Elisabeth M. McOmber (10615)
Katherine R. Nichols (16711)
Annika L. Jones (16483)
Snell & Wilmer L.L.P.
15 West South Temple, Suite 1200
Salt Lake City, Utah 84101
801.257.1900
emcomber@swlaw.com
knichols@swlaw.com
aljones@swlaw.com

Attorneys for Respondents Purdue Pharma L.P., Purdue Pharma Inc., and The Purdue Frederick Company

BEFORE THE DIVISION OF CONSUMER PROTECTION

OF THE UTAH DEPARTMENT OF COMMERCE

IN THE MATTER OF: PURDUE PHARMA L.P., PURDUE PHARMA INC., THE PURDUE FREDERICK COMPANY, RICHARD SACKLER, M.D., and KATHE SACKLER, M.D., Respondents.	**PURDUE'S RESPONSE TO THE UTAH DIVISION OF CONSUMER PROTECTION'S CITATION AND NOTICE OF AGENCY ACTION** DCP Legal File No. CP-2019-005 DCP Case No. 107102 Administrative Law Judge Bruce Dibb

RESPONSE

Respondents Purdue Pharma L.P., Purdue Pharma Inc., and The Purdue Frederick Company (together, "Purdue"), by and through counsel, hereby submit this Response to the Notice of Agency Action ("NoAA") filed by the Utah Division of Consumer Protection (the "Division") against Purdue and Dr. Richard Sackler and Dr. Kathe Sackler (together, "the Individual Respondents") (collectively with Purdue, "Respondents"). The Presiding Officer ordered this response by April 8, 2019, later extending the deadline to April 9, 2019. Purdue has also filed a motion to dismiss the NOAA and Administrative Citation. Because the ordered schedule does not provide an opportunity for the Presiding Officer to rule on the motion to dismiss before the filing

of a response, Purdue submits this response subject to, and without waiver of, any grounds for dismissal under Rule 12 of the Utah Rules of Civil Procedure or any applicable administrative rule or statute.

INTRODUCTION

This unprecedented and improper Division Agency Action violates the constitutional protections afforded citizens in Utah and the United States, exceeds the limitations of the Utah Consumer Sales Practices Act ("UCSPA"), and fails to state a claim against Purdue.

This dispute between the State and Purdue began in May 2018, when the State filed a highly publicized civil lawsuit (the "Civil Action") that sought to hold Purdue alone liable for an opioid abuse crisis in Utah. The State blamed this complex public health crisis on Purdue's marketing of opioid medications that the federal Food and Drug Administration ("FDA") approved as safe and effective to treat chronic non-cancer pain.

Rather than pursue the Civil Action in a forum suited to the complexities of the issues presented by the State's claims, the State changed course and dismissed the Civil Action in January 2019. On the same day, the Division issued its Administrative Citation (the "Citation") with virtually ***identical*** allegations, and initiated the present administrative proceeding ("Agency Action"). The Citation, like the Civil Action, alleged that Purdue's marketing violates the UCSPA. Notably, Purdue stopped marketing its opioid medications to healthcare professionals in February 2018—nearly a year before the Division issued the Citation. Purdue also discontinued the specific promotional and medical education statements referenced in the Citation—in most cases, this happened years ago.

Unfortunately, the rules that govern this Agency Action will not allow for a fair adjudication of the truth in a matter of this size and complexity. As explained in Respondents'

Motions to Dismiss, the rules governing this six to eight month administrative proceeding cannot provide the critical procedural safeguards needed to ensure due process in an action of this scope and complexity. Indeed, as the Attorney General admitted in a press release, the Division filed this expedited administrative proceeding not because it is a better way to determine the truth or to administer justice, but in an improper effort to gain leverage and force Purdue to settle this dispute as quickly as possible.[1] The State acknowledged that this is the true reason for its about-face: the State "felt like it would take far too long to get to a judgment" in traditional litigation,[2] whereas the administrative procedure would allow it to short-circuit the judicial process, "expedite legal proceedings against Purdue," and, most egregious of all, "to put new 'pressure' on defendants to be 'more reasonable.'"[3]

To be sure, there is an opioid abuse crisis in Utah, but the responsibility for this crisis cannot, as a matter of law, be tied to one company that manufactures a tiny fraction of the opioids prescribed and sold in Utah. In seeking to do so, the Division attempts to displace the medical judgments of public health experts at the FDA, and ignores the conduct of thousands of other third parties, including the independent medical judgment of prescribing physicians and the criminal activities of illicit drug rings. Patients may obtain Purdue's opioid medications only with a prescription from a licensed healthcare professional, who is obligated to exercise her or his

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[1] *See* Press Release, *Utah Office of the Attorney General, Utah Escalates Legal Action Against Purdue by Naming Executives and Expediting State's Claims* (Jan. 30, 2019), *available at* https://attorneygeneral.utah.gov/utah-escalates-legal-strategy-against-purdue-pharma/.

[2] Ben Winslow, *Utah Attorney General Drops Lawsuit, Files Administrative Action Against Purdue over Opioid Crisis*, Fox13 News, Jan. 30, 2019, *available at* https://fox13now.com/2019/01/30/utah-attorney-general-drops-opioid-lawsuit-files-administrative-action-against-purdue-over-opioid-crisis/.

[3] Katie McKellar, *Utah 'Streamlines' Legal Fight Against OxyContin Maker, Names Family in Filing*, Deseret News, Jan. 30, 2019 (quoting Attorney General Reyes), *available at* https://www.deseretnews.com/article/900053214/utah-streamlines-legal-fight-against-oxycontin-maker-names-family-in-filing.html.

independent medical judgment and make an individualized prescribing decision based on her or his training, experience, and evaluation of the benefits and risks of treatment for the individual patient. To be clear: This is not a public health problem caused by lawful prescriptions of Purdue's opioid medications to patients. Rather, other factors are far more significant causes, including the increase in illicit heroin and fentanyl use, and the use of medications that were not obtained through a lawful prescription, or were obtained from black-market sources or "pill mills." The Utah Department of Health ("UDH") has determined that the overwhelming majority of prescription opioid overdoses also involve other drugs, and even as opioid prescriptions decrease, illicit drug overdoses continue to rise. Yet, Purdue's OxyContin constitutes an exceedingly small percent of the opioids prescribed in the country (currently fewer than 2% and never more than 4%) and, thus, a tiny fraction of all opioids (legal and illicit) used and abused in Utah and elsewhere.

The Division's allegations primarily amount to an accusation that Purdue improperly marketed its medications for long-term therapy at high doses—the treatment doctors usually reserve for their patients who experience the worst, most intractable and debilitating pain. But the FDA has repeatedly approved Purdue's medicines to treat those patients. Indeed, in a 2013 response to a Citizen Petition that sought to limit opioid prescriptions to a shorter duration and lower daily dose, the FDA not only rejected those requests, but declined to impose warnings about increased risks due to longer therapy and higher doses—warnings the Division now asserts Purdue hid from Utah doctors. The Division cannot substitute its judgment over the FDA's and hold Purdue liable for not providing the warnings that the FDA, after its expert evaluation of the science, declined to impose.

Recognizing the weakness of its legal theories, the Division has resorted to the creation of a distorted or incomplete narrative. As set forth below, the Citation contains many inaccuracies

about Purdue and the Individual Respondents, including claims about Purdue's alleged promotion of higher doses of its medications, and Respondents' efforts to assist in combating the opioid abuse crisis.

In sum, the vast majority of the Division's allegations either: (1) are false; (2) relate to matters the truth or falsity of which Purdue has no knowledge—including, *inter alia*, the conduct of thousands of third parties over whom Purdue exercised no control; (3) state legal conclusions; (4) mischaracterize the contents of documents that speak for themselves; or (5) relate to lawful, truthful conduct. Purdue denies the Division's allegations, except as explicitly stated herein. And Purdue emphatically denies that it deceived the Utah medical community, controlled the conduct of any third parties or the contents or distribution of their alleged statements, or caused Utah's opioid abuse epidemic.

STATEMENT OF RELIEF REQUESTED

Purdue denies the Division's allegations, and respectfully asks the Presiding Officer to dismiss this action for the reasons summarized below and as set forth in Purdue's Motion to Dismiss filed prior to submission of this Response.

STATEMENT OF FACTS

A. The Respondents.

The Division correctly alleges that Purdue Pharma L.P. is a limited partnership existing under the laws of Delaware, Purdue Pharma Inc. is incorporated under the laws of New York, and The Purdue Frederick Company Inc. is incorporated under the laws of Delaware. Certain of the Purdue Respondents at relevant times were engaged in the business of manufacturing, marketing, selling, or distributing opioid medications in the United States, including but not limited to: OxyContin® (oxycodone hydrochloride controlled-release, FDA approved in 1995), Butrans® (buprenorphine, FDA approved in 2010), and Hysingla ER® (hydrocodone bitrate, FDA approved

in 2014). Purdue manufactures opioid medications that are approved by the FDA as safe and effective to treat chronic pain and, in the case of OxyContin, 12-hour dosing. The Individual Respondents were employed in some capacity by at least one of the Purdue entities at some time between 1971 and 2018. (*See* Citation ¶¶ 1–3, 5–6, 73 (denied except as specifically stated herein).)

B. Chronic Pain Is a Serious Public Health Problem, Which Purdue's FDA-Approved Opioids Help to Address.

Purdue's opioid medications OxyContin®, Butrans®, and Hysingla® are extended release, long-acting ("ER/LA") opioid analgesics that are indicated for and relieve chronic pain that is often severe and debilitating. The FDA has specifically approved each of these medications as safe and effective for the long-term treatment of chronic pain. The FDA's approval of OxyContin was based on six controlled clinical trials—two more than was then required by prevailing industry standards. These clinical trials involved over 700 patients, with only two patients demonstrating any evidence of abuse.[4] (Ex. A at § 6.1.)

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[4] Purdue attaches the following exhibits in connection with its Response: **(1)** the current FDA-approved labeling for OxyContin®, attached as **Exhibit A**; **(2)** Letter from Dr. Janet Woodcock, Director for Center of Drug Evaluation & Research, to Dr. Andrew Kolodny, President of Physicians for Responsible Opioid Prescribing ("PROP") (Sept. 1, 2013), attached as **Exhibit B**; **(3)** a presentation by Dr. Douglas C. Throckmorton entitled "FDA Perspective on Abuse-Deterrent Opioid Development," *available at* https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/DER/UCM545923.pdf, attached as **Exhibit C**; **(4)** a presentation by Dr. Douglas C. Throckmorton entitled "FDA's Actions To Address The Opioid Epidemic," *available at* https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM601178.pdf, attached as **Exhibit D**; **(5)** an FDA publication entitled "Abuse-Deterrent Opioid Analgesics," *available at* https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm600788.htm, attached as **Exhibit E**; **(6)** the 2012 "Citizen's Petition" submitted by Physicians for Responsible Opioid Prescribing ("PROP"), *available at* https://www.regulations.gov/document?D=FDA-2012-P-0818-0001, attached as **Exhibit F**; **(7)** UTAH DEP'T OF HEALTH., UTAH CLINICAL GUIDELINES ON PRESCRIBING OPIOIDS FOR TREATING PAIN 2–3 (2010), *available at* http://www.health.utah.gov/prescription/pdf/guidelines/final.04.09opioidGuidlines.pdf, attached as **Exhibit G**; **(8)** UTAH DEP'T OF H. PRESCRIPTION PAIN MEDICATION PROGRAM, HB 137 FINAL REPORT 30 (2009), *available at*

The FDA acknowledged that opioid medications like Purdue's OxyContin® serve an important public health role: "When prescribed and used properly, opioids can effectively manage pain and alleviate suffering—clearly a public health priority. Chronic pain is a serious and growing public health problem: it 'affects millions of Americans; contributes greatly to national rates of morbidity, mortality, and disability; and is rising in prevalence.'" (Ex. B at 2.) The FDA has approved and continues to approve the long-term use of ER/LA opioids to treat chronic pain. Indeed, for over twenty-three years, and with more than thirty labeling changes, OxyContin is FDA-approved for "long-term" use to this day. The FDA-approved labeling for OxyContin has always warned of the risk of abuse and misuse. In 2001, the FDA required Purdue to disclose in its FDA-approved labeling: "Opioids also have grave risks, the most well-known of which include addiction, overdose, and even death." (Ex. B at 2.) In 2001, the labeling also added a boxed warning (also known as a "black box"). This warning appeared in bolded, boxed text at the beginning of labeling, and warned healthcare professionals of the abuse and misuse risk with Purdue's opioid medications. For example, the current black box warning contains the following language:

> **WARNING: ADDICTION, ABUSE AND MISUSE . . .**
>
> - **OXYCONTIN exposes users to risks of addiction, abuse and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions.**

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http://health.utah.gov/prescription/pdf/2009final_programreport.pdf (last visited Apr. 4, 2019), attached as **Exhibit H**; **(9)** UTAH DEP'T OF H., PRESCRIPTION OPIOID DEATHS 3 (Apr. 2017), *available at* http://health.utah.gov/vipp/pdf/RxDrugs/PDODeaths2015.pdf, attached as **Exhibit I**; **(10)** Paul Reyes, *Rep. Paul Ray: Utah Is an Overdose Capital, and Fentanyl Must Be Stopped*, ATTORNEYGENERAL.UTAH.GOV (Mar. 13, 2019), https://attorneygeneral.utah.gov/utah-is-an-overdose-capital/, attached as **Exhibit J**; and **(11)** UTAH OFFICE OF LEGISLATIVE RESEARCH AND GENERAL COUNSEL, OPIOID MISUSE: OPTIONS FOR PREVENTION, IDENTIFICATION, & TREATMENT, *available at* https://le.utah.gov/interim/2016/pdf/00002098.pdf (last visited Apr. 4, 2019), attached as **Exhibit K**.

(Ex. A, at 1.)

Purdue continues to comply with FDA requirements, listing all these risks in the current OxyContin package insert. The Division does not allege to the contrary. Notwithstanding these warnings and the strict regulatory scheme under which Purdue marketed and sold these medications, the Division alleges that Purdue duped healthcare professionals with misrepresentations that "opioids were [safe] for the treatment of chronic pain," so as to "increase [ ] the number of opioids prescribed nationwide." (Citation ¶ 18.) But Purdue was (and is) permitted to market its opioid medications consistent with FDA-approved labeling, including for long-term treatment of chronic pain. That Purdue previously employed sales representatives to visit healthcare professionals and provide them with information about FDA-approved medications is not only legal, but is standard industry practice.

Furthermore, the FDA already addressed many of the same criticisms leveled by the Division, and concluded that no modification to OxyContin's labeling was necessary. In 2012, an independent group, Physicians for Responsible Opioid Prescribing, filed a Citizen Petition ("PROP Petition") with the FDA, requesting three major changes to the labeling for opioid analgesics: (1) strike "moderate" from the indication for non-cancer pain; (2) add a maximum daily dose for non-cancer pain; and (3) add a maximum duration of 90 days for continuous use for non-cancer pain. (Ex. F at 2.) The PROP Petition contended that ER/LA opioids' then-current "indication" (approved use)—for "moderate to severe pain when a continuous, around the clock analgesic is needed for an extended period of time"—was overly broad and implied that ER/LA opioids are safe and effective for long-term use. (*Id.* at 1.) PROP further claimed that the long-term safety and effectiveness of managing chronic non-cancer pain with opioids has not been established, and that chronic opioid therapy is associated with an increased risk of overdose death,

emergency room visits and fractures in the elderly. (*Id.* at 2.) Finally, PROP contended that two-thirds of patients who used opioids on a daily basis for 90 days were still taking them five years later. (*Id.*) In other words, the PROP Petition presented the FDA with the same assertions that the Division makes in its Citation.

For fourteen months, the FDA carefully reviewed the petition, evaluated the studies PROP cited, researched other available scientific literature, convened a two-day workshop, held a two-day public hearing, and considered over 2,500 public comments and the opinions of experts, medical associations, and patients. In September 2013, the FDA denied PROP's request to limit the indication for chronic opioid therapy to any particular duration or daily dose. The FDA concluded that available data and studies failed to show a causal relationship between higher doses/longer durations and higher risks to patients. (Ex. B at 12–16.) The FDA also did not require revision of the labeling to include additional risk information about a supposed "lack of evidence to support long-term use." (*Id.* at 12, 14–16.) To the contrary, the FDA recognized that "numerous uncontrolled studies . . . have evaluated patients on opioids for as long as a year" and "although some patients drop out of the studies over this period of time, many remain on opioid therapy, which may suggest that they continue to experience benefits that would warrant the risks of opioid use." (*Id.* at 10, n.40.) The FDA also did not direct Purdue to cease marketing the medications for long-term use. (*Id.* at 14–15) ("[T]he FDA has determined that limiting the duration of use for opioid therapy to 90 days is not supportable."). Finally, the FDA also refused to recommend a "maximum . . . duration of use." (*Id*. at 11.) Although the FDA did enhance some safety warnings related to abuse and addiction in response to the PROP Petition, the FDA expressly declined to add a warning that high doses and long durations of opioid treatment create greater risks to patients.

The Division mischaracterizes the FDA's response to the PROP Petition, asserting that the FDA's "findings" showed that "most opioid drugs have 'high potential for abuse.'" (*See* Citation ¶ 66.) Yet, the Division fails to mention that the FDA was quoting a federal statute, *see* 21 U.S.C. § 812(b)(2). In the "Background" section of the response, the FDA commented that opioids' status as a "controlled [substance] under Schedule II of the Controlled Substances Act" implicitly "reflects a finding that most opioid drugs have 'high potential for abuse.'" (Ex. B at 2–3.) In other words, the FDA "found" only that opioids' risk of abuse is reflected in and accounted for by the FDA's existing labeling and regulation of those medications. The Division further alleges that the FDA found that opioids had "known serious risks." (Citation ¶ 66; *accord id.* ¶ 71.) But, in fact, the FDA merely ordered opioid manufacturers to undertake "post-marketing requirements" ("PMRs") "to ***assess*** the known serious risks" of opioids—risks the Purdue labeling already disclosed. (Ex. B at 10.) Indeed, although the Division alleges the FDA found that opioids should be prescribed "only 'in patients for whom alternative treatment options' have failed," (Citation ¶ 66), the Division fails to acknowledge that this language is in Purdue's labeling. (Ex. B at 8.)

In short, when presented with the very same concerns about the enhanced risks of using opioids in high doses and long durations, the FDA chose neither to impose those limits on opioid use nor to add warnings about those risks. In the face of all of the science subsequently developed, the FDA has continued to find the product labeling appropriate.[5]

Finally, in connection with Purdue's 2007 plea agreement, Purdue agreed to enter into a five-year Corporate Integrity Agreement ("CIA") with the Office of the Inspector General of the U.S. Department of Health & Human Services ("OIG"). The CIA's key focus areas included sales,

[5] The FDA-approved labeling also discusses the concept of pseudoaddiction, distinguishing between "drug seeking behavior" and the fact that "[p]reoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control." (Ex. A. § 9.2.)

marketing, advertising, promotion, and dissemination of information and materials related to the selling of certain Purdue products. During the term of this five-year agreement, Purdue submitted annual reports to a designated OIG monitor, and engaged an Independent Review Organization that evaluated specified elements of Purdue's compliance program on a periodic basis to assess compliance with the terms of the CIA. One of the most glaring omissions in the Citation is its failure to recognize that Purdue successfully satisfied its obligations under the CIA, which ended in 2013.

C. The Opioid Abuse Crisis Is a Complex Issue with Several Contributing Factors.

The Citation's inaccurate narrative also fails to reflect that the opioid abuse crisis involves complex sociological and behavior health issues, various legal and illicit opioids, opioid diversion, and illegal drug rings.

Utah consumers can lawfully obtain opioid medications only through a licensed healthcare professional. *See, e.g.*, 21 C.F.R. §§ 1306.11, 1306.03(a)(1). Prescribers must take continuing medical educational courses on opioid medications, UTAH CODE ANN. § 58-37-6.5(6)(d). Healthcare professionals have a legal duty to know the risks associated with medications they prescribe, and to use their independent medical judgment, training, expertise, and evaluation of the specific patient before writing a prescription. *See Schaerrer v. Stewart's Plaza Pharm., Inc.*, 2003 UT 43, ¶¶ 20–22, 79 P.3d 922; *see also Downing v. Hyland Pharm.*, 2008 UT 65, ¶ 7, 194 P.3d 944. Utah regulations further prohibit a practitioner from "prescrib[ing] or administer[ing] a controlled substance without taking into account the drug's potential for abuse, the possibility the drug may lead to dependence, the possibility the patient will obtain the drug for a nontherapeutic use or to distribute to others, and the possibility of an illicit market for the drug." UTAH ADMIN. CODE R156-37-603(2). The UDH instructs prescribers to undertake a "comprehensive evaluation

. . . before initiating opioid treatment for chronic pain," including "screen[ing] for risk of abuse or addiction," in recognition of the fact that "[m]edicine is practiced one patient at a time and each patient is unique with individual needs and vulnerabilities." (Ex. G at 2–3.)

Not only does the Division's distorted narrative ignore the role of trained and licensed prescribers in limiting access to Purdue's medications, it also ignores the prevalence of other opioids. The vast majority (approximately 90%) of opioid prescriptions written in this country are for immediate release medications, not ER/LA medications. Of the small percent of prescriptions written for ER/LA products, only a very small portion are for abuse-deterrent products like Purdue's OxyContin. (*See* Ex. C at 25). OxyContin is one of just eight products for which the FDA currently approves labeling describing abuse-deterrent properties. (*See* Ex. E at 2–3.) Purdue's OxyContin currently accounts for fewer than 2% of opioid prescriptions nationwide. (Ex. D at 9.)

According to the UDH, in 2006 methadone was implicated in more overdoses than any other prescription opioid, (Ex. J at 30), and methadone continues to have the highest abuse-per-prescription rate of any prescription opioid. (Ex. I at 3.) In 2009, the UDH explained that "[r]ecreational use of prescriptions drugs is increasing," and stated that ***half*** "of individuals who died of an overdose of methadone had a valid prescription at the time of death. This is informative in showing that there are two distinct populations: individuals with a valid prescription and individuals who found prescription opioids from some other source." (Ex. H at 30.) The UDH further found that "[a]pproximately 60 percent of people who abuse prescription pain killers indicate that they got their prescription drugs from a friend or relative for free." (*Id.*) To this day, through its funding of the organization "Use Only as Directed," the State continues to acknowledge

the role that diversion of legitimate opioid prescriptions can play in opioid abuse.[6]

While prescription opioid abuse has declined in Utah for several years, heroin overdoses have been increasing since 2011. (*Id.* at 2.) In an article republished on the Attorney General's website, Utah Representative Paul Ray explained that overall opioid deaths "remain[] stubbornly high due to the spread of an illegally manufactured drug called fentanyl," which is produced in China and shipped through the Mexico-U.S. border. (Ex. J.)

Similarly, in a 2016 legislative think-piece, Utah's Office of Legislative Research and General Counsel ("OLRGC") recognized the multifaceted nature of this crisis by identifying numerous actors—including manufacturers, prescribers, dispensers, insurers, patients, the treatment community, and the State itself—that could help to combat opioid abuse. (Ex. K.) The OLRGC proposed only two strategies for manufacturers—"[i]mprov[ing] prescriber education" and "[i]ncreas[ing] production of abuse-deterrent opioids (extended-release and long-acting)." (*Id.* At 1.) The OLRGC proposed dozens of potential strategies, however, for others in the opioid supply chain, such as preventing diversion by "[using] secure prescribing pads" and "[reducing] drug sharing behaviors." (*Id.* At 1, 3.) The variety of actors and potential strategies mentioned in the document demonstrates the complex, multidimensional character of Utah's opioid abuse crisis.

D. The Division Attempts to Deflect from the State's Failures in This Complex Public Health Crisis with Sensationalist Mischaracterizations.

There is no doubt that the opioid abuse epidemic is a public health crisis. The State and Purdue agree on this point. Yet, although the Division now contends the overprescribing of opioid medications was a significant contributor, the State has failed to take several steps to address this alleged concern. For example, the State continues to reimburse opioid prescriptions for patients

[6] *See Safe Use*, USEONLYASDIRECTED.ORG, https://useonlyasdirected.org/opioid-safety/ (last visited Apr. 4, 2019).

with Medicare, Medicaid, or another state-sponsored healthcare plan. The State reimburses OxyContin 60mg, and reimburses for patients who need the medicine to treat chronic non-cancer pain. Moreover, before 2016, the State did not require prescribers to check a Prescription Drug Monitoring Program database—designed to help spot signs of diversion, abuse, or drug-seeking behavior—before prescribing opioids to a patient for the first time. Even after the State required prescribers to check patients against the database, the State left the frequency of these checks to "the prescriber's . . . professional judgment." UTAH CODE ANN. § 58-37f-304(2)(a) (2016) (amended May 8, 2018). Prior to last year, Utah prescribers were not required to check the database before first prescribing opioids for a patient when: (1) the prescription was for three days or fewer; (2) the prescriber had "prior knowledge of the patient's prescription history based on the prescriber's review of the patient's health record"; or (3) the prescription was a post-surgery prescription for thirty days or fewer. *See id.* § 58-37f-304(2)(c) (2017). Nor did the State require the Division of Occupational and Professional Licensing to review the database to identify "prescriber[s] who [have] a pattern of prescribing opioids not in accordance with the recommendations of" the CDC, Utah's Clinical Guidelines, and other published best practices. *Id.* § 58-37f-304(5)(a) (2019).

The Division therefore minimizes that the opioid abuse crisis is a complex, multifactorial societal and public health issue, and ignores the State's own role and failures to act. Instead, the State seeks to deflect from its own conduct and sets forth a misleading narrative in an attempt to litigate this case in the court of public opinion (while simultaneously trying to avoid litigating in a court of law). The number of inaccurate characterizations about Purdue and its executives and directors are too numerous to set out, but a few examples are illustrative of its broader strategy:

Higher Doses: The Division repeatedly asserts, without support, that Purdue inappropriately instructed its sales representatives to push doctors to prescribe higher doses of OxyContin. (*See, e.g.*, Citation ¶¶ 69–72.) In reality, Purdue has always sold OxyContin in a variety of doses that allow doctors more easily to titrate up and down to find the appropriate pain relief dose for a particular patient. (*See* Ex. A at § 2.5 ("Individually titrate OXYCONTIN to a dosage that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving OXYCONTIN to assess the maintenance of pain control, signs and symptoms of opioid withdrawal, and adverse reactions, as well as monitoring for the development of addiction, abuse and misuse . . .").) This is in line with the accepted medical practice of individualizing therapy to achieve pain relief through incremental dose escalation, as long as no serious risks emerge. Contrary to the Division's allegations, Purdue consistently issued warnings about the potential, well-known side effects of the highest OxyContin doses. Purdue specifically instructed that a patient should start with a low dose and that the highest doses were appropriate only for opioid tolerant patients. Indeed, OxyContin's FDA-approved labeling has always contained warnings about increasing dose levels.

Mischaracterizations About Respondents And Their Documents: The Division also makes numerous allegations about Respondents based on internal Purdue business documents that the Division grossly mischaracterizes and takes out of context. As one of many examples, the Division portrays Dr. Richard Sackler as heartlessly responding to "an article citing 59 deaths from OxyContin in Kentucky" by saying: "This is not too bad. It could have been far worse." (Citation ¶ 149.) When considered in context, however, Dr. Sackler merely forwarded to others at Purdue a New York Times article with the "subject" heading "NYTimes.com Article: Cancer Painkillers

Are Being Abused." Dr. Sackler's comments went to the nature of the press coverage—not the tragedy of overdose deaths.

As another example, the Division attempts to vilify Respondents for acquiring a patent for "a method of medication-assisted treatment for opioid addiction," alleging that "a change in the bottom line may have inspired a change of heart." (Citation ¶¶ 150, 160.) In other words, while alleging that Respondents did not do enough to combat the opioid abuse crisis, in the same breath the Division blames Respondents for attempting to help opioid abusers. It seems the Division wants to put Purdue in a no-win situation. Yet, this allegation also is inaccurate. Purdue long has attempted to help curb the opioid abuse epidemic. For example, in April 2010, the FDA approved a reformulated version of OxyContin developed by Purdue. The reformulation deterred abuse with the addition of a high molecular weight polymer, polyethylene oxide ("PEO"), which makes the tablet difficult to crush and very thick when exposed to liquid. Purdue worked for years to develop the new formulation, investing hundreds of millions of dollars, and it was the first FDA-approved opioid with abuse-deterrent properties. A 2017 report by a non-profit organization, the Institute for Clinical and Economic Review, showed that Purdue's abuse-deterrent formulas prevented thousands of cases of abuse.[7] Other scientific studies similarly establish that Reformulated OxyContin reduces OxyContin abuse.[8] Accordingly, in 2013, three years after its launch, the FDA

[7] Institute for Clinical and Economic Review, *Abuse-Deterrent Formulations of Opioids: Effectiveness and Value, Final Evidence Report* (Aug. 8, 2017).

[8] *See, e.g.*, Hui G. Cheng & Paul M. Coplan, *Incidence of Nonmedical Use of OxyContin and Other Prescription Opioid Pain Relievers Before and After the Introduction of OxyContin with Abuse Deterrent Properties*, POSTGRAD MED. (2018); Christopher M. Jones et al., *Trends in the Nonmedical Use of OxyContin, United States, 2006 to 2013*, CLIN. PAIN, Vol. 33, No. 5, 452-61 (May 2017); Stevan Geoffrey Severtson et al., *Sustained Reduction of Diversion and Abuse After Introduction of An Abuse-Deterrent Formulation of Extended Release OxyCodone*, DRUG ALCOHOL DEPEND., Vol 168, 219-29 (2016); PM Coplan et al., *The Effect of an Abuse-Deterrent Opioid Formulation (OxyContin) on Opioid Abuse-Related Outcomes in the Postmarketing Setting*, CLIN. PHARMACOL. THER., Vol. 100, No. 3, 275-86 (Sept. 2016); Theodore J. Cicero &

reviewed the available scientific data and approved the addition of abuse-deterrent information in the OxyContin labeling—the first abuse-deterrent labeling for an opioid.

These are just a handful of the inaccuracies that appear throughout the Division's Citation. The Division goes further astray in its mistaken narrative of this complex public health problem with vague references to Purdue "sponsoring" third-party publications without pleading any facts to establish that Purdue did anything apart from provide financial support to medical professional groups or researchers. The Division also does not identify any improper opioid prescriptions caused by Purdue's alleged conduct. The Division cannot succeed, either as a matter of fact, or as a matter of law, with vague, unsupported theories of "fraud in the air" that ignore what is actually happening in the State of Utah.

STATEMENT SUMMARIZING REASONS RELIEF REQUESTED SHOULD BE GRANTED

The Agency Action should be dismissed for three reasons. ***First***, it violates due process and would result in an unconstitutional excessive fine. ***Second***, the Agency Action ignores the limitations of the UCSPA, and conflicts with the FDA's federal regulatory scheme. ***Third***, the Agency Action, as pleaded, fails to state a claim, most notably because the Division does not even attempt to plead facts to show that any alleged deception caused harm.

A. This administrative proceeding violates due process and would result in an unconstitutional excessive fine.

This is not a typical enforcement action, where the Division might seek an expedited administrative proceeding to get a cease and desist order that would curb deceptive practices. A complex dispute of this magnitude demands constitutionally sound procedural protections that are

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Matthew S. Ellis, *Abuse-Deterrent Formulations and the Prescription Opioid Abuse Epidemic in the United States: Lessons Learned from OxyContin*, JAMA PSYCHIATRY, Vol. 72, No. 5, 424-29 (May 2015); Edward Michna et al., *Use of Prescription Opioids with Abuse-Deterrent Technology to Address Opioid Abuse,* CURR MED RES OPIN., Vol. 30, No. 8, 1589-1598 (2014).

commensurate with the action's scope and complexity. The rules that govern this administrative proceeding—a proceeding that must conclude within six to eight months—cannot provide the critical procedural safeguards needed to ensure due process. As the State itself acknowledges, the Division filed this administrative proceeding not because it is a better way to determine the truth or to administer justice, but in the hope that the State can secure massive statutory penalties—likely reaching hundreds of millions of dollars by the Division's calculations—as quickly as possible. Indeed, if the Division were to succeed on the merits in this abbreviated proceeding, it surely would result in a violation of Purdue's due process rights and an unconstitutionally excessive fine.

B The USCPA and federal law foreclose this Agency Action.

Apart from these due process and excessive fine violations, the Division's claims also impermissibly conflict with the extensive state and federal expert regulatory schemes through which Purdue's medications have been approved for the exact uses the Division now challenges. Because the FDA "specifically permitted" the conduct challenged by the Division—marketing an FDA-approved product for FDA-approved uses—the "safe harbor" provision of the UCSPA bars the Division's claims. And federal law preempts any state-law claim premised on the theory that Purdue could or should stop selling opioids for their FDA-approved and permitted uses. In the end, it would be improper to use the blunt tool of the UCSPA when there are other more specific and direct statutory and regulatory enforcement mechanisms available to the State, the FDA, the federal Drug Enforcement Agency ("DEA"), and the Department of Justice. In any event, the UCSPA does not permit enforcement actions as broad as this Agency Action because: (1) the version of the UCSPA in effect at the time Purdue was marketing its opioids permitted administrative actions only for present or ongoing violations; (2) the Division cannot bring

"unconscionability" claims in an administrative action; and (3) the UCSPA's enforcement reach does not extend to omissions.

