-Kettering Cancer Center - Pain & Palliative Care Service, Department of Neurology

- No conflicts to report

Jeffrey Fudin, BS, PharmD, DAAPM

Samuel S. Stratton Department of Veterans Affairs Medical Center, and Albany College of Pharmacy & Health Sciences

Fee Income:

- Speakers Bureaus for Advisory Boards: Abbott (less than \$10,000), Alpharma (less than \$10,000), Calloway Labs, Janssen, and Pricara (division of Ortho-McNeil)
- Janssen: Research support
- Teva Pharmaceuticals: Expert Witness

Appendix 1. Continued**Aaron M. Gilson, PhD**

University of Wisconsin Paul P. Carbone Comprehensive Cancer Center - Pain & Policy Studies Group

Fee Income:

- Consulting responsibilities for the American Cancer Society
- Honorarium payment for presentations at the Pharmacy Society of Wisconsin and the Federation of State Medical Boards of the U.S., and from Janssen Pharmaceuticals.
- The Pain & Policy Studies Group at The University of Wisconsin receives unrestricted educational grants from Alpharma, Endo Pharmaceuticals, and Purdue Pharma

Research Funding:

- Robert Wood Johnson Foundation, Federation of State Medical Boards of the U.S.
- Research projects at the Pain & Policy Studies Group at The University of Wisconsin are funded by grants from the American Cancer Society, Susan B. Komen for the Cure, U.S. Cancer Pain Relief Committee, and through a cooperative agreement with the Lance Armstrong Foundation
- Project funding is pending for R03 project at the Pain & Policy Studies Group

Alexander Kelter, MD

California Department of Health Services - Epidemiology & Prevention for Injury Control (EPIC) Branch (retired 2005)

- No conflicts to report

Alexander Mauskop, MD, FAAN

New York Headache Center

State University of New York, Downstate Medical Center

- No conflicts to report

Patrick G. O'Connor, MD, MPH

Yale University School of Medicine and Yale-New Haven Hospital - Section of General Internal Medicine

- No conflicts to report

Steven D. Passik, PhD, MA

Memorial Sloan-Kettering Cancer Center - Department of Psychiatry and Behavioral Sciences

Fee Income:

- Consultant/Speaker' Bureaus for Alpharma, Cephalon, Endo, King, Ligand, Lilly, and, Pricara pharmaceutical companies
- Honoraria for speaking on pain/addiction and risk management from Ligand, Cephalon, Endo, Alpharma, Purdue, and Mallinckrodt pharmaceutical companies

Research Funding:

- Have received grant/research support from Cephalon, Lilly, Amgen, Janssen, and Ligand companies

Gavril W. Pasternak, MD, PhD

Memorial Sloan-Kettering Cancer Center - Laboratory of Molecular Neuropharmacology

Fee Income:

- Consultant/Scientific Advisory Boards for Sarentis, Traxon, EpiCept, Limmerick, and QrxPahrma companies
- Honoraria from Adolor, Endo, Cephalon, and Ortho-McNeill pharmaceutical companies

Research Funding:

Have received grant/research support from Sarentis for preclinical evaluation of drug candidates

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Appendix 1. Continued

Russell K. Portenoy, MD

Beth Israel Medical Center - Department of Pain Medicine & Palliative Care

Fee Income:

- Consulting agreements with an extensive list of pharmaceutical companies, estimated to work with 4-5 within three year period (complete list available upon request)

Research Funding:

- Department at Beth Israel Medical Center has received research funding in amounts ranging from less than \$10,000 to over \$100,000 funding from several pharmaceutical companies, foundations, and other sources (complete list available upon request)

Ben A. Rich, JD, PhD

University of California, Davis - School of Medicine, Division of Bioethics

Fee Income:

- Speaker honoraria payments from Purdue Pharma, PharmaCon, Pharmacia/Pfizer
- Expert consultant/review payment from Purdue Pharma

Richard G. Roberts, MD, JD, FAAFP, FCLM

University of Wisconsin - School of Medicine and Public Health

Fee Income:

- Advisor Board membership payments (less than \$10,000 each) from Endo, Ortho-McNeill, and Pfizer

Knox H. Todd, MD, MPH, FACEP

Beth Israel Medical Center - Pain and Emergency Medicine Institute

Fee Income:

- Consulting payments from Johnson & Johnson, Alpharma, ALZA, and Ortho-McNeill pharmaceutical companies

Research Funding:

- Board of Director member for the American Chronic Pain Association, which has received research funding from Cephalon

Appendix 2. Grading Evidence and Recommendations (GRADE)**Grading evidence and recommendations - operationalization of GRADE methods⁵²****High-quality**

Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (at least two consistent, higher-quality randomized controlled trials*, or multiple, consistent observational studies with no significant methodological flaws showing large effects).

Moderate-quality

Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (at least one higher-quality trial* with >100 subjects; two or more higher-quality trials* with some inconsistency; at least two consistent, lower-quality trials*, or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects).

Low-quality

Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

*Or prospective studies on risk prediction or studies of diagnostic accuracy when appropriate

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Appendix 3. Risk Assessment Tool – Screener and Opioid Assessment for Patients with Pain (SOAPP)

Screener and Opioid Assessment for Patients with Pain (SOAPP)® Version 1.0 - 14Q

The Screener and Opioid Assessment for Patients with Pain (SOAPP)® Version 1.0 is a tool for clinicians to help determine how much monitoring a patient on long-term opioid therapy might require. Physicians remain reluctant to prescribe opioid medication because of concerns about addiction, misuse, and other aberrant medication-related behaviors, as well as liability and censure concerns. Despite recent findings suggesting that most patients are able to successfully remain on long-term opioid therapy without significant problems, physicians often express a lack of confidence in their ability to distinguish patients likely to have few problems on long-term opioid therapy from those requiring more monitoring.

SOAPP® version 1.0 is a quick and easy-to-use questionnaire designed to help providers evaluate the patients' relative risk for developing problems when placed on long-term opioid therapy. Version 1.0 -14Q is:

- A brief paper and pencil questionnaire
- Developed based on expert consensus regarding important concepts likely to predict which patients will require more or less monitoring on long-term opioid therapy (content and face valid)
- Preliminary reliability data (coefficient α) from 175 patients chronic pain patients
- Preliminary validity data from 100 patients (predictive validity)
- Simple scoring procedures
- 14 items
- 5 point scale
- <8 minutes to complete
- Ideal for documenting decisions about the level of monitoring planned for a particular patient or justifying referrals to specialty pain clinic.
- The SOAPP® is for clinician use only. The tool is not meant for commercial distribution.
- The SOAPP® is NOT a lie detector. Patients determined to misrepresent themselves will still do so. Other clinical information should be used with SOAPP® scores to decide on a particular patient's treatment.
- The SOAPP® is NOT intended for all patients. The SOAPP® should be completed by chronic pain patients being considered for opioid therapy.
- It is important to remember that all chronic pain patients deserve treatment of their pain. Providers who are not comfortable treating certain patients should refer those patients to a specialist.

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Appendix 3. Continued**SOAPP® Version 1.0-14Q**

Name: _____ Date: _____

The following are some questions given to all patients at the Pain Management Center who are on or being considered for opioids for their pain. Please answer each question as honestly as possible. This information is for our records and will remain confidential. Your answers alone will not determine your treatment. Thank you.

Please answer the questions below using the following scale:

0 = Never, 1 = Seldom, 2 = Sometimes, 3 = Often, 4 = Very Often

- | | |
|--|-----------------------|
| 1. How often do you have mood swings? | 0 1 2 3 4 |
| 2. How often do you smoke a cigarette within an hour after you wake up? | 0 1 2 3 4 |
| 3. How often have any of your family members, including parents and grandparents, had a problem with alcohol or drugs? | 0 1 2 3 4 |
| 4. How often have any of your close friends had a problem with alcohol or drugs? | 0 1 2 3 4 |
| 5. How often have others suggested that you have a drug or alcohol problem? | 0 1 2 3 4 |
| 6. How often have you attended an AA or NA meeting? | 0 1 2 3 4 |
| 7. How often have you taken medication other than the way that it was prescribed? | 0 1 2 3 4 |
| 8. How often have you been treated for an alcohol or drug problem? | 0 1 2 3 4 |
| 9. How often have your medications been lost or stolen? | 0 1 2 3 4 |
| 10. How often have others expressed concern over your use of medication? | 0 1 2 3 4 |

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Appendix 3. Continued**0 = Never, 1 = Seldom, 2 = Sometimes, 3 = Often, 4 = Very Often**

- | | |
|--|-----------------------|
| 11. How often have you felt a craving for medication? | 0 1 2 3 4 |
| 12. How often have you been asked to give a urine screen
for substance abuse? | 0 1 2 3 4 |
| 13. How often have you used illegal drugs (for example,
marijuana, cocaine, etc.) in the past five years? | 0 1 2 3 4 |
| 14. How often, in your lifetime, have you had legal problems or
been arrested? | 0 1 2 3 4 |

Please include any additional information you wish about the above answers. Thank you.

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Appendix 3. Continued**Scoring Instructions for the SOAPP® Version 1.0-14Q**

To score the SOAPP® V.1-14Q, simply add the ratings of all the questions:

A score of 7 or higher is considered positive.

Sum of Questions	SOAPP® Indication
> or = 7	+
< 7	-

What does the Cutoff Score Mean?

For any screening test, the results depend on what cutoff score is chosen. A score that is good at detecting patients at-risk will necessarily include a number of patients that are not really at risk. A score that is good at identifying those at low risk will, in turn, miss a number of patients at risk. A screening measure like the SOAPP® generally endeavors to minimize the chances of missing high-risk patients. This means that patients who are truly at low risk may still get a score above the cutoff. The table below presents several statistics that describe how effective the SOAPP® is at different cutoff values. These values suggest that the SOAPP® is a sensitive test. This confirms that the SOAPP® is better at identifying who is at high risk than identifying who is at low risk. Clinically, a score of 7 or higher will identify 91% of those who actually turn out to be at high risk. The Negative Predictive Value for a cutoff score of 7 is .90, which means that most people who have a negative SOAPP® are likely at low-risk. Finally, the Positive likelihood ratio suggests that a positive SOAPP® score (at a cutoff of 7) is nearly 3 times (2.94 times) as likely to come from someone who is actually at high risk (note that, of these statistics, the likelihood ratio is least affected by prevalence rates). All this implies that by using a cutoff score of 7 will ensure that the provider is least likely to miss someone who is really at high risk. However, one should remember that a low SOAPP® score suggests the patient is really at low-risk, while a high SOAPP® score will contain a larger percentage of false positives (about 30%), while at the same time retaining a large percentage of true positives. This could be improved, so that a positive score has a lower false positive rate, but only at the risk of missing more of those who actually do show aberrant behavior.

SOAPP® Cutoff Score	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio	Negative Likelihood Ratio
Score 7 or above	.91	.69	.71	.90	2.94	.13
Score 8 or above	.86	.73	.75	.86	3.19	.19
Score 9 or above	.77	.80	.77	.80	3.90	.28

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Appendix 4. Risk Assessment Tool – Opioid Risk Tool (ORT)

Date _____

Patient Name _____

OPIOID RISK TOOL

		Mark each box that applies	Item Score If Female	Item Score If Male
1. Family History of Substance Abuse	Alcohol	[]	1	3
	Illegal Drugs	[]	2	3
	Prescription Drugs	[]	4	4
2. Personal History of Substance Abuse	Alcohol	[]	3	3
	Illegal Drugs	[]	4	4
	Prescription Drugs	[]	5	5
3. Age (Mark box if 16 – 45)		[]	1	1
4. History of Preadolescent Sexual Abuse		[]	3	0
5. Psychological Disease	Attention Deficit Disorder	[]	2	2
	Obsessive Compulsive Disorder			
	Bipolar			
	Schizophrenia			
	Depression	[]	1	1
TOTAL		[]		

Total Score Risk Category

Low Risk 0 – 3 Moderate Risk 4 – 7

High Risk ≥ 8 Reproduced with permission from Lynn Webster¹³⁷

Appendix 5. Risk Assessment Tool - Score Diagnosis, Intractability, Risk Efficacy (D.I.R.E.)**D.I.R.E. Score: Patient Selection for Chronic Opioid Analgesia**

For each factor, rate the patient's score from 1-3 based on the explanations in the right hand column

Score	Factor	Explanation
	<u>Diagnosis</u>	1 = Benign chronic condition with minimal objective findings or no definite medical diagnosis. Examples: fibromyalgia, migraine headaches, non-specific back pain. 2 = Slowly progressive condition concordant with moderate pain, or fixed condition with moderate objective findings. Examples: failed back surgery syndrome, back pain with moderate degenerative changes, neuropathic pain. 3 = Advanced condition concordant with severe pain with objective findings. Examples: severe ischemic vascular disease, advanced neuropathy, severe spinal stenosis.
	<u>Intractability</u>	1 = Few therapies have been tried and the patient takes a passive role in his/her pain management process. 2 = Most customary treatments have been tried but the patient is not fully engaged in the pain management process, or barriers prevent (insurance, transportation, medical illness). 3 = Patient fully engaged in a spectrum of appropriate treatments but with inadequate response.
	<u>Risk</u>	(R= Total of P+C+R+S below)
	<u>Psychological:</u>	1 = Serious personality dysfunction or mental illness interfering with care. Example: personality disorder, severe affective disorder, significant personality issues. 2 = Personality or mental health interferes moderately. Example: depression or anxiety disorder. 3 = Good communication with clinic. No significant personality dysfunction or mental illness.
	<u>Chemical Health:</u>	1 = Active or very recent use of illicit drugs, excessive alcohol, or prescription drug abuse. 2 = Chemical coper (uses medications to cope with stress) or history of CD in remission. 3 = No CD history. Not drug-focused or chemically reliant.
	<u>Reliability:</u>	1 = History of numerous problems: medication misuse, missed appointments, rarely follows through. 2 = Occasional difficulties with compliance, but generally reliable. 3 = Highly reliable patient with meds, appointments & treatment.
	<u>Social Support:</u>	1 = Life in chaos. Little family support and few close relationships. Loss of most normal life roles. 2 = Reduction in some relationships and life roles. 3 = Supportive family/close relationships. Involved in work or school and no social isolation.
	<u>Efficacy score</u>	1 = Poor function or minimal pain relief despite moderate to high doses. 2 = Moderate benefit with function improved in a number of ways (or insufficient info- hasn't tried opioid yet or very low doses or too short of a trial). 3 = Good improvement in pain and function and quality of life with stable doses over time.

Total score = D + I + R + E

Score 7-13: Not a suitable candidate for long-term opioid analgesia

Score 14-21: Good candidate for long-term opioid analgesia

Reproduced with permission from Miles Belgrade⁴

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Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain

Appendix 6. Sample Informed Consent form**Consent for Chronic Opioid Therapy***A consent form from the American Academy of Pain Medicine*

Dr. _____ is prescribing opioid medicine, sometimes called narcotic analgesics, to me for a diagnosis of _____.

This decision was made because my condition is serious or other treatments have not helped my pain.

I am aware that the use of such medicine has certain risks associated with it, including, but not limited to: sleepiness or drowsiness, constipation, nausea, itching, vomiting, dizziness, allergic reaction, slowing of breathing rate, slowing of reflexes or reaction time, physical dependence, tolerance to analgesia, addiction and possibility that the medicine will not provide complete pain relief.

I am aware about the possible risks and benefits of other types of treatments that do not involve the use of opioids. The other treatments discussed included:

I will tell my doctor about all other medicines and treatments that I am receiving.

I will not be involved in any activity that may be dangerous to me or someone else if I feel drowsy or am not thinking clearly. I am aware that even if I do not notice it, my reflexes and reaction time might still be slowed. Such activities include, but are not limited to: using heavy equipment or a motor vehicle, working in unprotected heights or being responsible for another individual who is unable to care for himself or herself.

I am aware that certain other medicines such as nalbuphine (Nubain™), pentazocine (Talwin™), buprenorphine (Buprenex™), and butorphanol (Stadol™), may reverse the action of the medicine I am using for pain control. Taking any of these other medicines while I am taking my pain medicines can cause symptoms like a bad flu, called a withdrawal syndrome. I agree not to take any of these medicines and to tell any other doctors that I am taking an opioid as my pain medicine and cannot take any of the medicines listed above.

I am aware that addiction is defined as the use of a medicine even if it causes harm, having cravings for a drug, feeling the need to use a drug and a decreased quality of life. I am aware that the chance of becoming addicted to my pain medicine is very low. I am aware that the development of addiction has been reported rarely in medical journals and is much more common in a person who has a family or personal history of addiction. I agree to tell my doctor my complete and honest personal drug history and that of my family to the best of my knowledge.

Appendix 6. Continued

I understand that physical dependence is a normal, expected result of using these medicines for a long time. I understand that physical dependence is not the same as addiction. I am aware physical dependence means that if my pain medicine use is markedly decreased, stopped or reversed by some of the agents mentioned above, I will experience a withdrawal syndrome. This means I may have any or all of the following: runny nose, yawning, large pupils, goose bumps, abdominal pain and cramping, diarrhea, irritability, aches throughout my body and a flu-like feeling. I am aware that opioid withdrawal is uncomfortable but not life threatening.

I am aware that tolerance to analgesia means that I may require more medicine to get the same amount of pain relief. I am aware that tolerance to analgesia does not seem to be a big problem for most patients with chronic pain, however, it has been seen and may occur to me. If it occurs, increasing doses may not always help and may cause unacceptable side effects. Tolerance or failure to respond well to opioids may cause my doctor to choose another form of treatment.

(Males only) I am aware that chronic opioid use has been associated with low testosterone levels in males. This may affect my mood, stamina, sexual desire and physical and sexual performance. I understand that my doctor may check my blood to see if my testosterone level is normal.

(Females Only) If I plan to become pregnant or believe that I have become pregnant while taking this pain medicine, I will immediately call my obstetric doctor and this office to inform them. I am aware that, should I carry a baby to delivery while taking these medicines, the baby will be physically dependent upon opioids. I am aware that the use of opioids is not generally associated with a risk of birth defects. However, birth defects can occur whether or not the mother is on medicines and there is always the possibility that my child will have a birth defect while I am taking an opioid.

I have read this form or have it read to me. I understand all of it. I have had a chance to have all of my questions regarding this treatment answered to my satisfaction. By signing this form voluntarily, I give my consent for the treatment of my pain with opioid pain medicines.

Patient signature _____ Date _____

Witness to above _____

Approved by the AAPM Executive Committee on January 14, 1999.



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Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain

Appendix 7. Sample Medical Agreement

**SAMPLE FOR ADAPTATION AND REPRODUCTION
ON PHYSICIAN LETTERHEAD**

PLEASE CONSULT WITH YOUR ATTORNEY

Long-term Controlled Substances Therapy for Chronic Pain

SAMPLE AGREEMENT

A consent form from the American Academy of Pain Medicine

The purpose of this agreement is to protect your access to controlled substances and to protect our ability to prescribe for you.

The long-term use of such substances as opioids (narcotic analgesics), benzodiazepine tranquilizers, and barbiturate sedatives is controversial because of uncertainty regarding the extent to which they provide long-term benefit. There is also the risk of an addictive disorder developing or of relapse occurring in a person with a prior addiction. The extent of this risk is not certain.

Because these drugs have potential for abuse or diversion, strict accountability is necessary when use is prolonged. For this reason the following policies are agreed to by you, the patient, as consideration for, and a condition of, the willingness of the physician whose signature appears below to consider the initial and/or continued prescription of controlled substances to treat your chronic pain.

1. All controlled substances must come from the physician whose signature appears below or, during his or her absence, by the covering physician, unless specific authorization is obtained for an exception. (Multiple sources can lead to untoward drug interactions or poor coordination of treatment.)
2. All controlled substances must be obtained at the same pharmacy, where possible. Should the need arise to change pharmacies, our office must be informed. The pharmacy that you have selected is:

phone: _____

3. You are expected to inform our office of any new medications or medical conditions, and of any adverse effects you experience from any of the medications that you take.
4. The prescribing physician has permission to discuss all diagnostic and treatment details with dispensing pharmacists or other professionals who provide your health care for purposes of maintaining accountability.
5. You may not share, sell, or otherwise permit others to have access to these medications.
6. These drugs should not be stopped abruptly, as an abstinence syndrome will likely develop.
7. Unannounced urine or serum toxicology screens may be requested, and your cooperation is required. Presence of unauthorized substances may prompt referral for assessment for addictive disorder.

Appendix 7. Continued

8. Prescriptions and bottles of these medications may be sought by other individuals with chemical dependency and should be closely safeguarded. It is expected that you will take the highest possible degree of care with your medication and prescription. They should not be left where others might see or otherwise have access to them.
9. Original containers of medications should be brought in to each office visit.
10. Since the drugs may be hazardous or lethal to a person who is not tolerant to their effects, especially a child, you must keep them out of reach of such people.
11. Medications may not be replaced if they are lost, get wet, are destroyed, left on an airplane, etc. If your medication has been stolen and you complete a police report regarding the theft, an exception may be made.
12. Early refills will generally not be given.
13. Prescriptions may be issued early if the physician or patient will be out of town when a refill is due. These prescriptions will contain instructions to the pharmacist that they not be filled prior to the appropriate date.
14. If the responsible legal authorities have questions concerning your treatment, as might occur, for example, if you were obtaining medications at several pharmacies, all confidentiality is waived and these authorities may be given full access to our records of controlled substances administration.
15. It is understood that failure to adhere to these policies may result in cessation of therapy with controlled substance prescribing by this physician or referral for further specialty assessment.
16. Renewals are contingent on keeping scheduled appointments. Please do not phone for prescriptions after hours or on weekends.
17. It should be understood that any medical treatment is initially a trial, and that continued prescription is contingent on evidence of benefit.
18. The risks and potential benefits of these therapies are explained elsewhere [and you acknowledge that you have received such explanation].
19. You affirm that you have full right and power to sign and be bound by this agreement, and that you have read, understand, and accept all of its terms.

Physician Signature

Patient Signature

Date

Patient Name (Printed)

Approved by the AAPM Executive Committee on April 2, 2001.

AAPM
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 Glenview, IL 60025-1485
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 Web site <http://www.painmed.org>

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Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain

Appendix 8. Monitoring Tool – Pain Assessment and Documentation Tool (PADT)**A**

PROGRESS NOTE
Pain Assessment and Documentation Tool (PADT™)

Patient Stamp Here

Patient Name: _____ Record #: _____

Assessment Date: _____

Current Analgesic Regimen

Drug name	Strength (eg, mg)	Frequency	Maximum Total Daily Dose

The PADT is a clinician-directed interview; that is, the clinician asks the questions, and the clinician records the responses. The Analgesia, Activities of Daily Living, and Adverse Events sections may be completed by the physician, nurse practitioner, physician assistant, or nurse. The Potential Aberrant Drug-Related Behavior and Assessment sections must be completed by the physician. Ask the patient the questions below, except as noted.

Analgesia	
If zero indicates "no pain" and ten indicates "pain as bad as it can be," on a scale of 0 to 10, what is your level of pain for the following questions?	
1. What was your pain level on average during the past week? (Please circle the appropriate number)	
No Pain	0 1 2 3 4 5 6 7 8 9 10
Pain as bad as it can be	
2. What was your pain level at its worst during the past week?	
No Pain	0 1 2 3 4 5 6 7 8 9 10
Pain as bad as it can be	
3. What percentage of your pain has been relieved during the past week? (Write in a percentage between 0% and 100%) _____	
4. Is the amount of pain relief you are now obtaining from your current pain reliever(s) enough to make a real difference in your life?	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
5. Query to clinician: Is the patient's pain relief clinically significant?	
<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unsure	

Activities of Daily Living		
Please indicate whether the patient's functioning with the current pain reliever(s) is Better, the Same, or Worse since the patient's last assessment with the PADT.* (Please check the box for Better, Same, or Worse for each item below.)		
Better	Same	Worse
1. Physical functioning <input type="checkbox"/>		
2. Family relationships <input type="checkbox"/>		
3. Social relationships <input type="checkbox"/>		
4. Mood <input type="checkbox"/>		
5. Sleep patterns <input type="checkbox"/>		
6. Overall functioning <input type="checkbox"/>		
* If the patient is receiving his or her first PADT assessment, the clinician should compare the patient's functional status with other reports from the last office visit		

(Continued on reverse side)

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Appendix 8. Continued**B**

PROGRESS NOTE
Pain Assessment and Documentation Tool (PADT™)

Adverse Events					Potential Aberrant Drug-Related Behavior <small>This section must be completed by the physician.</small>																																												
						<i>Please check any of the following items that you discovered during your interactions with the patient. Please note that some of these are directly observable (eg, appears intoxicated), while others may require more active listening and/or probing. Use the "Assessment" section below to note additional details.</i>																																											
<p>1. Is patient experiencing any side effects from current pain reliever(s)? <input type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>Ask patient about potential side effects:</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 10%;">None</td> <td style="width: 10%;">Mild</td> <td style="width: 10%;">Moderate</td> <td style="width: 10%;">Severe</td> </tr> <tr> <td>a. Nausea</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>b. Vomiting</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>c. Constipation</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>d. Itching</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>e. Mental cloudiness</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>f. Sweating</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>g. Fatigue</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>h. Drowsiness</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>i. Other _____</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> <tr> <td>j. Other _____</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/></td> </tr> </table> <p>2. Patient's overall severity of side effects? <input type="checkbox"/> None <input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe</p>					None	Mild	Moderate	Severe	a. Nausea	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	b. Vomiting	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	c. Constipation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	d. Itching	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	e. Mental cloudiness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	f. Sweating	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	g. Fatigue	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	h. Drowsiness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	i. Other _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	j. Other _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> Purposeful over-sedation <input type="checkbox"/> Negative mood change <input type="checkbox"/> Appears intoxicated <input type="checkbox"/> Increasingly unkempt or impaired <input type="checkbox"/> Involvement in car or other accident <input type="checkbox"/> Requests frequent early renewals <input type="checkbox"/> Increased dose without authorization <input type="checkbox"/> Reports lost or stolen prescriptions <input type="checkbox"/> Attempts to obtain prescriptions from other doctors <input type="checkbox"/> Changes route of administration <input type="checkbox"/> Uses pain medication in response to situational stressor <input type="checkbox"/> Insists on certain medications by name <input type="checkbox"/> Contact with street drug culture <input type="checkbox"/> Abusing alcohol or illicit drugs <input type="checkbox"/> Hoarding (ie, stockpiling) of medication <input type="checkbox"/> Arrested by police <input type="checkbox"/> Victim of abuse Other: _____ _____
None	Mild	Moderate	Severe																																														
a. Nausea	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																																														
b. Vomiting	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																																														
c. Constipation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																																														
d. Itching	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																																														
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f. Sweating	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																																														
g. Fatigue	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																																														
h. Drowsiness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																																														
i. Other _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																																														
j. Other _____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																																														

Assessment: (This section must be completed by the physician.)

Is your overall impression that this patient is benefiting (eg, benefits, such as pain relief, outweigh side effects) from opioid therapy? Yes No Unsure

Comments: _____

Specific Analgesic Plan:

- | | |
|--|---|
| <input type="checkbox"/> Continue present regimen
<input type="checkbox"/> Adjust dose of present analgesic
<input type="checkbox"/> Switch analgesics
<input type="checkbox"/> Add/Adjust concomitant therapy
<input type="checkbox"/> Discontinue/taper off opioid therapy | Comments: _____

_____ |
|--|---|

Date: _____ Physician's signature: _____

Provided as a service to the medical community by Janssen Pharmaceutica Products, L.P. 

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Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain

Appendix 9. Monitoring Tool – Current Opioid Misuse Measure (COMM)**Current Opioid Misuse Measure (COMM)™**

The Current Opioid Misuse Measure (COMM)™ is a brief patient self-assessment to monitor chronic pain patients on opioid therapy. The COMM™ was developed with guidance from a group of pain and addiction experts and input from pain management clinicians in the field. Experts and providers identified six key issues to determine if patients already on long-term opioid treatment are exhibiting aberrant medication-related behaviors:

- *Signs & Symptoms of Intoxication*
- *Emotional Volatility*
- *Evidence of Poor Response to Medications*
- *Addiction*
- *Healthcare Use Patterns*
- *Problematic Medication Behavior*

The COMM™ will help clinicians identify whether a patient, currently on long-term opioid therapy, may be exhibiting aberrant behaviors associated with misuse of opioid medications. In contrast, the Screener and Opioid Assessment for Patients with Pain (SOAPP®) is intended to predict which patients, being considered for long-term opioid therapy, may exhibit aberrant medications behaviors in the future. Since the COMM™ examines concurrent misuse, it is ideal for helping clinicians monitor patients' aberrant medication-related behaviors over the course of treatment. The COMM™ is:

- A quick and easy to administer patient-self assessment
- 17 items
- Simple to score
- Completed in less than 10 minutes
- Validated with a group of approximately 500 chronic pain patients on opioid therapy
- Ideal for documenting decisions about the level of monitoring planned for a particular patient or justifying referrals to specialty pain clinic.
- The COMM™ is for clinician use only. The tool is not meant for commercial distribution.
- The COMM™ is **NOT** a lie detector. Patients determined to misrepresent themselves will still do so. Other clinical information should be used with COMM™ scores to decide if and when modifications to particular patient's treatment plan is needed.
- It is important to remember that all chronic pain patients deserve treatment of their pain. Providers who are not comfortable treating certain patients should refer those patients to a specialist.

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Appendix 9. Continued**COMM™**

Please answer each question as honestly as possible. Keep in mind that we are only asking about the **past 30 days**. There are no right or wrong answers. If you are unsure about how to answer the question, please give the best answer you can.

Please answer the questions using the following scale:	Never	Seldom	Sometimes	Often	Very Often
	0	1	2	3	4
1. In the past 30 days, how often have you had trouble with thinking clearly or had memory problems?	<input type="radio"/>				
2. In the past 30 days, how often do people complain that you are not completing necessary tasks? (i.e., doing things that need to be done, such as going to class, work or appointments)	<input type="radio"/>				
3. In the past 30 days, how often have you had to go to someone other than your prescribing physician to get sufficient pain relief from medications? (i.e., another doctor, the Emergency Room, friends, street sources)	<input type="radio"/>				
4. In the past 30 days, how often have you taken your medications differently from how they are prescribed?	<input type="radio"/>				
5. In the past 30 days, how often have you seriously thought about hurting yourself?	<input type="radio"/>				
6. In the past 30 days, how much of your time was spent thinking about opioid medications (having enough, taking them, dosing schedule, etc.)?	<input type="radio"/>				

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Appendix 9. Continued

Please answer the questions using the following scale:	Never	Seldom	Sometimes	Often	Very Often
	0	1	2	3	4
7. In the past 30 days, how often have you been in an argument?	<input type="radio"/>				
8. In the past 30 days, how often have you had trouble controlling your anger (e.g., road rage, screaming, etc.)?	<input type="radio"/>				
9. In the past 30 days, how often have you needed to take pain medications belonging to someone else?	<input type="radio"/>				
10. In the past 30 days, how often have you been worried about how you're handling your medications?	<input type="radio"/>				
11. In the past 30 days, how often have others been worried about how you're handling your medications?	<input type="radio"/>				
12. In the past 30 days, how often have you had to make an emergency phone call or show up at the clinic without an appointment?	<input type="radio"/>				
13. In the past 30 days, how often have you gotten angry with people?	<input type="radio"/>				
14. In the past 30 days, how often have you had to take more of your medication than prescribed?	<input type="radio"/>				
15. In the past 30 days, how often have you borrowed pain medication from someone else?	<input type="radio"/>				
16. In the past 30 days, how often have you used your pain medicine for symptoms other than for pain (e.g., to help you sleep, improve your mood, or relieve stress)?	<input type="radio"/>				

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Appendix 9. Continued

Please answer the questions using the following scale:	Never	Seldom	Sometimes	Often	Very Often
	0	1	2	3	4
17. In the past 30 days, how often have you had to visit the Emergency Room?	<input type="radio"/>				

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Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain

Appendix 9. Continued**Scoring Instructions for the COMM™**

To score the COMM™, simply add the rating of all the questions. A score of 9 or higher is considered a positive.

Sum of Questions	COMM Indication
> or = 9	+
< 9	-

As for any scale, the results depend on what cutoff score is chosen. A score that is sensitive in detecting patients who are abusing or misusing their opioid medication will necessarily include a number of patients that are not really abusing or misusing their medication. The COMM™ was intended to over-identify misuse, rather than to mislabel someone as responsible when they are not. This is why a low cut-off score was accepted. We believe that it is more important to identify patients who have only a possibility of misusing their medications than to fail to identify those who are actually abusing their medication. Thus, it is possible that the COMM™ will result in false positives – patients identified as misusing their medication when they were not.

The table below presents several statistics that describe how effective the COMM™ is at different cutoff values. These values suggest that the COMM™ is a sensitive test. This confirms that the COMM™ is better at identifying who is misusing their medication than identifying who is not misusing. Clinically, a score of 9 or higher will identify 77% of those who actually turn out to be at high risk. The Negative Predictive Values for a cutoff score of 9 is .95, which means that most people who have a negative COMM™ are likely not misusing their medication. Finally, the Positive likelihood ratio suggests that a positive COMM™ score (at a cutoff of 9) is over 2 times (2.26 times) as likely to come from someone who is actually misusing their medication (note that, of these statistics, the likelihood ratio is least affected by prevalence rates). All this implies that by using a cutoff score of 9 will ensure that the provider is least likely to miss someone who is really misusing their prescription opioids. However, one should remember that a low COMM™ score suggests the patient is really at low-risk, while a high COMM™ score will contain a larger percentage of false positives (about 34%), while at the same time retaining a large percentage of true positives. This could be improved, so that a positive score has a lower false positive rate, but only at the risk of missing more of those who actually do show aberrant behavior.

COMM™ Cutoff Score	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio	Negative Likelihood Ratio
Score 9 or above	.77	.66	.66	.95	2.26	.35

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EXHIBIT 36

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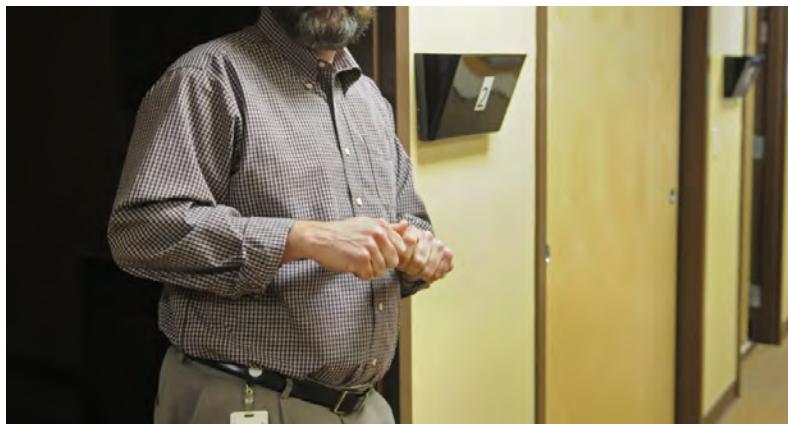
Even amid crisis, opioid makers plied doctors with perks

The practice raises ethical questions, and even fellow doctors frown upon Maine's top 2015 beneficiary, a Manchester physician who not only prescribes painkillers but also treats addiction.

BY [JOE LAWLER](#) STAFF WRITER

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Dr. Douglas Jorgensen of Manchester received \$42,522 in pharmaceutical industry payments from August 2013 through December 2015. *Andy Molloy/Kennebec Journal*

While the opioid crisis deepened in Maine over the past three years, drug companies selling opioids increasingly showed up on the doorsteps of physicians' offices – offering free food and beverages, consulting or speaking fees, discount coupons for drugs and other freebies. The total payments to doctors related to opioids doubled from 2014 to 2015.

The increased payments, documented in recently released federal data, occurred while the opioid crisis accelerated, and overdose deaths from prescription opioids and related illicit drugs such as heroin soared to record rates.



One physician –
Dr. Doug
Jorgensen of
Manchester –
stands out for both
prescribing
opioids for pain

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He is facing criticism from other doctors for accepting thousands of dollars from drug companies because of the conflicts that creates with prescribing medicine.

Jorgensen received 60 percent of all pharmaceutical company payments to doctors in Maine related to opioids, or \$42,522 from August 2013 through December 2015, the period for which data are available. He was paid \$28,519 in 2015 alone.

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[Explore payments from opioid manufacturers to Maine doctors, Aug. 2013 to Dec. 2015](#)

Overall, opioid industry spending on Maine doctors increased from \$21,654 in 2014 to \$42,550 in 2015. The data reporting requirement went into effect in August 2013, and for the August-through-December period of that year, payments from opiate manufacturers to Maine doctors totaled \$6,298.

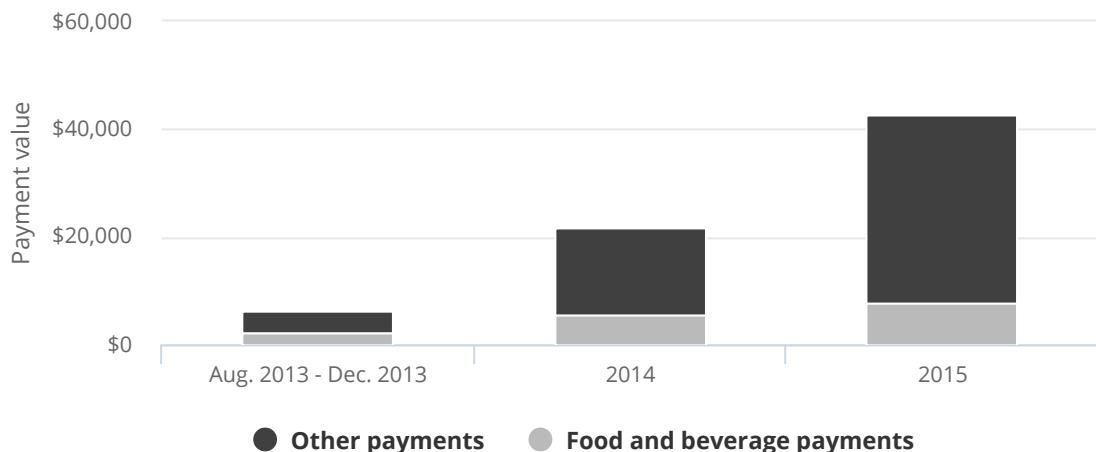
These numbers pale in comparison to the total payments to Maine doctors by all drug companies and manufacturers of medical devices. For 2013-2015, that grand total was \$11.9 million, ranking Maine behind 42 other states and the District of Columbia.

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But while the amount spent by opioid drug makers represents a fraction of total payments to doctors, the impact of opioid abuse has staggered the nation, emerging as one of the country's – and Maine's – major public health threats. And research shows even small amounts of money can have large effects on doctors' prescribing practices, experts say.

In Maine, the number of visits to doctors by pharmaceutical sales representatives for opioids like OxyContin, Subsys, Butrans and Hysingla ER has increased – from 440 visits to 125 doctors in 2014 to 569 visits to 117 doctors in 2015.

Payments from opioid manufacturers to Maine doctors, 2013-2015



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passing laws and trying to persuade doctors to minimize opioid prescribing in an attempt to alleviate the public health epidemic of addiction. Fueled by the opioid crisis, overdose deaths from heroin and other opioids jumped from 176 in 2013 to 272 in 2015 to 286 through the first nine months of this year.

Jorgensen is a physician at New England Sport and Spine in Manchester, which advertises pain relief for a number of maladies. At the same location, he's a doctor at the Maine Recovery Center to treat drug addiction. He's treating patients at the recovery center who may have become addicted to opioids he prescribed to them at the pain clinic.

In the spring, Jorgensen spoke out against what was then a proposed law that would make Maine one of the strictest states in the nation for prescribing opioids. The law passed.

Two other Maine physicians – Dr. Stephen Hull of Mercy Hospital in Portland and Dr. Noah Nesin of Penobscot Community Health Center in Bangor – question Jorgensen's ethical decisions in accepting the money.

They say for Jorgensen to take thousands of dollars in drug company money at the same time he was prescribing opioids is a dubious practice and an inherent conflict.

“There’s no way to reconcile the acceptance of

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important role a physician has, to advocate for their patients' best interests."

'PROFESSIONALLY IRRESPONSIBLE'

Nesin said doctors should never have a financial interest in prescribing a certain drug.

In one event recorded in the database and labeled as either a speaking fee or other promotional service, Jorgensen received \$7,220 on Nov. 21, 2015, from Purdue Pharma related to Hysingla, an extended-release opioid used to control severe pain, as well as opioids Butrans and OxyContin. The payment was categorized as a speaking, training and education engagement.

There were 10 additional payments of more than \$1,000 each to Jorgensen for opioids and 49 overall interactions or visits between Jorgensen and opioid pharmaceutical companies, according to the database, which is compiled by the U.S. Centers for Medicare and Medicaid Services. The data can be searched at openpaymentsdata.cms.gov. ProPublica, an independent, nonprofit journalism website, sorts and analyzes the federal data and offers its own search tool at ProPublica.org.

Hull said Jorgensen – who obtained a medical license in Maine in 1997 – is setting a bad example for other physicians.

"It's unfortunate to see doctors who are

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“Jorgensen raises questions about conflict of interest.”

It's rare for doctors to openly question the judgments other physicians make in practicing medicine, especially in the same state. The Maine Medical Association, which represents physicians, discourages such payments to doctors, although they are legal.

“This is pretty vexing,” said Dr. Eric Campbell, a medical ethics expert at Harvard Medical School, speaking broadly about the practice. “To be accepting payments for opioids in the face of the opioid epidemic in many ways can be viewed as professionally irresponsible.”

Jorgensen did not respond to multiple requests for comment from the Maine Sunday Telegram, including phone calls and emails.

In April, he wrote an op-ed for the Portland Press Herald opposing a strict new opioid prescribing law. Jorgensen's efforts failed, as the law was approved and doctors will now have to reduce opioid dosages for some patients and cap the length of prescriptions. They are also required to report opioid prescriptions to the state's Prescription Monitoring Program as a way to prevent “doctor shopping.”

Nesin questioned whether Jorgensen's attempts to defeat the bill were influenced by the payments he was receiving from the drug companies, which

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Jorgensen's lobbying efforts. "He's representing the interests of the people who are paying him money."

But one Maine doctor who accepted drug company money for opioids defended the practice.

EFFECTIVENESS OF EVEN MODEST GIFTS

Dr. Ganelia Guernelli, a Brunswick pain specialist for Mid Coast Hospital, was paid \$13,863 from August 2013 through December 2015, including \$6,667 in 2015. His total payments were second only to Jorgensen's.

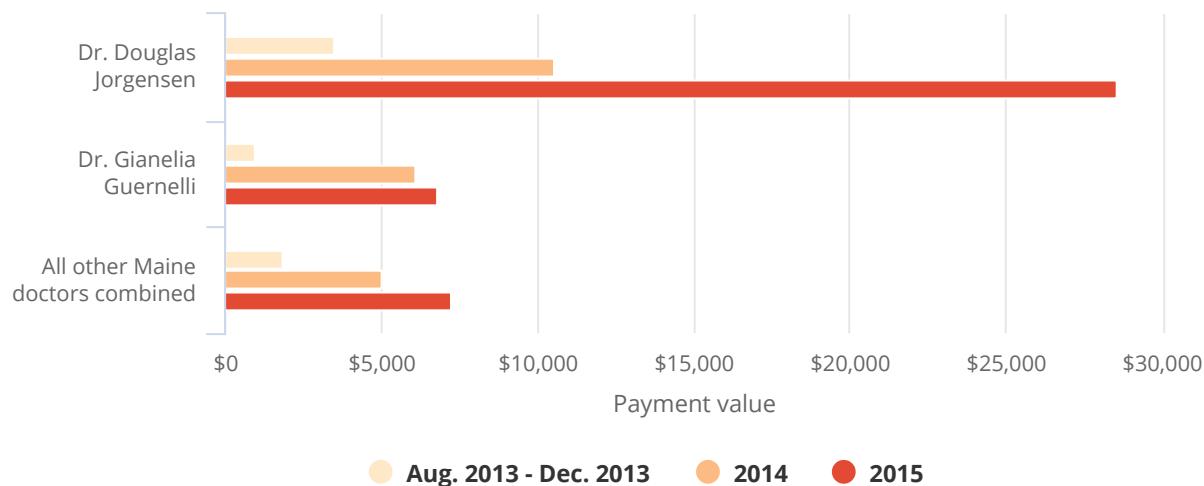
Guernelli, in an interview with the Telegram, said two large payments he received in 2015 – \$3,960 for consulting and \$2,475 for training – were justified. The payments were from Purdue Pharma, for training at the pharmaceutical giant's headquarters in Connecticut and for marketing purposes with other physicians about Hysingla Extended Release, an abuse-deterrant opioid that prevents patients from abusing the pills by crushing them and snorting the powder.

"They paid me for my training at Purdue Pharma and so I could do marketing talks for other doctors," Guernelli said, explaining the marketing talks were to promote Hysingla. He said that in general, the drug company training helps him

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SOURCE: [Centers for Medicare & Medicaid Services](#) | CHART:
Christian MilNeil

Guernelli said he sees nothing wrong with accepting money from pharmaceutical companies as long as it serves a useful purpose, and he said it does not affect how he prescribes medication.

“I do not see a direct correlation,” Guernelli said.

But Campbell, the Harvard Medical School professor who has studied industry payments to doctors, said studies point to a correlation between doctors accepting money and the types of drugs they prescribe.