C. The Division fails to state a claim.

In its Citation, the Division does not state a claim for four reasons. First, because the alleged deceptions relate to prescription medications and went to prescribing healthcare professionals rather than consumers, they were not the "subject of a consumer transaction." Second, the Division does not plead facts to show that these alleged deceptions caused harm. Third, although the Division relies on a number of alleged misrepresentations made by third parties, the Division has not pleaded facts to establish that these third parties were agents of Purdue. Finally, the Division has not pleaded its claims with the requisite particularity.

For all of these reasons, as explained in more detail in Purdue's Motion to Dismiss filed prior to this Response, the Agency Action should be dismissed in its entirety.

CONCLUSION

For the foregoing reasons, Purdue respectfully disputes the factual allegations set forth in the Citation and requests that the Citation and Agency Action be dismissed.

DATED this 9th day of April, 2019.

SNELL & WILMER L.L.P.

/s/ Elisabeth M. McOmber
Elisabeth M. McOmber
Katherine R. Nichols
Annika L. Jones

Attorneys for Respondents Purdue Pharma L.P., Purdue Pharma Inc., and The Purdue Frederick Company

CERTIFICATE OF SERVICE

I hereby certify that on this the 9th day of April, 2019, I served the foregoing on the parties of record in this proceeding set forth below by delivering a copy thereof by electronic means and U.S. Mail and/or as more specifically designated below, to:

Bruce L. Dibb, Presiding Officer
Administrative Law Judge
Heber M. Wells Building, 2nd Floor
160 East 300 South
Salt Lake City, Utah 84114
bdibb@utah.gov

Robert G. Wing, AAG
Kevin McLean, AAG
Assistant Attorneys General
Utah Attorney General's Office
160 East 300 South, 5th Floor
PO Box 140872
Salt Lake City, Utah 84114-0872
rgwing@agutah.gov
kmclean@agutah.gov

Patrick E. Johnson
Paul T. Moxley
Cohne Kinghorn, P.C.
111 E. Broadway, 11th Floor
Salt Lake City, Utah 84111
pjohnson@ck.law.com
pmoxley@ck.law.com
Attorneys for Respondents Richard Sackler, M.D. and Kathe Sackler, M.D.

Daniel R. S. O'Bannon – Director
Utah Division of Consumer Protection
160 East 300 South, 2nd Floor
Salt Lake City, Utah 84111
dobannon@utah.gov

/s/ Elisabeth M. McOmber

4818-4923-8931

EXHIBIT A

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use OXYCONTIN® safely and effectively. See full prescribing information for OXYCONTIN.

OXYCONTIN® (oxycodone hydrochloride) extended-release tablets, for oral use, CII
Initial U.S. Approval: 1950

WARNING: ADDICTION, ABUSE AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- **OXYCONTIN exposes users to risks of addiction, abuse and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.1)**
- **To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. (5.2)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow OXYCONTIN tablets whole to avoid exposure to a potentially fatal dose of oxycodone. (5.3)**
- **Accidental ingestion of OXYCONTIN, especially by children, can result in a fatal overdose of oxycodone. (5.3)**
- **Prolonged use of OXYCONTIN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.4)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of oxycodone. (5.5, 7, 12.3)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.6, 7)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	09/2018
Warnings and Precautions (5.2)	09/2018

----------INDICATIONS AND USAGE----------

OXYCONTIN is an opioid agonist 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 in:

- Adults; and
- Opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.

Limitations of Use

- Because of the risks of addiction, abuse and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve OXYCONTIN for use in patients for whom alternative treatment options (e.g. non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)
- OXYCONTIN is not indicated as an as-needed (prn) analgesic. (1)

----------DOSAGE AND ADMINISTRATION----------

- To be prescribed only by healthcare providers knowledgeable in use of potent opioids for management of chronic pain. (2.1)
- OXYCONTIN 60 mg and 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in patients in whom tolerance to an opioid of comparable potency has been established. (2.1)
- Patients considered opioid-tolerant are those taking, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid. (2.1)
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (2.1).
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Instruct patients to swallow tablets intact and not to cut, break, chew, crush, or dissolve tablets (risk of potentially fatal dose). (2.1, 5.1)
- Instruct patients to take tablets one at a time, with enough water to ensure complete swallowing immediately after placing in mouth. (2.1, 5.10)
- Do not abruptly discontinue OXYCONTIN in a physically dependent patient. (2.9)

Adults: For opioid-naïve and opioid non-tolerant patients, initiate with 10 mg tablets orally every 12 hours. See full prescribing information for instructions on conversion from opioids to OXYCONTIN, titration and maintenance of therapy. (2.2, 2.3, 2.5)

Pediatric Patients 11 Years of Age and Older

- For use only in pediatric patients 11 years and older already receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20 mg per day of oxycodone or its equivalent for at least two days immediately preceding dosing with OXYCONTIN. (2.4)
- See full prescribing information for instructions on conversion from opioids to OXYCONTIN, titration and maintenance of therapy. (2.4, 2.5)

Geriatric Patients: In debilitated, opioid non-tolerant geriatric patients, initiate dosing at one third to one half the recommended starting dosage and titrate carefully. (2.7, 8.5)

Patients with Hepatic Impairment: Initiate dosing at one third to one half the recommended starting dosage and titrate carefully. (2.8, 8.6)

----------DOSAGE FORMS AND STRENGTHS----------

Extended-release tablets: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg. (3)

----------CONTRAINDICATIONS----------

- Significant respiratory depression (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus (4)
- Hypersensitivity to oxycodone (4)

----------WARNINGS AND PRECAUTIONS----------

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.7)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.8)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of OXYCONTIN in patients with circulatory shock. (5.9)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of OXYCONTIN in patients with impaired consciousness or coma. (5.10)
- Risk of Obstruction in Patients who have Difficulty Swallowing or have Underlying GI Disorders that may Predispose them to Obstruction: Consider use of an alternative analgesic. (5.11)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence >5%) were constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, asthenia, and sweating. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Purdue Pharma L.P. at 1-888-726-7535 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- CNS Depressants: Concomitant use may cause hypotension, profound sedation, respiratory depression, coma, and death. If co-administration is required and the decision to begin OXYCONTIN is made, start with 1/3 to 1/2 the recommended starting dosage, consider using a lower dosage of the concomitant CNS depressant, and monitor closely. (2.6, 5.6, 7)
- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue OXYCONTIN if serotonin syndrome is suspected. (7)
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with OXYCONTIN because they may reduce analgesic effect of OXYCONTIN or precipitate withdrawal symptoms. (5.14, 7)
- Monoamine Oxidase Inhibitors (MAOIs): Can potentiate the effects of morphine. Avoid concomitant use in patients receiving MAOIs or within 14 days of stopping treatment with an MAOI. (7)

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: May cause fetal harm. (8.1)
Lactation: Not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

OXYCONTIN® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing OXYCONTIN and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)]*.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS):

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products *[see Warnings and Precautions (5.2)]*. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of OXYCONTIN. Monitor for respiratory depression, especially during initiation of OXYCONTIN or following a dose increase. Instruct patients to swallow OXYCONTIN tablets whole; crushing, chewing, or dissolving OXYCONTIN tablets can cause rapid release and absorption of a potentially fatal dose of oxycodone *[see Warnings and Precautions (5.3)]*.

Accidental Ingestion

Accidental ingestion of even one dose of OXYCONTIN, especially by children, can result in a fatal overdose of oxycodone *[see Warnings and Precautions (5.3)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of OXYCONTIN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of

neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.4)]*.

Cytochrome P450 3A4 Interaction
The concomitant use of OXYCONTIN with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving OXYCONTIN and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.5), Drug Interactions (7), Clinical Pharmacology (12.3)]*.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death *[see Warnings and Precautions (5.6), Drug Interactions (7)]*.

- **Reserve concomitant prescribing of OXYCONTIN and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

1 INDICATIONS AND USAGE

OXYCONTIN is 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 in:

- Adults; and
- Opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations *[see Warnings and Precautions (5.1)]*, reserve OXYCONTIN for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.

- OXYCONTIN is not indicated as an as-needed (prn) analgesic.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

OXYCONTIN should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

OXYCONTIN 60 mg and 80 mg tablets, a single dose greater than 40 mg, or a total daily dose greater than 80 mg are only for use in patients in whom tolerance to an opioid of comparable potency has been established. Adult patients who are opioid tolerant are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.

- Initiate the dosing regimen for each patient individually; taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*.

- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with OXYCONTIN and adjust the dosage accordingly *[see Warnings and Precautions (5.3)]*.

Instruct patients to swallow OXYCONTIN tablets whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth *[see Patient Counseling Information (17)]*. Instruct patients not to pre-soak, lick, or otherwise wet the tablet prior to placing in the mouth *[see Warnings and Precautions (5.11)]*. Cutting, breaking, crushing, chewing, or dissolving OXYCONTIN tablets will result in uncontrolled delivery of oxycodone and can lead to overdose or death *[see Warnings and Precautions (5.1)]*.

OXYCONTIN is administered orally every 12 hours.

2.2 Initial Dosage in Adults who are not Opioid-Tolerant

The starting dosage for patients who are not opioid tolerant is OXYCONTIN 10 mg orally every 12 hours.

Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression *[see Warnings and Precautions (5.3)]*.

2.3 Conversion from Opioids to OXYCONTIN in Adults

Conversion from Other Oral Oxycodone Formulations to OXYCONTIN
If switching from other oral oxycodone formulations to OXYCONTIN, administer one half of the patient's total daily oral oxycodone dose as OXYCONTIN every 12 hours.

Conversion from Other Opioids to OXYCONTIN
Discontinue all other around-the-clock opioid drugs when OXYCONTIN therapy is initiated.

There are no established conversion ratios for conversion from other opioids to OXYCONTIN defined by clinical trials. Initiate dosing using OXYCONTIN 10 mg orally every 12 hours.

It is safer to underestimate a patient's 24-hour oral oxycodone requirements and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral oxycodone dosage and manage an adverse reaction due to an overdose. While useful tables of opioid equivalents are readily available, there is substantial inter-patient variability in the relative potency of different opioids.

Close observation and frequent titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal and for signs of oversedation/toxicity after converting patients to OXYCONTIN.

Conversion from Methadone to OXYCONTIN
Close monitoring is of particular importance when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in the plasma.

Conversion from Transdermal Fentanyl to OXYCONTIN
Treatment with OXYCONTIN can be initiated after the transdermal fentanyl patch has been removed for at least 18 hours. Although there has been no systematic assessment of such conversion, start with a conservative conversion: substitute 10 mg of OXYCONTIN every 12 hours for each 25 mcg per hour fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to OXYCONTIN, as there is limited documented experience with this conversion.

2.4 Initial Dosage in Pediatric Patients 11 Years and Older

The following dosing information is for use only in pediatric patients 11 years and older already receiving and tolerating opioids for at least five consecutive days. For the two days immediately preceding dosing with OXYCONTIN, patients must be taking a minimum of 20 mg per day of oxycodone or its equivalent. OXYCONTIN is not appropriate for use in pediatric patients requiring less than a 20 mg total daily dose. Table 1, based on clinical trial experience, displays the conversion factor when switching pediatric patients 11 years and older (under the conditions described above) from opioids to OXYCONTIN.

Discontinue all other around-the-clock opioid drugs when OXYCONTIN therapy is initiated.

There is substantial inter-patient variability in the relative potency of different opioid drugs and formulations. Therefore, a conservative approach is advised when determining the total daily dosage of OXYCONTIN. It is safer to underestimate a patient's 24-hour oral oxycodone requirements and provide rescue medication (e.g., immediate-release opioid) than to

overestimate the 24-hour oral oxycodone requirements and manage an adverse reaction due to an overdose.

Consider the following when using the information in Table 1.

- This is not a table of equianalgesic doses.
- The conversion factors in this table are only for the conversion from one of the listed oral opioid analgesics to OXYCONTIN.
- The table cannot be used to convert from OXYCONTIN to another opioid. Doing so will result in an over-estimation of the dose of the new opioid and may result in fatal overdose.
- The formula for conversion from prior opioids, including oral oxycodone, to the daily dose of OXYCONTIN is mg per day of prior opioid x factor = mg per day of OXYCONTIN. Divide the calculated total daily dose by 2 to get the every-12-hour OXYCONTIN dose. If rounding is necessary, always round the dose down to the nearest OXYCONTIN tablet strength available.

Table 1: Conversion Factors When Switching Pediatric Patients 11 Years and Older to OXYCONTIN

Prior Opioid	Conversion Factor	
	Oral	Parenteral*
Oxycodone	1	--
Hydrocodone	0.9	--
Hydromorphone	4	20
Morphine	0.5	3
Tramadol	0.17	0.2

*For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

Step #1: To calculate the estimated total OXYCONTIN daily dosage using Table 1:

- For pediatric patients taking a single opioid, sum the current total daily dosage of the opioid and then multiply the total daily dosage by the approximate conversion factor to calculate the approximate OXYCONTIN daily dosage.
- For pediatric patients on a regimen of more than one opioid, calculate the approximate oxycodone dose for each opioid and sum the totals to obtain the approximate OXYCONTIN daily dosage.

- For pediatric patients on a regimen of fixed-ratio opioid/non-opioid analgesic products, use only the opioid component of these products in the conversion.

Step #2: If rounding is necessary, always round the dosage down to the nearest OXYCONTIN tablet strength available and initiate OXYCONTIN therapy with that dose. If the calculated OXYCONTIN total daily dosage is less than 20 mg, there is no safe strength for conversion and do not initiate OXYCONTIN.

Example conversion from a single opioid (e.g., hydrocodone) to OXYCONTIN: Using the conversion factor of 0.9 for oral hydrocodone in Table 1, a total daily hydrocodone dosage of 50 mg is converted to 45 mg of oxycodone per day or 22.5 mg of OXYCONTIN every 12 hours. After rounding down to the nearest strength available, the recommended OXYCONTIN starting dosage is 20 mg every 12 hours.

Step #3: Close observation and titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal or for signs of over-sedation/toxicity after converting patients to OXYCONTIN. [*see Dosage and Administration (2.5)]* for important instructions on titration and maintenance of therapy.

There is limited experience with conversion from transdermal fentanyl to OXYCONTIN in pediatric patients 11 years and older. If switching from transdermal fentanyl patch to OXYCONTIN, ensure that the patch has been removed for at least 18 hours prior to starting OXYCONTIN. Although there has been no systematic assessment of such conversion, start with a conservative conversion: substitute 10 mg of OXYCONTIN every 12 hours for each 25 mcg per hour fentanyl transdermal patch. Follow the patient closely during conversion from transdermal fentanyl to OXYCONTIN.

If using asymmetric dosing, instruct patients to take the higher dose in the morning and the lower dose in the evening.

2.5 Titration and Maintenance of Therapy in Adults and Pediatric Patients 11 Years and Older

Individually titrate OXYCONTIN to a dosage that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving OXYCONTIN to assess the maintenance of pain control, signs and symptoms of opioid withdrawal, and adverse reactions, as well as monitoring for the development of addiction, abuse and misuse *[see Warnings and Precautions (5.1)]*. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for the use of opioid analgesics.

Patients who experience breakthrough pain may require a dosage adjustment of OXYCONTIN or may need rescue medication with an appropriate dose of an immediate-release analgesic. If the level of pain increases after dose stabilization, attempt to identify the source of increased pain

before increasing the OXYCONTIN dosage. Because steady-state plasma concentrations are approximated in 1 day, OXYCONTIN dosage may be adjusted every 1 to 2 days.

If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

There are no well-controlled clinical studies evaluating the safety and efficacy with dosing more frequently than every 12 hours. As a guideline for pediatric patients 11 years and older, the total aily oxycodone dosage usually can be increased by 25% of the current total daily dosage. As a guideline for adults, the total daily oxycodone dosage usually can be increased by 25% to 50% of the current total daily dosage, each time an increase is clinically indicated.

2.6 Dosage Modifications with Concomitant Use of Central Nervous System Depressants

If the patient is currently taking a central nervous system (CNS) depressant and the decision is made to begin OXYCONTIN, start with one-third to one-half the recommended starting dosage of OXYCONTIN, consider using a lower dosage of the concomitant CNS depressant, and monitor patients for signs of respiratory depression, sedation, and hypotension *[see Warnings and Precautions (5.6), Drug Interactions (7)]*.

2.7 Dosage Modifications in Geriatric Patients who are Debilitated and not Opioid-Tolerant

For geriatric patients who are debilitated and not opioid tolerant, start dosing patients at one-third to one-half the recommended starting dosage and titrate the dosage cautiously *[see Use in Specific Populations (8.5]*.

2.8 Dosage Modifications in Patients with Hepatic Impairment

For patients with hepatic impairment, start dosing patients at one-third to one-half the recommended starting dosage and titrate the dosage carefully. Monitor for signs of respiratory depression, sedation, and hypotension *[see Use in Specific Populations, (8.6), Clinical Pharmacology (12.3)]*.

2.9 Discontinuation of OXYCONTIN

When the patient no longer requires therapy with OXYCONTIN, taper the dosage gradually, by 25% to 50% every 2 to 4 days, while monitoring for signs and symptoms of withdrawal. If a patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue OXYCONTIN *[see Warnings and Precautions (5.14), Drug Abuse and Dependence (9.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg.

- 10 mg film-coated extended-release tablets (round, white-colored, bi-convex tablets debossed with OP on one side and 10 on the other)
- 15 mg film-coated extended-release tablets (round, gray-colored, bi-convex tablets debossed with OP on one side and 15 on the other)
- 20 mg film-coated extended-release tablets (round, pink-colored, bi-convex tablets debossed with OP on one side and 20 on the other)
- 30 mg film-coated extended-release tablets (round, brown-colored, bi-convex tablets debossed with OP on one side and 30 on the other)
- 40 mg film-coated extended-release tablets (round, yellow-colored, bi-convex tablets debossed with OP on one side and 40 on the other)
- 60 mg film-coated extended-release tablets (round, red-colored, bi-convex tablets debossed with OP on one side and 60 on the other)
- 80 mg film-coated extended-release tablets (round, green-colored, bi-convex tablets debossed with OP on one side and 80 on the other)

4 CONTRAINDICATIONS

OXYCONTIN is contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.3)]*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.7)]*
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.12)]*
- Hypersensitivity (e.g., anaphylaxis) to oxycodone *[see Adverse Reactions (6.2)]*

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

OXYCONTIN contains oxycodone, a Schedule II controlled substance. As an opioid, OXYCONTIN exposes users to the risks of addiction, abuse, and misuse. Because extended-release products such as OXYCONTIN deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of oxycodone present *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed OXYCONTIN. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing OXYCONTIN, and monitor all patients receiving OXYCONTIN for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as OXYCONTIN, but use in such patients necessitates intensive counseling about the risks and proper use of OXYCONTIN along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse or misuse of OXYCONTIN by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of oxycodone and can result in overdose and death *[see Overdosage (10)]*.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing OXYCONTIN. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: www.fda.gov/OpioidAnalgesicREMSPCG .
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to www.opioidanalgesicrems.com. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint .

5.3 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of OXYCONTIN, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of OXYCONTIN.

To reduce the risk of respiratory depression, proper dosing and titration of OXYCONTIN are essential *[see Dosage and Administration (2)]*. Overestimating the OXYCONTIN dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of OXYCONTIN, especially by children, can result in respiratory depression and death due to an overdose of oxycodone.

5.4 Neonatal Opioid Withdrawal Syndrome

Prolonged use of OXYCONTIN during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1), Patient Counseling Information (17)]*.

5.5 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of OXYCONTIN with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression *[see Warnings and Precautions (5.3)]*, particularly when an inhibitor is added after a stable dose of OXYCONTIN is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in OXYCONTIN-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using OXYCONTIN with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in OXYCONTIN-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of OXYCONTIN until stable drug effects are achieved *[see Drug Interactions (7)]*.

Concomitant use of OXYCONTIN with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using OXYCONTIN with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur *[see Drug Interactions (7)]*.

5.6 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result if OXYCONTIN is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., non-benzodiazepines sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions (7)]*.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when OXYCONTIN is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7), Patient Counseling Information (17)]*.

5.7 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of OXYCONTIN in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: OXYCONTIN-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of OXYCONTIN *[see Warnings and Precautions (5.3)]*.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.3)]*.

Monitor such patients closely, particularly when initiating and titrating OXYCONTIN and when OXYCONTIN is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.3, 5.6)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.8 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.9 Severe Hypotension

OXYCONTIN may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7)]*. Monitor these patients for signs of hypotension after initiating or titrating the dosage of OXYCONTIN. In patients with circulatory shock, OXYCONTIN may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of OXYCONTIN in patients with circulatory shock.

5.10 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), OXYCONTIN may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure.

Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with OXYCONTIN.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of OXYCONTIN in patients with impaired consciousness or coma.

5.11 Difficulty in Swallowing and Risk for Obstruction in Patients at Risk for a Small Gastrointestinal Lumen

There have been post-marketing reports of difficulty in swallowing OXYCONTIN tablets. These reports included choking, gagging, regurgitation and tablets stuck in the throat. Instruct patients not to pre-soak, lick, or otherwise wet OXYCONTIN tablets prior to placing in the mouth, and to take one tablet at a time with enough water to ensure complete swallowing immediately after placing in the mouth.

There have been rare post-marketing reports of cases of intestinal obstruction, and exacerbation of diverticulitis, some of which have required medical intervention to remove the tablet. Patients with underlying GI disorders such as esophageal cancer or colon cancer with a small gastrointestinal lumen are at greater risk of developing these complications. Consider use of an alternative analgesic in patients who have difficulty swallowing and patients at risk for underlying GI disorders resulting in a small gastrointestinal lumen.

5.12 Risks of Use in Patients with Gastrointestinal Conditions

OXYCONTIN is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The oxycodone in OXYCONTIN may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.13 Increased Risk of Seizures in Patients with Seizure Disorders

The oxycodone in OXYCONTIN may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during OXYCONTIN therapy.

5.14 Withdrawal

Avoid the use of mixed agonist/antagonist (e.g.., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including OXYCONTIN. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

When discontinuing OXYCONTIN, gradually taper the dosage *[see Dosage and Administration (2.9)]*. Do not abruptly discontinue OXYCONTIN *[see Drug Abuse and Dependence (9.3)]*.

5.15 Risks of Driving and Operating Machinery

OXYCONTIN may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of OXYCONTIN and know how they will react to the medication *[see Patient Counseling Information (17)]*.

5.16 Laboratory Monitoring

Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative". Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.3)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.4)]*
- Interactions With Benzodiazepines and Other CNS Depressants *[see Warnings and Precautions (5.6)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.8)]*
- Severe Hypotension *[see Warnings and Precautions (5.9)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.11, 5.12)]*
- Seizures *[see Warnings and Precautions (5.13)]*
- Withdrawal *[see Warnings and Precautions (5.14)]*

6.1 Clinical Trial Experience

Adult Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of OXYCONTIN was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received OXYCONTIN in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

OXYCONTIN may increase the risk of serious adverse reactions such as those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, or shock *[see Overdosage (10)]*.

The most common adverse reactions (>5%) reported by patients in clinical trials comparing OXYCONTIN with placebo are shown in Table 2 below:

TABLE 2: Common Adverse Reactions (>5%)

Adverse Reaction	**OXYCONTIN (n=227) (%)**	**Placebo (n=45) (%)**
Constipation	(23)	(7)
Nausea	(23)	(11)
Somnolence	(23)	(4)
Dizziness	(13)	(9)
Pruritus	(13)	(2)
Vomiting	(12)	(7)
Headache	(7)	(7)
Dry Mouth	(6)	(2)
Asthenia	(6)	-
Sweating	(5)	(2)

In clinical trials, the following adverse reactions were reported in patients treated with OXYCONTIN with an incidence between 1% and 5%:

Gastrointestinal disorders: abdominal pain, diarrhea, dyspepsia, gastritis

General disorders and administration site conditions: chills, fever

Metabolism and nutrition disorders: anorexia

Musculoskeletal and connective tissue disorders: twitching

Psychiatric disorders: abnormal dreams, anxiety, confusion, dysphoria, euphoria, insomnia, nervousness, thought abnormalities

Respiratory, thoracic and mediastinal disorders: dyspnea, hiccups

Skin and subcutaneous tissue disorders: rash

Vascular disorders: postural hypotension

The following adverse reactions occurred in less than 1% of patients involved in clinical trials:

Blood and lymphatic system disorders: lymphadenopathy

Ear and labyrinth disorders: tinnitus

Eye disorders: abnormal vision

Gastrointestinal disorders: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, stomatitis

General disorders and administration site conditions: withdrawal syndrome (with and without seizures), edema, peripheral edema, thirst, malaise, chest pain, facial edema

Injury, poisoning and procedural complications: accidental injury

Investigations: ST depression

Metabolism and nutrition disorders: dehydration

Nervous system disorders: syncope, migraine, abnormal gait, amnesia, hyperkinesia, hypoesthesia, hypotonia, paresthesia, speech disorder, stupor, tremor, vertigo, taste perversion

Psychiatric disorders: depression, agitation, depersonalization, emotional lability, hallucination

Renal and urinary disorders: dysuria, hematuria, polyuria, urinary retention

Reproductive system and breast disorders: impotence

Respiratory, thoracic and mediastinal disorders: cough increased, voice alteration

Skin and subcutaneous tissue disorders: dry skin, exfoliative dermatitis

Clinical Trial Experience in Pediatric Patients 11 Years and Older

The safety of OXYCONTIN has been evaluated in one clinical trial with 140 patients 11 to 16 years of age. The median duration of treatment was approximately three weeks. The most frequently reported adverse events were vomiting, nausea, headache, pyrexia, and constipation.

Table 3 includes a summary of the incidence of treatment emergent adverse events reported in ≥5% of patients.

Table 3: Incidence of Adverse Reactions Reported in ≥ 5.0% Patients 11 to 16 Years

System Organ Class **Preferred Term**	**11 to 16 Years** **(N=140)** **n (%)**
Any Adverse Event >= 5%	71 (51)

GASTROINTESTINAL DISORDERS	56 (40)
Vomiting	30 (21)
Nausea	21 (15)
Constipation	13 (9)
Diarrhea	8 (6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	32 (23)
Pyrexia	15 (11)
METABOLISM AND NUTRITION DISORDERS	9 (6)
Decreased appetite	7 (5)
NERVOUS SYSTEM DISORDERS	37 (26)
Headache	20 (14)
Dizziness	12 (9)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	23 (16)
Pruritus	8 (6)

The following adverse reactions occurred in a clinical trial of OXYCONTIN in patients 11 to 16 years of age with an incidence between ≥1.0% and < 5.0%. Events are listed within each System/Organ Class.

Blood and lymphatic system disorders: febrile neutropenia, neutropenia

Cardiac disorders: tachycardia

Gastrointestinal disorders: abdominal pain, gastroesophageal reflux disease

General disorders and administration site conditions: fatigue, pain, chills, asthenia

Injury, poisoning, and procedural complications: procedural pain, seroma

Investigations: oxygen saturation decreased, alanine aminotransferase increased, hemoglobin decreased, platelet count decreased, neutrophil count decreased, red blood cell count decreased, weight decreased

Metabolic and nutrition disorders: hypochloremia, hyponatremia

Musculoskeletal and connective tissue disorders: pain in extremity, musculoskeletal pain

Nervous system disorders: somnolence, hypoesthesia, lethargy, paresthesia

Psychiatric disorders: insomnia, anxiety, depression, agitation

Renal and urinary disorders: dysuria, urinary retention

Respiratory, thoracic, and mediastinal disorders: oropharyngeal pain

Skin and subcutaneous tissue disorders: hyperhidrosis, rash

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of extended-release oxycodone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Abuse, addiction, aggression, amenorrhea, cholestasis, completed suicide, death, dental caries, increased hepatic enzymes, hyperalgesia, hypogonadism, hyponatremia, ileus, intentional overdose, mood altered, muscular hypertonia, overdose, palpitations (in the context of withdrawal), seizures, suicidal attempt, suicidal ideation, syndrome of inappropriate antidiuretic hormone secretion, and urticaria.

In addition to the events listed above, the following have also been reported, potentially due to the swelling and hydrogelling property of the tablet: choking, gagging, regurgitation, tablets stuck in the throat and difficulty swallowing the tablet.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in OXYCONTIN.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)]*.

7 DRUG INTERACTIONS

Table 4 includes clinically significant drug interactions with OXYCONTIN.

Table 4: Clinically Significant Drug Interactions with OXYCONTIN

Inhibitors of CYP3A4 and CYP2D6	
Clinical Impact:	The concomitant use of OXYCONTIN and CYP3A4 inhibitors can increase the plasma concentration of oxycodone, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of OXYCONTIN and CYP2D6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of OXYCONTIN is achieved *[see Warnings*

	and Precautions (5.5)]. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the oxycodone plasma concentration will decrease *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to oxycodone.
Intervention:	If concomitant use is necessary, consider dosage reduction of OXYCONTIN until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the OXYCONTIN dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
Examples	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of OXYCONTIN and CYP3A4 inducers can decrease the plasma concentration of oxycodone *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to oxycodone *[see Warnings and Precautions (5.5)]*. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the oxycodone plasma concentration will increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
Intervention:	If concomitant use is necessary, consider increasing the OXYCONTIN dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider OXYCONTIN dosage reduction and monitor for signs of respiratory depression.
Examples:	Rifampin, carbamazepine, phenytoin
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation *[see Dosage and Administration (2.6), Warnings and Precautions (5.6)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue OXYCONTIN if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine

	reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.3)]*.
Intervention:	The use of OXYCONTIN is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of OXYCONTIN and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Oxycodone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of OXYCONTIN and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when OXYCONTIN is used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.4)]*. There are no available data with OXYCONTIN in pregnant women to inform a drug-associated risk for major birth defects and miscarriage. In animal reproduction studies, there was no embryo-fetal toxicity when

oxycodone hydrochloride was orally administered to rats and rabbits, during the period of organogenesis, at doses 1.3 to 40 times the adult human dose of 60 mg/day, respectively. In a pre- and postnatal toxicity study, when oxycodone was orally administered to rats, there was transiently decreased pup body weight during lactation and the early post-weaning period at the dose equivalent to an adult dose of 60 mg/day. In several published studies, treatment of pregnant rats with oxycodone hydrochloride at clinically relevant doses and below resulted in neurobehavioral effects in offspring *[see Data]*. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.4)]*.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. OXYCONTIN is not recommended for use in women immediately prior to labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including OXYCONTIN, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Animal Data

Pregnant rats were treated with 0.5, 2, 4, and 8 mg/kg oxycodone hydrochloride (0.08, 0.3, 0.7, and 1.3 times the human daily dose of 60 mg/day, respectively based on a mg/m^2 basis) during the period of organogenesis. Oxycodone did not cause adverse effects to the fetus at exposures up to 1.3 times the human dose of 60 mg/day. The high dose produced maternal toxicity characterized by excessive gnawing on forelimbs and decreased body weight gain.

Pregnant rabbits were treated with 1, 5, 25, and 125 mg/kg oxycodone hydrochloride (0.3, 2, 8, and 40 times the human daily dose of 60 mg/day, respectively, based on a mg/m^2 basis) during the period of organogenesis. Oxycodone did not cause adverse effects to the fetus at exposures up to 40 times the human dose of 60 mg/day. The 25 mg/kg and 125 mg/kg doses high doses produced maternal toxicity characterized by decreased food consumption and body weight gain.

Pregnant rats were treated with 0.5, 2, and 6 mg/kg oxycodone hydrochloride (0.08, 0.32, and 1 times the human daily dose of 60 mg/kg, respective, based on a mg/m^2 basis, during the period of organogenesis through lactation. Decreased body weight was found during lactation and the early post-weaning phase in pups nursed by mothers given the highest dose used (6 mg/kg/day, equivalent to an adult human dose of 60 mg/day, on a mg/m^2 basis). However, body weight of these pups recovered.

In published studies, offspring of pregnant rats administered oxycodone hydrochloride during gestation have been reported to exhibit neurobehavioral effects including altered stress responses and increased anxiety-like behavior (2 mg/kg/day IV from Gestation Day 8 to 21 and Postnatal Day 1, 3, and 5; 0.3 times an adult human oral dose of 60 mg/day on a mg/m^2 basis), and altered learning and memory (15 mg/kg/day orally from breeding through parturition; 2.4 times an adult human oral dose of 60 mg/day on a mg/m^2 basis).

8.2 Lactation

Oxycodone is present in breast milk. Published lactation studies report variable concentrations of oxycodone in breast milk with administration of immediate-release oxycodone to nursing mothers in the early postpartum period. The lactation studies did not assess breastfed infants for potential adverse reactions. Lactation studies have not been conducted with extended–release oxycodone, including OXYCONTIN, and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with OXYCONTIN.

Clinical Considerations

Infants exposed to OXYCONTIN through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), Clinical Pharmacology (12.2)]*.

8.4 Pediatric Use

The safety and efficacy of OXYCONTIN have been established in pediatric patients ages 11 to 16 years. Use of OXYCONTIN is supported by evidence from adequate and well-controlled trials with OXYCONTIN in adults as well as an open-label study in pediatric patients ages 6 to 16 years. However, there were insufficient numbers of patients less than 11 years of age enrolled in this study to establish the safety of the product in this age group.

The safety of OXYCONTIN in pediatric patients was evaluated in 155 patients previously receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20 mg per day of oxycodone or its equivalent on the two days immediately preceding dosing with OXYCONTIN. Patients were started on a total daily dose ranging between 20 mg and 100 mg depending on prior opioid dose.

The most frequent adverse events observed in pediatric patients were vomiting, nausea, headache, pyrexia, and constipation *[see Dosage and Administration (2.4), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Trials (14)]*.

8.5 Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone was slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% *[see Clinical Pharmacology (12.3)]*. Of the total number of subjects (445) in clinical studies of oxycodone hydrochloride controlled-release tablets, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected adverse reactions were seen in the elderly patients who received oxycodone hydrochloride controlled-release tablets. Thus, the usual doses and dosing intervals may be appropriate for elderly patients. However, a dosage reduction in debilitated, non-opioid-tolerant patients is recommended *[see Dosage and Administration (2.7)]*.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who are not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of OXYCONTIN slowly in these patients and monitor closely for signs of central nervous system and respiratory depression. *[see Warnings and Precautions (5.7)]*.

Oxycodone is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

A study of OXYCONTIN in patients with hepatic impairment demonstrated greater plasma concentrations than those seen at equivalent doses in persons with normal hepatic function *[see Clinical Pharmacology (12.3)]*. Therefore, a dosage reduction is recommended for these patients *[see Dosage and Administration (2.8)]*. Monitor closely for signs of respiratory depression, sedation, and hypotension.

8.7 Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function *[see Clinical Pharmacology (12.3)]*. Follow a conservative approach to dose initiation and adjust according to the clinical situation.

8.8 Sex Differences

In pharmacokinetic studies with OXYCONTIN, opioid-naïve females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

OXYCONTIN contains oxycodone, a Schedule II controlled substance.

9.2 Abuse

OXYCONTIN contains oxycodone, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxymorphone, and tapentadol. OXYCONTIN can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)]*.

The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common in persons with substance use disorders. 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 healthcare provider(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers 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.

OXYCONTIN, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

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.

Risks Specific to Abuse of OXYCONTIN

OXYCONTIN is for oral use only. Abuse of OXYCONTIN poses a risk of overdose and death. The risk is increased with concurrent use of OXYCONTIN with alcohol and other central nervous system depressants. Taking cut, broken, chewed, crushed, or dissolved OXYCONTIN enhances drug release and increases the risk of overdose and death.

With parenteral abuse, the inactive ingredients in OXYCONTIN can be expected to result in local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis, valvular

heart injury, embolism, and death. Cases of thrombotic microangiopathy (a condition characterized clinically by thrombocytopenia and microangiopathic hemolytic anemia) associated with parenteral abuse have been reported.

Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV.

Abuse Deterrence Studies

OXYCONTIN is formulated with inactive ingredients intended to make the tablet more difficult to manipulate for misuse and abuse. For the purposes of describing the results of studies of the abuse-deterrent characteristics of OXYCONTIN resulting from a change in formulation, in this section, the original formulation of OXYCONTIN, which is no longer marketed, will be referred to as "original OxyContin" and the reformulated, currently marketed product will be referred to as "OXYCONTIN".

In Vitro Testing
In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the extended-release formulation. Results support that, relative to original OxyContin, there is an increase in the ability of OXYCONTIN to resist crushing, breaking, and dissolution using a variety of tools and solvents. The results of these studies also support this finding for OXYCONTIN relative to an immediate-release oxycodone. When subjected to an aqueous environment, OXYCONTIN gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle.

Clinical Studies
In a randomized, double-blind, placebo-controlled 5-period crossover pharmacodynamic study, 30 recreational opioid users with a history of intranasal drug abuse received intranasally administered active and placebo drug treatments. The five treatment arms were finely crushed OXYCONTIN 30 mg tablets, coarsely crushed OXYCONTIN 30 mg tablets, finely crushed original OxyContin 30 mg tablets, powdered oxycodone HCl 30 mg, and placebo. Data for finely crushed OXYCONTIN, finely crushed original OxyContin, and powdered oxycodone HCl are described below.

Drug liking was measured on a bipolar drug liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking and 100 represents maximum liking. Response to whether the subject would take the study drug again was also measured on a bipolar scale of 0 to 100 where 50 represents a neutral response, 0 represents the strongest negative response ("definitely would not take drug again") and 100 represents the strongest positive response ("definitely would take drug again").

Twenty-seven of the subjects completed the study. Incomplete dosing due to granules falling from the subjects' nostrils occurred in 34% (n = 10) of subjects with finely crushed OXYCONTIN, compared with 7% (n = 2) of subjects with finely crushed original OxyContin and no subjects with powdered oxycodone HCl.

The intranasal administration of finely crushed OXYCONTIN was associated with a numerically lower mean and median drug liking score and a lower mean and median score for take drug again, compared to finely crushed original OxyContin or powdered oxycodone HCl as summarized in Table 5.

Table 5: Summary of Maximum Drug Liking (E_{max}) Data Following Intranasal Administration

VAS Scale (100 mm)*		OXYCONTIN (finely crushed)	Original OxyContin (finely crushed)	Oxycodone HCl (powdered)
Drug Liking	Mean (SE)	80.4 (3.9)	94.0 (2.7)	89.3 (3.1)
	Median (Range)	88 (36-100)	100 (51-100)	100 (50-100)
Take Drug Again	Mean (SE)	64.0 (7.1)	89.6 (3.9)	86.6 (4.4)
	Median (Range)	78 (0-100)	100 (20-100)	100 (0-100)

* Bipolar scales (0 = maximum negative response, 50 = neutral response, 100 = maximum positive response)

Figure 1 demonstrates a comparison of drug liking for finely crushed OXYCONTIN compared to powdered oxycodone HCl in subjects who received both treatments. The Y-axis represents the percent of subjects attaining a percent reduction in drug liking for OXYCONTIN vs. oxycodone HCl powder greater than or equal to the value on the X-axis. Approximately 44% (n = 12) had no reduction in liking with OXYCONTIN relative to oxycodone HCl. Approximately 56% (n = 15) of subjects had some reduction in drug liking with OXYCONTIN relative to oxycodone HCl. Thirty-three percent (n = 9) of subjects had a reduction of at least 30% in drug liking with OXYCONTIN compared to oxycodone HCl, and approximately 22% (n = 6) of subjects had a reduction of at least 50% in drug liking with OXYCONTIN compared to oxycodone HCl.

Figure 1: Percent Reduction Profiles for E_{max} of Drug Liking VAS for OXYCONTIN vs. oxycodone HCl, N=27 Following Intranasal Administration

The results of a similar analysis of drug liking for finely crushed OXYCONTIN relative to finely crushed original OxyContin were comparable to the results of finely crushed OXYCONTIN relative to powdered oxycodone HCl. Approximately 43% (n = 12) of subjects had no reduction in liking with OXYCONTIN relative to original OxyContin. Approximately 57% (n = 16) of subjects had some reduction in drug liking, 36% (n = 10) of subjects had a reduction of at least 30% in drug liking, and approximately 29% (n = 8) of subjects had a reduction of at least 50% in drug liking with OXYCONTIN compared to original OxyContin.

Summary
The *in vitro* data demonstrate that OXYCONTIN has physicochemical properties expected to make abuse via injection difficult. The data from the clinical study, along with support from the *in vitro* data, also indicate that OXYCONTIN has physicochemical properties that are expected to reduce abuse via the intranasal route. However, abuse of OXYCONTIN by these routes, as well as by the oral route, is still possible.

Additional data, including epidemiological data, when available, may provide further information on the impact of the current formulation of OXYCONTIN on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate.

OXYCONTIN contains oxycodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, and oxymorphone. OXYCONTIN can be abused and is

subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.1)]*.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

OXYCONTIN should not be abruptly discontinued *[see Dosage and Administration (2.9)]*. If OXYCONTIN is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

Clinical Presentation

Acute overdose with OXYCONTIN can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression

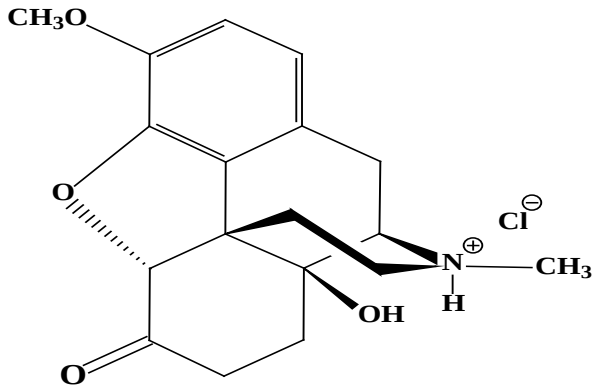
secondary to oxycodone overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose.

Because the duration of reversal is expected to be less than the duration of action of oxycodone in OXYCONTIN, carefully monitor the patient until spontaneous respiration is reliably reestablished. OXYCONTIN will continue to release oxycodone and add to the oxycodone load for 24 to 48 hours or longer following ingestion, necessitating prolonged monitoring. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

OXYCONTIN® (oxycodone hydrochloride) extended-release tablets is an opioid agonist supplied in 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg tablets for oral administration. The tablet strengths describe the amount of oxycodone per tablet as the hydrochloride salt. The structural formula for oxycodone hydrochloride is as follows:



$C_{18}H_{21}NO_4 \bullet HCl$ MW 351.83

The chemical name is 4, 5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Oxycodone is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL). It is slightly soluble in alcohol (octanol water partition coefficient 0.7).

The 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg tablets contain the following inactive ingredients: butylated hydroxytoluene (BHT), hypromellose, polyethylene glycol 400, polyethylene oxide, magnesium stearate, titanium dioxide.

The 10 mg tablets also contain hydroxypropyl cellulose.

The 15 mg tablets also contain black iron oxide, yellow iron oxide, and red iron oxide.

The 20 mg tablets also contain polysorbate 80 and red iron oxide.

The 30 mg tablets also contain polysorbate 80, red iron oxide, yellow iron oxide, and black iron oxide.

The 40 mg tablets also contain polysorbate 80 and yellow iron oxide.

The 60 mg tablets also contain polysorbate 80, red iron oxide and black iron oxide.

The 80 mg tablets also contain hydroxypropyl cellulose, yellow iron oxide and FD&C Blue #2/Indigo Carmine Aluminum Lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxycodone is a full opioid agonist and is relatively selective for the mu receptor, although it can bind to other opioid receptors at higher doses. The principal therapeutic action of oxycodone is analgesia. Like all full opioid agonists, there is no ceiling effect to analgesia for oxycodone. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

12.2 Pharmacodynamics

Effects on the Central Nervous System

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in CO_2 tension and electrical stimulation.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Overdosage (10)]*.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Oxycodone produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans *[see Adverse Reactions (6.2)]*. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6.2)]*.

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration –Efficacy Relationships

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall subjective "drug effect", analgesia and feelings of relaxation.

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance *[see Dosage and Administration (2.1, 2.5)]*.

Concentration –Adverse Reaction Relationships

There is a relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *[see Dosage and Administration (2.1, 2.5)]*.

12.3 Pharmacokinetics

The activity of OXYCONTIN is primarily due to the parent drug oxycodone. OXYCONTIN is designed to provide delivery of oxycodone over 12 hours.

Cutting, breaking, chewing, crushing or dissolving OXYCONTIN impairs the controlled-release delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone release from OXYCONTIN is pH independent. The oral bioavailability of oxycodone is 60% to 87%. The relative oral bioavailability of oxycodone from OXYCONTIN to that from immediate-release oral dosage forms is 100%. Upon repeated dosing with OXYCONTIN in healthy subjects in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours. Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life ($t_{½}$) of oxycodone following the administration of OXYCONTIN was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism.

Plasma Oxycodone Concentration over Time

Dose proportionality has been established for OXYCONTIN 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) *(see Table 6)*. Given the short elimination $t_{½}$ of oxycodone, steady-state plasma concentrations of oxycodone are achieved within 24-36 hours of initiation of dosing with OXYCONTIN. In a study comparing 10 mg of OXYCONTIN every 12 hours to 5 mg of immediate-release oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{max}, and similar for C_{min} (trough) concentrations.

TABLE 6

Mean [% coefficient of variation]

Regimen	Dosage Form	AUC (ng•hr/mL)*	C_{max} (ng/mL)	T_{max} (hr)
Single Dose†	10 mg	136 [27]	11.5 [27]	5.11 [21]
	15 mg	196 [28]	16.8 [29]	4.59 [19]
	20 mg	248 [25]	22.7 [25]	4.63 [22]
	30 mg	377 [24]	34.6 [21]	4.61 [19]
	40 mg	497 [27]	47.4 [30]	4.40 [22]
	60 mg	705 [22]	64.6 [24]	4.15 [26]
	80 mg	908 [21]	87.1 [29]	4.27 [26]

* for single-dose AUC = $AUC_{0\text{-}inf}$

†data obtained while subjects received naltrexone, which can enhance absorption

Food Effects

Food has no significant effect on the extent of absorption of oxycodone from OXYCONTIN.

Distribution

Following intravenous administration, the steady-state volume of distribution (V_{ss}) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk *[see Use in Specific Populations (8.4)]*.

Elimination

Metabolism

Oxycodone is extensively metabolized by multiple metabolic pathways to produce noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. Noroxycodone and noroxymorphone are the major circulating metabolites. CYP3A mediated *N*-demethylation to noroxycodone is the primary metabolic pathway of oxycodone with a lower contribution from CYP2D6 mediated *O*-demethylation to oxymorphone. Therefore, the formation of these and related metabolites can, in theory, be affected by other drugs *[see Drug Interactions (7)]*.

Noroxycodone exhibits very weak anti-nociceptive potency compared to oxycodone, however, it undergoes further oxidation to produce noroxymorphone, which is active at opioid receptors. Although noroxymorphone is an active metabolite and present at relatively high concentrations in circulation, it does not appear to cross the blood-brain barrier to a significant extent. Oxymorphone is present in the plasma only at low concentrations and undergoes further metabolism to form its glucuronide and noroxymorphone. Oxymorphone has been shown to be active and possessing analgesic activity but its contribution to analgesia following oxycodone administration is thought to be clinically insignificant. Other metabolites (α- and ß-oxycodol, noroxycodol and oxymorphol) may be present at very low concentrations and demonstrate limited penetration into the brain as compared to oxycodone. The enzymes responsible for keto-reduction and glucuronidation pathways in oxycodone metabolism have not been established.

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free and conjugated oxycodone 8.9%, free noroxycodone 23%, free oxymorphone less than 1%, conjugated oxymorphone 10%, free and conjugated noroxymorphone 14%, reduced free and conjugated metabolites up to 18%. The total plasma clearance was approximately 1.4 L/min in adults.

Specific Populations

Age: Geriatric Population

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects (age 21-45).

Age: Pediatric Population

In the pediatric age group of 11 years of age and older, systemic exposure of oxycodone is expected to be similar to adults at any given dose of OXYCONTIN.

Sex

Across individual pharmacokinetic studies, average plasma oxycodone concentrations for female subjects were up to 25% higher than for male subjects on a body weight-adjusted basis. The reason for this difference is unknown *[see Use in Specific Populations (8.9)]*.

Hepatic Impairment

Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than healthy subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The mean elimination $t_{½}$ for oxycodone increased by 2.3 hours.

Renal Impairment

Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) showed peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This was accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in mean elimination $t_{½}$ for oxycodone of 1 hour.

Drug Interaction Studies

CYP3A4 Inhibitors

CYP3A4 is the major isoenzyme involved in noroxycodone formation. Co-administration of OXYCONTIN (10 mg single dose) and the CYP3A4 inhibitor ketoconazole (200 mg BID) increased oxycodone AUC and C_{max} by 170% and 100%, respectively *[see Drug Interactions (7)]*.

CYP3A4 Inducers

A published study showed that the co-administration of rifampin, a drug metabolizing enzyme inducer, decreased oxycodone AUC and C_{max} values by 86% and 63%, respectively *[see Drug Interactions (7)]*.

CYP2D6 Inhibitors

Oxycodone is metabolized in part to oxymorphone via CYP2D6. While this pathway may be blocked by a variety of drugs such as certain cardiovascular drugs (e.g., quinidine) and antidepressants (e.g., fluoxetine), such blockade has not been shown to be of clinical significance with OXYCONTIN *[see Drug Interactions (7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate the carcinogenic potential of oxycodone have not been conducted.

Mutagenesis

Oxycodone was genotoxic in the in vitro mouse lymphoma assay. Oxycodone was negative when tested at appropriate concentrations in the in vitro chromosomal aberration assay, the in vitro bacterial reverse mutation assay (Ames test), and the in vivo bone marrow micronucleus assay in mice.

Impairment of Fertility

In a study of reproductive performance, rats were administered a once daily gavage dose of the vehicle or oxycodone hydrochloride (0.5, 2, and 8 mg/kg/day). Male rats were dosed for 28 days before cohabitation with females, during the cohabitation and until necropsy (2-3 weeks post-cohabitation). Females were dosed for 14 days before cohabitation with males, during cohabitation and up to Gestation Day 6. Oxycodone hydrochloride did not affect reproductive function in male or female rats at any dose tested (up to 8 mg/kg/day), up to 1.3 times a human dose of 60 mg/day.

14 CLINICAL STUDIES

Adult Clinical Study

A double-blind, placebo-controlled, fixed-dose, parallel group, two-week study was conducted in 133 patients with persistent, moderate to severe pain, who were judged as having inadequate pain control with their current therapy. In this study, OXYCONTIN 20 mg, but not 10 mg, was statistically significant in pain reduction compared with placebo.

Pediatric Clinical Study

OXYCONTIN has been evaluated in an open-label clinical trial of 155 opioid-tolerant pediatric patients with moderate to severe chronic pain. The mean duration of therapy was 20.7 days (range 1 to 43 days). The starting total daily doses ranged from 20 mg to 100 mg based on the patient's prior opioid dose. The mean daily dose was 33.30 mg (range 20 to 140 mg/day). In an extension study, 23 of the 155 patients were treated beyond four weeks, including 13 for 28 weeks. Too few patients less than 11 years were enrolled in the clinical trial to provide meaningful safety data in this age group.

16 HOW SUPPLIED/STORAGE AND HANDLING

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 10 mg are film-coated, round, white-colored, bi-convex tablets debossed with OP on one side and 10 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-410-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-410-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 15 mg are film-coated, round, gray-colored, bi-convex tablets debossed with OP on one side and 15 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-415-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-415-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 20 mg are film-coated, round, pink-colored, bi-convex tablets debossed with OP on one side and 20 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-420-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-420-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 30 mg are film-coated, round, brown-colored, bi-convex tablets debossed with OP on one side and 30 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-430-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-430-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 40 mg are film-coated, round, yellow-colored, bi-convex tablets debossed with OP on one side and 40 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-440-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-440-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 60 mg are film-coated, round, red-colored, bi-convex tablets debossed with OP on one side and 60 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-460-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-460-20**).

OXYCONTIN (oxycodone hydrochloride) extended-release tablets 80 mg are film-coated, round, green-colored, bi-convex tablets debossed with OP on one side and 80 on the other and are supplied as child-resistant closure, opaque plastic bottles of 100 (**NDC 59011-480-10**) and unit dose packaging with 10 individually numbered tablets per card; two cards per glue end carton (**NDC 59011-480-20**).

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Dispense in tight, light-resistant container.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Addiction, Abuse and Misuse

Inform patients that the use of OXYCONTIN, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share OXYCONTIN with others and to take steps to protect OXYCONTIN from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting OXYCONTIN or when the dosage is increased, and that it can occur even at recommended dosages *[see Warnings and Precautions (5.3)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

To guard against excessive exposure to OXYCONTIN by young children, advise caregivers to strictly adhere to recommended OXYCONTIN dosing.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.3)]*. Instruct patients to take steps to store OXYCONTIN securely and to dispose of unused OXYCONTIN by flushing the tablets down the toilet.

Interactions with Benzodiazepines or Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if OXYCONTIN is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider *[see Warnings and Precautions (5.6), Drug Interactions (7)]*.

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare provider if they are taking, or plan to take serotonergic medications *[see Drug Interactions (7)]*.

MAOI Interaction

Inform patients to avoid taking OXYCONTIN while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking OXYCONTIN *[see Drug Interactions (7)]*.

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.8)]*.

Important Administration Instructions

Instruct patients how to properly take OXYCONTIN, including the following:

- OXYCONTIN is designed to work properly only if swallowed intact. Taking cut, broken, chewed, crushed, or dissolved OXYCONTIN tablets can result in a fatal overdose *[see Dosage and Administration (2.1)]*.
- OXYCONTIN tablets should be taken one tablet at a time *[see Dosage and Administration (2.1)]*.
- Do not pre-soak, lick, or otherwise wet the tablet prior to placing in the mouth *[see Dosage and Administration (2.1)]*.
- Take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth *[see Dosage and Administration (2.1)]*.
- Do not discontinue OXYCONTIN without first discussing the need for a tapering regimen with the prescriber *[see Dosage and Administration (2.9)]*.

Hypotension

Inform patients that OXYCONTIN may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.9)]*.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in OXYCONTIN. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Adverse Reactions (6)]*.

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of OXYCONTIN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1)]*.

Embryo-Fetal Toxicity
Inform female patients of reproductive potential that OXYCONTIN can cause fetal harm and to inform their healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation:

Advise patients that breastfeeding is not recommended during treatment with OXYCONTIN *[see Use in Specific Populations (8.2)]*

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)]*.

Driving or Operating Heavy Machinery

Inform patients that OXYCONTIN may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.15)]*.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6)]*.

Disposal of Unused OXYCONTIN

Advise patients to flush the unused tablets down the toilet when OXYCONTIN is no longer needed.
Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

Purdue Pharma L.P.
Stamford, CT 06901-3431

U.S. Patent Numbers 6,488,963; 7,129,248; 8,309,060; 8,808,741; 8,821,929; 8,894,987; 8,894,988; 9,060,976; 9,073,933; 9,492,389, 9,492,391, 9,492,392, 9,492,393, and 9,522,919

Medication Guide
OXYCONTIN® (ox-e-KON-tin) (oxycodone hydrochloride) extended-release tablets, CII

OXYCONTIN is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not for use to treat pain that is not around-the-clock.
- Not for use in children less than 11 years of age and who are not already using opioid pain medicines regularly to manage pain severe enough to require daily around-the-clock long-term treatment of pain with an opioid.

Important information about OXYCONTIN:

- **Get emergency help right away if you take too much OXYCONTIN (overdose).** When you first start taking OXYCONTIN, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.
- Taking **OXYCONTIN** with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your OXYCONTIN. They could die from taking it. Store OXYCONTIN away from children and in a safe place to prevent stealing or abuse. Selling or giving away OXYCONTIN is against the law.

Do not take OXYCONTIN if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking OXYCONTIN, tell your healthcare provider if you have a history of:

- head injury, seizures
- problems urinating
- liver, kidney, thyroid problems
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of OXYCONTIN during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Not recommended during treatment with OXYCONTIN. It may harm your baby.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking OXYCONTIN with certain other medicines can cause serious side effects that could lead to death.

When taking OXYCONTIN:

- Do not change your dose. Take OXYCONTIN exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.
- Take your prescribed dose every 12 hours at the same time every day. Do not take more than your prescribed dose in 12 hours. If you miss a dose, take your next dose at your usual time.
- Swallow OXYCONTIN whole. Do not cut, break, chew, crush, dissolve, snort, or inject OXYCONTIN because this may cause you to overdose and die.
- OXYCONTIN should be taken 1 tablet at a time. Do not pre-soak, lick, or wet the tablet before placing in your mouth to avoid choking on the tablet.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking OXYCONTIN without talking to your healthcare provider.**
- After you stop taking OXYCONTIN, flush any unused tablets down the toilet.

While taking OXYCONTIN DO NOT:

- Drive or operate heavy machinery until you know how OXYCONTIN affects you. OXYCONTIN can make you sleepy, dizzy, or lightheaded.
- Drink alcohol, or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with OXYCONTIN may cause you to overdose and die.

The possible side effects of OXYCONTIN are:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

These are not all the possible side effects of OXYCONTIN. Call your doctor for medical advice about side effects.
You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

Manufactured by: Purdue Pharma L.P., Stamford, CT 06901-3431, **www.purduepharma.com or call 1-888-726-7535**

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 12/2016

OXYCONTIN® (II)
(OXYCODONE HCl) EXTENDED-RELEASE TABLETS

EXHIBIT B

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

SEP 10 2013

Andrew Kolodny, MD
President, Physicians for Responsible Opioid Prescribing
920 48th Street, Suite 1510
Brooklyn, NY 11219

Re: Docket No. FDA-2012-P-0818

Dear Dr. Kolodny:

This letter responds to the citizen petition submitted by Physicians for Responsible Opioid Prescribing (PROP), which was received by FDA on July 26, 2012 (Petition). The Petition describes PROP's concerns about the safety and efficacy of opioid analgesic drugs for long-term use in chronic non-cancer pain, and requests that the Food and Drug Administration (FDA or Agency): (1) "[s]trike the term 'moderate' from the indication [of opioid analgesics] for non-cancer pain"; (2) "[a]dd a maximum daily dose, equivalent to 100 milligrams of morphine for non-cancer pain"; and (3) "[a]dd a maximum duration of 90-days for continuous [daily] use" for non-cancer pain (Petition at 2).[1]

FDA has carefully reviewed PROP's Petition and the numerous comments submitted to the public dockets[2] by government entities, medical societies, healthcare providers, patients, and other members of the public. For the reasons described in detail in this response, the Petition is granted in part and denied in part.

Today, on the basis of the information discussed below, FDA has notified application holders for extended-release/long-acting (ER/LA) opioid analgesics that, pursuant to section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C 355(o)(4)), important safety labeling changes are needed to the labeling of ER/LA opioid analgesics.[3] It is the agency's intent that these changes, which are described more fully below, will help more effectively communicate the serious risks of misuse, abuse, neonatal opioid withdrawal syndrome (NOWS), addiction, overdose, and death associated with the use of ER/LA opioids overall, and during pregnancy. FDA has also determined that more data are needed about the safety of long-term use of opioids. Pursuant to section 505(o)(3) of the FD&C Act, FDA is therefore requiring all new drug application (NDA) sponsors of ER/LA opioids to conduct postapproval studies and clinical trials

[1] The Petition requests pertain to analgesia products; therefore, this response is limited to opioids with indications for analgesia.

[2] FDA received comments on the PROP citizen petition in the above-captioned docket and comments relevant to the PROP citizen petition in the docket for a part 15 hearing the agency held in February 2013, titled Impact of Approved Drug Labeling on Chronic Opioid Therapy (Part 15 Hearing) (*see* Docket No. FDA-2012-N-1172).

[3] Pursuant to section 505(o)(4) of the FD&C Act, FDA is notifying holders of approved NDAs and holders of approved ANDAs that reference a NDA that is not currently marketed.

(post-marketing requirements, or PMRs) to assess certain known serious risks of ER/LA opioid use: misuse, abuse, hyperalgesia, addiction, overdose, and death.

I. BACKGROUND

A. Opioids

Opioids are a class of powerful pain-relieving agents that includes oxycodone, hydrocodone, and morphine, among others. When prescribed and used properly, opioids can effectively manage pain and alleviate suffering—clearly a public health priority.[4] Chronic pain is a serious and growing public health problem: it "affects millions of Americans; contributes greatly to national rates of morbidity, mortality, and disability; and is rising in prevalence."[5] There is also evidence that pain is inadequately treated in many patients.[6] However, pain is a self-reported symptom that is difficult to quantify, and its treatment is complex.

Opioids also have grave risks, the most well-known of which include addiction, overdose, and even death. The labeling for these products contains prominent warnings about these risks. Moreover, the boxed warning states that all patients should be "routinely monitor[ed]...for signs of misuse, abuse, and addiction." Even proper use of opioids under medical supervision can result in life-threatening respiratory depression, coma, and death (see Boxed Warning and Section 5.3 of Warnings in current labeling). Indeed, a Centers for Disease Control and Prevention (CDC) analysis published in February 2013 documents an 11th straight year of increases in drug overdose deaths, with opioids being involved in 75% of pharmaceutical overdose deaths, either alone or in combination with other drugs.[7]

Most opioid-only drugs are controlled under Schedule II of the Controlled Substances Act.[8] By law, prescriptions for Schedule II drugs cannot be refilled; patients need a new prescription to obtain the drug beyond the initial number of doses prescribed.[9] There are also strict recordkeeping, reporting, and physical security requirements. This level of

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[4] *See* "Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research." Committee on Advancing Pain Research, Care, and Education; Institute of Medicine. 2011:1-364 (available at http://www.nap.edu/catalog.php?record_id=13172).

[5] *Id.* at p. 5.

[6] *Id.* at p. 1.

[7] Jones CM, Mack, KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. JAMA 2013; 309(7): 657-9.

[8] *See* 21 U.S.C. 801 *et seq*; 21 CFR 1308.12. There are some opioids in Schedule III (*e.g.*, buprenorphine, *see* 21 CFR 1308.13(e)(2)(i)) and Schedule IV (*e.g.*, butorphanol and pentazocine, *see* 21 CFR 1308.14(f)). Tramadol, a synthetic opioid, is not currently scheduled under the Controlled Substances Act, *see* www.deadiversion.usdoj.gov/drug_chem_info/tramadol.pdf.

[9] Although opioid drug labeling does not recommend a limit on the number of doses a patient should receive, the Schedule II status of most opioid drugs imposes certain restrictions on their availability. 21 CFR 1306.12(a). However, prescribers "may issue multiple prescriptions authorizing the patient to receive a total of up to a 90-day supply of a Schedule II controlled substance" as long as certain conditions are met. 21 CFR 1306.12(b)(1).

control reflects a finding that most opioid drugs have "high potential for abuse" and that "[a]buse of the drug . . . may lead to severe psychological or physical dependence."[10]

Opioid drugs have been approved for different conditions of use based on the data and information submitted by the sponsor of each drug product. Accordingly, product labeling may vary among approved opioid drugs, and such drugs may be prescribed to different patient populations.[11] The approved indications for ER/LA opioid analgesics are uniform, however. These drugs are currently indicated "for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time."[12] The current labeling for these drugs also contains a prominent statement that they are **not** for use:

- As an as-needed (prn) analgesic,
- For pain that is mild or not expected to persist for an extended period of time,
- For acute pain,
- In the immediate postoperative period, or
- For postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.[13]

The labeling for some ER/LA opioid analgesics also states that they are for use (or for use at higher doses) only in opioid-tolerant patients.[14]

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[10] 21 U.S.C. 812(b)(2).

[11] For example, indications for which particular IR opioid products have been approved include "the management of acute and chronic moderate to severe pain where the use of an opioid analgesic is appropriate" (Oxecta (oxycodone hydrochloride) labeling, available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/202080s001lbl.pdf); "the relief of mild to moderately severe pain where the use of an opioid analgesic is appropriate" (Codeine sulfate (NDA 022402) labeling, available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/022402s006lbl.pdf); and "the management of pain in patients where an opioid analgesic is appropriate" (Dilaudid (hydromorphone hydrochloride) labeling, available at www.accessdata.fda.gov/drugsatfda_docs/label/2007/019892s015lbl.pdf).

[12] OxyContin (oxycodone hydrochloride) extended-release tablets (NDA 022272) labeling, available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf.

[13] Labeling for OxyContin (oxycodone hydrochloride) extended-release tablets (NDA 022272), available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf (internal references omitted).

[14] *See, e.g.,* labeling for Exalgo (hydromorphone hydrochloride) (NDA 021217) and Duragesic (fentanyl) (NDA 019813). Further, certain opioid drugs also have limitations of use on the higher doses, with labeling stating that higher doses are for opioid-tolerant patients only. *See, e.g.,* labeling for Avinza (morphine sulfate) extended-release capsules (NDA 021260), available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/021260s017lbl.pdf and OxyContin (oxycodone hydrochloride) extended-release tablets (NDA 022272), available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf.