“It’s a form of self-delusion if they believe they’re not being affected,” Campbell said. “The drug companies do this because it works. It’s a way to pay doctors for prescribing.”

Campbell said it’s not so much the dollar amount that influences doctors – even small gifts or free food can change the way doctors prescribe

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difference, but they do. The small dollar value of the gifts makes it insidious. Because the gifts are modest, the doctors' guards are down and they may not realize they are being influenced, he said.

“At the most basic level, it’s unreasonable to believe the drug companies are throwing their money away,” Campbell said.

Top 10 doctors with the most “food and beverage” payments from opioid manufacturers, Aug. 2013 – Dec. 2015:



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Saba,
Lewiston 28 payments worth \$457.67

Dr. Gianelia
Guernelli,
Lewiston 27 payments worth \$308.02

CHART: Christian MilNeil | SOURCE: Centers for Medicare & Medicaid Services

For all drugs and medical devices across the United States, drug companies spent \$6.2 billion on 810,000 doctors, according to the federal data.

Nesin and Hull are part of a contingent of doctors trying to reduce the frequency with which Maine doctors prescribe opioids for pain – especially chronic pain – but their efforts are hindered by the one-on-one conversations between pharmaceutical reps and physicians. They are joined by the Maine Medical Association, which supported the new law and is trying to persuade doctors to prescribe fewer opioids, especially for chronic pain. There is no proof that opioids are effective in treating chronic pain, according to the U.S. Centers for Disease Control and Prevention. They do work in treating acute pain, such as immediately after surgery.

'DANGER IN THE STATUS QUO'

Gordon Smith, executive vice president of the Maine Medical Association, is criss-crossing the state touting the benefits of complying with the law and reducing or eliminating opioid prescribing, especially for chronic pain.

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Hull said there's no doubt that the salespeople are exaggerating the benefits of opioids while downplaying the risks.

People are much more likely to become addicted to opioids and die of a drug overdose if they are prescribed opioids, according to the CDC.

"There is danger in the status quo. The status quo is killing people," said Dr. Elisabeth Fowlie Mock, a Holden doctor who is also working to reduce Maine doctors' reliance on opioid prescribing.

Campbell said a financial incentive is likely a reason why the pharmaceutical reps were showing up in Maine in 2015 in much greater numbers than in 2013.

In 2015, Maine passed a law that required insurance companies to reimburse for abuse-deterrent drugs the same way that they reimburse for opioids that do not have abuse-deterrent formulations.

The abuse-deterrent drugs cost far more than regular opioids and produce more income for manufacturers.

When the law changed, the profit motive appeared, and so did the pharmaceutical reps touting abuse-deterrent opioids in Maine, Campbell said.

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Hysingla, for instance, is an abuse-deterrent opioid, and Jorgensen and Guernelli were paid thousands of dollars related to Hysingla.

The opioids – whether they are abuse-deterrent or not – still contain the same addictive properties. The difference is they can't be abused in ways other than taking them orally.

The data are collected by the U.S. Centers for Medicare and Medicaid Services and easily searched on the ProPublica.org website, but there's no way to track payments over a long period because the data have only been collected and made public since 2013, as one of the requirements of the Affordable Care Act.

Campbell said several studies show a clear correlation between doctors' willingness to prescribe certain drugs and receiving free food or other gifts from drug companies.

Campbell said he doesn't fault the drug companies, who are "merely doing what is in their best interest, to sell drugs," but he blames the medical profession for failing to have strong policies in place to stop the practice.

"The blame lies entirely with the medical profession," Campbell said.

Nesin said there is no value in the free food, speaking or consulting fees offered to doctors,

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research.

For instance, he said the “clinical trials” might show up in a marketing brochure – similar to “nine out of 10 dentists recommend a brand of toothpaste” – or never be used at all. It’s all an excuse to pay doctors to prescribe.

Nesin said even meeting with the sales reps to talk about the drug doesn’t have any value because better, independent information on when and how to prescribe is available online.

“There’s no reasonable excuse to have them in your practice at all,” Nesin said. “There is no value to it. The only reason to have them there is because you like what they’re giving to you.”

Fowlie Mock, the Holden doctor working to reduce opioid prescribing, runs a \$150,000-per-year state program that offers doctors neutral, academically based research on common prescribing topics. She said some doctors have naively been thinking that the sales techniques don’t work on them and don’t realize the extent to which they are being sold or marketed to.

“What makes a successful salesperson? You don’t learn that in medical school,” Fowlie Mock said.

She noted that the program she runs providing research and training on prescribing practices is now focusing on opioids.

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Many of the contacts between Maine doctors and drug companies are simply pharmaceutical sales representatives dropping off food and beverages – pastries, muffins, doughnuts or lunch.

Such hospitality may not seem egregious – how could two dozen pastries influence a doctor who earns a comfortable upper middle-class or better lifestyle? But the free lunches have a subtle way of psychologically influencing prescribing practices, experts say.

“There’s no such thing as a free lunch. It might not cost you any money, but it comes with strings attached,” Fowlie Mock said.

Fowlie Mock said the free food is pleasurable and opens the doctors up to conversations with the salespeople.

Nesin said he’s managed different practices over the past 10 years, and every time he switches jobs, he bans pharmaceutical reps from even entering the door. Nesin said there’s always some pushback from fellow doctors and employees, and he has to explain why it’s a bad idea to let them drop off the doughnuts.

“One doctor, when I refuted every last reason he gave me for allowing pharmaceutical reps in the practice, admitted to me that the real reason was he liked the sandwiches that they give you. I told

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doctors who receive free food and beverages from pharmaceutical companies are more likely to prescribe drugs from those companies than the generic equivalents, which are just as effective and less costly.

Nesin said something happens to the brain when you can get something for free, even if it's not of great value and even if you earn a comfortable living.

Nesin said he remembers attending a conference several years ago and he checked out a vendor room and watched as doctors would go to every table and get a card punched so they would qualify for a free Blu-ray player.

“You would see these highly compensated physicians scurrying around like lab rats for a free Blu-ray player that they could easily afford back home. It’s ludicrous,” Nesin said.

Hull said about 10 years ago, pharmaceutical reps were permitted to show up at the Mercy Pain Clinic he operates, and often they would drop off muffins or pastries. As time went on, he became uncomfortable even with accepting food or discount coupons for drugs, so he banned the practice.

“What they do influences you in very subtle ways,” Hull said.

Hull said at the time he was prescribing opioids

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says there is insufficient evidence that opioids help with chronic pain, and Hull said based on his extensive research and experiences helping patients with chronic pain, opioids are not useful for such pain.

STRICTER LAWS MAY BE NEEDED

Guernelli, the No. 2 recipient of drug company money for opioids in Maine, however, said that even though the evidence does not prove opioids are effective for chronic pain, doctors such as himself still prescribe opioids. He said the “science is evolving.”

“In the pain world, there is still a role for opioids to control chronic pain, as long as it’s done in a cautious and reasonable way,” said Guernelli, noting that the severity of chronic pain can vary widely depending on the condition of the patient.

Hull said opioids should be prescribed as little as possible because of their inherent risks, but that’s not what he heard from pharmaceutical reps, who would tout the drugs as effective in a number of pain control strategies.

Hull said pharmaceutical representatives do not give “unbiased, evidence-based information” and would never say that opioids are not effective for chronic pain. He said as a more frequent prescriber of opioids several years ago, he was targeted by the drug companies and offered all-expense-paid junkets, but he always refused.

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“... your professional advice,” Hull said. “I considered it to be a very thinly veiled strategy to convince me to prescribe their drugs.”

Campbell said ideally the solution would come from within the medical community, but stricter laws regulating drug companies at doctors’ offices may be needed.

“The medical field has not proven to be willing or able to self-regulate on this issue,” Campbell said.

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The speakers' bureau system: a form of peer selling

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Abstract

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Abstract

In the speakers' bureau system, physicians are recruited and trained by pharmaceutical, biotechnology, and medical device companies to deliver information about products to other physicians, in exchange for a fee. Using publicly available disclosures, we assessed the thesis that speakers' bureau involvement is not a feature of academic medicine in Canada, by estimating the prevalence of participation in speakers' bureaus among Canadian faculty in one medical specialty, cardiology. We analyzed the relevant features of an actual contract made public by the physician addressee and applied the Canadian Medical Association (CMA) guidelines on physician–industry relations to participation in a speakers' bureau. We argue that speakers' bureau participation constitutes a form of peer selling that should be understood to contravene the prohibition on product endorsement in the CMA Code of Ethics. Academic medical institutions, in conjunction with regulatory colleges, should continue and strengthen their policies to address participation in speakers' bureaus.

Physicians need to stay abreast of information about emerging drugs and devices, but the time pressures of clinical practice may limit their ability to do so independently. The companies that manufacture and sell these products have the resources and the motivation to “educate” physicians but cannot be expected to distinguish their marketing goals from physicians’ educational needs. Physicians’ professional associations and regulatory bodies, as well as medical journal publishers and editors, drug and device regulatory agencies, and academic medical institutions, have long debated their respective roles and responsibilities in ensuring the safety, efficacy, and probity of prescribing in light of these pressures and interests.¹

One current context of this long-standing struggle is the “speakers’ bureau” system, in which pharmaceutical, biotechnology, and medical device companies recruit and train physicians to deliver information about products to other physicians, in exchange for a fee or other considerations, such as professional development opportunities.² Participants in the system argue that physicians are best

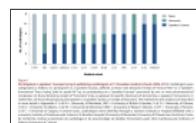
situated to deliver accurate information about new drugs and devices to other physicians and that industry is best placed to fund such communication. Critics reply that the speakers' bureau system raises significant concerns about ethics and professionalism and that it is part of a complex system of drug promotion^{3,4} and relationship-building with physicians⁵⁻⁷ that contributes to irrational prescribing,⁸ inflated health care costs,² and even harm to patients or society more generally. Some steps have been taken toward limiting participation in speakers' bureaus. The American Association of Medical Colleges (AAMC), in a report endorsed by the Association of Faculties of Medicine of Canada (AFMC),⁹ has stated that faculty participation in speakers' bureaus should be strongly discouraged and that faculty, residents, and students should be prohibited from attending such events.¹⁰ Furthermore, in the United States, lawsuit settlements and health care reform (i.e., the Physician Payment Sunshine Act, passed as a part of the Patient Protection and Affordable Care Act¹¹) are bringing some transparency to speakers' bureau arrangements.^{12,13}

Prevalence of participation in speakers' bureaus

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Industry seeks the aid of academic physicians to communicate its message to other physicians because these opinion leaders influence the prescribing behaviour of their peers.¹⁴ In a 2003–2004 survey of US physicians, 16% of respondents reported receiving payment for participation in speakers' bureaus.¹⁵ Cardiologists were more than twice as likely as family practitioners, and significantly more likely than certain other specialty physicians, to receive payments, including both speakers' bureau fees and other honoraria. In a 2007 survey of life sciences departments in the 50 US universities receiving the highest levels of funding from the National Institutes of Health, 23.8% of respondents reported being a “paid speaker” for industry, which ranked behind “consultant” (about 32%) as the second most common type of relationship with industry.¹⁶ These paid speakers were more likely to be from clinical departments, to be at the rank of full professor, and to produce more publications than those who were not paid speakers, which suggests that those participating in the speakers' bureau system are well positioned to influence others.

We are aware of no similar survey data for Canada, although a recent study suggested that financial conflicts of interest arising from relationships with industry are more common among authors of clinical practice guidelines in Canada than in the United States.¹⁷ For Canada, we found that 1 or more of the top 5 publishing cardiologists at each of 12 out of 13 Canadian medical schools had disclosed receipt of “lecture fees” or a “speaker's honorarium,” had been “paid to speak for,” and/or had participated on a speakers' bureau on one or more occasions (median 2 out of 5 faculty members) (see [Figure 1](#) and [Appendix A](#) for details).



[Figure 1](#)

Participation in speakers' bureaus by top 5 publishing cardiologists at 13 Canadian medical schools, 2006–2012.

Ethical and professional considerations

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Participation in a speakers' bureau involves 4 essential elements pertaining to control over the content to be delivered by the speaker and to the consideration upon which the agreement is contingent ([Box 1](#)). According to the conventions of contract law, the elements of any agreement may be explicit or implicit, but both parties must receive consideration in order for the contract to be binding.

[Box 1](#)

Profile of participation in speakers' bureaus: 4 essential elements

Box 1 Profile of participation in speakers' bureaus: 4 essential elements	
Content	<ul style="list-style-type: none"> ▪ Source of materials (i.e., company or speaker) ▪ Control of materials (i.e., ability to revise)
Consideration	<ul style="list-style-type: none"> ▪ Benefit to speaker (e.g., honorarium) ▪ Benefit to company (e.g., increased sales)

As an example, a Schering-Plough speakers' bureau agreement made public by Dr. Daniel Carlat¹⁸ followed this contract law convention, with both explicit and implicit terms and consideration going to each party (see [Box 1](#) and [Table 1](#)). With respect to content, the contract explicitly specified that the company would provide mandatory training and would supply educational materials to which the physician had to adhere: the intellectual content of the presentation was therefore almost entirely in the hands of the company. With regard to consideration, only the speaker's fee was explicit in the contract, but whether the physician would continue to serve on the speakers' bureau was entirely at the company's discretion. The implied term of the agreement was, therefore, that the speaker's performances must be in keeping with the company's interests and objectives—presumably, reputation, image, and, ultimately, sales. Indeed, industry “reps” often attend speakers' bureau events to build relationships with attending physicians, and industry tracks prescriptions of the product by attendees before and after the event.^{2,5,19}

Table 1	
	Key provisions of proposed agreement between Schering-Plough and Daniel J. Carlat regarding Saphris* speakers' bureau

In its Code of Ethics,²⁰ the Canadian Medical Association (CMA) has continuously prohibited product endorsements by physicians.²¹ In the United States, by contrast, physician product endorsement—apart from in-office sales with direct returns—is not addressed by the American Medical Association's Code of Medical Ethics.²² Historically, Canadian physicians have been disciplined in the courts for the endorsement of products to the public.^{23,24} In 2007, however, the CMA adopted a policy entitled “Guidelines for Physicians in Interactions with Industry,”²⁵ which states unequivocally that the prohibition on product endorsement extends beyond communication by physicians to the public to include communication among physicians:

Peer selling occurs when a pharmaceutical or medical device manufacturer or service provider engages a physician to conduct a seminar or similar event that focuses on its own products and is designed to enhance the sale of those products. This also applies to third party contracting on behalf of industry. This form of participation would reasonably be seen as being in contravention of the CMA's Code of Ethics, which prohibits endorsement of a specific product.

Speakers' bureau activities fall squarely within this definition of peer selling and hence product endorsement. Determining whether an event is designed to enhance sales involves considering both the explicit and the implicit terms of the contract. Attendance of company representatives at speakers' bureau events and the monitoring of sales^{2,5,19} after presentations make enhanced sales an implied term of the arrangement. Any participation by the same physician in events designed to enhance the sale of competitors' products is irrelevant to the question of whether a given act constitutes marketing. By the same token, becoming a member of multiple speakers' bureaus does not confer greater objectivity upon a physician's participation.²

Participation in a speakers' bureau is within the ambit of peer selling and should be the target of regulatory attention. The CMA's prohibition on product endorsement by physicians is not enough. In

the United States, where physicians are permitted to act as marketers, there is considerable movement toward regulatory oversight. Regulatory response to the practice remains weak in Canada.

Challenges to enforcement

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The Canadian medical profession, its regulatory colleges, continuing medical education (CME) accreditation bodies, and academic medical centres all have critical roles to play in bringing an end to peer selling, but thus far, each has struggled to do so.

Although provincial regulatory colleges are well placed to regulate speakers' bureau participation by adopting the CMA's 2007 guidelines on physician–industry relations,²⁵ uptake among colleges varies (see [Table 2](#)), and we found no record of any enforcement in published disciplinary proceedings. This is not surprising, given that college discipline is largely driven by complaints from the public, and speakers' bureau activities, taking place within the profession, are unlikely to come to the public's attention. Furthermore, physicians are generally reluctant to report their colleagues,^{33,34} and this may be particularly true when it comes to reporting prevalent and lucrative activities of influential members of the profession.

Update 2 Update of Canadian Medical Association (CMA) guidelines on physician liability indemnity – by physicians' regulatory bodies	
Physician College	Indemnity rate guidelines*
British Columbia**	Indemnity adopted
Alberta/Calgary***	Indemnity offloaded
Manitoba****/Manitoba	Revised premium-referenced independent adjustment, distinction between CIMA and non-CIMA
Saskatchewan, Nunavut, Newfoundland and Labrador, Prince Edward Island	Non-CIMA guidelines or policy available online.
Quebec*****	Rate guidelines of Canadian Medical Protective Association for liability and medical research. Health Insurance Act principles apply to all CIMA guidelines

Table 2

Uptake of Canadian Medical Association (CMA) guidelines on physician–industry relations by physicians’ regulatory colleges

Bodies that accredit and, in some cases, develop CME in Canada also have a role to play in addressing speakers' bureau participation. Such bodies consist of CME committees of national specialty societies, CME offices of faculties of medicine, and maintenance-of-certification programs of the Royal College of Physicians and Surgeons of Canada and the College of Family Physicians of Canada. We reviewed the posted policies and statements of the AFMC's Committee on Accreditation of Continuing Medical Education and Standing Committee on Continuing Professional Development (representing CME offices of faculties of medicine), the Royal College, the College of Family Physicians of Canada, and the Conseil de l'éducation médicale continue du Québec for their adoption of the CMA guidelines (see [Table 3](#)). We found that the CMA guidelines are widely endorsed. Furthermore, the Standing Committee on Continuing Professional Development has endorsed the AAMC recommendation that faculties of medicine should discourage speakers' bureau participation among their faculty.^{[36](#)}

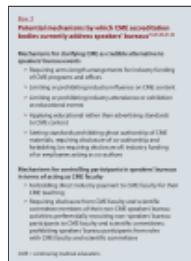
Table 2 Individual and household characteristics of the population by physical activity intensity – Australia 2006	
Characteristic	Description of characteristic
Demographic characteristics	Information on age, sex, marital status, education, income and family size.
Household characteristics	Information on household structure, number of children, employment status, industry of employer, and industry of household reference person.
Health and well-being	Information on self-assessed health, smoking, alcohol consumption, and chronic conditions.
Physical activity	Information on self-reported physical activity.
Household assets	Information on ownership of household assets.
Household income	Information on household income.
Household expenditure	Information on household expenditure.
Employment	Information on employment status.
Industry	Information on industry of employer.
Industry of household reference person	Information on industry of household reference person.
Chronic conditions	Information on self-assessed health.
Smoking	Information on smoking status.
Alcohol consumption	Information on alcohol consumption.
Self-assessed health	Information on self-assessed health.
Chronic conditions	Information on self-assessed health.
Employment	Information on employment status.
Industry	Information on industry of employer.
Industry of household reference person	Information on industry of household reference person.
Chronic conditions	Information on self-assessed health.
Smoking	Information on smoking status.
Alcohol consumption	Information on alcohol consumption.
Self-assessed health	Information on self-assessed health.

Table 3

Uptake of Canadian Medication Association (CMA) guidelines on physician–industry relations by selected CME accreditation bodies

Naturally, CME bodies cannot directly prohibit or limit speakers' bureau activities: given prohibitions on direct payment from industry to faculty in accredited CME, speakers' bureau activities fall, by definition, outside of accredited CME. However, CME accrediting bodies may prohibit or control speakers' bureau participants acting as faculty in CME, and these bodies do play an essential role in defining and maintaining the distinction between marketing and education that speakers' bureau activities blur. [Box 2](#) lists the approaches that CME bodies can take to achieve these goals, derived from guidelines of the CMA,²⁵ the US Accreditation Council for Continuing Medical Education,⁴¹ the Standing Committee on Continuing Professional Development of the AFMC,³⁶ and the AAMC.^{10,42} Assessing the extent to which Canadian CME bodies have availed themselves of all these mechanisms

is beyond the scope of this paper. However, we raise questions about two aspects of the approaches of Canadian CME bodies that pertain to the fundamental distinction between marketing and education.



Box 2

Potential mechanisms by which CME accreditation bodies currently address speakers' bureaus

The CMA guidelines prohibit industry membership on CME scientific planning committees; in the United States, the Accreditation Council for Continuing Medical Education more broadly prohibits any industry influence on content, whether direct or indirect.⁴³ In contrast, the Conseil de l'éducation médicale continue du Québec, in partnership with industry, has crafted its own code of ethics for CME.³² This document contains standards that were later embodied in the 2010 Code of Ethical Practices of Canada's Research-Based Pharmaceutical Companies (Rx&D),⁴⁴ the trade organization representing research-based pharmaceutical companies in Canada. Both documents explicitly assert the quid pro quo of industry funding for control of content as a principle of ethical partnership (on page 7 in the joint code³² and in section 4A 3.1 in the 2010 version of the Rx&D document⁴⁴). The Conseil de l'éducation médicale continue du Québec thus appears to maintain a standard requiring industry involvement, one that Rx&D itself abandoned in its 2012 code.³⁸ The Royal College of Physicians and Surgeons of Canada, by referencing the code authored by the Conseil de l'éducation médicale continue du Québec and Rx&D (see [Table 3](#)), appears to endorse this approach. By contrast, the College of Family Physicians of Canada cites the Rx&D code but gives the CMA guidelines priority, whereas the Committee on Accreditation of Continuing Medical Education and the Standing Committee on Continuing Professional Development of the AFMC indicate that the CMA guidelines should represent the minimum acceptable standard. Whether Canadian CME accrediting bodies tolerate "direct or indirect" influence in the form of a CME scientific planning committee seeking input or approval from industry appears to be an open question, or even a requirement in CME in Quebec, which raises significant questions about the independence of accredited CME.

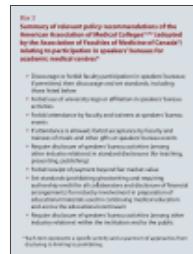
Furthermore, CME regulation and guidelines typically rely on several markers for distinguishing scientific and educational activities from marketing. For example, in both the United States and Canada, guidelines may refer to "satellite symposia" as well-known venues for industry-funded activities that resemble but must be distinguished from concurrent independent scientific meetings. A marker relevant to speakers' bureaus used in the United States is the Food and Drug Administration (FDA) restriction on marketing for off-label indications. As a matter of law, the FDA and Health Canada do not regulate the practice of medicine or the free speech of educators and scientists; rather, they regulate the sale of medical products. Thus, the presence of a responsibility to adhere to FDA-approved indications is one clear signal that a presenter is acting as a marketer rather than an educator under US policy.^{2,10} The 2012 Rx&D code,³⁸ however, states that materials that Rx&D member companies create or assist in creating for faculty who intend to use the materials in accredited CME must conform to the requirements set by the Pharmaceutical Advertising Advisory Board and the Advertising Standards Council—entities established to regulate advertising, not educational and scientific activities. CME bodies that adopt the Rx&D code³⁸ alongside the CMA guidelines²⁵ effectively adopt this same restriction. Prohibiting marketing materials in CME from violating marketing laws is very different from prohibiting marketing materials from being presented in CME at all. Ironically, then, through adoption of the Rx&D guidelines alongside the CMA guidelines, Canadian

physicians may come to see adopting marketing restrictions on materials they present as their ethical responsibility as educators, rather than a sign that they have taken on the role of marketers.