B. ER/LA Opioid Analgesic Risk Evaluation and Mitigation Strategy

FDA approved a shared-system Risk Evaluation and Mitigation Strategy (REMS) for ER/LA opioid analgesics on July 9, 2012 (ER/LA Opioid Analgesic REMS).[15] The goal of the ER/LA Opioid Analgesic REMS is to "reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of [ER/LA opioids] while maintaining patient access to pain medications."[16] Under the REMS, "[a]dverse outcomes of concern include addiction, unintentional overdose, and death."[17] The REMS is currently limited to ER/LA opioid products because FDA has concluded that there are disproportionate safety concerns associated with these products compared to immediate-release (IR) opioids.[18]

Currently, more than 30 products are subject to the ER/LA Opioid Analgesic REMS.[19] The ER/LA Opioid Analgesic REMS contains requirements for distribution of a Medication Guide with each prescription filled, as well as a requirement that training be made available to all those who prescribe ER/LA opioids. Prescriber education training is considered ER/LA Opioid Analgesic REMS-compliant if, among other things, it includes the elements described in the "FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics" (FDA Blueprint).[20] The FDA Blueprint provides guidance to prescribers to enable appropriate ER/LA opioid prescribing practices, as well as information prescribers can use in counseling patients about the risks and benefits of ER/LA opioid use.

C. Public Input

FDA has received a considerable amount of input from stakeholders and other commenters on issues pertaining to the benefits and risks of opioid use. For example, FDA participated in a two-day workshop in May 2012 hosted at the National Institutes of Health (NIH), called, "Assessment of Analgesic Treatment of Chronic Pain: A Scientific Workshop."[21] Several stakeholders and other members of the public gave presentations

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[15] *See* www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf (most recently modified in April, 2013).

[16] *Id.* at p. 2.

[17] *Id.*

[18] *See* http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm309742.htm#Q5; *see also, e.g.*, Dormitzer, C. Opioid Abuse and Misuse: Data from the National Survey on Drug Use and Health and the Drug Abuse Warning Network. Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). UMUC Inn and Conference Center by Marriott, Adelphi, MD, July 22-23, 2010 (available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM220950.pdf) (providing data showing growing harm associated with ER/LA opioids).

[19] The list of drugs required to have a REMS, grouped by application holder, may be found at www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM348818.pdf.

[20] Available at http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf.

[21] *See* Docket No. FDA-2012-N-0067; *see also* http://www.fda.gov/Drugs/NewsEvents/ucm283979.htm.

about issues relating to opioid treatment of chronic pain, and additional comments and subsequent input were posted to the public docket for that meeting.[22]

On February 7 and 8, 2013, FDA held a public hearing on chronic use of opioid drug products, titled, "Impact of Approved Drug Labeling on Chronic Opioid Therapy" (Part 15 Hearing).[23] FDA requested information, particularly scientific evidence, on issues pertaining to the use of opioid drugs in the treatment of chronic pain, including diagnosis and understanding of pain, understanding and adhering to the labeling of pain-treating products, and limiting opioid prescriptions and use.[24] The Agency received input from dozens of presenters, including patients, individuals who had lost loved ones due to opioids, clinicians, public health experts, professional associations, academicians, and others, including PROP. FDA also received over 600 comments to the Part 15 Hearing docket. The majority were from patients voicing concerns that labeling changes could make legitimate patient access to opioid analgesics more difficult.[25] The remainder reflected the same diversity of viewpoints and concerns presented during the hearing itself.

FDA also received more than 1900 comments on the PROP Petition. Many public health agencies and organizations supported the requests in the Petition, citing concerns about increased opioid use and abuse.[26] However, the majority of comments opposed PROP's requests. Many professional societies (*e.g.*, the American Academy of Pain Medicine, the American Medical Association, the American Society of Anesthesiologists, the American Pain Society) did not support the Petition and stated that the data cited by PROP did not support PROP's requests (particularly those requests for limits on dose and duration of use of opioids). Professional societies also expressed concern that the labeling changes requested by PROP were not supported by scientific evidence, and that a "one-size-fits-all" approach to a maximum dose or duration of treatment would be problematic and inconsistent with the need for individualized treatment and the variability among patient responses to opioids.[27]

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[22] *See* Docket No. FDA-2012-N-0067.

[23] *See* Docket No. FDA-2012-N-1172.

[24] *See* www.gpo.gov/fdsys/pkg/FR-2012-12-19/pdf/2012-30516.pdf.

[25] However, for privacy reasons, many comments from individual patients are not publicly available on www.regulations.gov. They nevertheless are considered to be included in the public docket.

[26] *See, e.g.*, comments from the New York City Department of Health and Mental Hygiene (Docket No. FDA-2012-P-0818-0785); County of Los Angeles Public Health (Docket No. FDA-2012-P-0818-0336); Denver Public Health (Docket No. FDA-2012-P-0818-0677); and the National Center on Addiction and Substance Abuse at Columbia University (Docket No. FDA-2012-P-0818-0691).

[27] *See, e.g.*, comments from the American Academy of Pain Medicine (Docket No. FDA-2012-P-0818-0165); the American Medical Association (Docket No. FDA-2012-P-0818-0783); the American Society of Anesthesiologists (Docket No. FDA-2012-P-0818-0246); the American Pain Society (Docket No. FDA-2012-P-0818-0187); the American Academy of Physical Medicine and Rehabilitation (Docket No. FDA-2012-P-0818-0658); the American Society of Regional Analgesia and Pain Medicine (Docket No. FDA-2012-P-0818-0276); the Texas Pain Society (Docket No. FDA-2012-P-0818-0331); and the Florida Academy of Pain Medicine (Docket No. FDA-2012-P-0818-0333). Some commenters submitted critiques of PROP's cited studies that identified the studies' limitations. *See, e.g.*, comments from the American Academy of Pain Medicine (Docket No. FDA-2012-P-0818-0165). For example, the Florida Academy of Pain Medicine states, "it appears that the petitioners are asking for changes to the indications for long-term

II. SAFETY LABELING CHANGES

After evaluating stakeholder and commenter input regarding opioid labeling, and based on FDA's review of relevant literature, FDA has determined that safety labeling changes to the labeling of ER/LA opioid analgesics are needed to more effectively communicate to prescribers the serious risks associated with these drugs, and to more clearly describe the population in whom these drugs should be used in light of these serious risks—thus encouraging better prescribing, monitoring, and patient counseling practices involving these drugs. FDA is therefore exercising its authority under section 505(o)(4) of the FD&C Act to notify application holders that modifications to ER/LA opioid analgesic labeling are needed.[28] It is the agency's intent that these changes will help reduce inappropriate prescribing[29] and help curb the increase in misuse, abuse, NOWS, addiction, overdose, and death associated with ER/LA opioid analgesic use.

These safety labeling changes apply only to ER/LA opioid analgesics, and, at present, FDA is not requesting or requiring that any labeling changes be made to IR opioids or opioid/non-opioid combination products (which include both an IR opioid and a non-opioid analgesic).[30] Much of the literature FDA reviewed assessed opioid use from all opioid sources, or did not necessarily separate data according to opioid formulation (*i.e.*, ER/LA versus IR or opioid/non-opioid combinations). However, FDA recognizes that ER/LA opioids, as a class of drugs, have disproportionate safety concerns compared to IR opioids or opioid/non-opioid combination products; indeed, the recognition of

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high-dose opioid therapy (LTHDOT) for non-cancer pain, based on a small number of studies with significant methodological shortcomings and findings that are not conclusive. In short, they are basing their request for label changes on the same kind of evidence they themselves, criticize as being insufficient to support the safety and efficacy of LTHDOT for non-cancer pain" (Docket No. FDA-2012-P-0818-0333).

[28] Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended the FD&C Act, as codified in section 505(o)(4) of the FD&C Act, to authorize FDA to require holders of approved drug applications to make safety labeling changes (SLCs) if the agency becomes aware of "new safety information" that FDA determines should be included in the labeling of the drug. *New safety information* is information derived from a clinical trial, an adverse event report, a post-approval study (including a study under section 505(o)(3) of the FD&C Act), or peer-reviewed biomedical literature; data derived from the post-market risk identification and analysis system under section 505(k) of the FD&C Act; or other scientific data deemed appropriate by the Agency about, among other things, a serious or an unexpected serious risk associated with use of the drug of which the Agency has become aware (that may be based on a new analysis of existing information) since the drug was approved, the REMS was approved, or since the last assessment of the approved REMS; or the effectiveness of the approved REMS for the drug obtained since the last assessment of such strategy. *See* section 505-1(b)(3) of the FD&C Act.

[29] Pain patients in the United States receive care from prescribers with different backgrounds and levels of experience and expertise in treating pain. IMS Health, Vector One®: National (VONA). Data Extracted September 2012. Weblink: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM337148.pdf. For example, some prescribers may not understand how to identify patients at risk for addiction, how to identify behaviors associated with misuse and abuse, and how to manage patients who are receiving opioids for chronic pain so as to reduce the risks of misuse, abuse, NOWS, addiction, overdose and death.

[30] Therefore, the agency denies PROP's Petition insofar as it requests labeling changes for IR opioids, or opioid/non-opioid combination products.

disproportionate safety concerns for ER/LA opioids informed FDA's decision to require the ER/LA Opioid Analgesic REMS. For example, data show that the risk for misuse and abuse is greater for ER/LA opioids.[31] Because they are intended to release the drug over a longer period of time, many ER/LA opioids contain higher doses of opioids compared to IR opioids or opioid/non-opioid combinations. This increases the risk of a fatal outcome in the event of an overdose, and may make ER/LA opioids more desirable in the eyes of opioid abusers and addicts. Furthermore, ER/LA opioids are often used in a chronic pain setting. Thus, in light of the risks posed by ER/LA opioids, and the totality of available data on both ER/LA opioids specifically and opioid drugs in general, the Agency has decided to make ER/LA opioid analgesics its current focus.

First, FDA is requiring changes to the boxed warning for ER/LA opioid analgesics to give greater emphasis and prominence to the risks of misuse, abuse, NOWS, addiction, overdose, and death. For example, the first sentence of the new boxed warning provides that ER/LA opioids "expose patients and other users to the risks of opioid addiction, abuse, and misuse which can lead to overdose and death." The new boxed warning also urges prescribers to "assess each patient's risk" before prescribing, and to "monitor all patients regularly for the development of these behaviors or conditions."

Second, FDA is requiring changes to the Indications and Usage section of the labeling. As noted above, ER/LA opioid analgesics currently are "indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time."[32] The Agency has concluded that use of terminology predicated only on a categorical "severity scale" (e.g., mild, moderate, severe) to characterize the intensity of pain for which ER/LA opioids are indicated does not sufficiently focus prescribers' attention on their responsibility to make an individualized assessment of patient needs in light of the serious risks of ER/LA opioids. Given these serious risks, especially those of overdose and death, the Agency believes that clarity as to the appropriate use of such drugs is of the utmost importance. The new language clearly communicates to prescribers that ER/LA opioid analgesics should be used only when alternative treatments are inadequate because of the serious risks of these drugs. The new language also identifies specific examples of alternative treatment options, namely, "non-opioid analgesics or immediate-release opioids," and provides additional guidance on when such treatments may be deemed inadequate to provide sufficient management of pain.

Furthermore, the new labeling language underscores that patients in pain should be assessed not only by their rating on a categorical pain intensity scale, but also based on a

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[31] Dormitzer, C. Opioid Abuse and Misuse: Data from the National Survey on Drug Use and Health and the Drug Abuse Warning Network. Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). UMUC Inn and Conference Center by Marriott, Adelphi, MD, July 22-23, 2010 (available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM220950.pdf).

[32] *See, e.g.*, OxyContin (oxycodone hydrochloride) extended-release tablets (NDA 022272) labeling, available at www.accessdata.fda.gov/drugsatfda_docs/label/2013/022272Orig1s014lbl.pdf.

more thoughtful determination that their pain — however it may be defined — is *severe enough* to require daily, around-the-clock, long-term opioid treatment, *and* for which alternative treatment options are inadequate. This framework better enables prescribers to make decisions based on a patient's individual needs, given the serious risks associated with ER/LA opioids, against a backdrop of alternatives such as IR opioids and non-opioid analgesics. It allows prescribers to make an assessment of pain relative to a patient's ability to perform daily activities or enjoy a reasonable quality of life, not only on where a patient's pain falls on an intensity scale, and assess if ER/LA opioids are needed after determining whether (a) the pain is severe enough to require daily, around-the-clock, long-term opioid treatment, and (b) if alternatives to ER/LA opioids are inadequate to manage such pain, in light of the serious risks associated with ER/LA opioid analgesics.

The revised indication language reads as follows:

> **"[Tradename] is 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.**
>
> **<u>Limitations of Use</u>**
> **• Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve [Tradename] for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.**
> **• [Tradename] is not indicated as an as-needed (prn) analgesic."**

This new language is intended to prompt prescribers to more closely assess each individual patient's condition, and carefully evaluate whether alternative treatment options such as non-opioid analgesics or IR opioids are appropriate. The new language is intended to reflect that ER/LA opioid analgesics should be prescribed only when the prescriber determines that such alternatives are ineffective, not tolerated, or would otherwise be inadequate.

Third, FDA is notifying application holders of the need for changes to the Dosage and Administration, Warnings and Precautions, Drug Interactions, and Use in Specific Populations sections of ER/LA opioid analgesic labeling. These changes are specifically intended to urge prescribers to weigh carefully whether the benefits of an ER/LA opioid outweigh its serious risks on a patient-by-patient basis. If an ER/LA opioid analgesic is prescribed, the labeling changes emphasize that prescribers should monitor patients carefully for signs of abuse and addiction. FDA is also notifying application holders of the need for changes to the Patient Counseling Information and the product-specific Medication Guides to improve the communication of risks to patients.[33] The Agency

[33] Following the approval of the safety labeling changes, a REMS modification will be required to incorporate the approved safety labeling changes into the REMS materials, as applicable.

believes that the changes will improve communication of serious risks associated with the use of these products and help improve the safe use of ER/LA opioid analgesics overall.

FDA intends these changes to enable not only a more careful and thorough approach to determining whether ER/LA opioid analgesics should be prescribed for a particular patient, but also allows prescribers to better assess whether the serious risks associated with ER/LA opioids, including the risks of misuse, abuse, addiction, overdose and death associated with ER/LA formulations, are offset by the benefits ER/LA opioids may provide in managing pain for an individual patient.

Accordingly, PROP's request that FDA remove the term "moderate" from the indication for ER/LA opioid analgesic drugs is granted for the reasons explained above. As explained above, the changes to the labeling also reflect a departure from an indication based solely on a severity scale, and transitions to an indication that facilitates careful prescribing decisions based on an individualized assessment of a patient's situation (*i.e.*, whether an individual's pain is severe enough to require daily, around-the-clock, long-term opioid treatment) and a heightened recognition that, because of the serious risks associated with the use of these drugs, ER/LA opioids should be used only when alternative treatment options are inadequate.[34]

All of PROP's labeling change requests are limited to "non-cancer" pain, a distinction that is not made in current ER/LA opioid analgesic labeling. It is FDA's view that a patient without cancer, like a patient with cancer, may suffer from chronic pain, and PROP has not provided scientific support for why labeling should recommend different treatment for such patients. In addition, FDA knows of no physiological or pharmacological basis upon which to differentiate the treatment of chronic pain in a cancer setting or patient from the treatment of chronic pain in the absence of cancer, and comments to the Petition docket reflect similar concerns.[35] FDA therefore declines to make a distinction between cancer and non-cancer chronic pain in opioid labeling.[36]

In accordance with section 505(o)(4) of the FD&C Act, the ER/LA opioid analgesic application holders are required to submit by October 10, 2013, a supplement proposing changes to the approved labeling to reflect the new safety information, or else notify the Agency that they do not believe labeling changes are warranted and submit a statement detailing the reasons why changes are not warranted.[37]

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[34] When other analgesics are contraindicated or ineffective, restricting the indication of opioid drugs to treatment of severe pain only could leave some patients with chronic pain with an impaired ability to carry out daily activities, resulting in a diminished quality of life. *See* National Pharmaceutical Council (2001): Pain: Current Understanding of Assessment, Management, and Treatments, http://www.npcnow.org/App_Themes/Public/pdf/Issues/pub_related_research/pub_quality_care/Pain-Current-Understanding-of-Assessment-Management-and-Treatments.pdf.

[35] *See, e.g.*, comments from National Hospice and Palliative Care Organization (Docket No. FDA-2012-P-0678); Purdue Pharma (Docket No. FDA-2012-P-0818-0707).

[36] FDA notes that some epidemiology studies make distinctions between cancer and non cancer pain. However, while such classifications may be standard in epidemiological research, FDA believes that they are not relevant to ER/LA opioid labeling.

[37] *See* section 505(o)(4)(B) of the FD&C Act.

If the ER/LA opioid application holders do not submit the requested safety labeling changes, or if FDA disagrees with alternative language that the companies propose, the FD&C Act provides timelines under section 505(o)(4) for discussions regarding the labeling changes.[38] At the conclusion of these discussions, section 505(o)(4)(E) authorizes FDA to issue an order directing labeling changes as appropriate.

III. POSTAPPROVAL SAFETY STUDIES AND CLINICAL TRIALS

ER/LA opioid drugs generally have been approved in part based on randomized, controlled clinical trials that lasted for a 12-week period. This is due, in part, to the fact that for chronic pain, it can be difficult to ensure subject participation in controlled trials beyond 12 weeks. Many commenters, including PROP, have voiced increasing concern about the lack of controlled clinical trial data evaluating opioid use longer than 12-weeks. FDA is not aware of adequate and well-controlled[39] studies of opioid use longer than 12 weeks.[40]

FDA has evaluated concerns pertaining to the serious risks of misuse, abuse, hyperalgesia,[41] addiction, overdose, and death associated with opioid use. The Agency acknowledges that the available data demonstrate an association—though not necessarily a causal relationship—between opioid dose and certain serious risks of opioid use. However, FDA also agrees that more data are needed regarding the relationship between opioid dose and adverse effects, and the relationship between opioid duration of use and adverse effects, before the Agency can determine whether additional action needs to be taken. More data are also needed on the point at which the risks of opioid use at escalating doses and longer durations of treatment may outweigh the benefits of opioid analgesic therapy.

Thus, FDA is exercising its authority under section 505(o)(3)(A) through (B) of the FD&C Act to require ER/LA opioid drug sponsors to conduct PMRs to assess the known serious risks of misuse, abuse, hyperalgesia, addiction, overdose, and death associated with the long-term use of opioid analgesics. FDA has established milestone dates for

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[38] *See* section 505(o)(4)(D) of the FD&C Act.

[39] In this setting, "well-controlled studies" exclude active-controlled trials because they lack assay sensitivity, and failure to detect a statistically significant difference is difficult to interpret—either both drugs had the desired effect or both drugs did not have the desired effect.

[40] There are numerous uncontrolled studies that have evaluated patients on opioids for as long as a year; although some patients drop out of the studies over this period of time, many remain on opioid therapy, which may suggest that they continue to experience benefits that would warrant the risks of opioid use.

[41] Hyperalgesia is a known serious risk associated with chronic opioid analgesic therapy in which the patient becomes more sensitive to certain painful stimuli over time. *See, e.g.*, Varney SM, Bebarta VS. Opioid-induced hyperalgesia--worsening pain in opioid-dependent patients . Am J Emerg Med. 2013 Feb;31(2):458.e5-6; Angst MS, Clark JD Opioid-induced Hyperalgesia A Qualitative Systematic Review. Anesthesiology 2006; 104:570–87. It also may lead to increased use of opioid analgesics. *See, e.g.*, Chapman CR, Davis J, Donaldson GW, Naylor J, Winchester D. Postoperative pain trajectories in chronic pain patients undergoing surgery: the effects of chronic opioid pharmacotherapy on acute pain. J Pain 2011;12:1240-6.

completion of these studies and clinical trials, and is encouraging ER/LA opioid application holders to work together on these studies and clinical trials to provide the best information possible. First, the sponsors will have the opportunity to discuss with the Agency the particulars of the design and conduct of these PMRs.[42] We expect that this process will be completed in time for sponsors to submit final protocols to FDA within one year (*i.e.*, no later than August 2014). Sponsors must periodically report on the status of the studies and clinical trials.[43] The milestones for completion vary by study, with some expected to be completed as early as August 2015 and others expected to be completed in 2018.

As with the safety labeling changes, FDA is requiring PMRs only of ER/LA opioid analgesic application holders. While a majority of the literature that FDA reviewed did not distinguish between opioid formulation and/or composition, such as ER/LA versus IR opioids, or single ingredient opioids versus opioid/non-opioid combination products, FDA has made the determination that PMRs should be required of ER/LA opioid analgesic application holders to assess the known serious risks of misuse, abuse, hyperalgesia, addiction, overdose and death. FDA is taking this approach for the same reasons the Agency has decided to require safety labeling changes for ER/LA opioid analgesics: as discussed in greater detail in section II, above, FDA recognizes that ER/LA opioids, as a class of drugs, have disproportionate safety concerns compared to IR opioids or opioid/non-opioid combination products[44] and because ER/LA opioids are often used in a chronic pain setting. Thus, in light of the serious risks of ER/LA opioids, and the totality of available data, the Agency has decided to make ER/LA opioid analgesics its current focus for requiring PMRs.

IV. REQUESTS FOR MAXIMUM DOSE AND DURATION OF USE

The Agency declines to specify or recommend a maximum daily dose or duration of use for any opioid at this time, for the reason described below. However, FDA has determined that PMRs are necessary to assess the known, serious risks of misuse, abuse, hyperalgesia, addiction, overdose, and death. These studies will address, among other things, the effect of dose and duration of opioid use on these serious risks.

A. Maximum Daily Dose

PROP requests that FDA "add a maximum daily dose" of the equivalent of 100 milligrams (mg) of morphine (100 mg morphine equivalent dose (MED)) to opioids

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[42] *See* Guidance for Industry, *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (April 2011) at 12.

[43] Section 505(o)(3)(iii) of the FD&C Act.

[44] *See, e.g.*, Dormitzer, C. Opioid Abuse and Misuse: Data from the National Survey on Drug Use and Health and the Drug Abuse Warning Network. Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM). UMUC Inn and Conference Center by Marriott, Adelphi, MD, July 22-23, 2010 (available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM220950.pdf).

(Petition at 2). In support of PROP's request, the Petition asserts that high-dose chronic opioid therapy is associated with increased risk of overdose death,[45] increased risk of emergency room visits,[46] and increased risk of fractures in the elderly,[47] (Petition at 2). PROP also maintains that "three large observational studies published in 2010 and 2011 found dose-related overdose risk" in patients on chronic opioid therapy (Petition at 2).

FDA agrees that adverse events and substance abuse of opioids occur at high doses—but adverse events can also occur at doses less than 100 mg MED. FDA also acknowledges that the available data do suggest a relationship between increasing opioid dose and risk of certain adverse events. However, the available information does not demonstrate that the relationship is necessarily a causal one. FDA has reviewed the studies cited in support of PROP's request, as well as studies cited in comments to the Petition docket and other studies described in the literature. For the reasons discussed in further detail below, the scientific literature does not support establishing a maximum recommended daily dose of 100 mg MED. Further, creating a maximum dose of 100 mg MED, or another dose ceiling, could imply a superior opioid safety profile under that set threshold, when there are no data to support such a conclusion. The Agency therefore denies PROP's request that opioid labeling specify a maximum daily dose.

1. Cited Data Do Not Define a Relationship between Opioid Dose and Risk of Fractures in the Elderly

FDA agrees that the Saunders study[48] PROP cites suggests a positive trend between opioid dose and fractures in the elderly. However, the elderly population is at risk for falls and fractures in general, and has more co-morbidities and more rapid fluctuations in health status than the overall adult population. The Saunders study did not take into account any co-morbidities in the elderly patients that arose after the initial patient visit when pain was diagnosed and an opioid was prescribed and the absence of that information may have confounded the results. Without additional data and a replication of the study's apparent finding, it would be premature to conclude that the risks of high-dose opioids outweigh their benefits in this population. Additionally, the highest dose-level in the Saunders study[40] was >50 mg MED, therefore, it did not directly address the 100 mg MED cutoff.

2. Cited Data Do Not Define a Relationship between Opioid Dose and Emergency Room Visits

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[45] *See* Gomes T, Mamdani MM, Dhalla IA, *et al.*, Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med, 2011; 171: 686-91.

[46] *See* Braden JB, Russo J, Fan MY, *et al.* Emergency department visits among recipients of chronic opioid therapy. Arch Intern Med 201 0; 170:1425-32.

[47] *See* Saunders KW, Dunn KM, Merrill JO, *et al.*, Relationship of opioid use and dosage levels to fractures in older chronic pain patients. J Gen Intern Med, 2010;25:310-5.

[48] Saunders KW, Dunn KM, Merrill JO, *et al.*, Relationship of opioid use and dosage levels to fractures in older chronic pain patients. J Gen Intern Med, 2010;25:310-5.

FDA does not agree with PROP's contention that the Braden study[49] demonstrated a clear dose-response relationship between high dose opioid therapy and emergency room visits for recipients of chronic opioid therapy for non-cancer pain. Braden *et al.* examined the association between opioid dose and emergency room visits in two populations: a national, commercially insured population and a state-based publicly insured population. The study categorized opioid dose according to 3 levels: (1) 0 MED to the median MED of the population at issue[50] (Category 1); (2) the median MED of the given population to 120 mg MED/day (Category 2); and (3) >120 mg MED/day (Category 3). When compared to Category 1 patients, Category 2 and Category 3 patients appeared to have an increased risk of emergency room visits—but only in one study population. Furthermore, Category 3 patients did not appear to have a greater risk of emergency room visits than Category 2 patients in that study population. Taken together, the findings of this study were inconclusive with respect to the relationship between opioid dose and emergency room visits. Furthermore, FDA is concerned that this study did not fully adjust for important factors that may confound the association between opioid dose and health services use, such as race and income.[51] FDA therefore concludes that the Braden study does not support PROP's request to limit the maximum daily dose of opioids.

3. *Cited Data Do Not Define a Relationship between Opioid Dose and Death*

PROP cites three observational studies (by Dunn, *et al.*,[52] Bohnert, *et al.*,[53] and Gomes, *et al*[54]) to support that higher doses of opioids are associated with higher risks of overdose-related death. Although these studies have several important limitations,[55] FDA agrees

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[49] Braden JB, Russo J, Fan MY, *et al.*, Emergency department visits among recipients of chronic opioid therapy. Arch Intern Med, 2010; 170:1425-32.

[50] Note that the mean MED was different in the two study populations.

[51] Examples of other potential confounders include past health service use, alcohol use, or numbers of total medications used concurrently with opioids. *See* Braden JB, Russo J, Fan MY, *et al.*, Emergency department visits among recipients of chronic opioid therapy. Arch Intern Med, 2010; 170:1425-32.

[52] Dunn KM, Saunders KW, Rutter CM, *et al.*, Opioid prescriptions for chronic pain and overdose: a cohort study. Annals of Internal Medicine, 2010; 152:85-92.

[53] Bohnert AS, Valenstein M, Bair MJ, et al., Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA, 2011; 305:1315-21.

[54] Gomes T, Mamdani MM, Dhalla IA, et al., Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med, 2011; 171: 686-91.

[55] For example, the Dunn and Gomes studies did not discuss the reason the patients had been prescribed opioid therapy. It is possible that the patients' underlying illnesses (or the severity thereof) may have increased the risk of death or other adverse events—and without additional information, FDA cannot evaluate PROP's assumption that these adverse events can be attributed to opioid use alone. None of the three studies—Dunn, Bohnert, or Gomes—examined the role of the opioid's formulation (e.g., IR vs. ER/LA opioids) in their analyses, and it is possible that different formulations may have differing impacts on overdose-related outcomes. In addition, none of the three studies included data about what doses the patients actually took (as opposed to the doses they were prescribed), or data about whether the patients complied with the instructions they received about proper opioid use. Indeed, in the Bohnert study, almost half of the decedent population experienced an unintentional opioid-related death when the maximum prescribed dose was equal to 0 mg per day—which raises questions not only about the amount of opioids

that these studies appear to credibly suggest a positive association between high-dose opioid use and the risk of overdose and/or overdose mortality. Indeed, these studies appear to demonstrate a statistically significantly higher risk of overdose death among those taking opioid doses of >100 mg MED compared to those taking opioid doses of 1-19 mg MED.

Unfortunately, the point at which the risk of overdose-related death increases enough to change the benefit-risk assessment of the studied opioids cannot be determined from these studies. Determining such a threshold would require a better understanding of how risk of overdose and/or overdose mortality changes along the continuum of opioid dose (from 0 mg through the highest doses taken by patients). This dose-response (*i.e.* overdose and/or overdose mortality) relationship should be analyzed treating opioid use as a continuous variable or using categories defined by small increments (*e.g.*, 1 mg MED, or per 5 mg MED). Thus, even though the aforementioned studies demonstrated a statistically significantly higher risk of overdose death for patients taking the highest studied doses compared with patients taking the lowest studied doses, the threshold for an increased risk associated with these drugs could actually be considerably lower or higher than a maximum daily dose of 100 mg MED.

B. Maximum Duration of Treatment

The PROP Petition requests that FDA "[a]dd a maximum duration of 90 days for continuous (daily) use" (Petition at 2). In support of this request, the Petition alleges that "[l]ong-term safety and effectiveness of managing [pain] with opioids has not been established." After a review of the literature cited in the Petition, and an assessment of other relevant information discussed below, FDA has determined that limiting the duration of use for opioid therapy to 90 days is not supportable. Thus, the Agency denies this request.

1. Treatment Guidelines

In support of its request, PROP cites to the American Pain Society-American Academy of Pain Medicine Opioids Guidelines. However, these guidelines state that chronic opioid therapy can be an effective therapy for carefully selected and monitored patients.[56] The guidelines recommend individualized care, management plans, and monitoring—not a maximum duration of treatment.[57] For example, they note that "proper patient selection is critical," requiring "a comprehensive benefit-to-harm evaluation that weighs the

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the patients actually took, but also the possibility that other causes of death may have mistakenly been assessed as opioid-related. Furthermore, the Dunn study described only 6 deaths in its discussion of 51 overdose-related outcomes, and it did not differentiate between deaths and other overdose outcomes in its analysis. Thus, it is less informative on the question of an association between opioid dose and death.

[56] *See* Chou R, Fanciullo GJ, Fine PG, *et al.*, American Pain Society- American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic non-cancer pain. J Pain, 2009; 10:113-130.

[57] *See generally id.*

potential positive effects of opioids on pain and function against potential risks."[58] The guidelines also strongly recommend that "[o]pioid selection, initial dosing, and titration . . . be individualized according to the patient's health status, previous exposure to opioids, attainment of therapeutic goals, and predicted or observed harms."[59] The decision whether to proceed with opioid therapy, according to the guidelines, "should be intentional and based on careful consideration of outcomes" of the initial course of opioid treatment, which should be treated as a "short-term, therapeutic trial lasting from several weeks to several months."[60]

These guidelines are consistent with the new indication for ER/LA opioids: a focus on treatment decisions that include a thorough patient-specific assessment of the appropriateness of ER/LA opioids for that patient, and that reflect careful thought by prescribers and patients alike.

2. Cited Data on Persistence of Chronic Pain and Long-Term Opioid Use Are Inconclusive

PROP cites surveys by Sullivan, *et al.*[61] and Eriksen, *et al.*[62] to support its assertion that "[r]ecent surveys of [chronic non-cancer pain] patients receiving [chronic opioid therapy] have shown that many continue to experience significant chronic pain and dysfunction" (Petition at 2). The Eriksen survey supports this assertion but is insufficient to conclude that chronic opioid therapy causes or contributes to chronic pain and dysfunction, or that it is ineffective in treating chronic pain and dysfunction. Although the survey found that the pain severity reported at the time of the survey was higher among respondents who were using opioids than those who were not using opioids, there was no assessment of pain severity prior to the time of the survey. Thus, patients who were using opioids could have suffered from higher levels of pain pre-survey than those who were not using opioids. Pain *improvement* was not measured.

The Sullivan survey found that patients with chronic non-cancer pain treated with chronic opioid therapy reported being in pain 162 of the past 180 days (90% of days), and 92% of that sample reported pain on at least 90 days. These data suggest that patients on chronic opioid therapy experienced significant chronic pain, and that they continued to experience pain throughout their therapy. However, the study did not survey similar patients who did *not* receive opioid treatment. Without such a comparison group, it is unclear what the patients' pain trajectory would have been had they not been on chronic opioid therapy. Thus, this survey does not address the question of whether chronic non-cancer pain patients fare better or worse on chronic opioid therapy.

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[58] *Id.* at 115.

[59] *Id.* at 117.

[60] *Id.*

[61] Sullivan MD, Von KM, Banta-Green C, Merrill JO, Saunders K. Problems and concerns of patients receiving chronic opioid therapy for chronic non-cancer pain. Pain 2010;149(2):345-353.

[62] Eriksen J, Sjogren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. Pain 2006;125(1-2):172-179.

3. *Cited Data on Long-term Opioid Use and Addiction Do Not Establish a Threshold for Maximum Duration of Use*

PROP's Petition contends that opioids should be given a maximum duration of use based in part on a study of "[a] large sample of medical and pharmacy claims records[, which] found that two-thirds of patients who took opioids on a daily basis for 90 days were still taking opioids five years later" (Petition at 2).

FDA disagrees with this statement.[63] Although the study follow-up lasted roughly 5 years, not all patients who were started on chronic opioid therapy were followed for that duration. Approximately half of the study population was followed two years or less (the median follow-up time was around 2 years). Throughout the course of the study period, some patients were censored due to death, disenrollment from health coverage, or other reasons. Patients who were censored may have had a different duration of therapy than those who continued to be followed. In FDA's view, the study showed that, among patients who were followed for 4.8 years, two-thirds were still taking opioids at the end of this period.

FDA also does not agree that these data necessarily reflect a safety concern specific to longer term use. Although some portion of these results certainly could be explained by adverse outcomes (*e.g.*, addiction in opioid therapy patients), other factors may also be associated with low discontinuation rates (*e.g.*, certain intractable or recalcitrant pain conditions that may require longer treatment periods). The referenced study did not collect data on why patients continued or discontinued opioid therapy, and without this information, it would be premature to restrict opioid use to a 90-day maximum duration treatment period.

The Petition also asserts that "[r]ecent surveys using [Diagnostic and Statistical Manual of Mental Disorders] DSM criteria found high rates of addiction in [chronic non-cancer pain] patients receiving [chronic opioid therapy]" (Petition at 2). FDA agrees with this assertion.[64] However, the cited surveys did not suggest that chronic opioid therapy causes addiction, or vice versa. Both addiction and chronic opioid therapy were measured at one point in time, so it is unknown which happened first: addiction or chronic opioid therapy.

The cited literature does not identify a duration threshold beyond which the risk of addiction outweighs the benefits of opioid treatment. PROP has selected a 90-day limit, but provides no evidence that addiction (however it is defined) increases significantly after 90 days of use such that it would support a labeling change. Nevertheless, the high

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[63] *See* Martin BC, Fan MY, Edlund MJ, DeVries A, Braden JB, Sullivan MD. Long-term chronic opioid therapy discontinuation rates from the TROUP study. J Gen Intern Med 2011;26(12):1450-1457.

[64] However, the recently published Diagnostic and Statistical Manual of Mental Disorders – V (DSM V) combines the substance abuse and substance dependence categories into a single disorder measured on a continuum, to try to avoid an inappropriate linking of "addiction" with "physical dependence," which are distinct issues. *See* American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition. Washington, DC: American Psychiatric Association, 2013.

rates of addiction shown in the cited literature are concerning enough to require further exploration in postapproval studies.

4. Cited Data Are Insufficient to Explain Association between Opioid Use and Mental Health Co-Morbidities

The Petition asserts that "[p]atients with mental health and substance abuse co-morbidities are more likely to receive [chronic opioid therapy] than patients who lack these risk factors, a phenomenon referred to as adverse selection." In support of this assertion, PROP cites to a study by Edlund *et al.*,[65] which examined trends in opioid prescribing among individuals with non-cancer pain, with and without mental health and substances disorders.

Although the Edlund study supports the association between current mental health and substance abuse co-morbidities and current use of chronic opioid therapy, FDA is unable to determine the reasons for this association in a cross-sectional analysis. This study only depicts the frequencies and prevalence of chronic opioid therapy in different sub-populations at one point in time, and the temporal relationship between mental health and substance abuse comorbidities and opioid therapy cannot be established. Thus, it is difficult to form any conclusions based on this study regarding the relationship between mental health/substance abuse disorders and the initiation, dose and duration of chronic opioid therapy. In sum, FDA agrees with the study's authors that the cited study does not conclude that the association between opioid use and mental/substance use disorder is due to any one specific factor.[66]

FDA acknowledges that patients with these co-morbid conditions may be at higher risk of adverse outcomes—possibly because they may be more likely to be treated with other psychoactive drugs. The results of the Edlund study thus underscore the need for prescribers to evaluate carefully whether and under what circumstances to prescribe opioids (particularly in high doses) to patients with these co-morbidities.[67] However, the findings of the Edlund study do not support PROP's argument that opioid labeling should include a maximum daily dose or a maximum duration of use.

---

[65] Edlund MJ, Fan MY, DeVries A, Braden JB, Martin BC, Sullivan MD. Trends in use of opioids for chronic non-cancer pain among individuals with mental health and substance use disorders: the TROUP Study. Clin J Pain 2010;26:1-8.

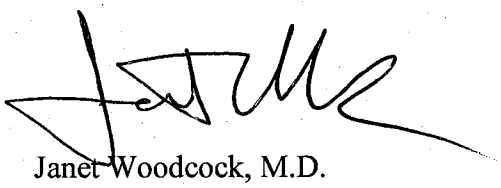
[66] The authors state that they "cannot definitively state why NCPC enrollees with MH [mental health]/SUDs [substances use disorders] were more likely to receive opioids than NCPC [non-cancer pain conditions] enrollees without MH/SUDs, and to receive them chronically[...]." *Id.* at 6.

[67] For example, section 5.1 of ER/LA opioid analgesic labeling, as provided for in the safety labeling change notification letters referred to above, contains the following language: "Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of [Tradename] for the proper management of pain in any given patient. Patients at increased risk may be prescribed modified-release opioid formulations such as [Tradename], but use in such patients necessitates intensive counseling about the risks and proper use of [Tradename] along with intensive monitoring for signs of addiction, abuse, and misuse."

V. CONCLUSION

For the reasons stated above, the Petition is granted in part and denied in part.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

EXHIBIT C

FDA Perspective on Abuse-Deterrent Opioid Development

Douglas C. Throckmorton, MD
Deputy Director for Regulatory Programs
CDER, FDA

CBI Abuse Deterrent
Formulations Summit

March 7-8, 2017

The opinions and information in this presentation are my own and do not necessarily reflect the views and policies of the FDA

Outline

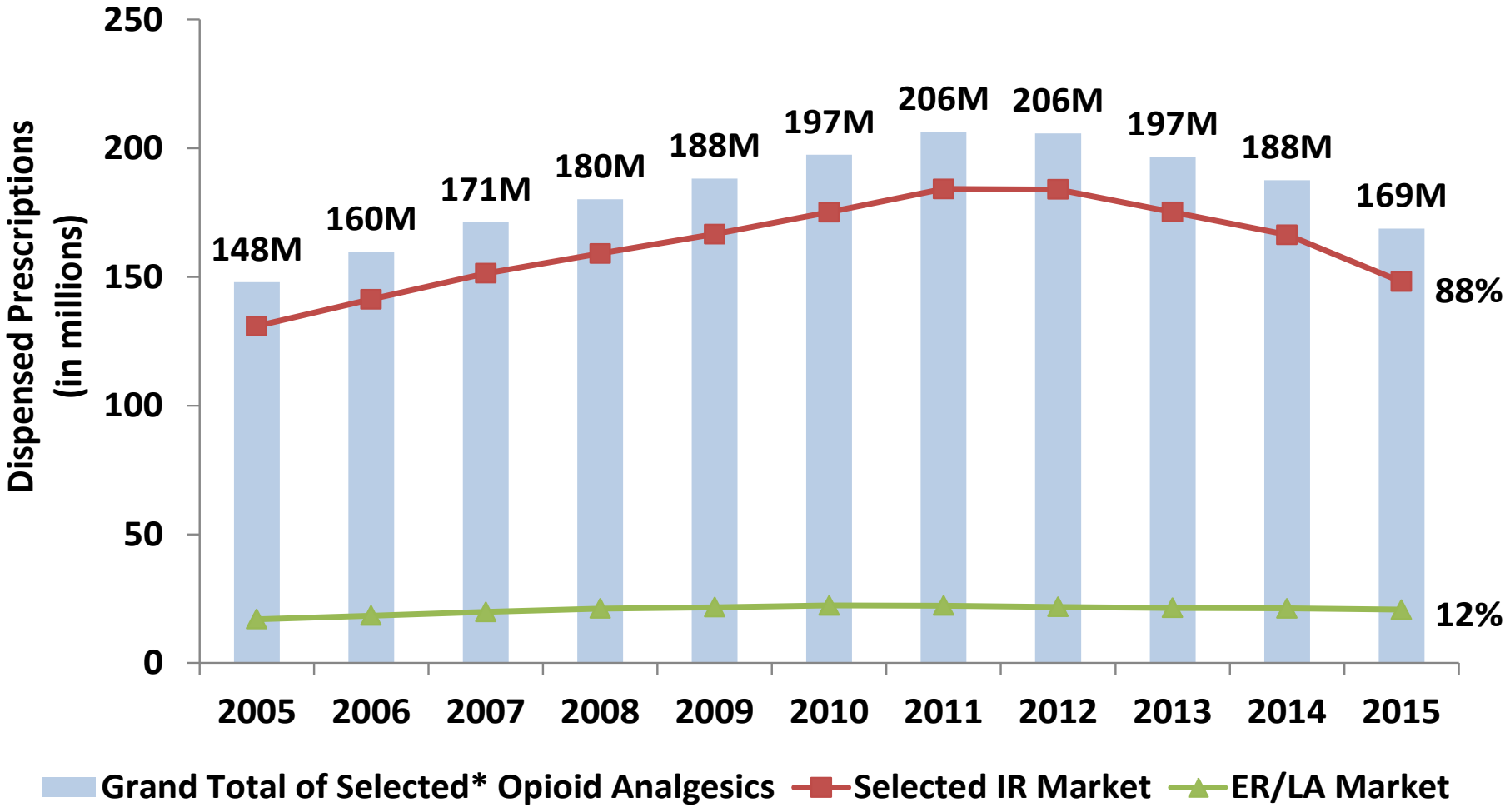
- Background on Epidemic
- Federal Context for FDA Efforts to Address Prescription Opioid Abuse
  - Other Federal Efforts
- FDA Action Plan
- FDA Focus on Abuse-Deterrent Formulations of Opioids

Overall Message

- The FDA work to improve the safe use of opioids is taking place within a larger policy framework aimed at addressing opioid abuse while assuring appropriate access to pain treatment
- Abuse Deterrent Opioids are one important part of FDA work to address opioid epidemic
- Ongoing and planned activities reflect the commitment by FDA to integrate the use of all of our available tools to achieve our goals related to the safe use of prescription opioids

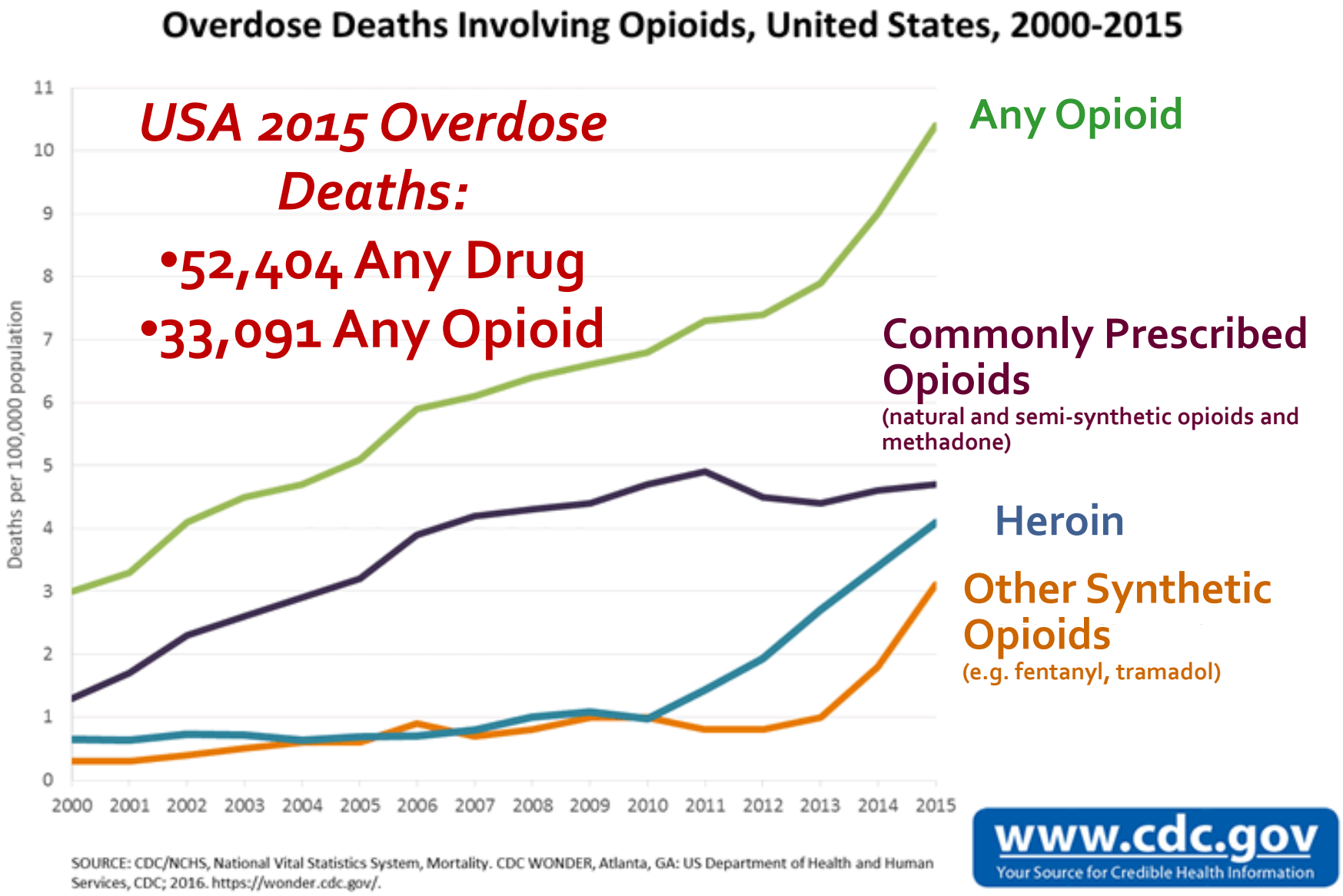
FDA U.S. FOOD & DRUG ADMINISTRATION

Nationally Estimated Number of Prescriptions Dispensed for Selected* Opioid Analgesics Oral Solids and Transdermal products from U.S. Outpatient Retail Pharmacies



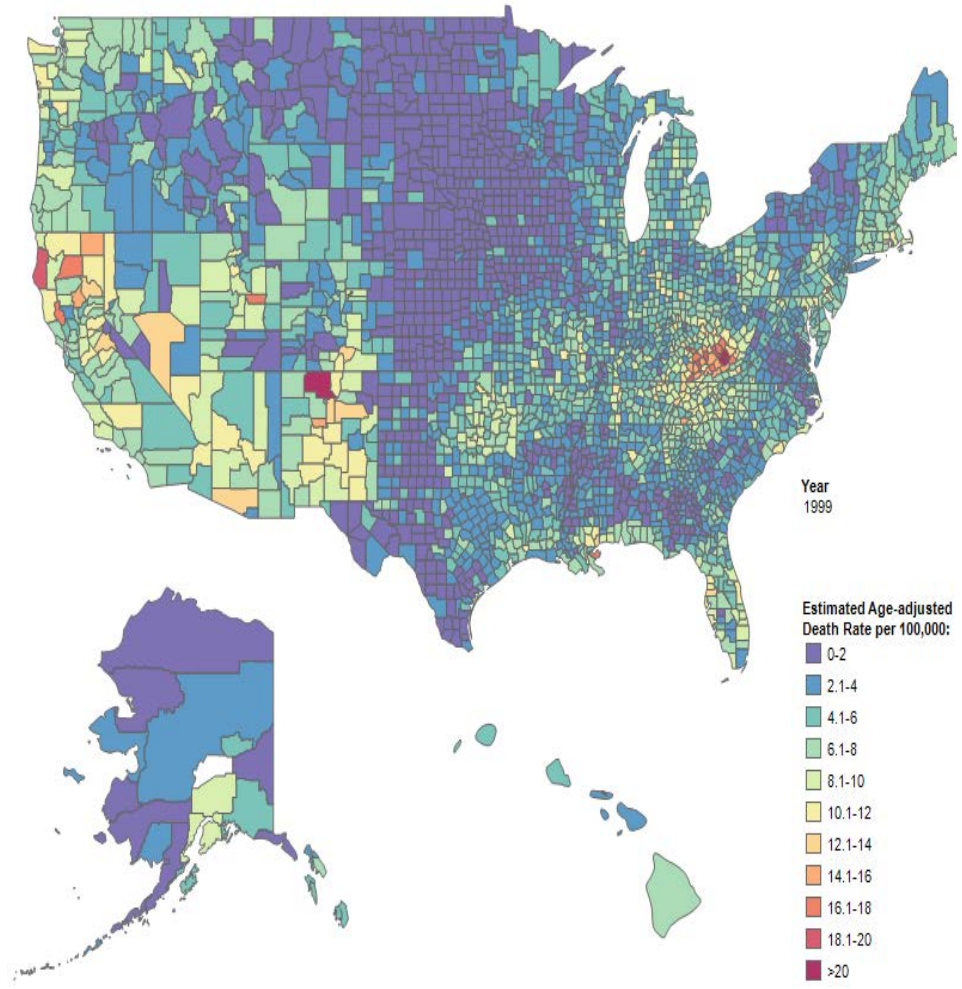
Source: National Prescription Audit (NPA). Extracted May 2015 (For 2005-2014 data) and November 2016 (For 2015 data).

Marked *Increases in Prescription Opioid and Heroin Overdose Deaths* in the USA 2000 to 2015

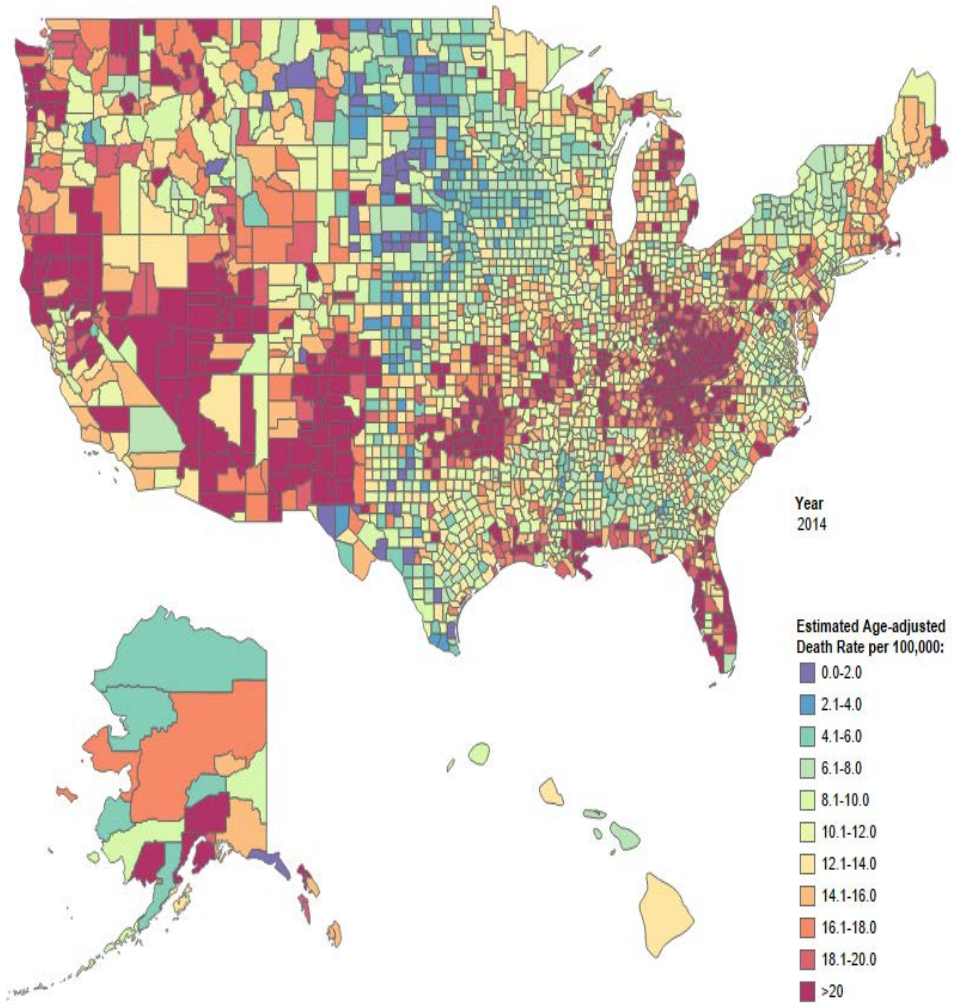


Overdose Death Rates

1999



2014

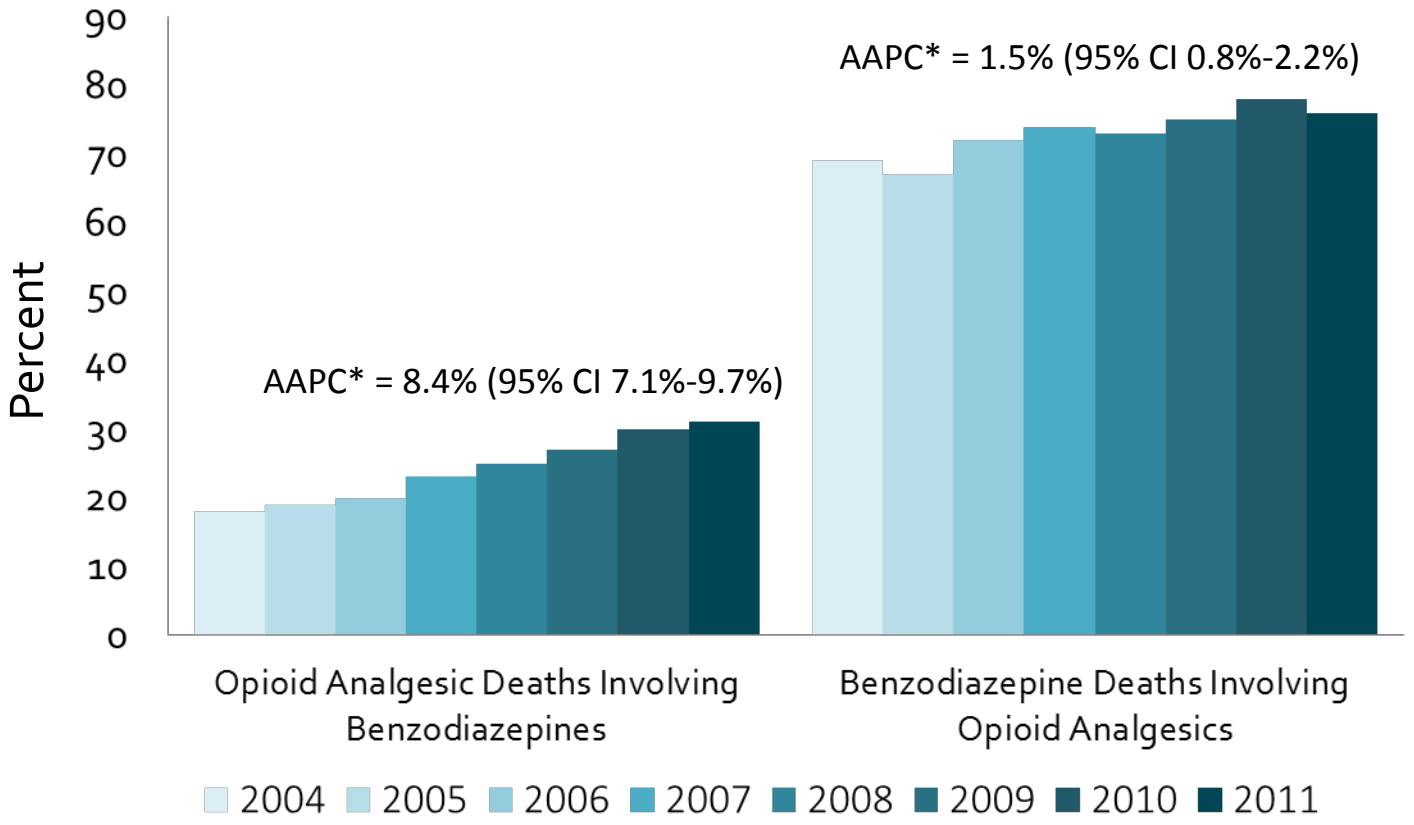


Designed by L. Rossen, B. Bastian & Y. Chong. SOURCE: CDC/NCHS, National Vital Statistics System

Science = Solutions

Overlap of *Benzodiazepines and Opioids*

Opioid OD Deaths Involving Benzodiazepines & Benzodiazepine OD Deaths Involving Opioids



*AAPC = Average annual percent change

Source: CM Jones, JK McAninch. *American Journal of Preventive Medicine* 2015;49:493-501.

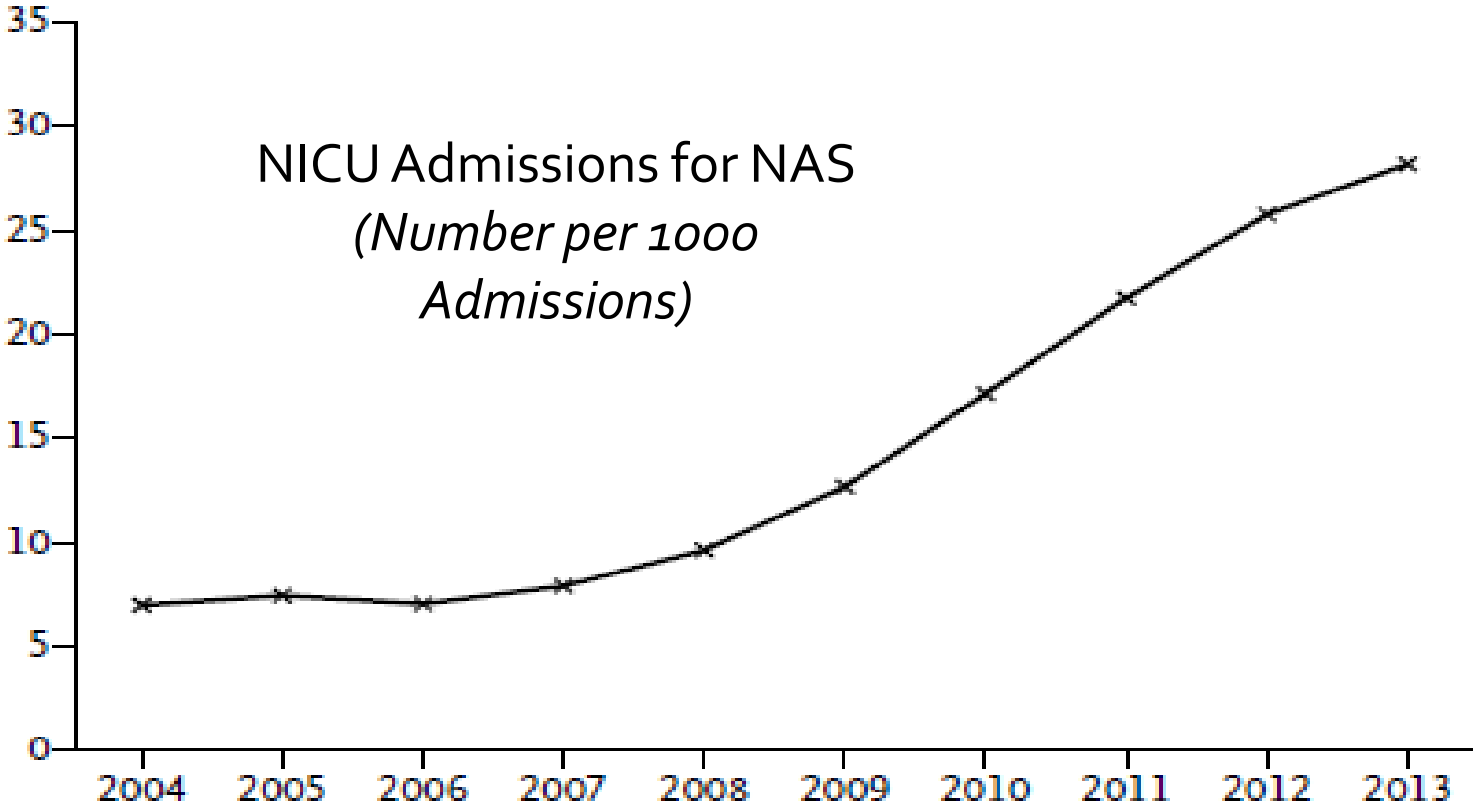
Science = Solutions

Outbreak of HIV Linked to IDU of Oxymorphone in Indiana, 2014-2015

- Through November 2015, **181 cases of HIV** identified in county of ~15,000
- 96% reported injection drug use
- Of these, **92% reported injecting prescription oxymorphone in past 12 months**
  - Frequently described preparing and injecting extended-release oxymorphone (Opana ER, Endo Pharmaceuticals)
- Public health emergency declared—syringe exchange program established

Source: Peters et al. *New England Journal of Medicine* 2016; 375:229-39.

Increasing
Neonatal Abstinence Syndrome



Source: Tolia VN, Patrick SW, et al. *NEJM* 2015;372:2118-2126

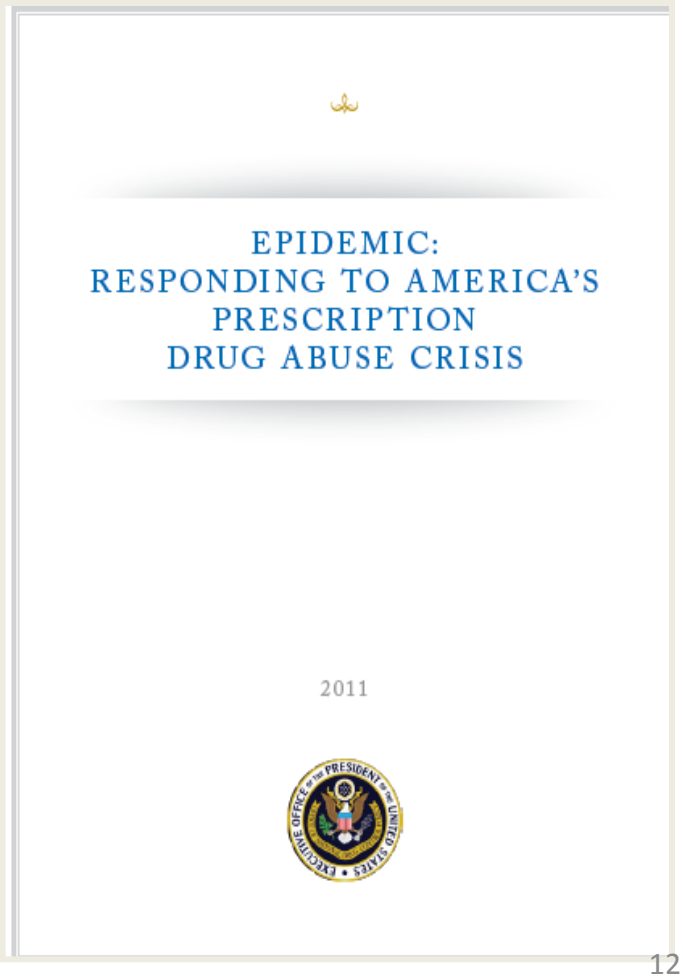
FDA is a Part of a Larger Governmental Response to Opioids Abuse

Office of the National Drug Control Policy (ONDCP) Plan

Health and Human Services (HHS) Secretary's Plan

ONDCP National Drug Abuse Prevention Plan

- Issued April 2011
- Four major areas of focus to reduce prescription drug abuse and other harm from drugs
  - Education
  - Monitoring
  - Proper medication disposal
  - Enforcement



HHS Secretary's Initiative to Combat Opioid Abuse

- Improving opioid prescribing practices to reduce opioid use disorders and overdose
- Expanding use and distribution of naloxone
- Expanding medication-assisted treatment (MAT) to reduce opioid use disorders and overdose

--http://aspe.hhs.gov/basic-report/opioid-abuse-us-and-hhs-actions-address-opioid-drug-related-overdoses-and-deaths

Other Critical U.S. Governmental Efforts FDA is Supporting

- **National Pain Strategy**
  - Focuses on key areas of pain and pain care, including professional education and training, public education and communication, service delivery and reimbursement
    - http://iprcc.nih.gov/docs/DraftHHSNationalPainStrategy.pdf
- **National Pain Research Strategy**
  - Strategic plan under development for pain research across federal agencies
- **Surgeon General's Call to End the Opioid Crisis**
  - Launched a new prescriber education campaign, Turn the Tide
  - Issued the first-ever Surgeon General's Report on Alcohol, Drugs and Health: Facing Addiction in America
- **CDC Guidelines for Prescribing Opioids for Chronic Pain**
  - Provides recommendations for the prescribing of opioid pain medication focused on the use of opioids in treating chronic pain
    - http://www.cdc.gov/drugoverdose/prescribing/guideline.html

U.S. FOOD & DRUG ADMINISTRATION

FDA Response to Opioids Abuse

FDA Action Plan (February 4, 2016)

- In response to the opioid abuse epidemic, FDA called for a far-reaching action plan to reassess the agency's approach to opioid medications. The plan focused on policies aimed at reversing the epidemic, while still providing patients in pain access to effective relief.