Clarity around communication about off-label uses is particularly important in the context of speakers' bureaus, as industry may employ physicians as speakers precisely to skirt (in a limited and perhaps legally defensible fashion) regulators' prohibitions related to promoting off-label uses of products. In the Schering-Plough contract,¹⁸ for example, a signatory would agree not to present off-label uses in industry-prepared materials, but would enjoy permission to discuss off-label uses based on clinical experience, after or in addition to the formal presentation, and this is more than company sales representatives may do.^{2-4,45} Again, a signatory to a speakers' bureau agreement may mistakenly understand standards for ethical marketing (an indication that the physician is now engaged in marketing) as standards for ethical education.

CME accreditors, following the example of the AAMC, should abandon misguided attempts to partner with industry in defining ethical standards for continuing education. CME accreditors are uniquely responsible for setting clear and credible standards that distinguish education from marketing. Given their leadership role within academic medical centres, Canadian CME accreditors should also take steps to prohibit or discourage speakers' bureau participants from acting as faculty in accredited CME, or to control any such activity.

Academic medical centres are well placed to take action on participation in speakers' bureaus, as most speakers are academics,¹³ and Canadian centres have formal ethical standards that apply in all teaching, whether in accredited CME or non-accredited events. The AFMC has endorsed the AAMC's Industry Funding of Medical Education report,⁹ which recommends that faculties forbid (or, if they do not forbid, then discourage and regulate) physicians' involvement in speakers' bureaus (see [Box 3](#) for key recommendations). An unpublished national analysis indicates, however, that Canadian faculties have been weak in implementing this particular AAMC recommendation (Joel Lexchin, Professor, School of Health Policy and Management, York University, personal communication by email, November 2012).



Box 3

Summary of relevant policy recommendations of the American Association of Medical Colleges (adopted by the Association of Faculties of Medicine of Canada) relating to participation in speakers' bureaus for academic medical centres

Although interactions between trainees and company representatives have been documented,⁴⁶⁻⁵³ the effects of trainees' interactions with faculty acting as marketers for companies is less well characterized. It is plausible that invitations to speakers' bureau events extended to residents and trainees by prominent faculty who participate in these events may be particularly flattering and thus even more influential than they would be for physicians already in practice. Faculty who are involved in speakers' bureaus may draw from their speakers' bureau materials for teaching at all levels, thus influencing a wider audience of trainees. Future generations of physicians may fail to identify and critically appraise materials prepared by or in collaboration with industry marketing departments when these are presented in an educational context.

Conclusion

Go to:

When the content of a physician's presentation to any audience of physicians or other health care providers does not rest exclusively in the hands of the speaker and she or he understands—whether

through an explicit term of a contract or an implied agreement—that the goal of the presentation is to increase uptake of a particular health care product, the physician is violating the CMA's guideline against peer selling and the prohibition on product endorsement in the CMA's Code of Ethics.

Although physician participation in promotional activities within the profession appears to be common, at least in some specialties, there is no record of disciplinary action in relation to this practice, even in provinces where regulatory colleges have adopted the CMA's prohibition on peer selling. Academic medical centres in Canada, unlike those in the United States, may rely on the strong guidance of the CMA Code of Ethics prohibition on product endorsement in crafting institutional policies; however, they are not showing leadership in forbidding faculty participation in speakers' bureaus. CME offices are in the process of clarifying and harmonizing policies, but they lack regulatory oversight of physicians' activities outside of accredited CME. The current non-enforcement of the CMA guideline against peer selling in Canada adds new fodder to age-old debates about the merits of self-regulation in medicine. The failure of academic medical institutions and regulatory colleges to enforce the guideline against peer selling and product endorsement bolsters the argument for stronger government oversight of physician–industry interactions.

Acknowledgments

[Go to:](#)

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Appendices

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Appendix A

Method for determining participation in speakers' bureaus by top 5 publishing cardiologists at Canadian academic centres

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Footnotes

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Contributors: Lynette Reid and Matthew Herder jointly conceived the project and contributed equally to the literature review and analysis, as well as to drafting and revising the manuscript. Lynette Reid analyzed changes to the Canadian Medical Association's Code of Ethics over time, reviewed recent policy changes in academic medicine, and reviewed mechanisms for continuing medical education. Matthew Herder collected data about participation in speakers' bureaus by Canadian cardiologists, created [Figure 1](#), and reviewed legal and regulatory precedents relating to physicians' commercial speech. Both authors analyzed the speakers' bureau contract described in the article, and revised one another's analyses. Lynette Reid wrote the first draft of the manuscript and is the guarantor of the work.

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EXHIBIT 38



Speakers' Bureaus:

Best Practices for Academic Medical Centers*

The Problem:

Pharmaceutical companies often recruit physicians to perform speeches or presentations for the purpose of marketing a specific drug. In 2010, 8.6% of physicians reported having received payments for participating in speakers' bureaus.¹ These speakers' bureaus leverage the credibility of physicians in order to promote the use of pharmaceutical products. The physicians are generally trained to present a certain message, or are provided with pre-produced slides.^{2, 3} The audience may assume that these presentations are objective, when in fact they are heavily biased towards the interests of the industry sponsor.

Speakers' bureaus may lead to the dissemination of false or biased information. Exposure to industry-sponsored speaking events is associated with decreased quality of prescribing.⁴ Additionally, the compensation provided for these engagements may influence the attitudes or judgment of the presenter.^{5, 6}

Best Policy Practices:

Prior approval must be required for participation in industry-sponsored speaking events.

Faculty members must be prohibited from participating in industry-sponsored speaking events for which marketing is the primary purpose.

Faculty members must maintain control over the content of speeches and/or presentations. They must prepare content without input from or prior review by the industry sponsor.

AMCs should take measures to distinguish between appropriate and inappropriate speaking engagements, and should ensure that faculty members understand the distinctions.

Model Policy

Johns Hopkins University:

The policy clearly defines specific standards for speaking engagements, stating that faculty members speaking at industry-sponsored events must “[retain] full control and authority over professional material”. Additionally, faculty cannot take part in any activity in which a company “creates the slide set (or other presentation materials) and has the final approval of all content and edits; [or] the faculty member...acts as the company’s employee or spokesperson for the purposes of dissemination of company-generated presentation materials”. Public disclosure is also required.

[http://
www.hopkinsmedicine.org/
Research/OPC/
Policy_Industry_Interaction/
policy_interaction_industry.html](http://www.hopkinsmedicine.org/Research/OPC/Policy_Industry_Interaction/policy_interaction_industry.html)

*These recommendations come out of an ongoing study by Columbia University's Center on Medicine as a Profession. The researchers will update their recommendations regularly to incorporate new policies and findings. These materials were made possible by a grant from the state Attorney General Consumer and Prescriber Education Grant Program, which is funded by the multi-state settlement of consumer fraud claims regarding the marketing of the prescription drug Neurontin.

Every speaker must disclose all sources of industry funding at the speaking event. ■

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Figure I.

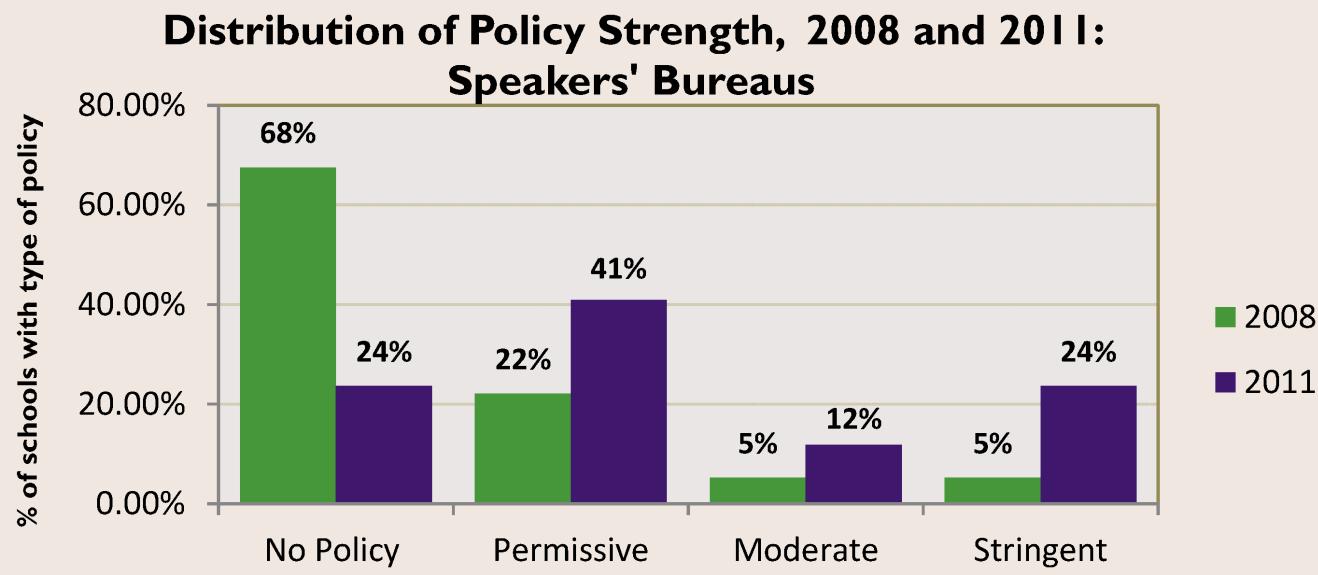


EXHIBIT 39

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Two Leaders in Pain Treatment Have Long Ties to Drug Industry

American Pain Foundation board members Scott Fishman and Perry Fine, both physicians, have lectured and authored publications funded by makers of narcotic painkillers. They say the support doesn't bias them.

by **Tracy Weber** and **Charles Ornstein**,
Dec. 23, 2011, 9:14 a.m. EST



Google Dr. Scott Fishman, chairman and president of the American Pain Foundation, or Dr. Perry Fine, a prominent board member, and it's quickly clear that their ties to the world of pain are legion.

[Here \(and at right\) is a photo of Fishman](#) at a forum with U.S. Surgeon General Regina Benjamin. [Here is his](#)

Two leaders in Pain Treatment Have Long Ties to Drug Industry - ProPublica
book about opioid prescribing that has been distributed to physicians in a couple of dozen states.

Multiple videos feature Fine delivering educational talks about the drugs. He appeared at the 2010 criminal trial of Anna Nicole Smith's boyfriend and two doctors accused of conspiracy in fostering the late celebrity's addiction to drugs. Fine testified that the 1,500 pills a month Smith was given did not make her an addict, according to news reports.

Fishman, chief of pain medicine at the University of California, Davis, and Fine, a professor of anesthesiology at the University of Utah School of Medicine, have authored articles on the foundation's website. They've testified in court cases and before state and federal committees, and each has been president of the American Academy of Pain Medicine, a doctors' group.

Last year, the pair and a third physician wrote a strongly worded column in The Seattle Times opposing a bill passed by Washington state lawmakers that required doctors and others to consult pain specialists before prescribing high doses of opioids to non-cancer patients. The governor signed it into law nonetheless.

Like the American Pain Foundation, both men have had longstanding ties to the pharmaceutical industry -- direct and indirect. The foundation received 88 percent of its \$5 million income last

Two leaders in pain treatment have long ties to drug industry — ProPublica
year from drug and medical-device makers.

This fall, the physicians acknowledged they had failed to disclose all their potential conflicts of interest in a letter to the editor of the Journal of the American Medical Association, which had been published in July. The journal requires all authors, even of letters, to disclose commercial ties.



In his correction, Fine listed 12 more companies for which he consulted, gave legal advice, delivered promotional talks or provided medical education. Among other things, he listed a 5 percent stake in a medical education company whose programs are funded by drugmakers.

Fine also appears to have played a role in launching a painkiller in 2009, ProPublica found. A subsidiary of Johnson & Johnson quoted him in its media release touting its new opioid.

ProPublica also found discrepancies in Fine's disclosures to his employer, the

University of Utah. For example, Fine told the university that he had received less than \$5,000 in 2010 from Johnson & Johnson for providing "educational" services. [On its website, however, the company says it paid Fine \\$32,017 for consulting, promotional talks, meals and travel that year.](#) (The University requires doctors to disclose all ties to drug companies, even situations in which they are not compensated.)

In an interview, Fine said he tries to be fully transparent about his industry ties. After reviewing his tax records, Fine said in an email, he discovered he had made several errors on his university disclosure and would amend it.

Fine said his relationships with drug companies add to his knowledge about their products. "Does it bias me and cause me to be prejudiced?" he said. "I really don't believe so."

Fine said he is a prominent speaker and teacher on pain because it remains undertreated. "Chronic pain is sort of the modern day leprosy," he said. "It's been sort of hidden away. There are a lot of people affected."

In his initial JAMA disclosure, Fishman said he had written a book about responsible opioid prescribing but received no royalties. [In his correction](#), he acknowledged receiving fees for teaching medical education courses, some of which were funded by drug-company grants.

Two leaders in pain treatment have long ties to drug companies — ProPublica
Over time, Fishman has had relationships with at least eight companies, including OxyContin maker Purdue Pharma, for which he was a consultant, paid speaker and recipient of research support. In an email to ProPublica, Fishman said he had stopped taking money from drug companies in recent years to avoid the perception of a conflict of interest.

He does appear to maintain some ties. Last year, for example, he and Fine appeared in videos on a website sponsored by drugmaker Cephalon to educate patients about the safe use of prescription pain pills. [Fishman's video was removed from the site after this story was published.] Fishman's opioid book, written for the Federation of State Medical Boards, was financed in large part by drug companies. The federation would not provide specific dollar amounts.

Fishman, who is stepping down as chairman of the pain foundation this month, said he often receives honoraria for teaching medical education courses but doesn't discuss them with drug-company funders and completely controls the content.

Fishman also said his position on opioids has evolved. He now believes they are overused, often in cases in which the risks outweigh the benefits. "Opioids represent only a small part of the spectrum on options for mitigating pain, but they carry a disproportionate level of risk," he wrote to ProPublica.

Fine's defense of doctors who prescribe opioids [was criticized last year by a top U.S. Drug Enforcement Administration official](#).

The agency's deputy administrator slammed Fine for his testimony in support of a Utah physician accused of doling out pain medication indiscriminately, several times after sexual activity with a patient.

In revoking the doctor's ability to prescribe narcotics, the official called Fine's testimony "patently disingenuous."

Asked whether it would be outside the standard of practice for a doctor to "go to the home of his patient, have her take off her clothes, digitally penetrate her vagina and then issue her a controlled substance prescription," Fine initially said no, according to a revocation of registration for the accused physician, published in the Federal Register in August 2010.

Although Fine "eventually acknowledged" it was wrong, the administrative law judge in the case said Fine's testimony was "evasive" and "bias[ed] in favor of assuming the correctness of the actions of any doctor," according to the revocation notice in the Federal Register. The judge found a colleague of Fine's from the University of Utah, who had testified against the accused doctor, to be more believable.

Fine went on to testify at the doctor's criminal trial in federal court in Salt Lake City this year. The doctor was convicted of two counts of distributing a controlled substance resulting in death, as well as 38 other counts.

In an interview, Fine defended his participation in both cases, saying he did not believe the doctor's conduct was criminal. He said the prosecution had to attack him or its case would have fallen apart.

"They had to cast me in a bad light; of course they did," Fine said. "They were too deep into this." As for his colleague who testified for the other side, Fine said, "I believe he's wrong."

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Tracy Weber

Tracy Weber is a senior editor at ProPublica. Previously, Weber was a senior reporter covering health care issues at ProPublica and, before that, she reported for the Los Angeles Times, the Los Angeles Herald Examiner and the Orange County Register.

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🐦 [@tracyweber](https://twitter.com/tracyweber)



Charles Ornstein

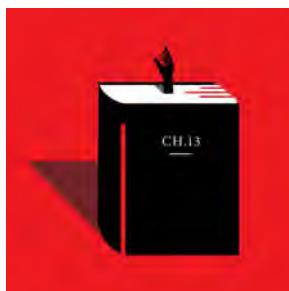
Charles Ornstein is a senior reporter at ProPublica, covering health care and the pharmaceutical industry.

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EXHIBIT 40

Entertainment

Doctor: 1,500 pills don't prove Smith was addicted



Originally published September 22, 2010 at 5:16 pm Updated September 22, 2010 at 7:31 pm


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A pain-management doctor testified Wednesday that Anna Nicole Smith was not a drug addict, rebuffing a prosecutor who suggested the model's prescriptions for 1,500 pills in a single month amounted to an addiction.

By [LINDA DEUTSCH](#)

AP Special Correspondent

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a drug
pills in

ction,"

Fine, who testified as a defense witness, said there might be a toxicity risk if Smith took all the drugs but added that her medical records showed no indication of actual harm.

The definition of an addict is central to the case against Dr. Sandeep Kapoor, Dr. Khristine Eroshevich and Howard K. Stern, who have pleaded not guilty to providing drugs to an addict and other charges. They are not charged in Smith's drug overdose death in 2007.

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Stern is a lawyer who was the late celebrity model's boyfriend.

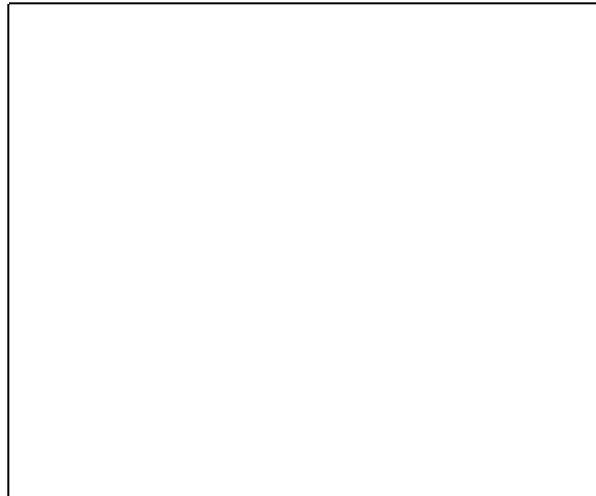
Fine said he believed Smith had a high tolerance for drugs but was not addicted. He said medical records showed she had suffered fractured ribs and was seeking relief from chronic pain.

"She woke up and functioned from day to day," Fine said. "She was in recovery from rib fractures, and anyone's function would be highly limited."

Deputy District Attorney David Barkhurst had asked Fine whether Smith's prescriptions for 1,500 drug tablets in June 2004 might help determine if Smith was an addict.

Fine agreed with Superior Court Judge Robert Perry that it was a lot of drugs but said it was antiquated thinking to equate the number of pills with addiction. The pills included various opiates, muscle relaxants and other drugs.

"The disease of addiction is viewed as largely present in genetic factors, and it takes social and environmental factors to bring it out," he said.



Fine said a typical addict would be driven to compulsive drug use to seek a sense of

aw no

ief from

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ub with

ed to

hide Smith's nakedness.

Prosecutors contend the video supports their theory that Smith was drugged during that time and unable to function normally. The judge told jurors to evaluate whether the actions on screen were relevant to testimony they have heard.

Stern, operating the camera for the home movie, could be heard talking to Smith and to the infant.

Smith's speech was slow and somewhat slurred, but she communicated with Stern, asking for a bottle of baby soap, waving the baby's hand at Stern and blowing kisses.

At one point the baby howls, but she eventually settles down on Smith's stomach as the new mother scoops water over her. For a brief moment, Smith sings a little song to the infant who appeared to be about 2 to 3 months old.

LINDA DEUTSCH

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EXHIBIT 41

MEDPAGE TODAY®

Neurology > Pain Management

Follow the Money: Pain, Policy, and Profit

by [John Fauber](#), Reporter, Milwaukee Journal Sentinel/MedPage Today

February 19, 2012

The Federation of State Medical Boards, often develops guidelines that serve as the basis for model policies with the stated goal of improving medical practice -- but after its guideline for the use of opioids to treat chronic pain patients was adopted as a model policy, it asked Purdue Pharmaceuticals for \$100,000 to help pay for printing and distribution that policy to 700,000 practicing doctors.

That \$100,000 was just a small downpayment on the \$3.1 million that the Federation's foundation estimated it would cost for its campaign to get out the word about "safe" use of opioid analgesics in treatment of chronic pain.

The federation, which functions as a trade group representing some 70 allopathic and osteopathic medical boards, won't say how much money it received from industry, but the \$100,000 request was detailed in a document obtained by the *Milwaukee Journal Sentinel/MedPage Today* from University of Wisconsin School of Medicine and Public Health.

Why a Pain Policy?

Why the FSMB would turn to a pharmaceutical company to underwrite the cost of producing and distributing a book about its opioid prescribing policy -- and why the FSMB undertook developing such a policy in the first place -- is part of a much larger story that has unfolded over the last decade, culminating with the Centers for Disease Control and Prevention's stark warning about [spiraling risk of death from prescription painkillers](#).

An FSMB spokesperson said there were many reasons for it to codify a position on the prescribing of opioids, and among those reasons was a project supported by the Robert Wood Johnson Foundation to seek some common ground in the treatment of chronic pain.

A *Journal Sentinel/MedPage Today* investigation suggests it was the \$693,000 grant from the Robert Wood Johnson Foundation to University of Wisconsin that started the ball

rolling down this slippery slope. That grant went to the UW Pain & Policy Studies Group.

Last year, the *Journal Sentinel/MedPage Today* reported that the UW Pain group had received \$2.5 million from Purdue and several other opioid makers between 1999 and 2010.

After the story ran last April, the UW Pain group said it had decided to stop taking money from the drug industry.

But that decision does not change the time line for the FSMB pain management policy -- at nearly every step along the way, financial connections between the FSMB policy and companies that make the drugs can be found.

For example:

- The RWJ-funded project started with an advisory committee that recruited several pain experts who had ties to makers of opioids -- a core group that included J. David Haddox, DDS, MD, then a member of the Purdue Pharma speakers' bureau, who went on to become a Purdue employee. Purdue is the maker of OxyContin.
- FSMB's involvement started with a guideline written in 1998, and then with its model policy, which was adopted in 2004. With that policy in hand, the FSMB decided to spread the word to the nation's physicians by translating the policy into a book and it delegated that task to Scott Fishman, MD, a University of California Davis physician with extensive financial ties to pharmaceutical companies that market opioids.
- FSMB not only asked Purdue for money, it also reached out to a total of six opioid makers for money to produce and distribute "Responsible Opioid Prescribing: A Physician's Guide," but it won't disclose how much each company contributed.
- In 2009 the University of Wisconsin School of Medicine and Public Health decided to offer an online CME course based on the FSMB book, and to fund the activity it sought and received a \$119,000 grant from Endo Pharmaceuticals (one the six companies that chipped in to pay for the book's printing and distribution). As course reviewer, UW chose Aaron Gilson, PhD, a UW employee, who had been paid to help another opioid maker, Cephalon, with a new drug application to the FDA.