--http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm484765.htm

FDA Opioids Action Plan

- Expand the use of advisory committees
- Develop warnings and safety information for immediate-release (IR) opioid labeling
- Strengthen postmarket requirements to get needed data
- Update Risk Evaluation and Mitigation Strategy (REMS) Program for Prescription Opioids
- **Expand access to abuse-deterrent formulations (ADFs) to discourage abuse**
- Support better treatment for prescription opioid abuse and overdose
- Reassess the risk-benefit approval framework for opioid use

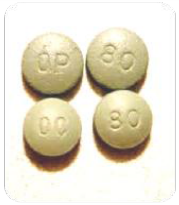
--www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm484714.htm

FDA and Abuse-Deterrent Formulations of Opioids

Part of Larger FDA/HHS Efforts to Improve Tools for Pain Management

Development of New Pain Treatments

Abuse-deterrent Opioid formulations



Pro-drugs

Crush/extraction resistant formulation

Drug combinations with adverse effects if injected

Non-Opioid based analgesics
Cannabinoids;
Inflammatory mediators;
Ion channel blockers

Non-pharmacological treatments
Surgical interventions;
Neural stimulation;
Spinal cord stimulation

Transcranial Magnetic Stimulation

Spurring Development of Abuse-Deterrent (AD) Opioids: FDA Goals

- Incentivize the development of opioid medications with progressively better AD properties and support their widespread use
- Assure appropriate development and availability of generics, reflecting their importance in U.S. healthcare
  - Generic drugs play a critical role in U.S. healthcare, including important role in controlling costs and expanding access

FDA Tools to Support AD Formulation Development

- **Scientific Research**
- **Regulatory Activities**
  - Decisions on applications
  - Sponsor discussions as a part of individual product development
- **Guidances**
  - Final guidance on developing AD formulations of opioids issued April 2015
  - Draft guidance on generics development and testing issued March 2016
- **Public Discussion and Comment**
  - Public meetings, including meeting held October 2014 and 2016
  - Comments on draft guidance
  - Citizen petitions

Policy Development: Generic AD Opioids

- Generic drugs play a critical role in U.S. healthcare, including important role in controlling costs and expanding access
- March, 2016: FDA released draft guidance: "General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products"
- October, 2016: FDA held a 2-day meeting to discuss draft guidance and standardization of in vitro testing for AD opioids
- FDA plans to publish a final guidance to the March 2016 draft in 2017 in accordance with the requirements of the Comprehensive Addiction and Recovery Act of 2016.

Regulatory Activity: Supporting AD Opioid Development

- **9** new opioids approved with abuse-deterrent formulations (latest January, 2017)

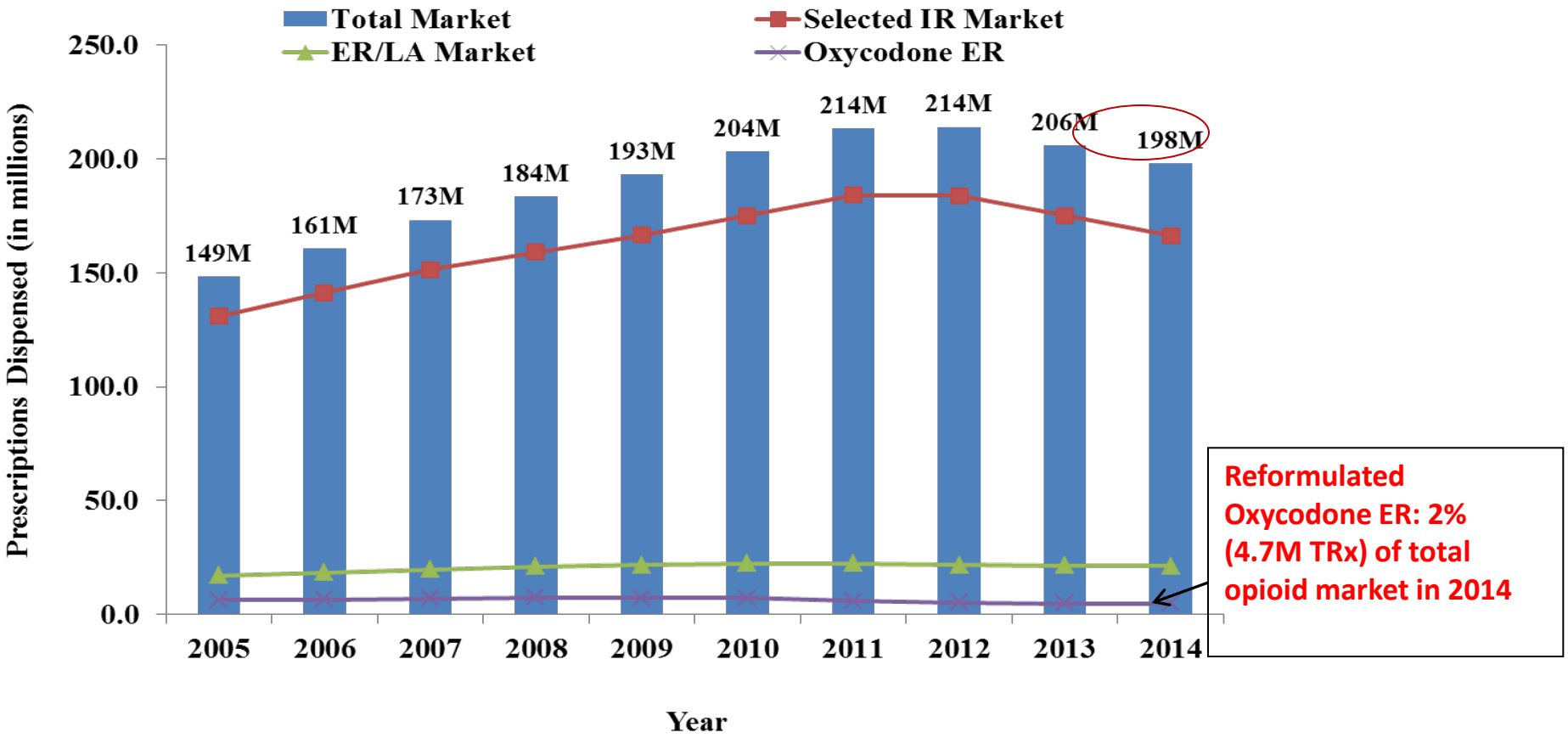
  (OxyContin, Targiniq ER, Embeda, Hysingla ER, MorphaBond, Xtampza ER, Troxyca ER, Arymo ER, Vantrela ER)

  - Work to date has often focused on use of crush/extraction-resistant and agonist/antagonist technologies, but many new approaches being explored
  - More than 30 active investigational new drug applications (INDs) being discussed for AD formulations
    - New technologies being explored by industry (e.g., pro-drugs that require activation to prevent IV abuse and snorting)

Next Steps: Need for Assessment of Impact on Real-world Abuse

- Current labels based on clinical and in vitro data to predict the formulation will reduce abuse
- Real-world assessment needed (and ongoing) as we know AD formulations are not silver bullets and can be defeated
- DECIDE WHAT WORKS AND WHAT DOESN'T

IR and ER/LA Opioid Prescriptions



Nationally estimated number of prescriptions dispensed for selected IR and ER/LA opioid analgesics from U.S. outpatient retail pharmacies

- No prescriptions captured for Hysingla ER or Embeda in 2014

Source: IMS Health, National Prescription Audit ™ Extracted May and August 2015

Challenges in Getting to the Future for AD Opioids

- Incentivizing innovation: Current FDA incentives include product labeling and Hatch-Waxman exclusivity
- Encouraging iterative development and use of effective abuse-deterrent formulations
  - Challenge to assess impact of individual formulations
  - Challenge to encourage uptake of effective products by payers
- Managing expectations: abuse-deterrent opioid--
  - Are part of larger effort on opioids
  - Will not ‘prevent’ abuse, and are not ‘silver bullets’

Summary and Conclusions

- FDA working to address opioids epidemic as a part of the larger HHS response
  - One of the FDA's highest priorities
- FDA Opioids Action Plan provides framework for FDA response to the challenge of opioids abuse epidemic
- Supporting development and use of progressively better abuse deterrent opioids one important FDA goal within the Action Plan
  - FDA looks forward to the day, not far in the future, when the majority of opioids on the market are known to be abuse deterrent

Thank you


FDA
U.S. FOOD & DRUG
ADMINISTRATION

EXHIBIT D

FDA's Actions to Address the Opioid Epidemic

Douglas C. Throckmorton, MD
Deputy Director for Regulatory Programs
Center for Drug Evaluation and Research
FDA

CBI Abuse-Deterrent Formulation Summit

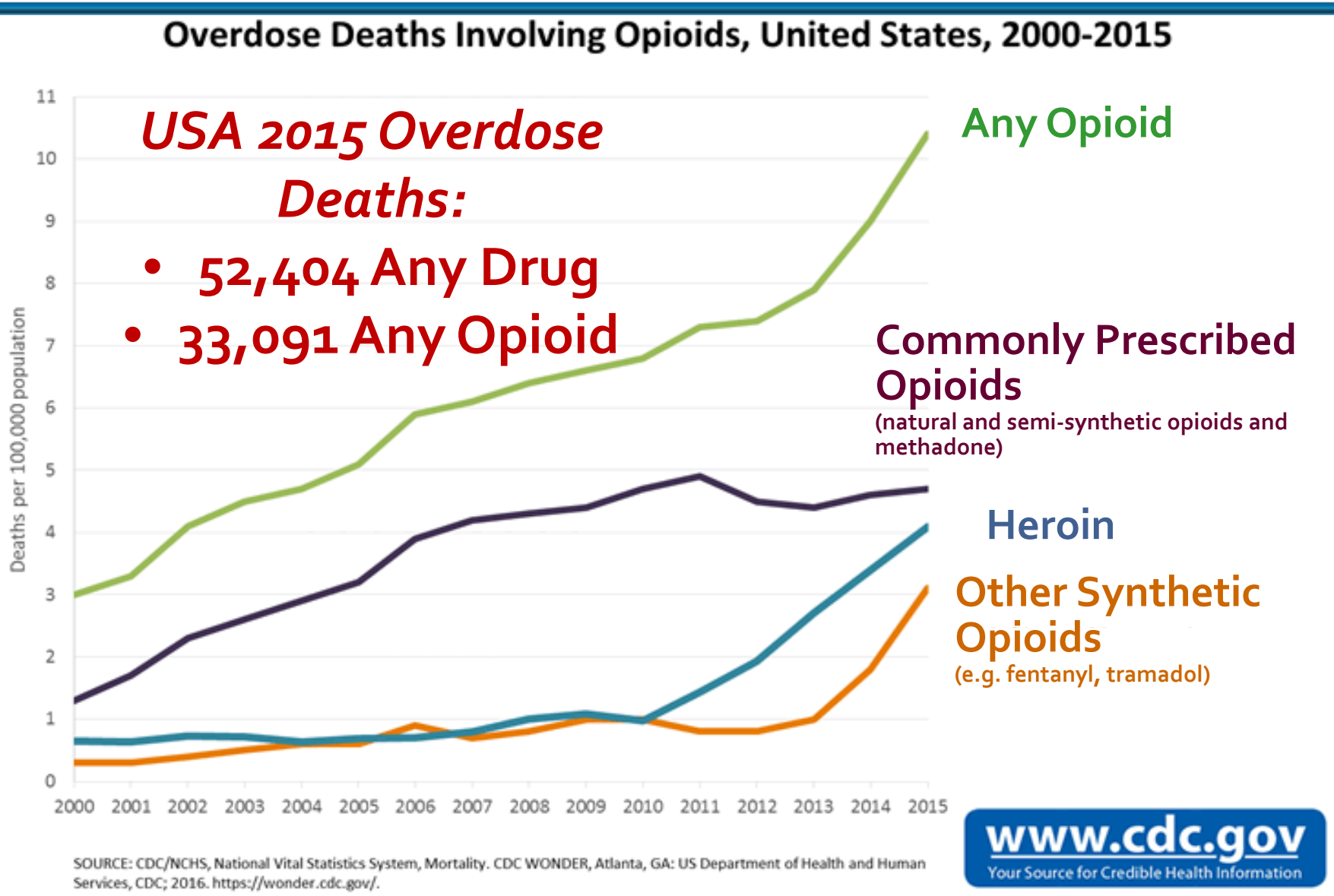
March 14, 2018

The opinions and information in this presentation are my own and do not necessarily reflect the views and policies of the FDA

Overall Messages

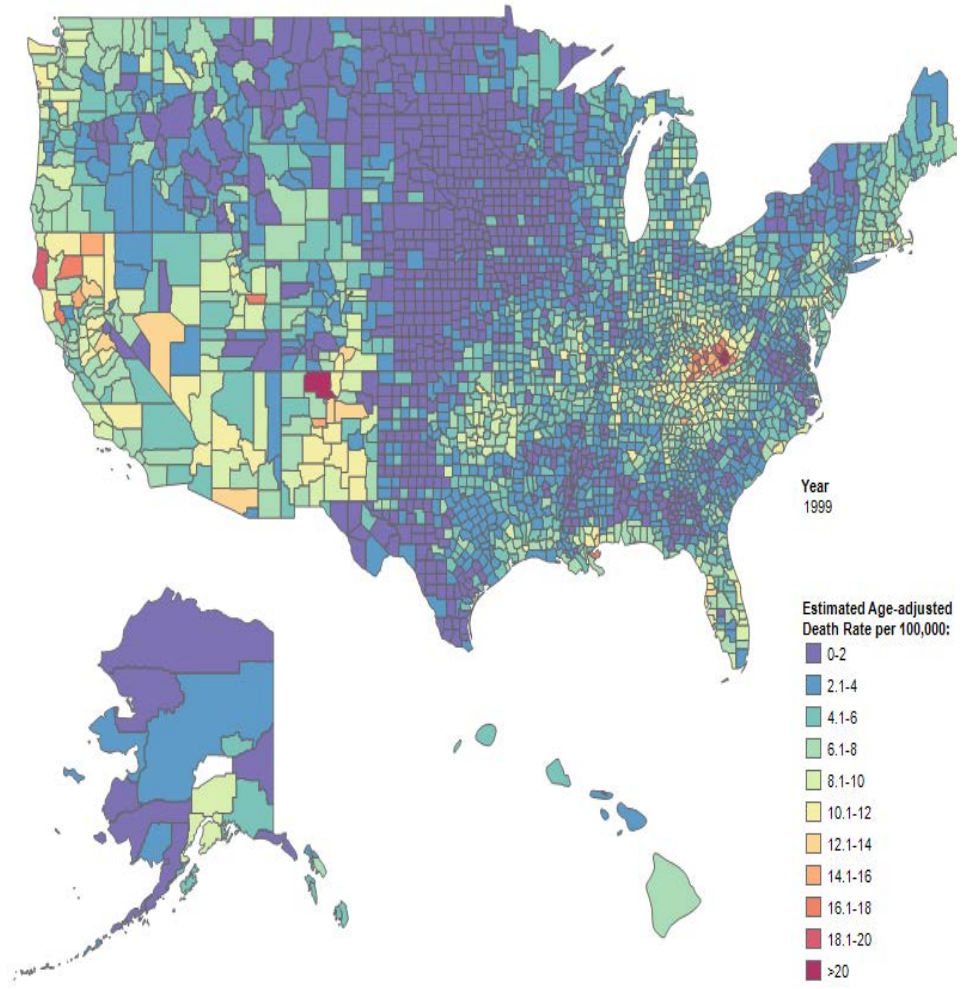
- The FDA work to improve the safe use of opioids is taking place within a larger policy framework aimed at addressing opioid abuse while assuring appropriate access to effective pain treatment
- Ongoing and planned activities reflect the commitment by FDA to use of all of our available tools to appropriately manage pain while also addressing the opioids crisis

Marked *Increases in Prescription Opioid and Heroin Overdose Deaths* in the USA 2000 to 2015

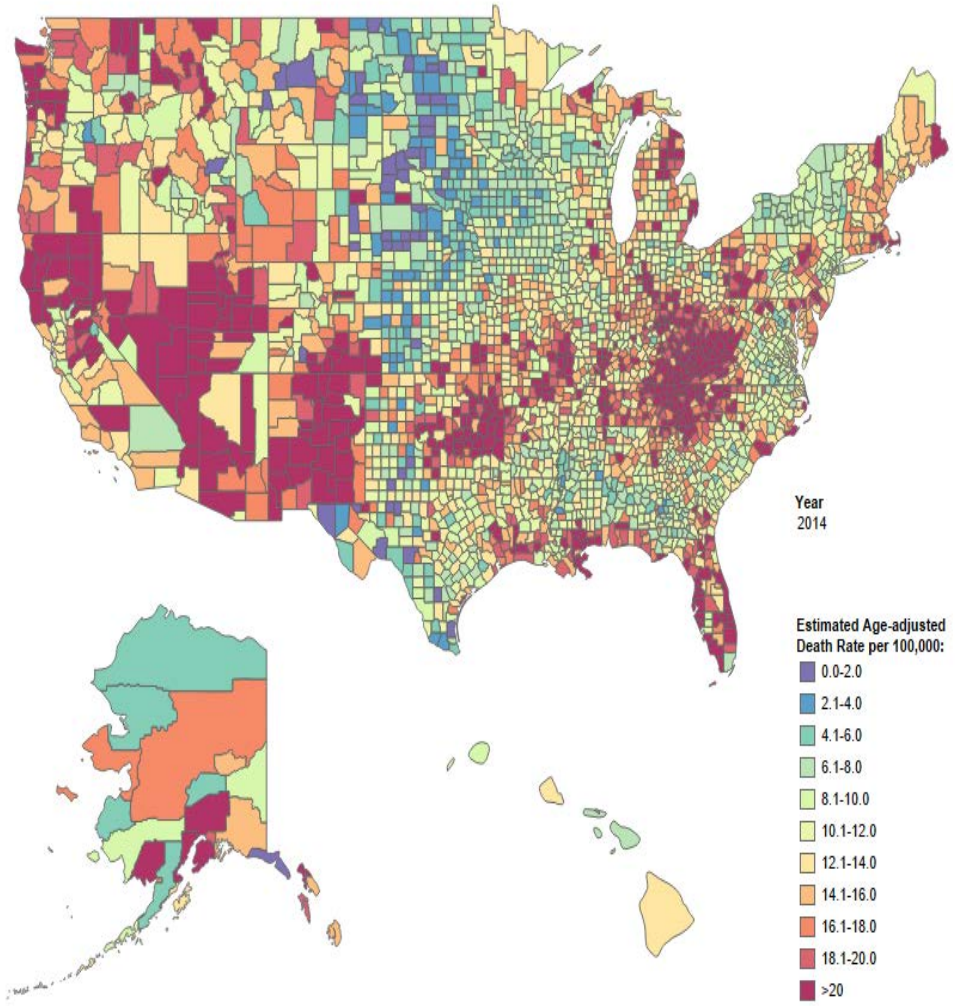


Overdose Death Rates

1999



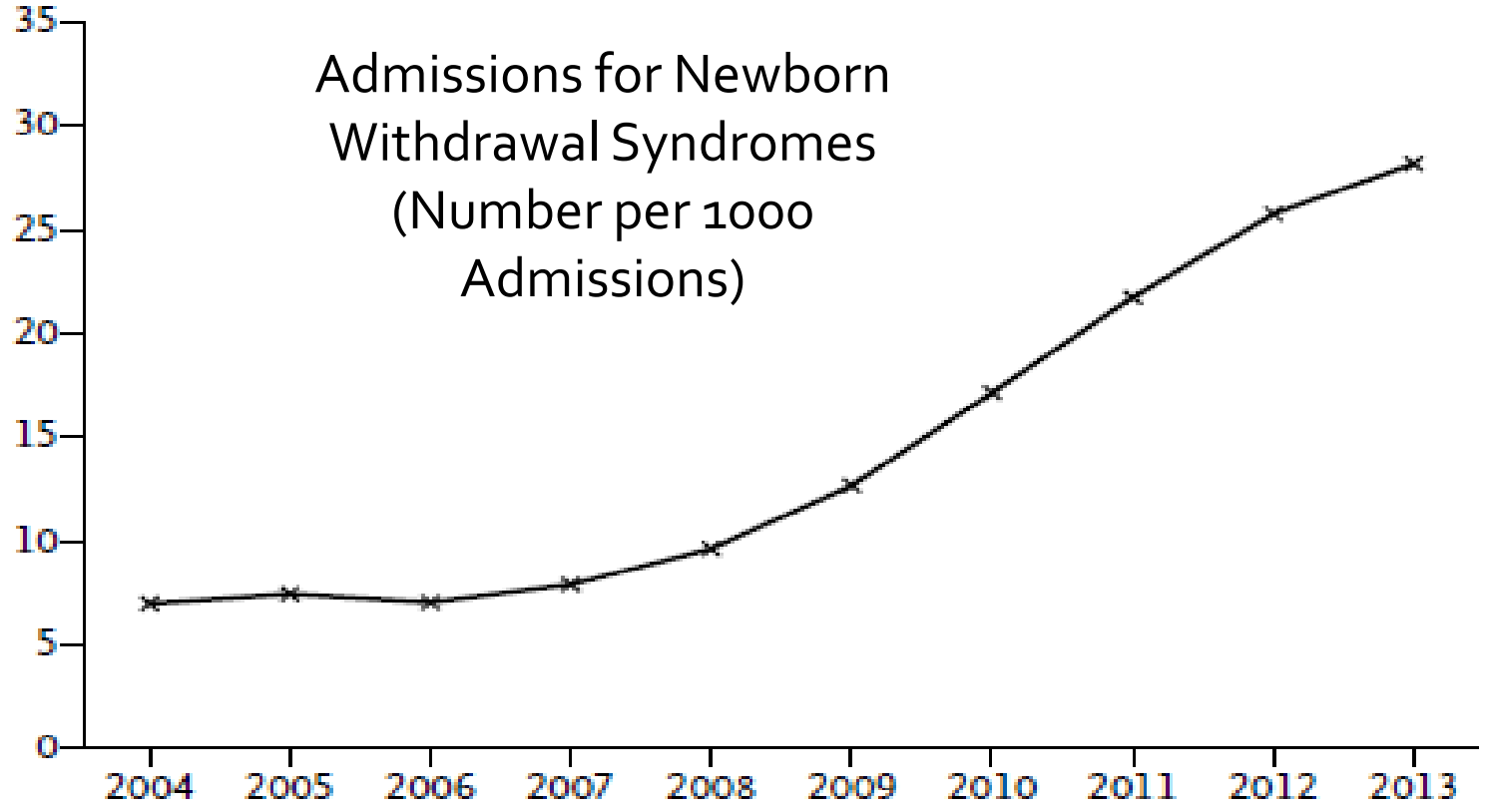
2014



Designed by L. Rossen, B. Bastian & Y. Chong. SOURCE: CDC/NCHS, National Vital Statistics System

Science = Solutions

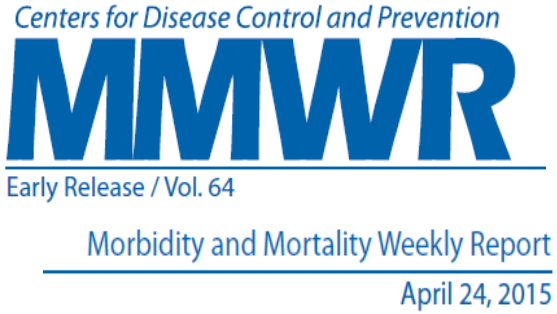
Impact of Crisis: Increasing Prenatal Exposure



Tolia VN, Patrick SW, et al. NEJM 2015;372:2118-2126

Impact of Crisis: Infectious Disease Transmission

HIV and Hepatitis C Outbreak Linked to Oxymorphone Injection Use in Indiana, 2015



Peters et al.

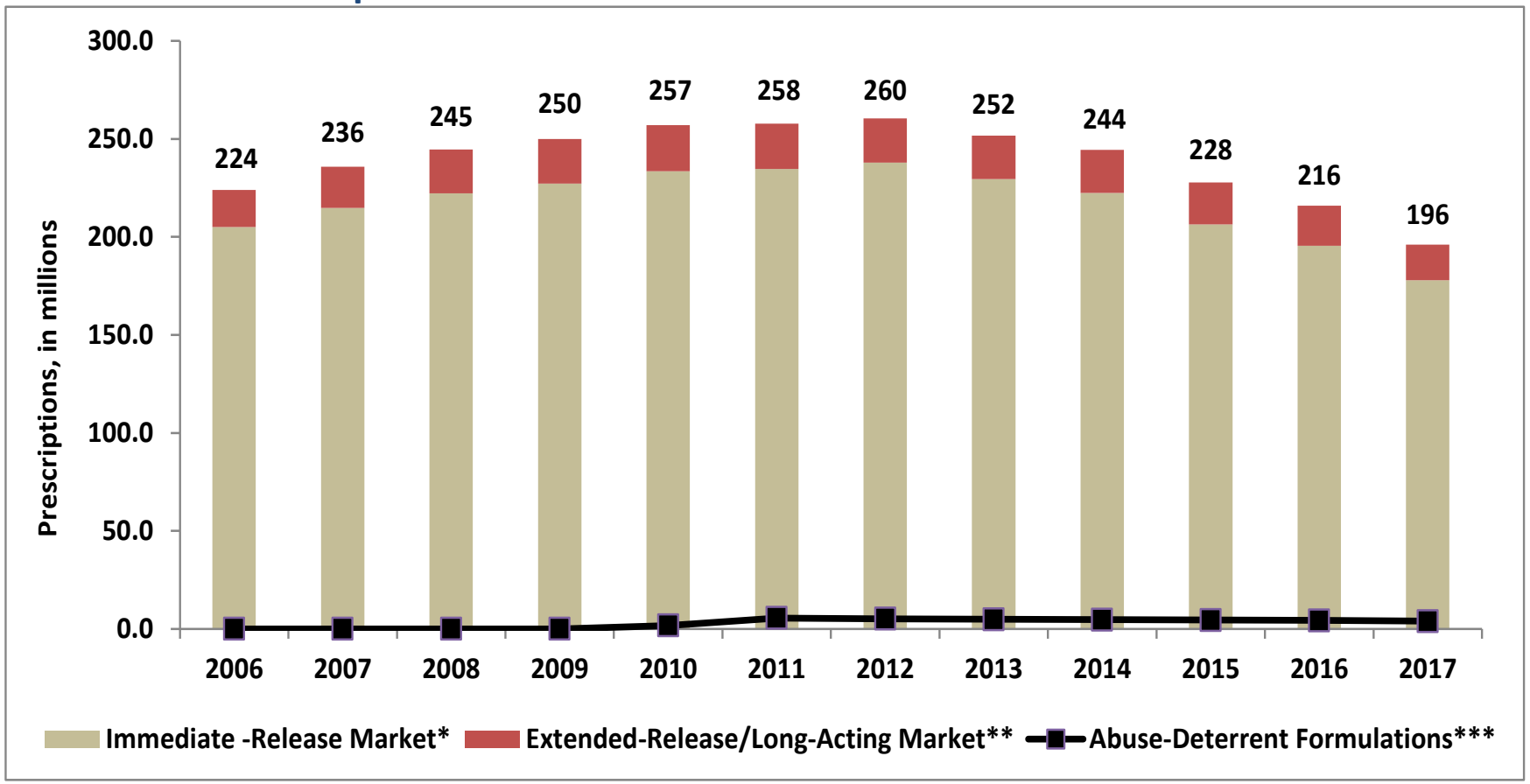
The New England Journal of Medicine

2016;375:229-239

U.S. Prescribing Rates - Trends

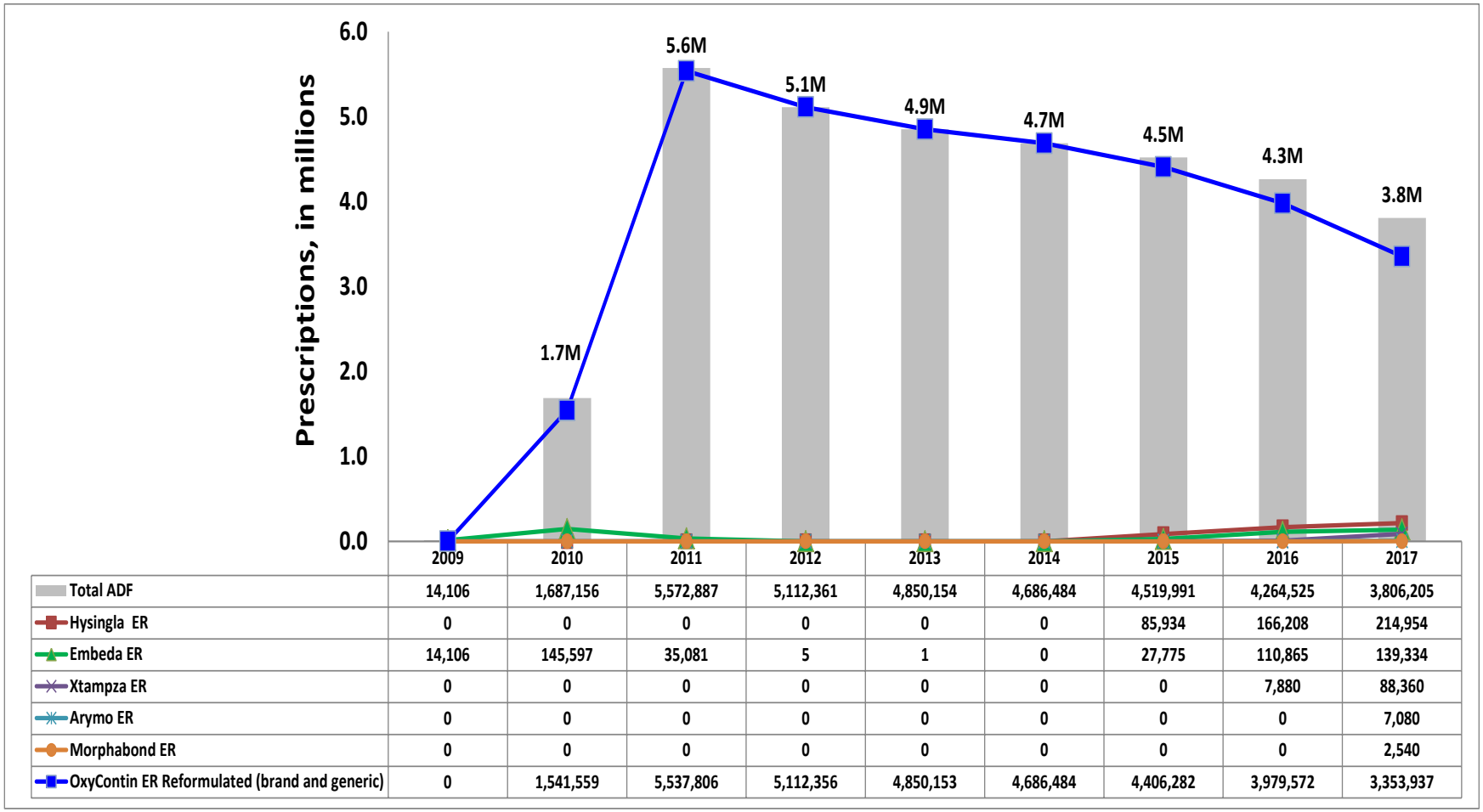
- U.S. prescribing rates peaked in 2012 at 81.3 prescriptions per 100 persons[11]
  - Total: 255 million prescriptions
- Opioid prescribing has been decreasing between 2012 and 2016.
- U.S. prescribing rate in 2016 was 66.5 prescriptions per 100 people
  - 214 million prescriptions
- Rates continue to vary widely
  - Some counties had rates 7 times the national average

Nationally Estimated Number of Prescriptions Dispensed for Opioid Analgesics Products from U.S. Outpatient Retail Pharmacies



Source: IQVIA, National Prescription Audit (NPA) and static data 2006-2011. January 2006-December 2017.
Static data extracted March 2017 and 2012-2017 data extracted February 2018.
*Immediate-Release formulations include oral solids, oral liquids, rectal, nasal, and transmucosal
**Extended-Release/Long-Acting formulations include oral solids and transdermal patches
***Abuse-deterrent formulation opioid products include Arymo ER, Embeda ER, Hysingla ER, Morphabond ER, Xtampza ER, OxyContin ER Reformulated (Approval in April 2010)
Note: Include opioid analgesics only, excluding injectable formulations as well as opioid-containing cough-cold products and opioid-containing medication-assisted treatment (MAT) products

Nationally Estimated Number of Prescriptions Dispensed for Abuse-Deterrent Formulation (ADF) Opioid Analgesic Products* from U.S. Outpatient Retail Pharmacies



	2009	2010	2011	2012	2013	2014	2015	2016	2017
Total ADF	14,106	1,687,156	5,572,887	5,112,361	4,850,154	4,686,484	4,519,991	4,264,525	3,806,205
Hysingla ER	0	0	0	0	0	0	85,934	166,208	214,954
Embeda ER	14,106	145,597	35,081	5	1	0	27,775	110,865	139,334
Xtampza ER	0	0	0	0	0	0	0	7,880	88,360
Arymo ER	0	0	0	0	0	0	0	0	7,080
Morphabond ER	0	0	0	0	0	0	0	0	2,540
OxyContin ER Reformulated (brand and generic)	0	1,541,559	5,537,806	5,112,356	4,850,153	4,686,484	4,406,282	3,979,572	3,353,937

Source: IQVIA, National Prescription Audit™, Years 2009-2017. Data Extracted February 2018.

*ADF Products not marketed during study period: RoxyBond (Oxycodone IR) - Approved 04/2017; Targiniq ER (oxycodone/naloxone ER) - Approved 07/2014; Troxyca ER (Oxycodone/naltrexone ER) - Approved 08/2016; Vantrela ER (Hydrocodone ER) - Approved 01/2017

Equally Critical Social and Medical Issue: Pain in America

- From the Functioning and Disability Supplement of the 2012 National Health Interview Survey
  - 126.1 million adults reported some pain in the previous 3 months
  - 25.3 million adults (11.2%) suffering from daily (chronic) pain
  - 23.4 million (10.3%) reporting a lot of pain.
  - Based on the persistence and bothersomeness of their pain, 14.4 million adults (6.4%) were classified as having the highest level of pain, category 4, with an additional 25.4 million adults (11.3%) experiencing category 3 pain.

Nahin RL, J.Pain, 2015 Aug;16(8):769-80

Pain in America (cont)

- Treatment options for pain: pharmacologic, physical medicine, behavioral medicine, neuromodulation, interventional, and surgical
- Optimal patient outcomes often result from a comprehensive multidisciplinary approach where pharmacologic treatment is not the sole focus
- Patients experience ongoing barriers to adequate pain management
  - "many related to non-existent or insufficient insurance coverage and reimbursement for evidence- and consensus-based therapies"

    -American Academy of Pain Medicine, 2014
- As a result, treatments have largely focused on prescription drugs, mainly opioids, and procedures, at least, in part, because of the reimbursement structure of our healthcare system

FDA Response to this Crisis

"Unquestionably, our greatest immediate challenge is the problem of opioid abuse. This is a public health crisis of staggering human and economic proportion … we have an important role to play in reducing the rate of new abuse and in giving healthcare providers the tools to reduce exposure to opioids to only clearly appropriate patients, so we can also help reduce the new cases of addiction."

- Scott Gottlieb, FDA Commissioner
  Address to FDA staff, May 15, 2017

The Opioid Crisis: An FDA Priority

Take immediate steps to reduce the scope of the epidemic of opioid addiction

- **May 2017:** Established an FDA Opioid Policy Steering Committee (OPSC)
- **2017-2018:** Soliciting public input on how **FDA authorities** can or should be **used to address the crisis**
  - **Sept 2017, January 2018: Public meetings**
  - **December 2017: Packaging solutions**
  - **February 2018: Healthcare system solutions**

The Opioid Crisis: FDA's Priorities

1. Decreasing Exposure & Prevent New Addiction

2. Supporting the Treatment of Those With Opioid Use Disorder

3. Fostering the Development of Novel Pain Treatment Therapies

4. Improving Enforcement & Assessing Benefit-Risk

FDA Priorities align to HHS Strategic Priorities and other National Activities

HHS STRATEGIC PRIORITIES	*FDA PRIORITIES*	*OTHER ACTIVITIES*
Strengthening public health surveillance	1. Decreasing Exposure & Prevent New Addiction	President's Commission on Combating Drug Addiction
Targeting availability and distribution of overdose-reversing drugs	2. Supporting the Treatment of Those With Opioid Use Disorder	Office of National Drug Control Policy Recommendations
Supporting cutting-edge research	3. Fostering the Development of Novel Pain Treatment Therapies	Comprehensive Addiction and Recovery Act (CARA)
Improving access to treatment and recovery services	4. Improving Enforcement & Assessing Benefit-Risk	National Pain Strategy Recommendations
Advancing the practice of pain management		National Public Health Emergency

1. Decreasing Exposure and Prevent New Addiction

	HOW?	*WHAT?*
Appropriate Dose/Duration Labeling	• **Facilitate appropriate prescribing** of opioid analgesics. • Evaluate **indication specific doses**.	• **Jan 30, 2018:** FDA **public meeting** to gain input on how FDA's authorities could **facilitate appropriate prescribing**. • **Feb 15, 2018:** Duke Margolis **public workshop** – "Strategies for Promoting the **Safe Use** and **Appropriate Prescribing** of Prescription Opioids".
Appropriate Packaging, Storage, and Disposal	• Explore how opioid analgesic drug products are **packaged, stored, and discarded**. • Examine use of packaging strategies, such as **unit-of-use packaging** to improve opioid analgesic safety.	• **Jun 1, 2017:** FDA/Duke Margolis **workshop and white paper** on packaging, storage, and disposal solutions. • **Dec 11-12, 2017:** FDA **public workshop** to gain input on **packaging strategies**.

1. Decreasing Exposure and Prevent New Addiction

Health Care Provider Education

HOW?	*WHAT?*
• Consider appropriateness of **mandatory education** and **how FDA would operationalize** such a requirement. • Ensure **training** is made **available to non-physician prescribers**, including nurses and pharmacists.	• **May 9-10, 2017:** FDA **public workshop** on pain management training. Issued **revised Blueprint**. • **Sept 28, 2017:** FDA issued **letters** notifying sponsors of IR opioids their drugs will be subject to more stringent set of requirements under REMS & should be approved Sept 2018. The **training** must be made available to **health care providers** who prescribe **IR opioid analgesics**.

2. Supporting the Treatment of Those With Opioid Use Disorder

	HOW?	*WHAT?*
Naloxone	• Exploring ways to **expand access** to naloxone and **facilitate the switch** to **OTC naloxone**.	• **Precedent setting research**: **FDA-led labeling study** to facilitate the **switch** from prescription to **OTC naloxone**.
Medication Assisted Treatment (MAT)	• Facilitate the development of **new MAT options**. • Take steps **promote the more widespread use** of existing, safe and effective, FDA approved therapies. • Join efforts to **break the stigma** associated with medications used for treatment of addiction.	• Issuing Guidances for product developers to **facilitate the development of new treatments**. • NIH **collaboration** to identify **new endpoints** in MAT drug development and **facilitate new formulations**.

3. Fostering the Development of Novel Pain Treatment Therapies

	HOW?	*WHAT?*
Partnerships & Meetings	• Expand use of partnerships with **non-profit organizations**, **public** meetings, and **Advisory Committee** meetings. • **Collaborate** across HHS.	• **FDA grant** supporting Drug-Free Kids campaign. • **Public-private-partnership (PPP) with NIH and developers** under the Critical Path initiative. • **Jul 2017:** Commissioned NASEM **consensus report**. • **Feb 14, 2018: Advisory Committee** meeting for Hydexor (hydrocodone/APAP/promethazine) – for short term **management** of **acute pain** while **preventing** and **reducing** opioid-induced **nausea** and **vomiting**.

3. Fostering the Development of Novel Pain Treatment Therapies

	HOW?	WHAT?
Abuse Deterrent Formulations (ADFs)	• Support development of **innovative** ADFs, **data** to inform benefit-risk assessment, and **transition to an ADF-prominent market**. • Ensure ADF **label nomenclature** enables providers to adequately distinguish between the risk of abuse and the risk of addiction.	• **Jul 2017: Public workshop** for postmarketing **ADF data and evaluation methods**. • Issued final **guidance** on **generic ADFs**. • **2018:** Contracts to improve **data for ADF assessment** and understand **nomenclature**.
Pain Treatment Alternatives	• Explore use of Fast Track and Breakthrough Therapy Designations. • Encourage novel therapies, including **medical devices**.	• **Summer 2017:** FDA/NIH **meeting series** on pain treatment alternatives.

4. Improving Enforcement & Assessing Benefit-Risk

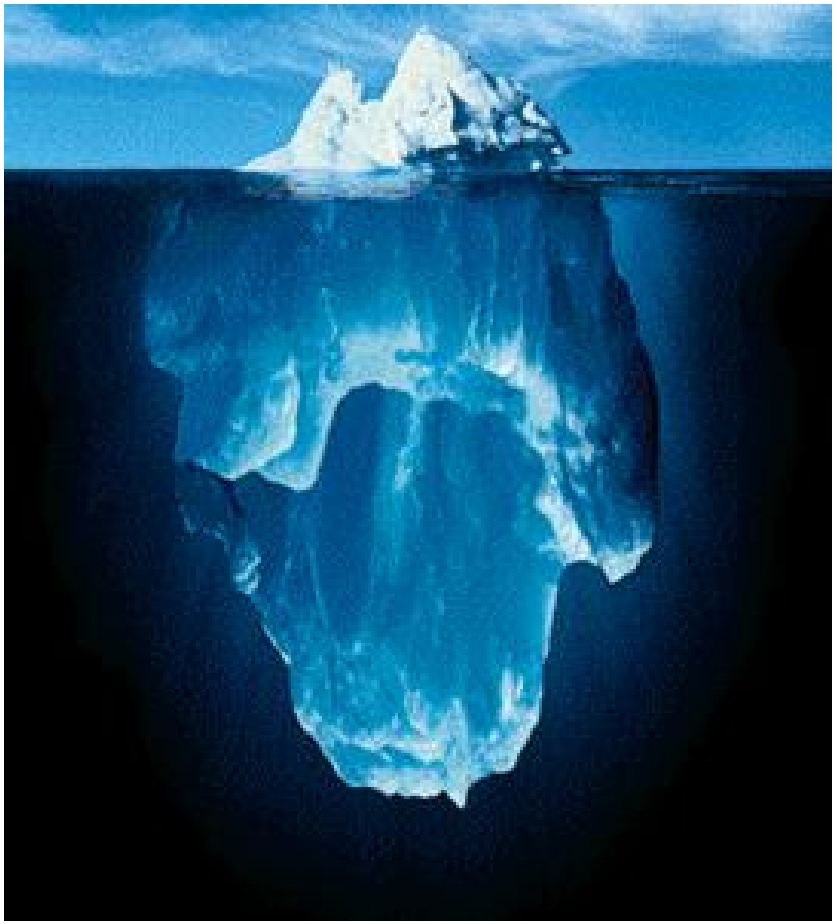
	HOW?	*WHAT?*
Improving Enforcement	• Consider how to fully **leverage** FDA's current **seizure authorities**. • Increase oversight of **Illicit** trade.	• **Collaboration** with Customs and Border Protection to **increase FDA staff** stationed at international mail facilities (IMFs) to increase **seizure of opioids** being smuggled into the United States through **international mail facilities (IMFs)**.
Assessing Benefit-Risk	• **Take action**, including product market **withdrawal recommendation**. • **Improve robustness** of **benefit-risk assessment framework** for opioid analgesic formulations.	• **Jun 2017:** Requested market **withdrawal** of Opana ER due to **abuse risks**. • **Sep 2017:** Pediatric **Advisory Committee** for hydrocodone or codeine containing cough treatment in **pediatric patients**.

FDA Will Use All of its Available Tools to Accomplish These Goals

- Improving the safe use of opioids through careful and appropriate regulatory activities
- Improving the safe use of opioids through careful and appropriate policy development
- Improving the treatment of pain through improved science
- Improving the safe use of opioids through communication, partnership and collaboration

Solutions Must Come from Many Sources

- FDA is one of many Federal agencies addressing issues involving opioids
- Many Federal Agencies working together on issue
- Each state has programs to address opioids
- Guidelines and educational programs are available from specialty societies and State Medical Boards
- Healthcare institutions
- Advocacy groups
- Individual providers (n = 800,000+)
- Patients (n = millions)



Summary and Conclusions

- FDA working to address opioid epidemic as a part of the larger HHS response
  - One of the FDA's very highest priorities
  - FDA one of many groups focused on the issue
- Going forward, FDA is committed to taking decisive actions, grounded in the available science and appropriate public input to address this critical challenge to the US health and welfare
- Our focus is addressing opioid abuse while assuring appropriate access to effective pain treatment

Thank You

EXHIBIT E

Abuse-Deterrent Opioid Analgesics

The FDA is encouraging the development of prescription opioids with abuse-deterrent formulations (ADFs) to help combat the opioid crisis. The agency recognizes that abuse-deterrent opioids are not abuse- or addiction-proof but are a step toward products that may help reduce abuse. The FDA fully supports efforts to better understand the impact of these products in the real-world setting and convened a **public workshop on July 10-11, 2017 (/Drugs/NewsEvents/ucm540845.htm)**, to discuss the current data and methods for evaluating ADF products postmarketing and what can be done to improve national data and methods moving forward.

The FDA also supports the development of innovative formulations that have the potential to make abuse of these products more difficult or less rewarding. This does not mean a product is impossible to abuse or that abuse-deterrent properties necessarily prevent addiction, overdose, and death. Notably, currently marketed technologies do not effectively deter one of the most common forms of opioid abuse -- swallowing the tablet or capsule. Because opioid medications must in the end be able to deliver the opioid to the patient, there may always be some potential for addiction and abuse of these products.

What does abuse-deterrent really mean?
Abuse-deterrent formulations target the known or expected routes of abuse, such as crushing in order to snort or dissolving in order to inject, for the specific opioid drug substance. The science of abuse deterrence is relatively new, and both the formulation technologies and the analytical, clinical, and statistical methods for evaluating those technologies are rapidly evolving. The FDA is working with many drug makers to support advancements in this area and helping drug makers navigate the regulatory path to market as quickly as possible. In working with industry, the FDA is taking a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products.

Opioids with FDA-Approved Labeling Describing Abuse-Deterrent Properties
FDA has approved these opioids with labeling describing abuse-deterrent properties consistent with the FDA's Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling:

- **OxyContin (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=022272)**
- **Targiniq ER (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=205777)**
- **Embeda (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=022321)**
- **Hysingla ER (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=206627)**
- **MorphaBond ER (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=206544)**
- **Xtampza ER (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=208090)**
- **Arymo ER (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=208603)**

- **RoxyBond (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=209777)**

There are currently NO generic opioids with FDA-approved abuse-deterrent labeling.

How does the FDA decide what drugs are considered abuse-deterrent?
To meet the FDA's standards, it is essential that every opioid with labeling describing its abuse-deterrent properties be grounded in science and supported by evidence. Any claims regarding abuse-deterrent properties must be truthful and not misleading based on a product's labeling, and supported by sound science taking into consideration the totality of the data for the particular drug. Absent sufficient science, there can be no claim of abuse deterrence. Permitting insufficiently proven claims does not serve the public health.

The FDA has issued two guidances to help industry understand how the agency currently is evaluating these innovative products.

- "**Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling (/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf)**" (final guidance) explains the FDA's current thinking about the studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties. It also makes recommendations about how those studies should be performed and evaluated, and discusses what labeling claims may be approved based on the results of those studies.
- "**General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products (/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM492172.pdf)**" (final guidance) includes recommendations about the studies that should be conducted to demonstrate that a generic opioid is no less abuse-deterrent than the brand name product, with respect to all potential routes of abuse.

How will abuse-deterrent opioids help with the epidemic?
Because abuse-deterrent products are expected to reduce abuse compared to non-abuse-deterrent products, the agency is very interested in exploring new methods for analyzing and evaluating abuse-deterrent features; evaluating the nomenclature use to describe abuse-deterrent features; facilitating development of science for generic versions of these drugs; and taking new steps to encourage the conversion of the market to effective ADFs as part of the FDA's Opioid Policy Work Plan. The FDA looks forward to a future in which most or all opioid medications are available in formulations that are less susceptible to abuse than the formulations that are on the market today. To achieve this goal, FDA is taking steps to incentivize and support the development of opioid medications with progressively better abuse-deterrent properties. These steps include working with individual sponsors on promising abuse-deterrent technologies; developing appropriate testing methodologies for both innovator and generic products; and publishing guidance on the development and labeling of abuse-deterrent opioids.

We continue to encourage the development of innovative abuse-deterrent technologies, and we are also prioritizing the need for data that will help determine the impact of products incorporating abuse-deterrent technology on misuse and abuse. To collect this important information, all the companies that have brand name opioids with abuse-deterrent labeling claims are being required to conduct post-market studies to determine the impact those products are having in the real world. Having that information is critical and will allow us to take the next important steps in this area.

In addition, FDA supports the development of assessment tools to evaluate packaging, storage, delivery, and disposal solutions, as well as product formulations, designed to prevent and deter misuse and abuse of opioids. To further this effort, the agency held a **public workshop on December 11-12, 2017 (/Drugs/NewsEvents/ucm571797.htm)**, regarding the role of packaging, storage, and disposal options within the larger landscape of activities aimed at addressing abuse, misuse, or inappropriate access of prescription opioid

drug products. **A Broad Agency Agreement was amended (https://www.fbo.gov/index?s=opportunity&mode=form&id=62f0f64bbb3aff58da7ba3569f099485&tab=core&_cview=1)** to add this additional area of research to those previously noted to be of interest to FDA to address our current knowledge gap in this area.

More in Postmarket Drug Safety Information for Patients and Providers (/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm)

Index to Drug-Specific Information (/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111085.htm)

EXHIBIT F

PROP
PHYSICIANS FOR RESPONSIBLE OPIOID PRESCRIBING

2012 JUL 25 P 1:48

July 25, 2012

Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville MD 20852

The undersigned clinicians, researchers and health officials from fields that include Pain, Addiction, Primary Care, Internal Medicine, Anesthesiology, Psychiatry, Neurology, Emergency Medicine, Toxicology, Rheumatology, and Pubic Health submit this petition under Section 21 CFR 10.20 and 21 CFR 10.30 and other pertinent sections of the Federal Food, Drug and Cosmetic Act or any other statutory provision which authority has been delegated to the FDA Commissioner to regulate labeling of opioid analgesics.

At present, the FDA-approved indication for nearly all instant-release opioid analgesics is "moderate to severe pain". For extended-release opioids, the indication is for "moderate to severe pain when a continuous, around-the clock analgesic is needed for an extended period of time." These overly broad indications imply a determination by FDA that they are safe and effective for long-term use. As outlined below, an increasing body of medical literature suggests that long-term use of opioids may be neither safe nor effective for many patients, especially when prescribed in high doses.

Unfortunately, many clinicians are under the false impression that chronic opioid therapy (COT) is an evidence-based treatment for chronic non-cancer pain (CNCP) and that dose-related toxicities can be avoided by slow upward titration. These misperceptions lead to over-prescribing and high dose prescribing. By implementing the label changes proposed in this petition, FDA has an opportunity to reduce harm caused to chronic pain patients as well as societal harm caused by diversion of prescribed opioids. In addition, FDA will be able to reinforce adherence to dosing limits that have been recommended by the United States Centers for Disease Control[1], the state of Washington[2] and the New York City Department of Health and Mental Hygiene[3].

The Federal Food, Drug and Cosmetic Act established that a drug intended to treat a condition must be proven safe and effective for use as labeled.[4]The current label on opioid analgesics does not comply with this law. By taking the actions requested in this petition, FDA will be able to exercise its regulatory responsibility over opioid manufacturers by prohibiting the marketing of opioids for conditions in which their use has not been proven safe and effective.

FDA-2012-P-0818

CP

920 48th Street, Suite 1510
Brooklyn, NY 11219
Office: 718.283.7557
Fax: 718.283.6540
www.responsibleopioidprescribing.org
info@responsibleopioidprescribing.org

2012-6360

SPECIFIC ACTIONS REQUESTED FOR CHANGES TO OPIOID ANALGESIC LABELS:

1. Strike the term "moderate" from the indication for non-cancer pain.
2. Add a maximum daily dose, equivalent to 100 milligrams of morphine for non-cancer pain.
3. Add a maximum duration of 90-days for continuous (daily) use for non-cancer pain.

STATEMENTS OF SCIENTIFIC BASIS FOR PETITION:

1. Over the past decade, a four-fold increase in prescribing of opioid analgesics has been associated with a four-fold increase in opioid related overdose deaths and a six-fold increase in individuals seeking treatment for addiction to opioid analgesics.[5]

2. Prescribing of opioids increased over the past 15 years in response to a campaign that minimized risks of long-term use for CNCP and exaggerated benefits.[6,7,8]

3. Long-term safety and effectiveness of managing CNCP with opioids has not been established.[9]

4. Recent surveys of CNCP patients receiving COT have shown that many continue to experience significant chronic pain and dysfunction.[10,11]

5. Recent surveys using DSM criteria found high rates of addiction in CNCP patients receiving COT.[12,13]

6. A large sample of medical and pharmacy claims records found that two-thirds of patients who took opioids on a daily basis for 90 days were still taking opioids five years later.[14]

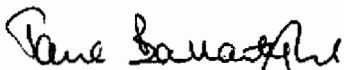
7. Patients with mental health and substance abuse co-morbidities are more likely to receive COT than patients who lack these risk factors, a phenomenon referred to as *adverse selection.*[15]

8. Three large observational studies published in 2010 and 2011 found dose-related overdose risk in CNCP patients on COT.[16,17,18]

9. COT at high doses is associated with increased risk of overdose death[18], emergency room visits[19] and fractures in the elderly[20].

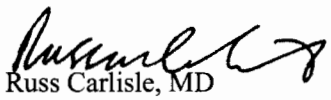
There is no environmental impact associated with this Citizen's Petition and we wish to be excluded under 21 CFR Sec. 25.24.

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petition which are unfavorable to the petition (21 CFR Sec.10.30b).

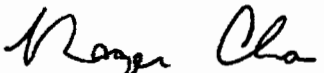


Jane C. Ballantyne, MD, FRCA
UW Professor of Education and Research
Department of Anesthesiology and Pain Medicine
Seattle, Washington

Miles Belgrade, MD
Medical Director, Fairview Pain Center
Adjunct Professor, Department of Neurology,
University of Minnesota Medical Center
Minneapolis, Minnesota

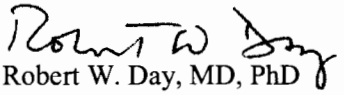


Russ Carlisle, MD
Medical Director, Emergency Department
Swedish Cherry Hill Medical Center
Seattle, Washington

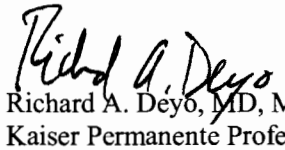


Roger Chou, MD, FACP
Associate Professor of Medicine
Dept. of Medicine and Dept. of Medical
Informatics and Clinical Epidemiology
Oregon Health & Science University

Edward C. Covington, MD
Director, Neurological Center for Pain
Cleveland Clinic
Cleveland, Ohio

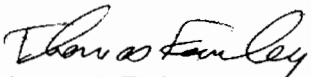


Robert W. Day, MD, PhD
President Emeritus
Fred Hutchinson Cancer Research Center
Seattle, Washington



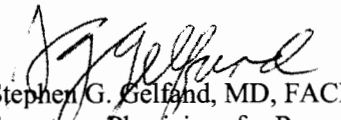
Richard A. Deyo, MD, MPH
Kaiser Permanente Professor of Evidence-Based
Family Medicine, Dept. of Family Medicine
Department of Medicine Director, OCTRI
Community and Practice Research Program
Oregon Health and Science University

Irfan Dhalla, MD, MSc
Assistant Professor, University of Toronto
Toronto, Ontario

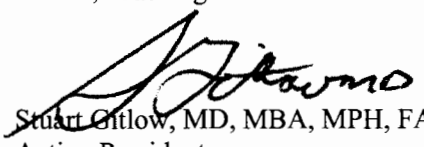


Thomas A. Farley, MD, MPH
Commissioner, Department of Health
City of New York

Gary M. Franklin, MD, MPH
Research Professor, University of Washington
Director, Occupational Epidemiology and Health
Outcomes Program
Seattle, Washington



Stephen G. Gelfand, MD, FACP
Secretary, Physicians for Responsible Opioid
Prescribing
Myrtle Beach, South Carolina



Stuart Gitlow, MD, MBA, MPH, FAPA
Acting President
American Society of Addiction Medicine
Chevy Chase, Maryland

Roland W. Gray, MD, FASAM
Medical Director, Tennessee Medical Foundation
Physician's Health Program
Brentwood, Tennessee

Erik Gunderson, MD, FASAM
Assistant Professor, Dept. of Psychiatry &
Neurobehavioral Sciences and Dept. of Medicine
Director, Clinical Pharmacological Research Unit
University of Virginia

W. Michael Hooten, MD
Associate Professor of Anesthesiology
Mayo Clinic
Rochester, Minnesota

David Juurlink, MD, PhD
Head, Division of Clinical Pharmacology and
Toxicology, University of Toronto
Toronto, Ontario

Andrew Kolodny, MD
President, Physicians for Responsible Opioid
Prescribing; Chair, Dept. of Psychiatry
Maimonides Medical Center
Brooklyn, New York

Thomas R. Kosten, MD
Waggoner Chair and Professor of Psychiatry,
Neuroscience, Pharmacology
Baylor College of Medicine,
Micheal E DeBakey VAMC
Houston, Texas

Kurt Kroenke, MD
Professor of Medicine, Indiana University Research
Scientist, VA HSR&D Center for Implementing
Evidence-Based Practice, Regenstrief Institute
Indianapolis, Indiana

Eric B. Larson, MD, MPH
Vice President for Research, Group Health
Exec. Director, Group Health Research Institute
Seattle, Washington

Petros Levounis, MD, MA
Director, The Addiction Institute of New York
Associate Chair for Clinical Services, Dept. of
Psychiatry, St. Luke's & Roosevelt Hospitals
New York, New York

Elinore F. McCance-Katz, MD, PhD
Professor, Department of Psychiatry
University of California San Francisco
San Francisco, California

Lewis Nelson, MD
Associate Professor, Dept. of Emergency Medicine
New York University School of Medicine
New York, New York

Rosemary Orr, MD
Professor of Anesthesiology, Seattle Children's
Hospital and University of Washington
Seattle, Washington

William Phillips, MD, MPH, FAAP
Theodore J. Phillips Endowed Professor in Family Medicine, University of Washington
Seattle, Washington

Charles Reznikoff, MD
Internal Medicine and Addiction Medicine,
Hennepin County Medical Center
Minneapolis, Minnesota

Roger Rosenblatt, MD, MPH, MFR
Professor & Vice Chair, Dept. of Family Medicine
University of Washington School of Medicine
Seattle, Washington

Nirav R. Shah, MD, MPH
Commissioner
New York State Department of Health
Albany, New York

Harris Silver, MD
Policy Analyst, Senate Memorial 18 New Mexico Drug Policy Task Force, Robert Wood Johnson Foundation Center for Health Policy
University of New Mexico

Kurt C. Stange, MD, PhD
Professor of Family Medicine & Community Health, Epidemiology & Biostatistics, Oncology and Sociology, Case Western Reserve University
Cleveland, Ohio

Jon Streltzer, MD
Program Director, Addiction Psychiatry
Professor of Psychiatry, University of Hawaii
Honolulu, Hawaii

Mark Sullivan, MD, PhD
Professor, Dept. of Psychiatry and Behavioral Sciences; Adjunct Professor Bioethics and Humanities; Adjunct Professor, Anesthesiology and Pain Medicine University of Washington
Seattle, Washington

Barbara J. Turner MD, MSED, MA, MACP
Professor of Medicine; Director, ReACH Center
Director, Health Outcomes Improvement
University of Texas Health Science Center
San Antonio, Texas

Judith Turner, PhD
Professor, University of Washington, Dept. of Psychiatry and Behavioral Sciences

Michael Von Korff, ScD
Senior Investigator
Group Health Research Institute
Seattle, Washington

Sidney M. Wolfe, MD
Director
Public Citizen's Health Research Group
Washington, DC

Art Van Zee, MD
Stone Mountain Health Services
St. Charles Clinic
Charles, Virginia

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EXHIBIT G

Utah Clinical Guidelines on Prescribing Opioids for Treatment of Pain

Utah Department of Health
2009

David N. Sundwall, MD
Executive Director

Robert T. Rolfs, MD, MPH
State Epidemiologist

Erin Johnson, MPH
Program Manager

State of Utah

JON M. HUNTSMAN, JR.
Governor

GARY R. HERBERT
Lieutenant Governor

Utah Department of Health
Executive Director's Office

DAVID N. SUNDWALL, M.D.
Executive Director

A. RICHARD MELTON, Dr.P.H.
Deputy Director

W. DAVID PATTON, Ph.D
Deputy Director

February, 2009

I am pleased to provide a copy of "Utah Clinical Guidelines on Prescribing Opioids for Pain." This document represents the results of many months of work on the part of many people, all of whom contributed considerable time, effort, experience, and expertise. This effort is an attempt to address what I consider one of the most pressing and challenging public health problems—premature deaths, dependency and disability associated with misuse and/or abuse of prescription drugs, especially, narcotic medications.

Utah's Medical Examiner, Dr. Todd Grey, brought to my attention soon after I assumed my position as Executive Director of the Utah Department of Health in 2005, the alarming increase in deaths in our state related to misuse of prescription drugs. In recent years, prescription medications used alone, in combination, or mixed with illicit drugs, has resulted in the death of hundreds of our fellow citizens. For the past 17 years, prescription drug-related deaths have increased and now exceed deaths resulting from automobile crashes in our state. In fact, it is now the **number one cause of unintentional death.**

These guidelines are meant to be just that—suggestions on how to properly use and prescribe opioid medication. As with any effort to achieve consensus, there were members who participated in the preparation of this document who disagree at both ends of the spectrum, i.e., some believe that the guidelines are too lax, others believe they impose barriers to access of much needed narcotic medications for the control of pain. It is our hope that the guidance in this document will educate both the public and clinicians about appropriate use of these medications which will, if followed, significantly reduce deaths from misuse and abuse, but at the same time allow for the control of chronic pain with proper use of opioid medications.

I want to thank the many individuals and organizations that contributed to the preparation of this document. Thousands of hours were spent in meetings and in reviewing related literature. I particularly want to acknowledge the outstanding work of Dr. Robert Rolfs, Utah State Epidemiologist and Erin Johnson, Prescription Pain Medication Program Manager. I would also like to acknowledge that the Utah State Legislature directed the Department of Health by law to produce this report on, "Medical Treatment and Quality Care Guidelines that are Scientifically Based; and Peer Reviewed," and provided the necessary funds. Additional encouragement and strong support was provided along with matching funds from the Labor Commission Workplace Safety Fund.

I'm hopeful that these guidelines will prove to be a "living document" that will be updated over time to reflect new knowledge and science and thereby improve the public's health in our state.

Sincerely,

David N. Sundwall, MD
Executive Director

288 North 1460 West, PO Box 141000, Salt Lake City, Utah, 84114-1000
Telephone 801-538-6111 • Fax 801-538-6306

Corresponding Author:

Robert T. Rolfs, MD, MPH

PO Box 142104
Salt Lake City, Utah, 84114-2104

phone (801) 538-6191
fax (801) 538-9923
email: rrolfs@utah.gov

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Table of Contents

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The Department of Health is grateful for the leadership in addressing this issue by Representative Bradley Daw who introduced House Bill 137: Pain Medication Management and Education, which was passed by the 2007 Utah legislature providing funding and directing production of these guidelines.

Steering Committee

Robert Rolfs, MD, MPH, Bureau of Epidemiology, Utah Department of Health*

Noel Taxin, Utah Division of Occupational and Professional Licensing

Kim Bateman, MD, HealthInsight

Martin Caravati, MD, MPH, Utah Poison Control Center

Alan Colledge, MD, Utah Labor Commission

Perry Fine, MD, Professor of Anesthesiology, Pain Research Center

Teresa Garrett, RN, Division of Epidemiology & Laboratory Services, Utah Department of Health

Craig PoVey, MSW, LCSW, Division of Substance Abuse, Utah Department of Human Services

Doug Springmeyer, JD, Attorney General's Office

Terri Rose, HealthInsight

Guideline Recommendation Panel

Marc Babitz, MD, Primary Care*
Jay Aldous, DDS, MS Dental
John Barbuto, MD, Neurology
Alan Colledge, MD, Occupational Medicine
David Cole, MD, Emergency Medicine
Michael Crookston, MD, Psychiatry
Robert Finnegan, MD, Anesthesiology
Kathy Hogan, FNP, Primary Care
Jerry Shields, RPh, MBA, Pharmacy
Roger Stuart, MD, Occupational Medicine
Peter Taillac, MD, Emergency Medicine
Lynn Webster, MD, Pain Management

Implementation & Tool Panel

Kim Bateman, MD, Family Practice*
Bennion Buchanan, MD, Emergency Medicine
Mark Foote, MD, Psychiatry
Edward Holmes, MD, Occupational Medicine
Kathy Goodfellow, PharmD, Pharmacy
Mark Lewis, MD, Internal Medicine
Kerry Strateford, MD, Family Practice
Tom Kurrus, MD, Internal Medicine
Robert Rolfs, MD, MPH, Internal Medicine

* Indicates the panel or committee chair-person

Disclosure of Funding

These Guidelines are based on research conducted at the Utah Department of Health with funding from the Utah State Legislature. Additional funds were contributed to the program by the Utah Labor Commission (from the Utah Workplace Safety Account) and by the Worker's Compensation Fund of Utah.