Policy Prompting Practice

Deborah Grady, MD, a professor of medicine at the University of California, San Francisco, said she believes the federation's policy as well as CME courses such as the one offered by UW contributed to the marked increase in opioid use.

That policy also helped establish the idea that denying high doses of opioids to patients is a bad medical practice, she said.

"The sad fact is that for many patients, the pain is never controlled, despite very high, dangerous doses of opioids that may actually result in more side effects than benefit," Grady said.

The model policy, which describes how opioids should be used to treat pain, has been adopted in full or in part by nearly 30 state medical boards.

Instead of protecting patients from over-prescribing doctors, many of those medical boards have been "duped" by the federation's "pharma-funded campaign" into encouraging aggressive prescribing, said Andrew Kolodny, MD, a New York psychiatrist, addiction specialist and critic of the opioid industry.

States that want to go after pill mill operators and reckless doctors are unable to do so because they've adopted the policy, he added.

What's more, many of those medical boards purchased the opioid guide book and gave it to doctors, he said.

He said the book promotes aggressive prescribing. More than 160,000 copies of the book have been distributed.

In a statement, Lisa Robin, the federation's chief advocacy officer, said its efforts are not intended to advocate for opioid therapy.

"Far from encouraging opioid use, the policy and book have provided a much-needed warning to physicians that opioids are potentially dangerous, that the use of opioids for other than legitimate medical purposes poses a threat to the individual and society ... Such medications must be used with great caution."

She said the policy urges physicians to seek balance, "recognizing the fact that millions of legitimate patients rely on these medications for pain relief, while incorporating safeguards into their practices to minimize the potential for the abuse and diversion of controlled substances."

Several doctors contacted for this story were critical of the book because it failed to point out the lack of science supporting the use of opioids for chronic, non cancer pain. Instead, the book says the drugs may be essential for chronic pain.

In a statement, UW said the book and the CME course are not clinical practice guidelines. They are a response to the issue of opioid abuse and how to reduce it, said UW spokeswoman, Lisa Brunette.

The book's content was reviewed for accuracy and balance by 20 experts, including 14 who had no financial relationships with drug companies, she said.

She said Gilson, who reviewed UW's CME course, is a widely published expert on pain policy issues. He had no financial relationship to the Endo Pharmaceuticals, which funded the course, she said.

In a statement, Fishman, the book's author, said he was not paid for his work on the book and does not receive royalties.

He acknowledged that when the first edition of the book was written in 2006, the science on the effectiveness of opioids "was not robust" and data on the severe risks "had yet to emerge."

Since then, new data on risks, including unintended overdose deaths, have emerged, he said.

The new risk information will be included in an expanded version of the book that will be published by the spring, he said.

EXHIBIT 42

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United States Senate
 COMMITTEE ON FINANCE
 WASHINGTON, DC 20510-6200

May 8, 2012

Catherine Underwood
 Executive Director
 American Pain Society
 4700 W. Lake Avenue
 Glenview, IL 60025

Dear Ms. Underwood:

As Chairman and a senior member of the Senate Finance Committee, we have a responsibility to the more than 100 million Americans who receive health care under Medicare, Medicaid, and CHIP. As part of that responsibility, this Committee has investigated the marketing practices of pharmaceutical and medical device companies as well as their relationships with physicians and non-profit medical organizations.

It is clear that the United States is suffering from an epidemic of accidental deaths and addiction resulting from the increased sale and use of powerful narcotic painkillers such as Oxycontin (oxycodone), Vicodin (hydrocodone), and Opana (oxymorphone). According to CDC data, “more than 40% (14,800)” of the “36,500 drug poisoning deaths in 2008” were related to opioid-based prescription painkillers.¹ Deaths from these drugs rose more rapidly, “from about 4,000 to 14,800” between 1999 and 2008, than any other class of drugs,² and now kill more people than heroin and cocaine combined.³ More people in the United States now die from drugs than car accidents as a result of this new epidemic.⁴ Additionally, the CDC reports that improper “use of prescription painkillers costs health insurers up to \$72.5 billion annually in direct health care costs.”⁵

In Montana, prescription drug abuse is characterized by the state’s Department of Justice as an “invisible epidemic” killing at least 300 people per year and contributing to increases in

¹ Center for Disease Control, “Drug Poisoning Deaths in the United States, 1980-2008, NCHS Data Brief, No. 81, December 2011 at <http://www.cdc.gov/nchs/data/databriefs/db81.pdf>.

² Id.

³ CDC Press Release, “Prescription painkiller overdoses at epidemic levels,” November 1, 2011 at http://www.cdc.gov/media/releases/2011/p1101_flu_pain_killer_overdose.html.

⁴ LA Times, “Drug deaths now outnumber traffic fatalities in U.S., data show,” September 17. 2011 at <http://articles.latimes.com/2011/sep/17/local/la-me-drugs-epidemic-20110918>.

⁵ International Business Times, “Prescription Painkiller Overdoses Cost Insurers \$72.5 Billion Yearly: CDC,” November 3, 2011 at <http://www.ibtimes.com/articles/242437/20111103/prescription-painkiller-overdoses-cost-insurers-72-5.htm>.

addiction and crime.⁶ The University of Montana Bureau of Business and Economic Research estimated that prescription drug abuse is costing the state \$20 million annually in additional law enforcement, social services, and lost productivity.⁷

In Iowa, “the use of opioid painkillers such as hydrocodone and oxycodone has increased dramatically in the last decade,” according to the Governor’s Office of Drug Control Policy. Annual overdose deaths from opioids “increased more than 1,233% from 3 deaths in 2000 to 40 deaths in 2009.”⁸ Data from Iowa’s prescription drug monitoring program demonstrates that in 2010, 89,500,000 doses of hydrocodone and oxycodone were prescribed totaling nearly 40% of all controlled substance prescriptions.⁹

Concurrent with the growing epidemic, the *New York Times* reports that, based on federal data, “over the last decade, the number of prescriptions for the strongest opioids has increased nearly fourfold, with only limited evidence of their long-term effectiveness or risks” while “[d]ata suggest that hundreds of thousands of patients nationwide may be on potentially dangerous doses.”¹⁰

There is growing evidence pharmaceutical companies that manufacture and market opioids may be responsible, at least in part, for this epidemic by promoting misleading information about the drugs’ safety and effectiveness. Recent investigative reporting from the *Milwaukee Journal Sentinel/MedPage Today* and *ProPublica* revealed extensive ties between companies that manufacture and market opioids and non-profit organizations such as the American Pain Foundation, the American Academy of Pain Medicine, the Federation of State Medical Boards, the University of Wisconsin Pain and Policy Study Group, and the Joint Commission.

In a *ProPublica* story published in the *Washington Post*, the watchdog organization examined the American Pain Foundation, a “health advocacy” organization that received “nearly 90 percent of its \$5 million funding from the drug and medical device industry.”¹¹ *ProPublica* wrote that its review of the American Pain Foundation’s “guides for patients, journalists, and policymakers play down the risks associated with opioids and exaggerate their benefits. Some of the foundation’s materials on the drugs include statements that are misleading or based on scant or disputed research.”¹²

According to the *Milwaukee Journal Sentinel/MedPage Today*, a “network of national organizations and researchers with financial connections to the makers of narcotic painkillers...helped create a body of dubious information” favoring opioids “that can be found in prescribing guidelines, patient literature, position statements, books and doctor education

⁶ See the Montana Department of Justice website at <http://doj.mt.gov/prescriptionabuse/>.

⁷ Bureau of Business and Economic Research, “The Economic Cost of Prescription Drug Abuse in Montana”, June 2011 at <http://mbcc.mt.gov/PlanProj/Projects/PDMP/Prescription%20Drug%20Abuse%2020110629.pdf>.

⁸ Iowa Governor’s Office of Drug Control Policy, “Iowa Drug Control Strategy: 2012,” November 1, 2011 at http://www.iowa.gov/odcp/drug_control_strategy/Strategy2012.Final.pdf

⁹ Id.

¹⁰ NY Times, “Tightening the Lid on Pain Prescriptions,” April 8, 2012 at <http://www.nytimes.com/2012/04/09/health/opioid-painkiller-prescriptions-pose-danger-without-oversight.html>.

¹¹ ProPublica, “The Champion of Painkillers,” December 23, 2011 at <http://www.propublica.org/article/the-champion-of-painkillers>.

¹² Id.

courses.”¹³ Specifically, a patient guide funded by three drug companies and available on the American Pain Foundation website states that “there is no ceiling does for opioids as long as they are not combined with other drugs such as acetaminophen.”¹⁴ However, a 2011 Archives of Internal Medicine paper “found that the risk of death for high-dose patients was three times greater than in lower-dose patients.”¹⁵

Although it is critical that patients continue to have access to opioids to treat serious pain, pharmaceutical companies and health care organizations must distribute accurate and unbiased information about these drugs in order to prevent improper use and diversion to drug abusers.

As part of our effort to understand the relationship between opioid manufacturers and non-profit health care organizations, please provide the following information:

- 1) Provide a detailed account of all payments/transfers received from corporations and any related corporate entities and individuals that develop, manufacture, produce, market, or promote the use of opioid-based drugs from 1997 to the present.¹⁶ For each payment identified, provide:
 - a. Date of payment.
 - b. Payment description (general support, project specific etc.).
 - c. Amount of payment.
 - d. Year end or year-to-date payment total and cumulative total payments for each organization or individual.
 - e. For each year a payment was received, the percentage of funding from organizations identified above relative to total revenue.
- 2) Has the American Pain Society received any funding from the federal government? If yes, describe the year, amount, and purpose of this funding.
- 3) In addition to financial support, identify and describe any collaborative activity between the organizations identified in request #1 and the American Pain Society from 2007 to the present.
- 4) In the event any activity identified in request #3 above pertains to information distributed to physicians and patients concerning prescription pain medications, please identify any materials developed, in whole or in part, by organizations identified in request #1 and provide copies of these materials.

¹³ Milwaukee Journal Sentinel/MedPage Today, “Follow the Money: Pain, Policy, and Profit,” February 19, 2012 at <http://www.medpagetoday.com/Neurology/PainManagement/31256>.

¹⁴ Milwaukee Journal Sentinel, “Painkiller Boom Fueled by Networking,” February 18, 2012 at <http://www.jsonline.com/watchdog/watchdogreports/painkiller-boom-fueled-by-networking-dp3p2rn-139609053.html>

¹⁵ Id.

¹⁶ Include any charitable foundation established by a pharmaceutical company.

- 5) Please identify the name, job title, job description, and dates employed of any American Pain Society employees who communicated with any organization identified in question #1 regarding the content of any materials distributed to patients and physicians pertaining to opioid use from 2007 to the present.

In cooperating with the Committee's review, no documents, records, data, or other information related to these matters, either directly or indirectly, shall be destroyed, modified, removed, or otherwise made inaccessible to the Committee.

We look forward to hearing from you by no later than June 8, 2012. All documents responsive to this request should be sent electronically, on a disc, in searchable PDF format to my staff. If you have any questions, please do not hesitate to contact Christopher Law with Senator Baucus at (202) 224-4515 or Erika Smith with Senator Grassley at (202) 224-5225.

Sincerely,



Charles E. Grassley
Senator



Max Baucus
Chairman

EXHIBIT 43

STAT

Senators Hatch and Wyden: Do your jobs and release the sealed opioids report

By Paul D. Thacker

June 27, 2016



Senators Ron Wyden (left) and Orrin Hatch of the Senate Finance Committee. Gabriella Demczuk/Getty Images

Like many Americans, I want to know how we got to the point that nearly 30,000 of our fellow countrymen and women died last year from [overdosing on opioids](#)¹. Answers, lots of answers, are to be found in a report written by staff working in the US Senate. But the senators overseeing the report have failed to release it.

In 2012, the chair and ranking member of the Senate Finance Committee, Max Baucus (D-Mont.) and Chuck Grassley (R-Iowa), launched an investigation into financial ties between drug manufacturers and medical organizations that were setting guidelines for opioid use. When the investigation began, the federal government had already reported that opioid overdoses were killing more people each year than car accidents. Many staffers working for Baucus considered his home state of Montana to be ground zero for the epidemic of opioid addiction.

The committee focused on the American Pain Foundation, the Center for Practical Bioethics, and five other organizations. It also targeted three leading opioid makers: [Purdue Pharma](#)² (OxyContin), Endo Pharmaceuticals (Percocet), and Johnson & Johnson (Duragesic). The committee demanded to see documents and get answers to its questions.

Over the course of many months, congressional investigators collected and analyzed a mountain of material. These documents, and the report that was drafted from them almost a year later, have never seen the light of day. Instead, they remain sealed in the Senate Finance Committee's office.

[Read More:](#)² [Purdue Pharma files appeal of decision to unseal OxyContin records](#)²

As a former investigator who helped the Senate Finance Committee uncover corruption in science and medicine, I know firsthand the hard work that goes into these inquiries. Making information public can change policy, without needing to pass new laws. The public, the press, and lawmakers deserve to know what the committee learned about how the drug industry influenced opioid prescribing practices.

I also have personal reasons for wanting to see the report and learn more about the causes of the opioid epidemic. I have lost two cousins to opioids, and my father unwittingly became addicted to [fentanyl](#)³. His personal physician had prescribed this painkiller for back pain without warning him that it is a powerful and addictive opioid. After a while, my father decided to stop taking the medication. That led to his being rushed to the emergency room in the middle of the night with severe abdominal pain and a feeling that fire was shooting up his arms and into his hands. The emergency doctors explained that he was experiencing [opioid withdrawal](#)⁴, and put him on a morphine drip. Shocked that he was now a “junkie,” he restarted fentanyl the next day, and slowly tapered off the drug.

The players

The [American Pain Foundation](#)⁵ was a nonprofit that described itself as America's largest organization for pain patients. Yet its guidance on opioid use for patients and policymakers exaggerated the benefits of these drugs while downplaying the risks. At one point, pharmaceutical and medical device companies provided 90 percent of the foundation's funding. Days after the Senate investigation began, [ProPublica reported](#)⁶ that the foundation had shut down “due to irreparable economic circumstances.” Senate investigators later combed through a treasure trove of the foundation's documents, which helped explain how the foundation, affiliated physicians, and drug companies helped fuel prescriptions for opioids.

[Read More:](#)⁷ [Opioid crisis puts pharmacists on the front line, pressed to serve as drug cops](#)⁷

The Finance Committee also targeted the [Center for Practical Bioethics](#)⁸, a nonprofit which bills itself as an independent national leader in helping policymakers and corporate leaders struggle with health care decisions. The [Kansas City Star reported](#)⁹ that Purdue Pharma had showered the center with funds, providing seed money to create the center's \$1.5 million chair in pain management, held by [Myra Christopher](#)¹⁰, one of the center's founders, and donating a sizable amount to the group's annual dinner and symposium.

In 2008, Christopher [coauthored a study](#)¹¹ to calm physicians' fears that they might be criminally prosecuted or disciplined for inappropriately prescribing opioids. In 2011, as money from pharmaceutical companies continued to pour into the center, she [wrote a commentary](#)¹² titled “It's Time for Bioethics to See Chronic Pain as an Ethical Issue” for the American Journal of Bioethics, which was then housed at the Center for Practical Bioethics. The commentary [failed to disclose](#)¹³ that the center had received

Senators must do their jobs and release sealed opioid report
funding from the pharmaceutical industry and was one of many articles promoting opioid use the journal published. By the time the Senate launched its investigation, the journal had changed homes and sought to distance itself from the center.

Change of leadership further threatens the report

Baucus left the Senate in January 2014 to become the US [ambassador to China](#)¹⁴. Grassley lost his leadership position with the Senate Finance Committee after becoming chairman of the Senate Judiciary Committee. They were succeeded by Senator Orrin Hatch (R-Utah), who now chairs the Senate Finance Committee, and Senator Ron Wyden (D-Ore.), its ranking Democrat. These new leaders are likely to do little to release the opioid report.

When Hatch took over the committee, he promised to lead aggressive investigations, just as Grassley had done. He has broken that promise. While Grassley zealously investigated nonprofits across the political spectrum, Hatch avoids rankling corporate America with aggressive investigations into corruption and, as I was told by one staffer, Hatch wants to keep his hands off nonprofits. Why? Hatch holds to an ideological conviction that government is bad and can be replaced by more efficient nonprofits. Releasing a report that hints at how corrupt some of these nonprofits can be would harm that ideology — even as it would help his home state. According to the Utah Department of Public Health, opioid poisoning kills about [30 people each month](#)¹⁵, more than die from firearms, falls, or auto accidents.

Senator W yden responds

Senators Baucus and Grassley did not compose a written report related to the investigation they launched in 2012. Senate rules prohibit the release of documents collected in the course of an investigation outside the context of an official report or other official action. Senator Wyden, now the ranking member of the minority, is [deeply committed](#)¹⁶ to curtailing the crisis of opioid addiction, and that includes holding accountable those who contributed to its rise in the first place. The documents related to the 2012 investigation are currently being reviewed by Democratic investigations staff. Senator Wyden intends to take official action related to this investigation.

Taylor Harvey
Spokesperson for Senator Ron Wyden

Voters in Oregon, which has had the [second highest rate](#)¹⁷ of opioid abuse in the country, shouldn't expect much better from Wyden. Like many Democrats, Wyden has no love for corporate corruption. But this is balanced by an aversion to the pain and drudgery required to hold wrongdoers accountable through congressional investigations. Instead of investigating and laboriously tinkering to improve the system we have, the senator seems to prefer writing new pieces of legislation onto which he can solder the Wyden nameplate.

Do the right thing

Last September, [dozens of public health advocates](#)¹⁸ pleaded with both senators to release the findings of the opioid prescribing report. They noted that many of the companies and groups targeted [by the](#)

Senators must do their jobs and release sealed opioid report
investigation¹⁹ “have continued to promote aggressive opioid use and continue to block federal and state interventions that could reduce overprescribing.” In response, Hatch said¹⁹ he would bring up the possibility of releasing the report with other senators. That hasn’t happened.

[Read More:](#)⁴ ‘Like you’re living in hell’: A survivor on what opioid withdrawal did to his body⁴

Every day, an estimated 78 Americans die from an opioid overdose and more than 1,000 are treated in emergency departments²⁰ for misusing prescription opioids. Medical evidence tells us that these overdoses are “accidents.” A sense of justice tells us that they aren’t. Instead, they are preventable incidents tied to corporate profit. Those at fault should be named and held accountable.

Senators Hatch and Wyden have sponsored new legislation to control the societal impact of opioid addiction. These are Band-Aids that treat the symptoms of the opioid epidemic while ignoring the parasitic elements that caused the disease.

Release the report, senators. Americans deserve to know who created the national scourge of opioid addiction.

Paul D. Thacker, a former investigator on the United States Senate Finance Committee, is a writer living in Spain.

A previous version of this article incorrectly stated that opioid poisoning is Utah’s leading cause of death.

About the Author

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EXHIBIT 44

Health +

Live TV

manufacturers

By Nadia Kounang, CNN

① Updated 11:06 AM ET, Wed March 29, 2017

**Photos:** Opioids: Addictive painkillers

Prescription and illegal opioids are commonly abused because they are so addictive.

Opioid medications bind to the areas of the brain that control pain and emotions, driving up levels of the good hormone dopamine in the brain's reward areas and producing an intense feeling of euphoria.

As the brain becomes used to the feelings, it often takes more and more of the drug to produce the same levels of pain relief and well-being, leading to dependence and, later, addiction.

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Drug
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Investigation questions role of pharmaceuticals in opioid epidemic

(CNN) — Missouri Senator Claire McCaskill has launched an investigation into some of the country's leading prescription drug manufacturers, demanding documents and records dating back the past five years which indicate just what the companies knew of the drugs' risk for abuse as well as documents detailing marketing practices and sales

presentations. Her office has sent [letters](#) to the heads of Purdue, Janssen/Johnson & Johnson, Insys, Mylan, and Depomed.

The companies were targeted based on their role in manufacturing some of the opioid painkillers with the highest sales in 2015.

Overdose deaths quadrupled since 1999

The United States is in the midst of an opioid epidemic. According to the United States Centers for Disease Control and Prevention, since 1999, the number of drug overdose deaths involving prescription drugs has [quadrupled](#). During the same time period, the sales of prescription drugs have also increased four-fold. In 2014, nearly 2 million Americans abused or depended on prescription drugs.



McCaskill is the senior Democrat on the Senate Homeland Security and Governmental Affairs Committee. This is not her first effort in attempting to uncover what has contributed to this epidemic. Earlier this year, she [requested](#) the Department of Justice Office of the Inspector General open an investigation into the role of drug distributors in the opioid epidemic. In addition, she's also been involved in investigating Medicare Part D's role in preventing abuse of prescription narcotics.

Related Article: Prescriptions may hold clues to who gets hooked on opioids, study says

'Single-handedly destroying families'

"I hear it everywhere I go: 'Drug overdose deaths, the vast majority of them related to prescription opioids or heroin, are single-handedly destroying families and communities across Missouri and the country,' and I refuse to just stand by and watch, we have an obligation to everyone devastated by this epidemic to find answers," McCaskill said in a statement.

This is not the first time the Senate has investigated the relationship of drug manufacturers in the opioid epidemic. In [2012](#) the Senate Finance Committee began looking into the relationship between drug manufacturers and pain organizations that advocated for their use. The [findings](#) have yet to be released.

In addition, counties and cities across the country have begun filing lawsuits against manufacturers for their roles in the drug epidemic. In Cabell County, West Virginia a [complaint was filed](#) (PDF) earlier this month alleging that between 2007 and

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Related Article: Why opioid overdose deaths seem to happen in spurts

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prescriptions nationally, but we are an industry leader in the development of abuse-deterrent technology and advocating for the use of prescription drug monitoring programs. We are reviewing Senator McCaskill's letter and will respond accordingly."

CNN's Debra Goldschmidt contributed to this report



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to county pharmacies. The county population during those years grew from just over 94,000 to just over 96,000 people. Similarly, nearby Kanawha County, West Virginia, [filed a lawsuit](#) (PDF) at the same time alleging the drug companies sold 66 million doses of these medications during the same time period when the county population ranged from about 191,000 to 192,000 residents.

The cities of [Everett, Washington](#) and [Chicago, Illinois](#) (PDF) have also filed similar complaints, alleging aggressive marketing and deceptive messaging about the risks of opioid painkillers.

"All of this didn't happen overnight. It happened one prescription and marketing program at a time. The vast majority of the employees, executives, sales representatives, scientists, and doctors involved with this industry are good people and responsible actors, but some are not. This investigation is about finding out whether the same practices that led to this epidemic still continue today, and if decisions are being made that harm the public health," said McCaskill.

In response to the investigation, Purdue Pharma issued the following comment: "The opioid crisis is among our nation's top health challenges, which is why our company has dedicated itself for years to being part of the solution.

OxyContin accounts for only 2% of the opioid analgesic prescriptions nationally, but we are an industry leader in the development of abuse-deterrent technology and advocating for the use of prescription drug monitoring programs. We are reviewing Senator McCaskill's letter and will respond accordingly."

EXHIBIT 45

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How big pharma got people hooked on dangerous opioids — and made tons of money off it

America is in the middle of a big drug epidemic. Drug companies are a large reason why.

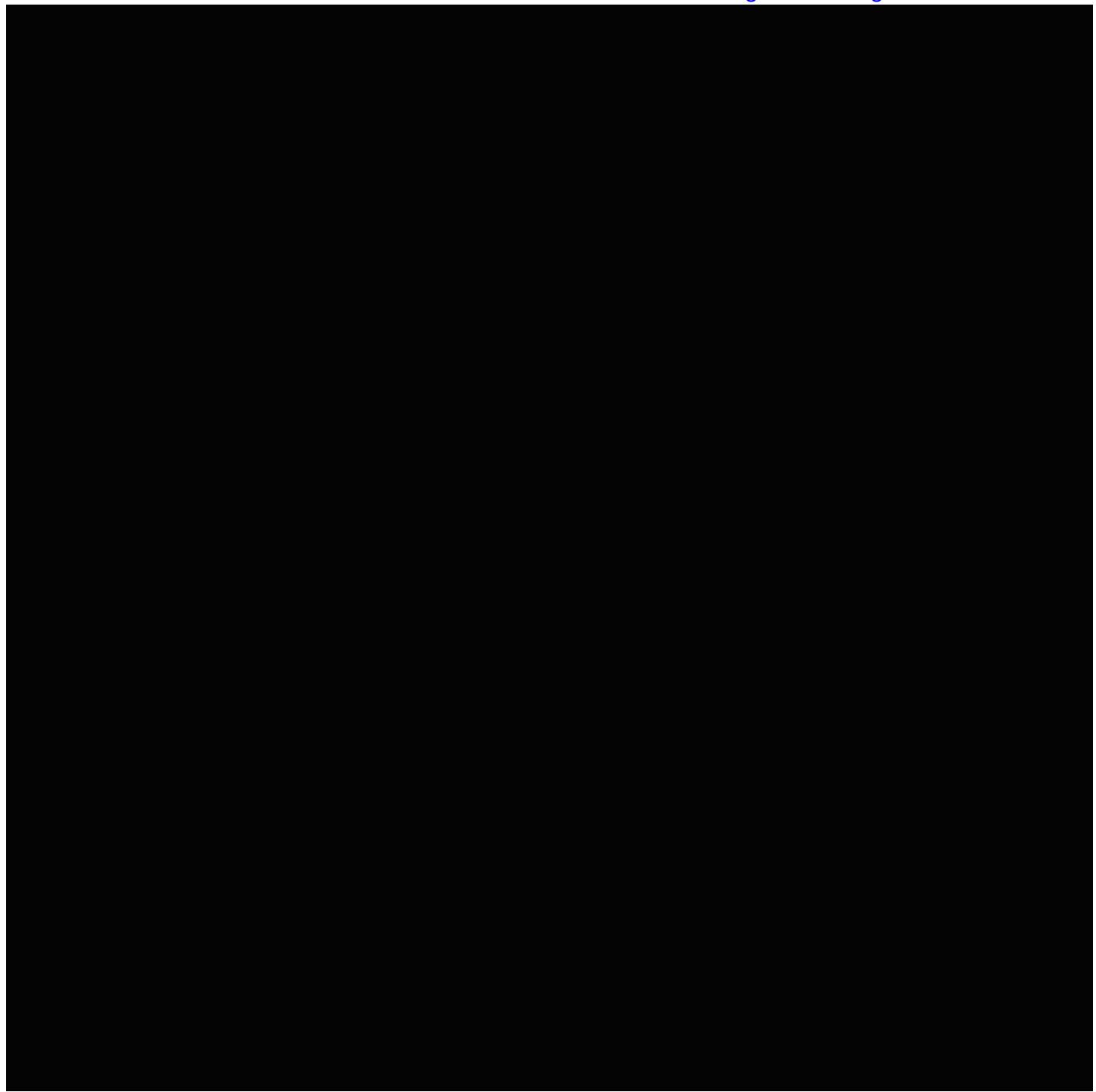
Updated by German Lopez | @germanrlopez | german.lopez@vox.com | Sep 22, 2016, 3:00pm EDT



How did America get to a point where legal opioid painkillers, marketed as medicine, were involved in **nearly 19,000 overdose deaths** in 2014?

One alarming explanation: The drug companies behind these opioids wanted more people to buy their product, so they led a misleading campaign to get doctors to prescribe their drugs.

The result: Drug companies profited as more and more people got addicted and died of overdoses. This chart, from a 2015 study published in the ***Annual Review of Public Health***, tells the story:



Annual Review of Public Health

Let's back up. The opioid epidemic began in the 1990s when doctors prescribed a tremendous amount of opioid painkillers to help treat pain — a serious problem, given that chronic pain alone afflicts **about 100 million Americans**.

But one reason doctors were so willing to prescribe these painkillers, despite the clear risks of addiction and overdose, is heavy marketing from the pharmaceutical industry.

Andrew Kolodny and other public health experts **explained** the history in the *Annual Review of Public Health*, detailing Purdue Pharma's involvement after it put OxyContin on the market in the 1990s:

Between 1996 and 2002, Purdue Pharma funded more than 20,000 pain-related educational programs through direct sponsorship or financial grants and launched a multifaceted campaign to encourage long-term use of [opioid painkillers] for chronic non-cancer pain. As part of this campaign, Purdue provided financial support to the American Pain Society, the American Academy of Pain Medicine, the Federation of State Medical Boards, the Joint Commission, pain patient groups, and other organizations. In turn, these groups all advocated for more aggressive identification and treatment of pain, especially use of [opioid painkillers].

Often, these campaigns propagated highly misleading claims. Such as claims that OxyContin and other new opioid painkillers were safer than other medications on the market — as we're now seeing, they aren't. Or assertions that opioid painkillers can treat chronic pain — in reality, the **evidence** for opioids treating long-term, chronic pain is **very weak**, despite their effectiveness for acute, short-term pain.

The claims were so misleading, in fact, that Purdue Pharma eventually **paid** hundreds of millions of dollars in fines for them. The Associated Press **reported** in 2007:

Purdue Pharma, its president, top lawyer and former chief medical officer will pay \$634.5 million in fines for claiming the drug was less addictive and less subject to abuse than other pain medications, U.S. Attorney John Brownlee said in a news release....

Purdue learned from focus groups with physicians in 1995 that doctors were worried about the abuse potential of OxyContin. The company then gave false information to its sales representatives that the drug had less potential for addiction and abuse than other painkillers, the U.S. attorney said.

But in the midst of the misinformation campaigns, doctors prescribed hundreds of millions of prescriptions for opioids — in 2012, enough to give a bottle of pills to **every adult in the country**. And as people became addicted to opioid painkillers, they also began turning to a cheaper, more potent opioids — such as heroin and fentanyl — to satiate their cravings.

The result: In 2014, there were a record 47,000 drug overdose deaths in the US, nearly two-thirds of which were opioid-related, according to **federal data**. (For more on the drug epidemic, read **Vox's explainer**.)

Pain patients thought they were being helped, and doctors thought they were helping their patients. But really, people's lives were put in danger — largely so drug companies could make some money.



THE WAR ON DRUGS, EXPLAINED

How does the US decide which drugs are regulated or banned?

The US uses what's called the drug scheduling system (<http://www.vox.com/2014/9/25/6842187/drug-schedule-list-marijuana>). Under the Controlled Substances Act (<https://www.law.cornell.edu/uscode/text/21/812>), there are five categories of controlled substances known as schedules, which weigh a drug's medical value and abuse potential.

Medical value is typically evaluated through scientific research, particularly large-scale clinical trials similar to those used by the Food and Drug Administration for pharmaceuticals. Potential for abuse isn't clearly defined by the Controlled



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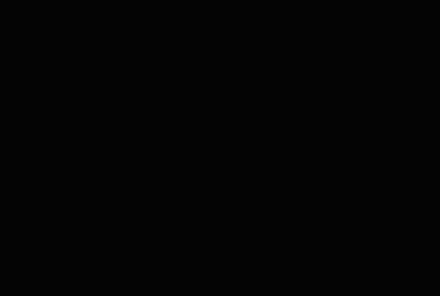
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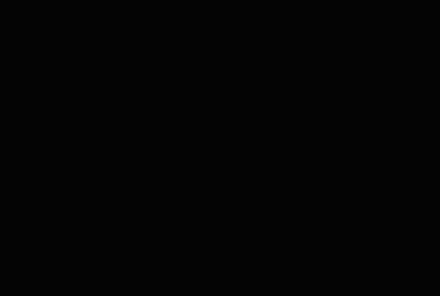
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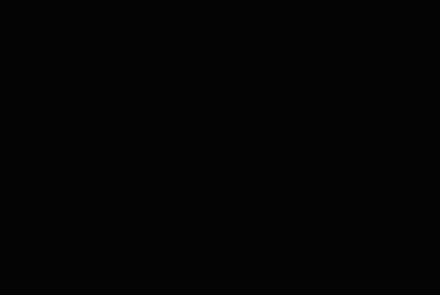
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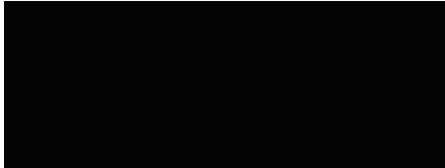
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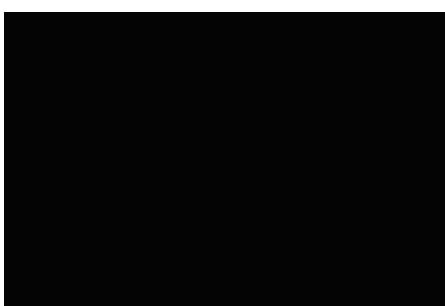
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The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy

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Abstract

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I focus on issues surrounding the promotion and marketing of controlled drugs and their regulatory oversight. Compared with noncontrolled drugs, controlled drugs, with their potential for abuse and diversion, pose different public health risks when they are overpromoted and highly prescribed. An in-depth analysis of the promotion and marketing of OxyContin illustrates some of the associated issues.

Modifications of the promotion and marketing of controlled drugs by the pharmaceutical industry and an enhanced capacity of the Food and Drug Administration to regulate and monitor such promotion can have a positive impact on the public health.

CONTROLLED DRUGS, WITH their potential for abuse and diversion, can pose public health risks that are different from—and more problematic than—those of uncontrolled drugs when they are overpromoted and highly prescribed. An in-depth analysis of the promotion and marketing of OxyContin (Purdue Pharma, Stamford, CT), a sustained-release oxycodone preparation, illustrates some of the key issues. When Purdue Pharma introduced OxyContin in 1996, it was aggressively marketed and highly promoted. Sales grew from \$48 million in 1996 to almost \$1.1 billion in 2000.¹ The high availability of OxyContin correlated with increased abuse, diversion, and addiction, and by 2004 OxyContin had become a leading drug of abuse in the United States.²

Under current regulations, the Food and Drug Administration (FDA) is limited in its oversight of the marketing and promotion of controlled drugs. However, fundamental changes in the promotion and marketing of controlled drugs by the pharmaceutical industry, and an enhanced capacity of the FDA to regulate and monitor such promotion, can positively affect public health.

OxyContin's commercial success did not depend on the merits of the drug compared with other available opioid preparations. The Medical Letter on Drugs and Therapeutics concluded in 2001 that oxycodone offered no advantage over appropriate doses of other potent opioids.³ Randomized double-blind studies comparing OxyContin given every 12 hours with immediate-release oxycodone given 4 times daily showed comparable efficacy and safety for use with chronic back pain⁴ and cancer-related

The promotion and marketing of OxyContin, Commercial Triumph In Public Health Transparency
 pain.^{5,6} Randomized double-blind studies that compared OxyContin with controlled-release morphine for cancer-related pain also found comparable efficacy and safety.⁷⁻⁹ The FDA's medical review officer, in evaluating the efficacy of OxyContin in Purdue's 1995 new drug application, concluded that OxyContin had not been shown to have a significant advantage over conventional, immediate-release oxycodone taken 4 times daily other than a reduction in frequency of dosing.¹⁰ In a review of the medical literature, Chou et al. made similar conclusions.¹¹

The promotion and marketing of OxyContin occurred during a recent trend in the liberalization of the use of opioids in the treatment of pain, particularly for chronic non–cancer-related pain. Purdue pursued an “aggressive” campaign to promote the use of opioids in general and OxyContin in particular.^{1,12-17} In 2001 alone, the company spent \$200 million¹⁸ in an array of approaches to market and promote OxyContin.

PROMOTION OF OXYCONTIN

[Go to:](#)

From 1996 to 2001, Purdue conducted more than 40 national pain-management and speaker-training conferences at resorts in Florida, Arizona, and California. More than 5000 physicians, pharmacists, and nurses attended these all-expenses-paid symposia, where they were recruited and trained for Purdue's national speaker bureau.^{19(p22)} It is well documented that this type of pharmaceutical company symposium influences physicians' prescribing, even though the physicians who attend such symposia believe that such enticements do not alter their prescribing patterns.²⁰

One of the cornerstones of Purdue's marketing plan was the use of sophisticated marketing data to influence physicians' prescribing. Drug companies compile prescriber profiles on individual physicians—detailing the prescribing patterns of physicians nationwide—in an effort to influence doctors' prescribing habits. Through these profiles, a drug company can identify the highest and lowest prescribers of particular drugs in a single zip code, county, state, or the entire country.²¹ One of the critical foundations of Purdue's marketing plan for OxyContin was to target the physicians who were the highest prescribers for opioids across the country.^{1,12-17,22} The resulting database would help identify physicians with large numbers of chronic-pain patients. Unfortunately, this same database would also identify which physicians were simply the most frequent prescribers of opioids and, in some cases, the least discriminate prescribers.

A lucrative bonus system encouraged sales representatives to increase sales of OxyContin in their territories, resulting in a large number of visits to physicians with high rates of opioid prescriptions, as well as a multifaceted information campaign aimed at them. In 2001, in addition to the average sales representative's annual salary of \$55 000, annual bonuses averaged \$71 500, with a range of \$15 000 to nearly \$240 000. Purdue paid \$40 million in sales incentive bonuses to its sales representatives that year.¹⁹

From 1996 to 2000, Purdue increased its internal sales force from 318 sales representatives to 671, and its total physician call list from approximately 33 400 to 44 500 to approximately 70 500 to 94 000 physicians.¹⁹ Through the sales representatives, Purdue used a patient starter coupon program for OxyContin that provided patients with a free limited-time prescription for a 7- to 30-day supply. By 2001, when the program was ended, approximately 34 000 coupons had been redeemed nationally.¹⁹

The distribution to health care professionals of branded promotional items such as OxyContin fishing hats, stuffed plush toys, and music compact discs (“Get in the Swing With OxyContin”) was unprecedented for a schedule II opioid, according to the Drug Enforcement Administration.¹⁹

Purdue promoted among primary care physicians a more liberal use of opioids, particularly sustained-release opioids. Primary care physicians began to use more of the increasingly popular OxyContin; by

The Promotion and Marketing of OxyContin, Commercial Triumph in Public Health Tragedy

2003, nearly half of all physicians prescribing OxyContin were primary care physicians.¹⁹ Some experts were concerned that primary care physicians were not sufficiently trained in pain management or addiction issues.²³ Primary care physicians, particularly in a managed care environment of time constraints, also had the least amount of time for evaluation and follow-up of patients with complicated chronic pain.

Purdue “aggressively” promoted the use of opioids for use in the “non-malignant pain market.”¹⁵(p187) A much larger market than that for cancer-related pain, the non–cancer-related pain market constituted 86% of the total opioid market in 1999.¹⁷ Purdue’s promotion of OxyContin for the treatment of non–cancer-related pain contributed to a nearly tenfold increase in OxyContin prescriptions for this type of pain, from about 670 000 in 1997 to about 6.2 million in 2002, whereas prescriptions for cancer-related pain increased about fourfold during that same period.¹⁹ Although the science and consensus for the use of opioids in the treatment of acute pain or pain associated with cancer are robust, there is still much controversy in medicine about the use of opioids for chronic non–cancer-related pain, where their risks and benefits are much less clear. Prospective, randomized, controlled trials lasting at least 4 weeks that evaluated the use of opioids for chronic, non–cancer-related pain showed statistically significant but small to modest improvement in pain relief, with no consistent improvement in physical functioning.^{24–38} A recent review of the use of opioids in chronic back pain concluded that opioids may be efficacious for short-term pain relief, but longer-term efficacy (> 16 weeks) is unclear.³⁹

In the long-term use of opioids for chronic non–cancer-related pain, the proven analgesic efficacy must be weighed against the following potential problems and risks: well-known opioid side effects, including respiratory depression, sedation, constipation, and nausea; inconsistent improvement in functioning; opioid-induced hyperalgesia; adverse hormonal and immune effects of long-term opioid treatment; a high incidence of prescription opioid abuse behaviors; and an ill-defined and unclarified risk of iatrogenic addiction.⁴⁰

MISREPRESENTING THE RISK OF ADDICTION

[Go to:](#)

A consistent feature in the promotion and marketing of OxyContin was a systematic effort to minimize the risk of addiction in the use of opioids for the treatment of chronic non–cancer-related pain. One of the most critical issues regarding the use of opioids in the treatment of chronic non–cancer-related pain is the potential of iatrogenic addiction. The lifetime prevalence of addictive disorders has been estimated at 3% to 16% of the general population.⁴¹ However, we lack any large, methodically rigorous prospective study addressing the issue of iatrogenic addiction during long-term opioid use for chronic nonmalignant pain.⁴²

In much of its promotional campaign—in literature and audiotapes for physicians, brochures and videotapes for patients, and its “Partners Against Pain” Web site—Purdue claimed that the risk of addiction from OxyContin was extremely small.^{43–49}

Purdue trained its sales representatives to carry the message that the risk of addiction was “less than one percent.”⁵⁰(p99) The company cited studies by Porter and Jick,⁵¹ who found iatrogenic addiction in only 4 of 11 882 patients using opioids and by Perry and Heidrich,⁵² who found no addiction among 10 000 burn patients treated with opioids. Both of these studies, although shedding some light on the risk of addiction for acute pain, do not help establish the risk of iatrogenic addiction when opioids are used daily for a prolonged time in treating chronic pain. There are a number of studies, however, that demonstrate that in the treatment of chronic non–cancer-related pain with opioids, there is a high incidence of prescription drug abuse. Prescription drug abuse in a substantial minority of chronic-pain patients has been demonstrated in studies by Fishbain et al. (3%–18% of patients),⁵³ Hoffman et al. (23%),⁵⁴ Kouyanou et al. (12%),⁵⁵ Chabal et al. (34%),⁵⁶ Katz et al. (43%),⁵⁷ Reid et al. (24%–

The Promotion and Marketing of OxyContin: Commercial Triumph or Public Health Tragedy
31%),⁵⁸ and Michna et al. (45%).⁵⁹ A recent literature review showed that the prevalence of addiction in patients with long-term opioid treatment for chronic non–cancer-related pain varied from 0% to 50%, depending on the criteria used and the subpopulation studied.⁶⁰

Misrepresenting the risk of addiction proved costly for Purdue. On May 10, 2007, Purdue Frederick Company Inc, an affiliate of Purdue Pharma, along with 3 company executives, pled guilty to criminal charges of misbranding OxyContin by claiming that it was less addictive and less subject to abuse and diversion than other opioids, and will pay \$634 million in fines.⁶¹

Although research demonstrated that OxyContin was comparable in efficacy and safety to other available opioids,^{11,63} marketing catapulted OxyContin to blockbuster drug status. Sales escalated from \$44 million (316 000 prescriptions dispensed) in 1996 to a 2001 and 2002 combined sales of nearly \$3 billion (over 14 million prescriptions).¹⁹

The remarkable commercial success of OxyContin, however, was stained by increasing rates of abuse and addiction. Drug abusers learned how to simply crush the controlled-release tablet and swallow, inhale, or inject the high-potency opioid for an intense morphinelike high.⁶⁴ There had been some precedence for the diversion and abuse of controlled-release opioid preparations. Purdue's own MS Contin had been abused in the late 1980s in a fashion similar to how OxyContin was later to be; by 1990, MS Contin had become the most abused prescription opioid in one major metropolitan area.⁶⁵ Purdue's own testing in 1995 had demonstrated that 68% of the oxycodone could be extracted from an OxyContin tablet when crushed.⁶⁶

Opioid prescribing has had significant geographical variations. In some areas, such as Maine, West Virginia, eastern Kentucky, southwestern Virginia, and Alabama, from 1998 through 2000, hydrocodone and (non-OxyContin) oxycodone were being prescribed 2.5 to 5.0 times more than the national average. By 2000, these same areas had become high OxyContin-prescribing areas—up to 5 to 6 times higher than the national average in some counties (Table 1).⁶⁷ These areas, in which OxyContin was highly available, were the first in the nation to witness increasing OxyContin abuse and diversion, which began surfacing in 1999 and 2000.²³ From 1995 to 2001, the number of patients treated for opioid abuse in Maine increased 460%, and from 1997 to 1999 the state had a 400% increase in the number of chronic hepatitis C cases reported.⁶⁸ In eastern Kentucky from 1995 to 2001, there was a 500% increase in the number of patients entering methadone maintenance treatment programs, about 75% of whom were OxyContin dependent (Mac Bell, administrator, Narcotics Treatment Programs, Kentucky Division of Substance Abuse, written communication, March 2002). In West Virginia, the first methadone maintenance treatment program opened in August 2000, largely in response to the increasing number of people with OxyContin dependence. By October 2003, West Virginia had 7 methadone maintenance treatment clinics with 3040 patients in treatment (M. Moore, Office of Behavioral Health Services, Office of Alcoholism and Drug Abuse, West Virginia, written communication, March 16, 2004). In southwestern Virginia, the first methadone maintenance treatment program opened in March 2000, and within 3 years it had 1400 admissions (E. Jennings, Life Center of Galax, Galax, Virginia, written communication, March 12, 2004).

TABLE 1 Distribution of OxyContin, Oxycodone (Excluding OxyContin), and Hydrocodone per 100 000 Population: Virginia, West Virginia, and Kentucky, 2000			
State and County	Distribution in Deaths per 100 000 Population		
	OxyContin	Oxycodone (Excluding OxyContin)	Hydrocodone
Virginia			
Dalton	28 801	8 777	18 888
Lee	23 988	8 030	8 445
Buchanan	18 149	4 930	13 988
Roanoke	17 856	2 868	17 273
			7 201

TABLE 1
Distribution of OxyContin, Oxycodone (Excluding OxyContin), and Hydrocodone per 100 000 Population:
Virginia, West Virginia, and Kentucky, 2000

With increasing diversion and abuse, opioid-related overdoses escalated. In southwest Virginia, the number of deaths related to opioid prescriptions increased 830%, from 23 in 1997 to 215 in 2003 (William Massello III, MD, assistant chief medical examiner, Office of Chief Medical Examiner,

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Western District, Virginia Department of Health, written communication, January 12, 2007). The high availability of OxyContin in these 5 regions seemed to be a simple correlate of its abuse, diversion, and addiction.

With the growing availability of OxyContin prescriptions, the once-regional problem began to spread nationally. By 2002, OxyContin accounted for 68% of oxycodone sales.⁶⁹ Lifetime nonmedical use of OxyContin increased from 1.9 million to 3.1 million people between 2002 and 2004, and in 2004 there were 615 000 new nonmedical users of OxyContin.⁷⁰ By 2004, OxyContin had become the most prevalent prescription opioid abused in the United States.²

The increasing OxyContin abuse problem was an integral part of the escalating national prescription opioid abuse problem. Liberalization of the use of opioids, particularly for the treatment of chronic non–cancer-related pain, increased the availability of all opioids as well as their abuse. Nationwide, from 1997 to 2002, there was a 226%, 73%, and 402% increase in fentanyl, morphine, and oxycodone prescribing, respectively (in grams per 100 000 population). During that same period, the Drug Abuse Warning Network reported that hospital emergency department mentions for fentanyl, morphine, and oxycodone increased 641%, 113%, and 346%, respectively.⁷¹ Among new initiates to illicit drug use in 2005, a total of 2.1 million reported prescription opioids as the first drug they had tried, more than for marijuana and almost equal to the number of new cigarette smokers (2.3 million).⁷² Most abusers of prescription opioids get their diverted drugs directly from a doctor's prescription or from the prescriptions of friends and family.⁷³

In terms of illicit drug abuse, prescription opioids are now ahead of cocaine and heroin and second only to marijuana.⁷² Mortality rates from drug overdose have climbed dramatically; by 2002, unintentional overdose deaths from prescription opioids surpassed those from heroin and cocaine nationwide.⁷⁴ Nationally, as well as regionally, the high availability of OxyContin and all prescription opioids was correlated with high rates of abuse and diversion.

THE FOOD AND DRUG ADMINISTRATION

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Under the Food, Drug, and Cosmetics Act and implementing regulations, the FDA regulates the advertising and promotion of prescription drugs and is responsible for ensuring that prescription drug advertising and promotion are truthful, balanced, and accurately communicated. There is no distinction in the act between controlled and noncontrolled drugs regarding the oversight of promotional activities. Although regulations require that all promotional materials for prescription drugs be submitted to the FDA for review when the materials are initially disseminated or used, it is generally not required that these materials be approved by the FDA prior to their use. The FDA has a limited number of staff for overseeing the enormous amount of promotional materials. In 2002, for example, 39 FDA staff members were responsible for reviewing roughly 34 000 pieces of promotional materials.¹⁹ This limited staffing significantly diminishes the FDA's ability to ensure that the promotion is truthful, balanced, and accurately communicated.

In 1998, Purdue distributed 15 000 copies of an OxyContin video to physicians without submitting it to the FDA for review, an oversight later acknowledged by Purdue. In 2001, Purdue submitted to the FDA a second version of the video, which the FDA did not review until October 2002—after the General Accounting Office inquired about its content. After its review, the FDA concluded that the video minimized the risks from OxyContin and made unsubstantiated claims regarding its benefits to patients.¹⁹

When OxyContin entered the market in 1996, the FDA approved its original label, which stated that iatrogenic addiction was “very rare” if opioids were legitimately used in the management of pain. In July 2001, to reflect the available scientific evidence, the label was modified to state that data were not

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available for establishing the true incidence of addiction in chronic-pain patients. The 2001 labeling also deleted the original statement that the delayed absorption of OxyContin was believed to reduce the abuse liability of the drug.¹⁹ A more thorough review of the available scientific evidence prior to the original labeling might have prevented some of the need for the 2001 label revision.

CONCLUSIONS

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OxyContin appears to be as efficacious and safe as other available opioids and as oxycodone taken 4 times daily.^{11,63} Its commercial success, fueled by an unprecedented promotion and marketing campaign, was stained by escalating OxyContin abuse and diversion that spread throughout the country.^{2,75} The regions of the country that had the earliest and highest availability of prescribed OxyContin had the greatest initial abuse and diversion.^{23,67} Nationally, the increasing availability of OxyContin was associated with higher rates of abuse, and it became the most prevalent abused prescription opioid by 2004.²

Compared with noncontrolled drugs, controlled drugs, with their potential for abuse and diversion, pose different public health risks when overpromoted and highly prescribed. Several marketing practices appear to be especially questionable.

The extraordinary amount of money spent in promoting a sustained-release opioid was unprecedented. During OxyContin's first 6 years on the market, Purdue spent approximately 6 to 12 times more on promoting it than the company had spent on promoting MS Contin, or than Janssen Pharmaceutical Products LP had spent on Duragesic, one of OxyContin's competitors.¹⁹ Although OxyContin has not been shown to be superior to other available potent opioid preparations,^{11,63} by 2001 it had become the most frequently prescribed brand-name opioid in the United States for treating moderate to severe pain.¹⁹ Carefully crafted limits on the marketing and promotion of controlled drugs would help to realign their actual use with the principles of evidence-based medicine.

Physicians' interactions with pharmaceutical sales representatives have been found to influence the prescribing practices of residents and physicians in terms of decreased prescribing of generic drugs, prescribing cost, nonrational prescribing, and rapid prescribing of new drugs.⁷⁶ Carefully crafted limits on the promotion of controlled drugs by the pharmaceutical sales force and enhanced FDA oversight of the training and performance of sales representatives would also reduce over- and misprescribing.

Although there are no available data for evaluating the promotional effect of free starter coupons for controlled drugs, it seems likely that the over- and misprescribing of a controlled drug are encouraged by such promotional programs and the public health would be well served by eliminating them.

The use of prescriber profiling data to influence prescribing and improve sales is imbedded in pharmaceutical detailing. Very little data are publicly available for understanding to what extent this marketing practice boosts sales. One market research report indicated that profiling improved profit margins by as much as 3 percentage points and the initial uptake of new drugs by 30%.⁷⁷ The use of prescriber profiling data to target high-opioid prescribers—coupled with very lucrative incentives for sales representatives—would seem to fuel increased prescribing by some physicians—perhaps the most liberal prescribers of opioids and, in some cases, the least discriminate. Regulations eliminating this marketing tool might decrease some potential overprescribing of controlled drugs.

The public health would be better protected if the FDA reviewed all advertising and promotional materials as well as associated educational materials—for their truthfulness, accuracy, balance, and scientific validity—before dissemination. Such a change would require a considerable increase in FDA support, staffing, and funding from what is currently available. Public monies spent on the front end of the problem could prevent another such tragedy.

The pharmaceutical industry's role and influence in medical education is problematic. From 1996 through July 2002, Purdue funded more than 20 000 pain-related educational programs through direct sponsorship or financial grants,¹⁹ providing a venue that had enormous influence on physicians' prescribing throughout the country. Particularly with controlled drugs, the potential for blurring marketing and education carries a much higher public health risk than with uncontrolled drugs. At least in the area of controlled drugs, with their high potential for abuse and diversion, public health would best be served by severing the pharmaceutical industry's direct role and influence in medical education.

Marketing and promotion by the pharmaceutical industry have considerably amplified the prescription sales and availability of opioids. A number of factors have contributed to the marked growth of opioid abuse in the United States, but one factor is certainly the much increased availability of prescription opioids.⁷⁸ The public interest and public health would be better served by a redefinition of acceptable and allowable marketing practices for opioids and other controlled drugs.

Acknowledgments

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EXHIBIT 47



Opioid Painkiller Prescribing

Where You Live Makes a Difference

On this Page

- Problem
- Infographic
- What Can Be Done
- Science Behind the Issue
- Related Pages

July 2014

Vital signs™



46

Each day, 46 people die from an overdose of prescription painkillers* in the US.



259 M

Health care providers wrote 259 million prescriptions for painkillers in 2012, enough for every American adult to have a bottle of pills.



10

10 of highest prescribing states for painkillers are in the South.

Health issues that cause people pain don't vary much from place to place—not enough to explain why, in 2012, health care providers in the highest-prescribing state wrote almost 3 times as many opioid painkiller prescriptions per person as those in the lowest prescribing state in the US. Or why there are twice as many painkiller prescriptions per person in the US as in Canada. Data suggest that where health care providers practice influences how they prescribe. Higher prescribing of painkillers is associated with more overdose deaths. More can be done at every level to prevent overprescribing while ensuring patients' access to safe, effective pain treatment. Changes at the state level show particular promise.

States can

- Consider ways to increase use of prescription drug monitoring programs, which are state-run databases that track prescriptions for painkillers and can help find problems in overprescribing. Use of these programs is greater when they make data available in real-time, are universal (used by all prescribers for all controlled substances), and are actively managed (for example, send alerts to prescribers when problems are identified).
- Consider policy options (including laws and regulation) relating to pain clinics (facilities that specialize in pain treatment) to reduce prescribing practices that are risky to patients.

Problem

An increase in painkiller prescribing is a key driver of the increase in prescription overdoses.

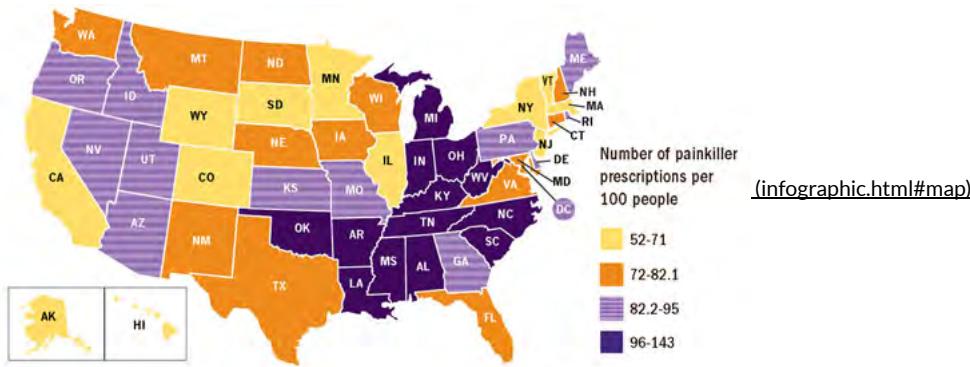
Health care providers in some states prescribed far more painkillers than those in other states in 2012.

- Southern states had the most prescriptions per person for painkillers, especially Alabama, Tennessee, and West Virginia.
- The Northeast, especially Maine and New Hampshire, had the most prescriptions per person for long-acting and high-dose painkillers.
- Nearly 22 times as many prescriptions were written for oxymorphone (a specific type of painkiller) in Tennessee as were written in Minnesota.

What might be causing this?

- Health care providers in different parts of the country don't agree on when to use prescription painkillers and how much to prescribe.
- Some of the increased demand for prescription painkillers is from people who use them nonmedically (using drugs without a prescription or just for the high they cause), sell them, or get them from multiple prescribers at the same time.
- Many states report problems with for-profit, high-volume pain clinics (so-called "pill mills") that prescribe large quantities of painkillers to people who don't need them medically.

Some states have more painkiller prescriptions per person than others.



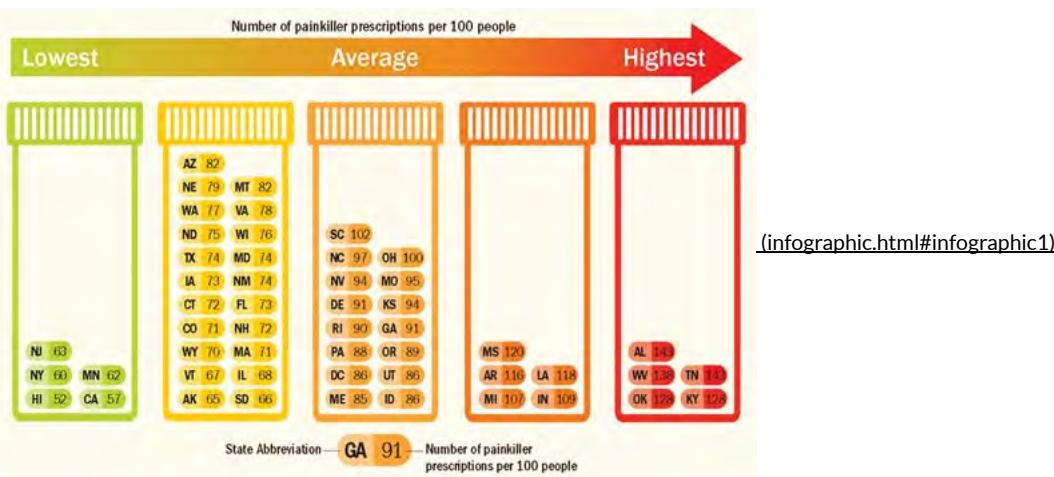
SOURCE: IMS, National Prescription Audit (NPA™), 2012.

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Infographic

Health care providers in different states prescribe at different levels.



SOURCE: IMS, National Prescription Audit (NPA™), 2012.

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Making a Difference: State Successes



SOURCES: NY, TN: PDMP Center of Excellence at Brandeis University, 2014. FL: Vital Signs Morbidity and Mortality Weekly Report, July 1, 2014.

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What Can Be Done

Federal government is

- Supporting states that want to develop programs and policies to prevent prescription painkiller overdose, while ensuring patients' access to safe, effective pain treatment.
- Improving patient safety by supplying health care providers with data, tools, and guidance for decision making based on proven practices.
- Increasing access to mental health and substance abuse treatment through the Affordable Care Act.

States can

- Consider ways to increase use of prescription drug monitoring programs, which are state-run databases that track prescriptions for painkillers and can help find problems in overprescribing. Use of these programs is greater when they make data available in realtime, are universal (used by all prescribers for all controlled substances), and are actively managed (for example, send alerts to prescribers when problems are identified).
- Consider policy options (including laws and regulation) relating to pain clinics to reduce prescribing practices that are risky to patients.
- Evaluate their own data and programs and consider ways to assess their Medicaid, workers' compensation programs, and state-run health plans to detect and address inappropriate prescribing of painkillers.
- Identify opportunities to increase access to substance abuse treatment and consider expanding first responder access to naloxone, a drug used when people overdose.

Health care providers can

- Use prescription drug monitoring programs to identify patients who might be misusing their prescription drugs, putting them at risk for overdose.
- Use effective treatments such as methadone or buprenorphine for patients with substance abuse problems.
- Discuss with patients the risks and benefits of pain treatment options, including ones that do not involve prescription painkillers.
- Follow best practices for responsible painkiller prescribing, including:
 - Screening for substance abuse and mental health problems.
 - Avoiding combinations of prescription painkillers and sedatives unless there is a specific medical indication.
 - Prescribing the lowest effective dose and only the quantity needed depending on the expected length of pain.

Everyone can

- Avoid taking prescription painkillers more often than prescribed.
- Dispose of medications properly, as soon as the course of treatment is done, and avoid keeping prescription painkillers or sedatives around "just in case."
- Help prevent misuse and abuse by not selling or sharing prescription drugs. Never use another person's prescription drugs.
- Get help for substance abuse problems 1-800-662-HELP. Call Poison Help 1-800-222-1222 if you have questions about medicines.

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Science Behind the Issue

- MMWR
- Science Clips (<http://www.cdc.gov/library/>)

Related Pages

- 2:17-cv-19334-JCO-EAS Doc # 1-48 Filed 10/12/17 Pg 5 of 5 Pg ID 1341**
- Vital Signs: Prescription Painkiller Overdoses: A Growing Epidemic Especially Among Women (<http://www.cdc.gov/vitalsigns/prescriptionpainkilleroverdoses/index.html>)
 - Vital Signs: Prescription Painkiller Overdoses: Use and Abuse of Methadone as a Painkiller (<http://www.cdc.gov/vitalsigns/methadoneoverdoses/index.html>)
 - Vital Signs: Prescription Painkiller Overdoses in the US (<http://www.cdc.gov/vitalsigns/PainkillerOverdoses/index.html>)
 - Prescription Drug Overdose (<http://www.cdc.gov/homeandrecreationsafety/overdose/index.html>)
 - Policy Impact: Prescription Painkiller Overdoses (<http://www.cdc.gov/homeandrecreationsafety/rxbrief/>)
 - Common Elements in Guidelines for Prescribing Opioids for Chronic Pain (<http://www.cdc.gov/HomeandRecreationalSafety/overdose/guidelines.html>)

On Other Web Sites

- MedlinePlus - Prescription Drug Abuse (<http://www.medlineplus.gov/prescriptiondrugabuse.html>)
- MedlinePlus - Pain Relievers (<http://www.medlineplus.gov/painrelievers.html>)
- The White House - Office of National Drug Control Policy (<http://www.whitehouse.gov/ondcp>)
- SAMHSA - Substance Abuse and Mental Health Services Administration (<http://www.samhsa.gov/>)
 - Medication-Assisted Treatment for Opioid Addiction: Facts for Families and Friends (<http://store.samhsa.gov/product/Medication-Assisted-Treatment-for-Opioid-Addiction-Facts-for-Families-and-Friends/SMA09-4443>)
 - Opioid Overdose Prevention Toolkit (<http://store.samhsa.gov/product/Opioid-Overdose-Prevention-Toolkit/SMA13-4742>)
 - Buprenorphine Treatment Locator (http://buprenorphine.samhsa.gov/bwns_locator/)
 - Mental Health Treatment Locator (<http://findtreatment.samhsa.gov/MHTreatmentLocator/faces/quickSearch.jspx>)
- Drug Enforcement Administration - Office of Diversion Control (<http://www.deadiversion.usdoj.gov/>)
- National Institute on Drug Abuse (<http://www.drugabuse.gov/>)
 - Drugs, Brains, and Behavior: The Science of Addiction (<http://www.drugabuse.gov/publications/science-addiction>)
 - Opioid and Pain Management CMEs/CEs (<http://www.drugabuse.gov/opioid-pain-management-cmesces>)
- Prescription Drugs (<http://www.nida.nih.gov/drugpages/prescription.html>)
- U.S. Food and Drug Administration - Drugs Information (<http://www.fda.gov/Drugs/default.htm>)
- National Institute of Mental Health (<http://www.nimh.nih.gov/>)
 - Mental health medications (<http://www.nimh.nih.gov/health/publications/mental-health-medications/index.shtml>)
- PDMP Center of Excellence, Brandeis University (<http://www.pdmpexcellence.org/>)
- The Dartmouth Atlas of Health Care (<http://www.dartmouthatlas.org/>)
- National Alliance for Model State Drug Laws (<http://www.namsdl.org/>)
- Office of the National Coordinator for Health Information Technology (ONC) - Linking PDMPs to Health IT (<http://www.healthit.gov/PDMP>)
- Prescription Drug Monitoring Program Initiative (<http://wiki.siframework.org/Prescription+Drug+Monitoring+Program+Initiative>)
- National Action Plan for Adverse Drug Event Prevention (<http://www.health.gov/hai/ade.asp>)
- CMS Improvements to Medicare Drug and Health Plans (<http://www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2014-Fact-sheets-items/2014-05-19.html>)

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EXHIBIT 48

FORTUNE

OxyContin: Purdue Pharma's painful medicine

By **Katherin Eban** Nov 9th, 2011 10:00 AM ET

What the strange saga of Purdue and its \$3 billion drug tells us about our national dependence on painkillers.

FORTUNE — We have become a nation of pill poppers. Pain tablets are the prime culprits — more specifically, opioids. You may have never heard the word “opioid,” which refers to a broad category of drugs derived from natural or synthetic forms of opium or morphine. You have, however, likely heard of many of the medications in the group, which includes everything from Percocet to Vicodin to Fentanyl. Their chemical composition is such that the U.S. is just a few carbon molecules from being a nation of heroin addicts.

Consider these statistics, all for 2010: 254 million prescriptions for opioids were filled in the U.S., according to Wall Street analysts Cowen & Co. Enough painkillers were prescribed to “medicate every American adult around the clock for a month,” the federal Centers for Disease Control reported on Nov. 1. It estimated that “nonmedical use of prescription painkillers costs health insurers up to \$72.5 billion annually in direct health care costs.” Opioids generated \$11 billion in revenues for pharmaceutical companies, says market research firm Frost & Sullivan.

Sellers include giants such as Abbott Labs ([ABT, -0.60%](#)) , Novartis ([NVS, -0.38%](#)) , Johnson & Johnson ([JNJ, +0.23%](#)) , and (in the future) Pfizer ([PFE, +0.25%](#)) , as well as smaller fry like Endo Pharmaceuticals ([ENDP, -1.05%](#)) in Newark, Del., which makes Percocet, and UCB of Belgium, which makes Lortab. Most opioids are made by big generics companies such as Watson Pharmaceuticals ([WPI, +0.00%](#)) , with companywide sales of \$3.6 billion last year, and Covidien ([COV, +0.00%](#)) of Ireland, with \$10.4 billion.

Two decades ago opioid sales were a small fraction of today’s figures, as such drugs were reserved for the worst cancer pain. Why? Because drugs whose chemical composition

resemble heroin's are nearly as addictive as heroin itself, and doctors generally wouldn't use such powerful meds on anybody but terminal cancer patients. But that changed years ago, and ever since, addiction to painkillers has become a staple of news headlines. There are periodic lurid crimes, such as the quadruple homicide in a Long Island pharmacy this summer committed by an addict desperate for hydrocodone. More often, there are the celebrities, such as Rush Limbaugh, who admitted on his radio show years ago that he was addicted to painkillers, or actor Heath Ledger, who was found dead with oxycodone in his system, or rapper Eminem, who entered rehab to address his reliance on Vicodin and other pills.

The celebrity in rehab and the addict holding up pharmacies have both become such clichés that it's easy to view painkiller calamities as things that happen only to criminals and celebrities. But the numbers are broad and disturbing: Some 15,000 Americans died of opioid overdoses in 2008 — triple the number for 1999, according to the new CDC findings. That's more than from heroin and cocaine combined. As Dr. Irfan Dhalla, a physician and drug-safety researcher, puts it, "That's four 9/11s a year."

The other reason it's easy to brush off opioid dependence is that unlike with heroin or cocaine, most people swallow the pills, at least initially, because their doctor tells them to. You could call it **the invisible addiction**: countless Americans — including all manner of businesspeople — taking medication prescribed to them who discover, months or years later, that they can't stop. According to Physicians for Responsible Opioid Prescribing, more than 25% of opioid users meet the criteria for addiction.

A field guide to the 6 best-known opioids

Among the sellers of opioids, none has been more successful — or controversial — than Purdue Pharma, maker of the No. 1 drug in the class: OxyContin, which generated \$3.1 billion in revenue in 2010. Purdue and its marketing prowess are the biggest reasons such drugs are now widely prescribed for all sorts of pain, says Dhalla: "Purdue played a very large role in making physicians feel comfortable about opioids." And as we'll see, Purdue's past and present go a long way toward explaining how so many Americans came to be in the grip of potent painkillers.

OxyContin. Purdue Pharma's painful medicine. Fortune

When it was introduced in the late '90s, OxyContin was touted as nearly addiction-proof — only to leave a trail of dependence and destruction. Its marketing was misleading enough that [Purdue pleaded guilty in 2007](#) to a federal criminal count of misbranding the drug "with intent to defraud and mislead the public," paid \$635 million in penalties, and today remains on the corporate equivalent of probation.

OxyContin's bad reputation, however, has obscured a significant step. Last year Purdue began selling a reformulated version that should help reduce the worst form of abuse. The original drug had a time-release mechanism that could be defeated by crushing the pill and snorting it, smoking it, or adding water to the powder and injecting it for a heroin-like high. (Purdue's claims that the time-release process reduced the addiction risk were crucial in making doctors feel comfortable prescribing a powerful addictive drug.) By contrast, the new version breaks into chunks rather than a powder; if water is added, the result is a gelatinous goop.

So far the new OxyContin appears to be withstanding attempts to crush, snort, or inject it. The "street price" — what addicts are willing to pay on the black market — has dropped from \$0.73 per milligram for the old version to \$0.52 for the new, according to data from Radars (Researched Abuse, Diversion, and Addiction-Related Surveillance), a program originally designed and funded by Purdue that collects data on prescription-drug abuse. As one disgusted abuser wrote on an addiction chat site called Bluelight after a failed effort to mince the new version with a razorblade, "Purdue won. I knew the oxy was inside, but I could not break into the safe."

Purdue has taken a worthwhile step, but one that only highlights the paradox of opioids. There's no question that making it harder to crush OxyContin will cut down on a pernicious form of misuse (not incidentally, the one that most resembles what people think of as "drug abuse"). But at the same time, taking that step lifts a stigma from the drug and may make doctors more comfortable prescribing it, an outcome Purdue is hoping for. The result could be an even greater number of invisible addicts.

Purdue's own drug war

Purdue is a private company in both senses of the word: It's family-owned, and it's reticent when it comes to discussing its business. But this summer, after much reluctance

and multiple requests, Purdue agreed to let me visit its offices in Stamford, Conn. The mere presence of a reporter in the building seemed to disrupt Purdue's systems: An intercom started blaring, and the phones and Internet service crashed. Technicians scurried to fix the problem, and I soon found myself in a conference room, where my e-mailed query to Purdue was projected on the wall and two executives waited with stacks of documents.

Though they were wary, Alan Must, Purdue's VP for state government and public affairs, and Mark Geraci, its chief security officer, seemed eager to get a chance to speak for the company. "We are well aware of detractors," says Must. "For those individuals who think we're evil ... I don't think there's anything we can do that is going to change their opinion."

"Obviously," he says later, "the idea that our business model is based on getting patients addicted and dependent is absurd," though he acknowledges it's "not unusual for patients to become physically dependent." In the company's view, Americans have long suffered from an epidemic of pain, and Purdue provides profound relief. Says Must: "At the end of the day, I am very proud to work for this company and proud of the things we have done."

Ironically, Purdue views itself as waging a drug war. On one side sits the company and its intended patients, who need OxyContin to alleviate real pain. On the other side are the "bad" patients who misuse painkillers to get high or cross state lines to shop for pliant doctors willing to write a prescription. Must and Geraci say Purdue has everything to gain if OxyContin is sold properly and abuse minimized. "One might argue that your sales might actually go up," Must says, "because now physicians have some confidence that when they're prescribing this product, they're not being scammed." He adds, "We are trying to be part of the solution."

Purdue is deploying large sums of money (the company won't give specifics) on programs to fight abuse and lawbreaking. The company operates Rx Patrol, a website that circulates police reports on drug crimes. Purdue offers rewards for citizens who help bring perpetrators to justice. The company distributes brochures that fit in the visors of police cars with photographs and names of frequently abused prescription drugs to make it easy to identify them. It pays for addiction hotlines, brochures that help parents figure out if their children are pilfering from the medicine cabinet, and DVDs that describe the perils of addiction. Purdue has even given thousands of height charts to pharmacies to help

witnesses guess the height of robbers. (That seems an unfortunate bit of brand linkage, given that the height charts suggest — accurately — that dispensing OxyContin may increase the chance of [a robbery in your store](#).)

One of the company's most substantial programs consists of seminars to train police on how to recognize and respond to the abuse and [diversion of prescription drugs](#). That's why, on a September morning, I find myself in a ballroom at the Marriott Hotel in Austin. The seats are filled with wide-shouldered Texas lawmen, many in cowboy boots, most with guns holstered on hips. The teachers are two retired officers, Landon Gibbs and Ed Cartwright, now Purdue employees wearing company polo shirts. They're part of a six-person team that travels the country holding free seminars. Purdue is the only drug company to offer such a service.

Over four hours the men lead the attendees through a disturbing real-life topography of abuse and addiction: the operating-room nurse who stole anesthetic from patients before surgery, leaving them to writhe in agony on the surgical table; the drug-addicted relatives who peel painkilling Fentanyl patches off the skin of their loved ones in nursing homes; the "pharm" parties where kids empty their parents' medicine cabinets, dump the haul into a bowl, and ingest random pills.

The presenters neither avoid nor focus on problems related to OxyContin. If they're selling anything, it's the staggering scale of the problem, with prescription-drug abuse responsible for one-third of the overdose visits to the nation's emergency rooms. "Once those pills leave those pharmacies, where are they?" Cartwright asks the group. "We don't know."

During a coffee break, I ask the participants what they think of the workshop. One attendee, an investigator with the Drug Enforcement Administration, tacitly acknowledges the tension his agency has had with the company. He tells me: "Our supervisors didn't prevent us from coming." There was a time not that long ago when they would have.

The brothers Sackler

If you're an art aficionado or a denizen of the academic world, there's a good chance you recognize the name Sackler. The glorious Egyptian Temple of Dendur at New York's Metropolitan Museum of Art resides in the Sackler Wing; galleries at the Smithsonian, at Harvard, Oxford, and Peking University, as well as institutes at Clark, Tufts, and New York University, all bear the name of the family that brought the world OxyContin.

It's an impressive philanthropic legacy and all the more striking for the family's humble origins. Brothers Arthur, Mortimer, and Raymond Sackler were born in the second decade of the 20th century to Eastern European immigrants who ran a grocery store in Brooklyn. (Only Raymond, 91, is alive; he still goes to Purdue's offices.) All three brothers became psychiatrists and worked at a mental hospital in Queens in the 1940s, where their insights would later be hailed. The three "helped pioneer research of the biology of psychiatric illnesses," *BMJ* (formerly the *British Medical Journal*) wrote last year, "research that helped open the door decades later toward drug treatments."

Leveraging their scientific prowess, the brothers branched into business. In 1952, Mortimer and Raymond bought a 60-year-old drug company called Purdue Frederick. Its principal product was a sherry-based "medicinal tonic" called Gray's Glycerine, whose earlier owner was federally charged in 1914 for overstating the tonic's curative powers. Purdue then expanded into selling earwax removers, laxatives, and antiseptics.

Meanwhile, the brilliant eldest brother, Arthur, joined a small advertising agency that specialized in marketing pharmaceuticals. (He also funded his brothers' purchase of Purdue, according to a 2003 book by *New York Times* reporter Barry Meier called *Pain Killer: A Wonder Drug's Trail of Addiction and Death*.) Arthur was so successful that in 1997 he was one of the first people named to the Medical Advertising Hall of Fame, whose website credits him with helping "shape pharmaceutical promotion as we know it today." As early as the 1950s he was experimenting with TV marketing, and according to the entry, Arthur's scientific knowledge and ability to expand the uses for Valium helped turn it into the first \$100 million drug ever. Arthur's philosophy was to sell drugs by lavishing doctors with fancy junkets, expensive dinners, and lucrative speaking fees, an approach so effective that the entire industry adopted it.

Purdue itself remained a backwater. But the brothers had ambitions, and Arthur's research told them that pain medicine was a growth area. In 1984 Purdue took an old drug

OxyContin. Purdue Pharma's painful medicine. Fortune for cancer pain, morphine sulfate, added a time-release formula, and began selling it as MS Contin. Over the next decade sales exceeded \$475 million, and they spun the pain unit into its own company: Purdue Pharma. By then Arthur Sackler had died. Still, his brothers knew that if they wanted a mega-hit with a pain medication, they'd need to find a way to sell to a market much broader than dying cancer patients.

OxyContin's dark side

Purdue's breakthrough would be one of marketing rather than medicine. The painkiller in OxyContin was not remotely new. Its active ingredient was oxycodone, a strong, partly modified form of an opiate alkaloid called thebaine invented in Germany in 1916. The patent had run out decades before, and the generic form was sold by a number of companies.

But with its new time-release mechanism, Purdue won FDA approval to sell OxyContin in late 1995. Purdue immediately set out to promote its new drug, following Arthur Sackler's template. The company pushed for its use in a broad range of chronic pain: everything from backaches to arthritis. Purdue knew it needed to overcome doctors' fears about addiction, so it treated the time-release formula as a magic bullet. It claimed the drug would give pain patients steadier 12-hour coverage, avoid withdrawal, and frustrate addicts seeking a euphoric rush. As one 1998 Purdue promotional video stated, the rate of addiction for opioid users treated by doctors is "much less than 1%."

The pitch worked, and sales took off: from \$45 million in 1996 to \$1.5 billion in 2002 to nearly \$3 billion by 2009. The key: Nearly half of those prescribing OxyContin were primary-care doctors rather than, say, cancer specialists, the General Accounting Office reported. Purdue had succeeded in vastly expanding the market for its drug.

But evidence quickly emerged of OxyContin's dark side. Doctors discovered that the drug lasted around eight hours rather than 12, and that patients would crash, needing more and higher doses. Patients who took moderate amounts for backaches or arthritis could find themselves hooked. Addicts saw they could easily get high by crushing the pills and then snorting, chewing, or injecting them.

In congressional testimony, Purdue's top executives would later say they first learned of problems with OxyContin in 2000, after the U.S. attorney in Maine warned of rampant abuse. But for at least three years prior, internal records show, company executives were aware of the abuse allegations. In October 1997, for example, a Purdue marketing executive e-mailed several people, including then-COO Michael Friedman, stating that references to OxyContin abuse on addiction chat sites were "enough to keep a person busy all day." He added, "We have three people that visit the site chat rooms." (A lawyer for Friedman and two other former Purdue executives says that "substantial levels of abuse did not begin until 2000 and 2001," and cites DEA data showing the numbers of cases reported to the government first spiked in those years.)

As addiction rates began rising in the early 2000s, prosecutors and plaintiffs lawyers circled. The case grew so serious, *Fortune* has learned, that federal prosecutors formally recommended charging Purdue and its three top executives (but none of the Sacklers) with multiple felonies including conspiracy, mail and wire fraud, and money laundering, in addition to misbranding.

But Purdue dodged the worst charges. The company hired an all-star defense team, including Mary Jo White, a former U.S. attorney, and Rudolph Giuliani, then the Republican Party's presumptive presidential front-runner. The company was able to appeal above the heads of the prosecutors on the case and met with the head of the Justice Department's criminal division.

Eventually the two sides agreed that Purdue would plead guilty to a single felony count of misbranding. In May 2007 the company agreed to pay a \$600.5 million fine, and its top three executives were fined \$34.5 million (though the company picked up the tab) and subsequently left Purdue. Each of the three pleaded guilty to a misdemeanor count of misbranding. Jonathan Abram, a lawyer for the three executives — then-CEO Michael Friedman, chief medical officer Paul Goldenheim, and general counsel Howard Udell — asserts his clients bore no personal responsibility for wrongdoing. He says the lead prosecutor admitted that the government had found "no evidence against the three individuals to support charges based on any sort of knowing or intentional misconduct. That's why they were charged with only a strict liability misdemeanor." Abram asserts the three were "leaders" in the company's efforts to address abuse.

In its plea Purdue acknowledged that its promotional materials had contained misleading or inaccurate data and that its sales force made claims unsupported by science that falsely downplayed the addiction risks.

Are opioids worth it in the end?

Long before Purdue was penalized by the government, the company sensed that the extent of OxyContin abuse and addiction threatened its franchise. By 2001 the DEA had raised the idea of imposing quotas on the drug and allowing only pain specialists to prescribe it. A Purdue medical director wrote in an e-mail that “the threat of cutting back the quotas to 1996 levels is ghastly ... [We] really are in a battle.” The company’s best defense became a commitment to security, which could show it was policing itself. Purdue aimed to convince key government officials, an internal strategic plan explained, that its “voluntary program to safeguard the use of OxyContin is the only effective means to proscribe it without interfering with the doctor-patient relationship.”

Almost a decade later, Purdue appears to be following that approach (a contention that company spokesman James Heins disputes: “The purpose of our anti-diversion efforts has been to prevent or reduce the abuse of OxyContin and other prescription medications.”) In August 2010 its new formulation debuted. Because of past marketing abuses and ongoing federal scrutiny, not to mention litigation risk and a history of bad press, Purdue has refrained from making proclamations about the new version. But Heins is adamant that the company began work on a reformulation long before its criminal case.

Eventually sales of the harder-to-abuse version of OxyContin will provide a barometer of sorts as to what portion of its business is attributable to those who snort or inject it, since they’ll probably abandon the painkiller in favor of another. The new formulation seems likely to dent sales, argues Dr. Andrew Kolodny, chair of psychiatry at Maimonides Medical Center and president of Physicians for Responsible Opioid Prescribing. “Even many pain patients who are addicted and don’t realize it,” he says, “are actually complaining about the new formulation because it has better time release.” Kolodny views Purdue as benefiting from addiction. As he puts it, “Once you’ve got a patient who’s addicted or physically dependent, and they’re going to be too sick to stop taking it, that’s a very good business model.”

The FDA is encouraging other painkiller manufacturers to develop tamper-resistant formulas, according to a recent report by Cowen & Co. For example, Pfizer, which is planning to get into the generic oxycodone game in coming years, is expected to use such a formula.

But the use of tamper-resistant pills is hardly going to slow the painkiller juggernaut. Analysts expect the opioid market to maintain its rapid growth. Frost & Sullivan projects an increase from today's \$11 billion to \$15.3 billion by 2016.

Meanwhile an increasing number of physicians are wondering whether opioids are worth it. "I have come to question whether the long-term treatment of nonmalignant pain is causing more harm than good," wrote a San Francisco public health internist named Mitchell Katz in a journal article last year. He subtitled it "A Believer Loses His Faith." A little less faith in painkillers right now would do the country a lot of good.

-Reporter associate Doris Burke contributed to this article.

This article is from the November 21, 2011 issue of Fortune.

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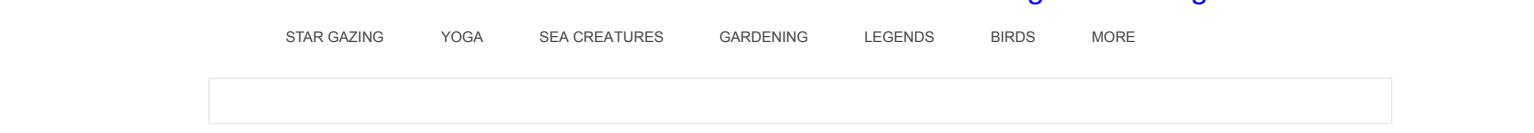
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MEDICATIONS & VITAMINS

Q: What is the difference between agonist and antagonist drugs?

A: [QUICK ANSWER](#)

Agonist drugs activate neurotransmitter receptors to produce a certain response. Antagonist drugs work to prevent the binding of other chemicals to neurotransmitters to block a certain response, according to the Merck Manual. [CONTINUE READING](#)

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Addictive drugs give the desired effect by interacting with neurotransmitters and altering brain chemistry, says the Merck Manual. The brain naturally produces a balance of chemicals to bind and block these receptors, and there are two types of agonist drugs that bind the receptors. Most agonist drugs are conventional agonists, which increase the number of active neurotransmitters. Inverse agonists work similarly to antagonist drugs and keep the receptors stabilized in an inactive conformation so that compounds cannot activate them.

Antagonist drugs are introduced chemicals that block receptor activation to produce the desired effect, the Merck Manual describes. These drugs can either directly block neurotransmitters or bind to the chemicals meant to attach to those receptors and prevent them from binding. There are two types of antagonist drugs: reversible and irreversible. Irreversible antagonist drugs bind the receptor and remain tightly associated to prevent the binding of other chemicals, while reversible antagonists readily dissociate from their receptor. Agonist and antagonist drugs can both be bound to the same receptor, but the antagonist drug binding reduces or prevents the unction of the agonist drug.

[LEARN MORE ABOUT MEDICATIONS & VITAMINS](#)

Sources: merckmanuals.com



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A: Trimix is a combination of three separate drugs, which are combined to create a sterile injection used to treat erectile dysfunction, according to The Comp... [FULL ANSWER >](#)

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A: Some common anticoagulant drugs include warfarin, enoxaparin and heparin, explains National Jewish Health. The U.S. Food and Drug Administration approves o... [FULL ANSWER >](#)

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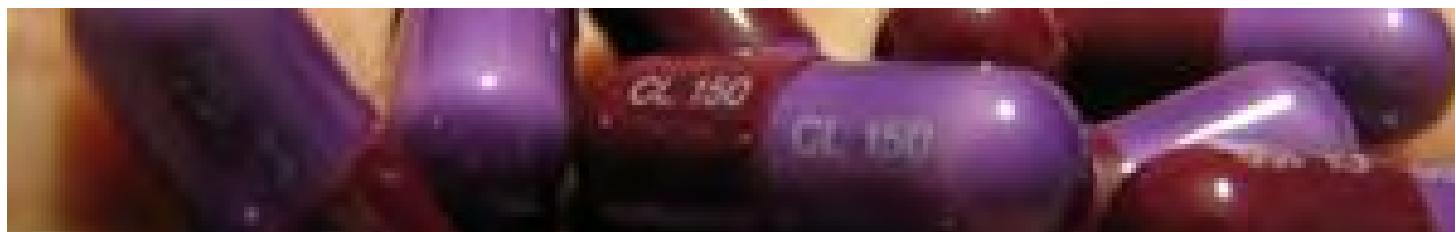
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DILAUDID ADDICTION

What is Dilaudid?

While the potent prescription pain killer Dilaudid may not be as well-known as some of its more popular contemporaries like **OxyContin** and Vicodin, it still has the potential to be very dangerous and highly addictive drug. Dilaudid, also known as hydromorphone, is an analgesic that is used in the treatment of severe and chronic pain. Because of its powerful and addictive nature, Dilaudid should only be taken as prescribed, and is generally not prescribed for an extended period of time. Dilaudid can sometimes be prescribed for chronic coughing and is 8 times more potent than morphine.

Dilaudid is a very powerful pain killer that acts similar to morphine on the body. Dilaudid not only soothes severe pain but also creates a high level of euphoria. Dilaudid is highly addictive and can cause long term addiction and dependency.

History of Dilaudid

Dilaudid was invented in 1924 by a group of German scientists and was then subsequently marketed a few years later by a drug company

Dilauidid Addiction - Dilauidid Dependence and Withdrawal Symptoms
named Knoll. Dilauidid was created in hopes of developing a superior chronic pain reliever to morphine, with much less severe side effects. Even though Dilauidid was derived from morphine, scientists hoped that it would be less prone to long-term addiction and dependency. However, it didn't take long to realize that Dilauidid is actually as addictive, if not more addictive than morphine, and has since become a popular substitute for dangerous street drugs like **heroin** and OxyContin.

Dilauidid Addiction

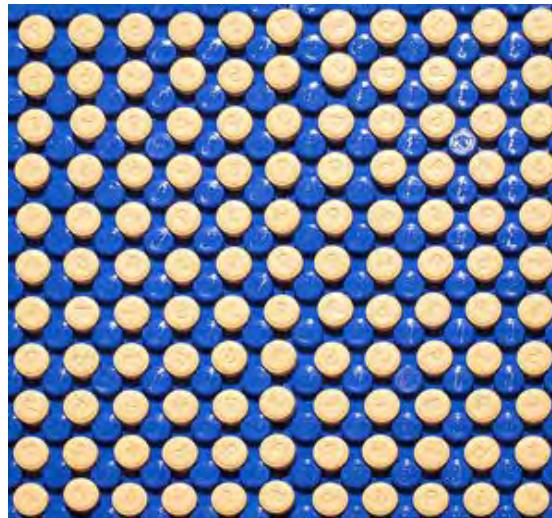
The truth is that while Dilauidid is a semi-popular recreational drug, most Dilauidid addictions actually come from people using the drug legally for pain and then becoming addicted to it. Because Dilauidid works by targeting pain pathways in the central nervous system that alter pain perceptions, it can have a profound lasting impact on the way the body copes with pain in the future, thus having the ability to cause long-term dependency and withdrawal symptoms.

Common symptoms of a Dilauidid addiction include:

- **Anorexia**
- Nervousness
- Constipation
- Mental or Physical Impairment
- Low breathing rate
- Sleepiness
- Dizziness
- Depression
- Withdrawal Symptoms

Dilauidid Dependence and Withdrawal Symptoms

Since Dilauidid is a powerful synthetic opiate, it does come with the risk of long-term dependency and withdrawal. Because the body builds up a tolerance to Dilauidid over time, more and more of the drug will be needed to receive the same powerful effects. After time, the body can become physically dependent to the drug and painful physical withdrawal symptoms can soon occur.



Dilauidid withdrawal

symptoms include:

- Flu-like symptoms
- Nausea
- Vomiting
- Lack of Energy
- Sweating
- Runny Nose
- Goosebumps
- Diarrhea
- Agitation

Seeking Help

If you, or someone you care about, are currently suffering from a Dilaudid addiction, do not hesitate to speak with them right away about their addiction. It is important not to come off as judgmental, accusing, or aggressive; but instead let them know you're coming from a place of love and assistance. Once you have gotten their attention, make an appointment with a California drug rehab facility that can offer a medically assisted detox plan with something like **Suboxone**, to help them get through terrible pain withdrawal symptoms. After the withdrawal symptoms have subsided the individual will begin an intensive physical and mental drug rehabilitation program that will get them on the road to recovery and sobriety in no time.



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