Statutory Authority

These Guidelines were authorized by the Utah Legislature which directed the Utah Department of Health to produce "medical treatment and quality care guidelines that are scientifically based; and peer reviewed" (§26-1-36 Utah Code Annotated).

Disclosure of Conflicts

Alan L. Colledge, MD, is the Medical Director of the Labor Commission of Utah which oversees the care of approximately 60,000 injured individuals a year provided by over 250 different insurance and payer sources.

Edward B. Holmes, MD, MPH, is an appointed member of the Utah Labor Commission Workers Compensation Advisory Council. He is also Chief Medical Consultant for Disability Determination Services for Social Security.

Roger K. Stuart, MD, is employed by the Worker's Compensation Fund of Utah.

Jerry A. Shields, RPh, MBA, is a clinical pharmacy consultant for Regence Blue Cross Blue Shield of Utah which is an insurance provider.

Lynn R. Webster, MD, conducts research for the following pharmaceutical companies: Abbott Laboratories, Ameritox, Merck & Co., Inc., Arryra, AstraZeneca, Boehringer Ingelheim, Elite Pharmaceuticals, King Pharmaceuticals, Medtronic, Merck & Co., Inc., Durect Corp., Nektar, NeurogesX, Inc., PTI, Purdue Pharma, QRZ, Respironics, Takeda Pharmaceuticals, TorreyPines Therapeutics, Wyeth, and Zars Pharma. He also conducts research for Nervo and Advanced Bionics (device companies), Ameritox (urine drug testing company), and Respironics (manufacturer of sleep apnea machines). Dr. Webster is a consultant for Advanced Bionics, Alpharma Pharmaceuticals, LLC, Cephalon, Inc., King Pharmaceuticals, Medtronic, Nektar, and Nervo. He is also an advisor to Purdue Pharma.

Background and Introduction

Unintentional fatalities due to prescription medications are an increasing problem in the United States and Utah. In the year 2000, the Utah Medical Examiner noted an increase in the number of deaths occurring due to an overdose of prescription opioid medications that are typically used for pain management. Epidemiologic studies conducted in Utah using death certificate data, Office of the Medical Examiner data, emergency department encounter data, and data from the Utah Controlled Substances Database confirmed the increases and uncovered an alarming problem.

During the years 1999–2007 deaths attributed to poisoning by prescription pain medications increased by over 500%, from 39 to 261. Deaths of Utah residents from non-illicit drug poisoning (unintentional or intent not determined) have increased from about 50 deaths per year in 1999 to over 300 in 2007. The increase was mostly due to increased numbers of deaths from prescription opioid pain medications, including methadone, oxycodone, hydrocodone, and fentanyl (CDC, 2005).

Prescribing of opioid medications has substantially increased over the past 10-15 years, including greater use for treating acute and chronic pain. Distribution to Utah of opioids such as hydrocodone, oxycodone, and methadone increased 6-fold from 1997-2002. In addition, national data document an increase in non-medical use of prescription opioids during the past several years (Substance Abuse and Mental Health Services Administration [SAMHSA], 2004; SAMHSA, 2007). From 1990 to 2002, the number of people in the U.S. who reported using prescription pain medications non-medically for the first time that year increased from 600,000 to over 2 million people (SAMHSA, 2004).

In 2007, recognizing the need for intervention, the Utah State Legislature passed House Bill 137 appropriating funding to the Utah Department of Health (UDOH) to establish a program aimed at reducing deaths and other harm from prescription opiates. Additionally, the program's charge was to develop medical treatment and quality care guidelines for the state of Utah. The resulting Prescription Pain Medication Program is being led by the Utah Department of Health in collaboration with the Utah Attorney General, the Labor Commission, the Division of Occupational and Professional Licensure, Department of Commerce, and Division of Substance Abuse and Mental Health, Department of Human Services.

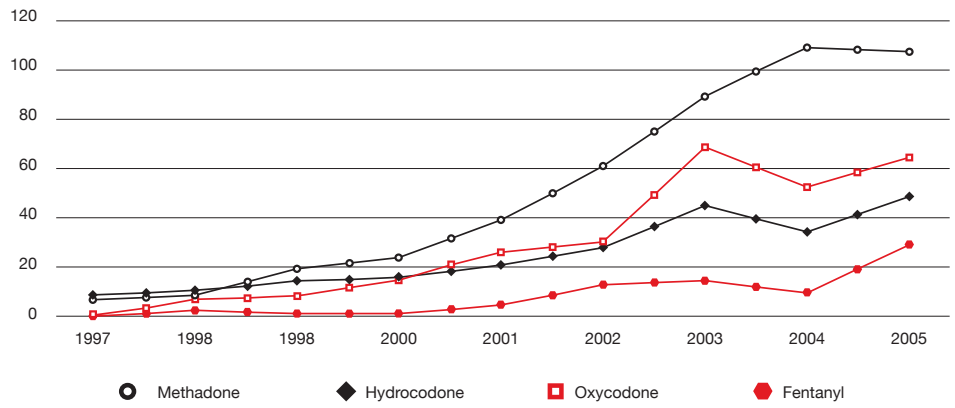
A key goal of this Guideline is to seek a balance between appropriate treatment of pain and safety in the use of opioids for that purpose. The Model Policy for the Use of Controlled Substances for the Treatment of Pain[1] (Federation of State Medical Boards, 2004) acknowledged that "undertreatment of pain is…a serious public health problem," but also sought to establish the importance of balance in treating pain as stated in the following sentence:

"…the inappropriate treatment of pain includes nontreatment, undertreatment, overtreatment, and the continued use of ineffective treatments."

As of the time these Utah Guidelines were produced, **adequate evidence was not available to determine the benefits of long-term treatment with opioids for persons with chronic pain due to musculoskeletal and other non-cancer causes on patient function and quality of life** (Von Korff & Deyo, 2004). Despite that lack of evidence, the use of these medications for treatment of these conditions has increased substantially in recent years. In the absence of adequate evidence to determine the true benefits and best practices in use of these medications,

[1] The Model Policy for the Use of Controlled Substances for the Treatment of Pain was developed by the Federation of State Medical Boards and endorsed by the Division of Occupational and Professional Licensing on recommendation of the Physicians Licensing Board.

Figure 1. *Number of Utah Deaths by Year and Drug: Accidental and Undetermined Cause*



these Guidelines were developed to assist physicians who choose to use opioids to treat patients with pain to manage that treatment as safely as possible.

The principal focus of these Guidelines is on the use of opioids in the long term treatment of chronic pain, especially chronic, non-cancer pain[2]. These guidelines were not developed to guide treatment of patients with malignant cancer or for patients in hospice or palliative care settings and should not limit treatment for patients for whom pain relief is the primary goal and improved function is not expected.

The diversion of opioid medications to non-medical uses also has contributed to the increased numbers of deaths. Therefore, these guidelines also include several recommendations on the use of opioids to treat acute pain to help address that public health problem. For purposes of these guidelines, acute pain is considered to be an episode of pain lasting six weeks or less and chronic pain to be pain lasting more than three months. Episodes of pain lasting from one to three months are sometimes referred to as subacute pain and were not explicitly addressed by these guidelines, however many of the recommendations are applicable to subacute pain.

The Utah Department of Health and its advisors recognized that clinicians have many demands on their time and have attempted to make these guidelines as practical and concise as possible. However, long-term use of opioid medications to treat chronic pain carries substantial risks and the benefits of this treatment approach have not been adequately established by appropriate studies. The time commitment required to safely manage patients on these medications should be considered when they are prescribed. The Utah Department of Health agrees with Von Korff and Deyo (2004) that,

"Long-term opioid therapy should only be conducted in practice settings where careful evaluation, regular follow-up and close supervision are ensured."

Medicine is practiced one patient at a time and each patient is unique with individual needs and vulnerabilities. The Guidelines have attempted to guide clinicians but not to inappropriately constrain practice. The art of medicine is recognized. However, these Guidelines were based on evidence or consensus recommendations by experts. They are intended to improve outcomes of patient care and in particular to prevent deaths due to opioid use. Departures from these recommendations will be appropriate for some patients, but should be justified and documented.

[2] This Guideline uses the term chronic non-cancer pain to refer to chronic pain that is not associated with active cancer or occurs at the end of life (Chou et al., 2009). Some of the tools and references included in this Guideline use the term, "chronic non-malignant pain" to describe a similar or identical set of conditions.

Summary of Recommendations

Opioid Treatment for Acute Pain

1) Opioid medications should only be used for treatment of acute pain when the severity of the pain warrants that choice and after determining that other non-opioid pain medications or therapies will not provide adequate pain relief.

2) When opioid medications are prescribed for treatment of acute pain, the number dispensed should be no more than the number of doses needed based on the usual duration of pain severe enough to require opioids for that condition.

3) When opioid medications are prescribed for treatment of acute pain, the patient should be counseled to store the medications securely, to not share with others, and to dispose of medications properly when the pain has resolved in order to prevent non-medical use of the medications.

4) Long duration-of-action opioids should not be used for treatment of acute pain, including post-operative pain, except in situations where monitoring and assessment for adverse effects can be conducted. Methadone is rarely if ever indicated for treatment of acute pain.

5) The use of opioids should be reevaluated carefully, including assessing the potential for abuse, if persistence of pain suggests the need to continue opioids beyond the anticipated time period of acute pain treatment for that condition.

Opioid Treatment for Chronic Pain

1) A comprehensive evaluation should be performed before initiating opioid treatment for chronic pain.

2) Alternatives to opioid treatment should be tried (or adequate trial of such treatment by a previous provider documented), before initiating opioid treatment.

3) The provider should screen for risk of abuse or addiction before initiating opioid treatment.

4) When opioids are to be used for treatment of chronic pain, a written treatment plan should be established that includes measurable goals for reduction of pain and improvement of function.[3]

5) The patient should be informed of the risks and benefits and any conditions for continuation of opioid treatment, ideally using a written and signed treatment agreement.

6) Opioid treatment for chronic pain should be initiated as a treatment trial, usually using short-acting opioid medications.

7) Regular visits with evaluation of progress against goals should be scheduled during the period when the dose of opioids is being adjusted (titration period).

8) Once a stable dose has been established (maintenance period), regular monitoring should be conducted at face-to-face visits during which treatment goals, analgesia, activity, adverse effects, and aberrant behaviors are monitored.

9) Continuing opioid treatment after the treatment trial should be a deliberate decision that considers the risks and benefits of chronic opioid treatment for that patient. A second opinion or consult may be useful in making that decision

10) An opioid treatment trial should be discontinued if the goals are not met and opioid treatment should be discontinued at any point if adverse effects outweigh benefits or if dangerous or illegal behaviors are demonstrated.

11) Clinicians treating patients with opioids for chronic pain should maintain records documenting the evaluation of the patient, treatment plan, discussion of risks and benefits, informed consent, treatments prescribed, results of treatment, and any aberrant behavior observed.

12) Clinicians should consider consultation for patients with complex pain conditions, patients with serious co-morbidities including mental illness, patients who have a history or evidence of current drug addiction or abuse, or when the provider is not confident of his or her abilities to manage the treatment.

13) Methadone should only be prescribed by clinicians who are familiar with its risks and appropriate use, and who are prepared to conduct the necessary careful monitoring.

[3] "Function" as used here is defined broadly to include physical, emotional, cognitive, psychological and social function.

Methods

Purpose and Target Audience

These Guidelines provide recommendations for the use of opioids for management of pain that are intended to balance the benefits of use against the risks to the individual and society, and to be useful to practitioners. The target audience for these Guidelines includes all clinicians who prescribe opioids in their practice.[4]

Guideline Evidence Review

The steering committee of the Utah Department of Health's Prescription Pain Medication Program developed the key questions, scope, and inclusion criteria used to guide the evidence review process. The process began with a literature review to identify existing guidelines on pain, chronic pain, opioids, pain management, and related topics. Guidelines were identified through electronic databases, reference lists from evaluated guidelines, and recommendations from experts. Electronic databases that were searched include: PubMed, Medline, CINAHL, and the National Guideline Clearinghouse. Investigators identified and evaluated 40 individual guidelines.

Grading of the Evidence and Recommendations

As guidelines were identified they were reviewed for key information. They were evaluated based on the following categories:

- Title
- Year Published: Guidelines were included only if they were published after the year 1999. Articles published before 2000 were merely noted in the grid by their title and date with no additional information.
- Sponsorship and funding
- Medical Perspective
- Target Audience
- The Process: This describes how the guidelines were created. Most guidelines fell into two categories: "evidence-based" and/or "consensus"
- The Rating Scale: This was based on the quality of research that went into the development of the guidelines. Explicit evidence-based guidelines received higher ratings and less explicit, consensus-based guidelines received lower ratings

The complete evaluation matrix of the 40 guidelines is available from the Utah Department of Health, Bureau of Epidemiology upon request.

In total, 40 guidelines for pain management were reviewed and evaluated. As each guideline was reviewed, it received a rating from 1-10 (for a breakdown of the rating scale, see Appendix A). Guidelines that received scores of seven (7) or lower were excluded. Four (4) sets of guidelines received scores of eight (8) or above. Three (3) public health professionals reviewed the ratings to ensure that the scores were consistent with the rating scale.

Panel Composition

The Utah Department of Health convened two multidisciplinary panels (see page 4 for complete list of panel members). The Guideline Recommendation Panel convened on four (4) occasions between May and July 2008. Their purpose was to review the evidence and formulate recommendations based on the evidence in the selected guidelines. Each member signed a Conflict of Interest disclosure. Conflicts were reported as described below (See Disclosure of Conflicts on page ii). The Guideline Implementation and Tool Panel convened twice (2) between July and August 2008 to review the recommendations to ensure that they were implementable as well as to identify tools needed in order to put the recommendations into use. The first panel consisted of twelve (12) experts and the second consisted of nine (9) experts from throughout the state of Utah.

Recommendation Development Process

The Guideline Recommendation Panel met in person on four occasions between May and July 2008. The purpose of the first meeting was to provide panel members with copies of the selected, high-scoring guidelines and to present the purpose and plan for developing the guidelines. Prior to the second meeting, panel members were asked to review the four guidelines for commonalities. The recommendations that were supported by multiple guidelines created the basis of the first draft of the recommendations used by the Guideline Recommendation Panel. Consideration was given to adopting one of the existing evidence-based guidelines outright, but the panel

[4] In Utah as of January 2009 (R156-37), clinicians who can be licensed to prescribe controlled substances as part of practice (human) includes physicians and surgeons, osteopathic physicians and surgeons, podiatrists, dentists, physician assistants, advanced practice registered nurses, certified nurse midwives, certified nurse anesthetists, and optometrists.

felt that no single guideline represented sufficiently what was desired of the Utah guidelines. The panel voted to include two (2) additional sets of guidelines that had not met the inclusion criteria for consideration while drafting the recommendations. In total, content for the Utah guidelines was drawn from six (6) guidelines. The key topics to be developed into specific recommendations were posted on a website where the Guideline Recommendation Panel members posted comments and edited the text. The panelists' postings were the basis on which content was selected from the chosen guidelines. This content was then used to create a draft of actual recommendation statements and supporting paragraphs. At the third meeting, a straw poll was taken on the recommendation draft. Through discussion and rewording, consensus on content was achieved for all of the recommendations discussed over the course of the two meetings. Outside the meetings, non-content editing of the recommendations and supporting statements was performed, based on the panel's discussions, to create the final draft of the recommendations and supporting paragraphs.

Tool Development Process

The Guideline Implementation and Tools Panel met in person on two occasions between July and August 2008. Prior to the first meeting, a book was compiled that included all tools that were identified in the forty (40) guidelines. Sample tools were solicited from panel members as well. In total, the workbook contained forty-seven (47) tools. At the first meeting, the panel reviewed the draft recommendations and discussed whether any specific recommendations were impossible or burdensome to implement. Panel members were each given a book containing all the tools. In between the first and second meeting, panel members reviewed and graded each tool according to usefulness and whether or not it should be included in the guidelines. Votes and rating were tallied prior to the second meeting. Tools that received an average rating of below two (2) were eliminated. At the second meeting, the remaining tools were discussed and it was determined which of the remaining tools should be included, modified, or eliminated.

Following the final panel meetings, Utah Department of Health staff formally drafted the complete guidelines document. Drafts of the complete guidelines were then distributed to all panel members and several Utah Department of Health internal staff for feedback and revisions. External peer reviewers were solicited for additional comments. The final draft recommendations were posted for public comment during November–December 2008 and revisions were made based on consideration of those comments (copies of comments are available online at **health.utah.gov/prescription**). Prior to publication, the Guideline was submitted to the Utah Department of Health Executive Director for approval.

Recommendations

Previously published evidence-based or consensus-based guidelines have been used as the foundation for many of the Utah recommendations. Each guideline has been assigned a number. After each recommendation, the numbers of the guidelines with similar or supporting recommendations are listed.

Reference Guidelines:

1. Department of Veterans Affairs, Department of Defense. (2003). *VA/DoD clinical practice guideline for the management of opioid therapy for chronic pain*
2. College of Physicians and Surgeons of Ontario. (2000). *Evidence-based recommendations for medical management of chronic non-malignant pain*
3. American College of Occupational and Environmental Medicine's Occupation Medicine Practice Guidelines. (2008).
4. *Opioids in the Management of Chronic Non-Cancer Pain: An Update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines.* (2008).
5. Washington State Agency Medical Directors' Group. (2007). *Interagency guideline on opioid dosing for chronic non-cancer pain: An educational pilot to improve care and safety with opioid treatment*
6. Federation of State Medical Boards of the United States, Inc. (2004). *Model policy for the use of controlled substances for the treatment of pain*

Opioid treatment recommendations for acute pain:

Acute Pain Recommendation 1:
Opioid medications should only be used for treatment of acute pain when the severity of the pain warrants that choice and after determining that other non-opioid pain medications or therapies will not provide adequate pain relief. *Reference Guidelines: 3*

Most acute pain is better treated with non-opioid medications (e.g., acetaminophen, non-steroidal anti-inflammatory drugs (NSAID), or therapies such as exercise, or specific stretching) than opioid medications which have less desirable adverse effect profiles in acute pain patients. Care should be taken to assure that use of opioid pain treatment does not interfere with early implementation of functional restoration programs such as exercise and physical therapy. The developing brain may be more susceptible to addiction when exposed to opioid medications and nonmedical use is more common among younger people. Those risks should be considered when prescribing to an adolescent.

Acute Pain Recommendation 2:
When opioid medications are prescribed for treatment of acute pain, the number dispensed should be no more than the number of doses needed based on usual duration of pain severe enough to require opioids for that condition.

Prescribing more medications than the amount likely to be needed leads to unused medications being available for non-medical use or abuse. Use of opioid pain medications should be stopped when pain severity no longer requires opioid medications.

Acute Pain Recommendation 3:
When opioid medications are prescribed for treatment of acute pain, the patient should be counseled to store the medications securely, not share with others, and to dispose of properly when the pain has resolved in order to prevent non-medical use of the medications.

It is important that patients understand the need to store medications securely. Encourage patients to keep medications in a locked environment rather than in typical locations, such as the bathroom or kitchen cabinet, where they are accessible to unsuspecting children, curious teenagers, and can be a target for theft. Tell the patient that if they have leftover medication after they have recovered, they should dispose of their medication immediately to help protect them from being a target for theft as well as protect others from getting into the medications. The Federal Guidelines on Proper Disposal of Prescription Drugs are included in the Tool Section.

Acute Pain Recommendation 4:
Long duration-of-action opioids should not be used for treatment of acute pain, including post-operative pain, except in situations where adequate monitoring and assessment for adverse effects can be conducted. Methadone is rarely if ever indicated for treatment of acute pain.

Acute Pain Recommendation 5:
The use of opioids should be reevaluated if persistence of pain suggests the need to continue opioids beyond the anticipated time period of acute pain treatment for that condition.

Patients with acute pain who fail to recover in a usual timeframe or otherwise deviate from the expected clinical course for their diagnosis should be carefully evaluated. The continuation of opioid treatment in this setting may represent the initiation of opioid treatment for a chronic pain condition without being recognized as such at the time. The diagnosis and appropriateness of interventions should be reevaluated and the patient's medical history should be reviewed for comorbidities that could interact with opioid treatment and for risk factors for problems during opioid treatment, including substance abuse or history of substance abuse. It is recommended that the provider check the Utah Controlled Substances Database at this time as well.

Opioid treatment recommendations for chronic pain:

Before prescribing opioid treatment for chronic pain:

1. Comprehensive initial evaluation/assessment of patient

1.1 Recommendation:
A comprehensive evaluation should be performed before initiating opioid treatment for chronic pain. *Reference Guidelines: 1, 2, 4, 6*

There are many reasons for using caution when initiating opioid therapy, therefore the recommended comprehensive initial evaluation is very important. A major goal when prescribing opioids should be to provide greater benefit than harm to patients. Potential for serious harm exists, up to and including death, due either to overdose or to dangerous behaviors that occur while under the influence of these medications. The patient may be harmed, but others may also be harmed through diversion or because of an act performed by the patient on opioids. The most frequent harms are diversion, misuse, abuse, addiction, and overdose and predicting which patients will be affected by these harms is difficult. Initiating opioid treatment often results in short term relief, but that relief might not be maintained. Long-term use of opioid medications to treat chronic pain safely requires the commitment of adequate resources to regularly monitor and evaluate outcomes and identify occurrence of adverse consequences.

The goal of the comprehensive evaluation is to determine the nature of the patient's pain, evaluate how the pain is affecting the patients function and quality of life, identify other conditions or circumstances that could affect the choice of treatment or the approach to managing that treatment, assess and evaluate prior approaches to pain management, and serve as a basis for establishing a plan for treatment and evaluation of treatment outcomes.

The evaluation should specifically address these issues:

1) Assess pain and prior treatment of pain.
   - Determine the cause of the pain and whether the pain is acute or chronic.
   - Assess previous treatment approaches and trials for appropriateness, adequacy, and outcome.

2) Assess presence of social factors, and medical or mental health conditions that might influence treatment especially those that might interfere with appropriate and safe use of opioid therapy (Department of Veterans Affairs & Department of Defense [VA/DOD], 2003):
   - Obtain history of substance use, addiction or dependence (if present, refer to Recommendations 12.2 and 12.3).
   - Identify psychiatric conditions that may affect pain or treatment of pain (if present, refer to Recommendation 12.4).
   - Identify use of other medications that might interact with medications used to treat the pain. Particular attention should be given to benzodiazepines and other sedative medications.
   - Assess social history, including employment, social network, marital history, and any history of legal problems especially illegal use or diversion of controlled substances.
   - Assess for presence of medical conditions that might complicate treatment of the pain, including medication allergy, cardiac or respiratory disease, and sleep apnea or risk factors for sleep apnea.
   - Central sleep apnea is common among persons treated with methadone and other opioid medications, especially at higher dosages. Some clinicians recommend that all patients who are considered for long-term opioid treatment receive a sleep study prior to therapy or when higher dosages are considered.

3) Assess the effects of pain on the person's life and function.
   - Assess the severity of pain, functional status of the patient, and the patient's quality of life using a method/instrument that can be used later to evaluate treatment effectiveness.

Tools to accompany Recommendation 1:
- Sheehan Disability Tool
- Pain Management Evaluation Tool

2. Consider alternative treatment options

2.1 Recommendation:
Alternatives to opioid treatment should be tried (or an adequate trial of such treatments by a previous provider documented) before initiating opioid treatment. *Reference Guidelines: 1, 2, 3, 4, 5*

Opioid medications are not the appropriate first line of treatment for most patients with chronic pain. Other measures, such as non-opioid analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants, antiepileptic drugs, and non-pharmacologic therapies (e.g., physical therapy), should be tried and the outcomes of those therapies documented first. Opioid therapy should be considered only when other potentially safer and more effective therapies have proven inadequate. This approach is consistent with the World Health Organization's Pain Relief Ladder (WHO).

2.2 Recommendation:
Clinicians should refer to disease-specific guidelines for recommendations for treatment of chronic pain related to specific diseases or conditions.

Tools to accompany Recommendation 2:

- Non-opioid Pain Management Tool

3. Screening for risk of addiction or abuse

3.1 Recommendation:
Use a screening tool to assess the patient's risk of misuse prior to prescribing an opioid medication long-term for chronic pain. *Reference Guidelines: 3*

A number of screening tools have been developed for assessing a patient's risk of misuse of medications. Several of these are included in the Tool Section. The screening tool results are intended to assist the clinician in determining whether opioid therapy is appropriate and in determining the level of monitoring appropriate for the patient's level of risk.

3.2 Recommendation:
Consider performing drug screening before initiating long term opioid treatment for chronic pain.

Research and experience have shown that drug testing can identify problems, such as use of undisclosed medications, non-use of reported medications (i.e., diversion), undisclosed use of alcohol, or use of illicit substances, that are not identified without that testing. Several experts involved in the development of these guidelines recommended that drug screening be done on all patients before initiating opioid treatment for chronic pain. However, drug testing can damage a provider-patient relationship, the results of testing can be difficult to interpret, and that recommendation attracted a substantial number of negative comments during the public comment period. It is recommended that drug testing be strongly considered and conducted especially when other factors suggest caution.

The drug screening should be either a urine drug screen or another laboratory test that can screen for the presence of illegal drugs, unreported prescribed medication, or unreported alcohol use. It is recommended that this testing be considered for all patients. When screening is limited to situations when there is suspicion of substance misuse, some misuse may be missed. In one study, testing results at first admission to a pain clinic did not correlate with reported medication use for nearly one-fourth of patients. Most of these discrepancies involved finding substances not reported by the patient; a small minority reported taking medications that were not found on testing (Berndt, Maier, & Schutz, 1993).

The clinician may consider testing for illegal substances (See list of Urine Drug Testing Devices in the Tool Section) in addition to screening for opioids.

A positive drug screen indicates the need for caution, but does not preclude opioid use for treatment of pain. Consideration should be given to referral to substance abuse counseling and/or to a pain management specialist. If opioid medication is subsequently prescribed, the patient should be more carefully monitored and conditions

under which opioids are being prescribed should be well documented in the treatment plan (See Recommendations 5, 6, 8, 12).

Immunoassays can be done in the office. These can determine if opioids are present but do not identify specific ones, which can subsequently be determined by confirmatory laboratory testing. However, in many cases, going over the results of the initial in-office test carefully with the patient can eliminate the need for confirmation testing. It is extremely important to keep in mind that immunoassays have both false positive and false negative results. Over-the-counter medication, for example, can cause a positive result (Washington State Agency Medical Directors' Group [WSAMDG], 2007).The prescriber may want to consider confirmatory testing or consultation with a certified Medical Review Officer if drug test results are unclear (WSAMDG, 2007).

3.3 Recommendation:
The prescriber should check Utah's Controlled Substance Database before prescribing opioids for chronic pain.

Most patients who request treatment for pain are legitimately seeking relief of the pain. However, a subset of patients who present seeking treatment for pain are seeking drugs for recreational use, to support an established addiction, or for profit. Information about past patterns of controlled substance prescriptions filled by the patient, such as obtaining medications from multiple providers or obtaining concurrent prescriptions, can alert the provider to the potential for problems.

The State of Utah's Division of Occupational and Professional Licensing (DOPL) maintains the Controlled Substance Database Program, which is a searchable record of all prescriptions that are filled in the state for controlled substances. The Utah Controlled Substance Database Program was legislatively created and put into effect in 1995. It is used to track and collect data on the dispensing of Schedule II-V drugs by all retail, institutional, and outpatient hospital pharmacies, and in-state/out-of-state mail order pharmacies. Access to the data is provided to authorized individuals and used to identify potential cases of drug over-utilization, misuse, and potential abuse of controlled substances throughout the state. This database is accessible to all controlled substance prescribers online at **www.csdb.utah.gov**. A "Getting Started" presentation is available to help orient users to the site and to appropriate uses of the database.

Tools to accompany Recommendation 3:

- SOAPP-R
- Opioid Risk Tool
- Prescription Drug Use Questionnaire
- List of Recommended Urine Drug Screens

Establishing Treatment Goals and a Written Treatment Plan:

4. Establish treatment goals

4.1 Recommendation:
When opioids are to be used for treatment of chronic pain, a written treatment plan should be established that includes measurable goals for reduction of pain and improvement of function.

The treatment plan should be tailored to the patient's circumstances and the characteristics and pathophysiology of the pain. The pathophysiology helps to predict whether opioid medication is likely to help reduce pain or to improve function and therefore should be considered when establishing treatment goals. Non-opioid treatment modalities should be included in the treatment plan whenever possible, to maximize the likelihood of achieving treatment goals.

4.2 Recommendation:
Goals for treatment of chronic pain should be measurable and should include improved function and quality of life as well as improved control of pain. *Reference Guidelines: 1, 3, 5*

For most chronic pain conditions, complete elimination of pain is an unreasonable goal (College of Physicians and

Surgeons of Ontario, 2000). Goals for treatment of chronic pain should include improvement in the tolerability of the pain and in function (College of Physicians and Surgeons of Ontario, 2000). The clinician should counsel the patient on reasonable expectations for treatment outcomes so that together they can agree on achievable treatment goals addressing pain, function, and quality of life.

The pathophysiologic basis of the pain can help establish a prognosis for future improvement (or worsening) in function and pain and should influence the goals of treatment. Goals for functional improvement and measures to track progress against those goals should be established and documented to serve as a basis of evaluating treatment outcome (VA/DOD, 2003; Hegmann, Feinberg, Genovese, Korevaar, & Mueller, 2008). These include:

- Objective physical findings obtained by the examining clinician (e.g., improved strength, range of motion, aerobic capacity);
- Functional status at work (e.g., increase in physical output, endurance, or ability to perform job functions); and
- Functional status at home (e.g., increased ability to perform instrumental activities of daily living, and frequency and intensity of conditioning).

Targets for improved quality of life should also be identified and documented to serve as a basis for evaluating treatment outcomes. These may include:

- Patient rating of quality of life on a measurement scale
- Psychosocial status (e.g., increased social engagement or decreased emotional distress)
- Familial status (e.g., improved relationships with or decreased burden on family members)
- Physical status (e.g., increased ability to exercise, perform chores, or participate in hobbies).

Pain intensity should be assessed at each visit using a standard instrument such as the Numerical Rating Scale. See the Pain Management Evaluation Tool, Patient Pain and Medication Tracking Chart, Sheehan Disability Scale, and Brief Pain Inventory Form in the Tool Section or page 17 of VA/DOD guidelines.

Clinicians should consider cultural differences in assessing function, quality of life, and pain intensity (See **http://prc.coh.org/culture.asp** for examples). These measures of improvement could be reported by the patient, family members, and/or the employer. Permission to discuss the patient's condition with these persons should have previously been obtained and documented (See Recommendation 5.5).

4.3 Recommendation:
Treatment goals should be developed jointly by patient and clinician. *Reference Guidelines: 2*

Engage patients in their own healthcare. Clinicians have observed that when patients assume a significant portion of the responsibility for their rehabilitation they are more likely to improve and that when they participate in goal setting they are more likely to achieve the goals. As with any other chronic illness (such as diabetes or heart disease), the clinician should focus not just on pain control, but also on treating the patient's underlying diseases and encouraging them to engage in ownership of their own health.

Tools to accompany Recommendation 4:

- Pain Management Evaluation Tool
- Patient Pain and Medication Tracking Chart
- Sheehan Disability Scale
- Brief Pain Inventory Form
- Sample Treatment Plan for Prescription Opioids
- Cultural considerations in assessing function, quality of life, and pain intensity: **http://prc.coh.org/culture.asp**

5. Informed consent and formulation of a treatment plan

5.1 Recommendation:
The patient should be informed of the risks and benefits and any conditions for continuation of opioid treatment, ideally using a written and signed treatment agreement. *Reference Guidelines: 4*

The patient should be counseled about appropriate use of the medication, possible adverse effects, and the risks of developing tolerance, physical or psychological dependence, and withdrawal symptoms (Trescot et al., 2008; WSAMDG, 2007). Adverse effects can include nausea, constipation, decreased libido, sexual dysfunction, hypogonadism with secondary osteoporosis (Hegmann et al., 2008), opioid-induced hyperalgesia (Hegmann et al., 2008; WSAMDG, 2007), allodynia (WSAMDG, 2007), abnormal pain sensitivity (WSAMDG, 2007), and depression (Daniell, 2007).

Patients should be informed not to expect complete relief from pain. The excitement and euphoria of initial pain relief that may occur with a potent opioid can lead the patient to expect long term complete pain relief. Without careful guidance this may lead the patient to seek excessive dosing of opioids and to disappointment.

Sedation and cognitive impairment may occur when patients are taking opioid medication. Therefore, discuss with patients the need for caution in operating motor vehicles or equipment or performing other tasks where impairment would put them or others at risk.[5]

Ensure the patient does not have any absolute contraindications and review risks and benefits related to any relative contraindications with the patient.

Absolute contraindications for opioid prescribing:

- Allergy to an opioid agent (may be addressed by using an alternative agent)
- Co-administration of drug capable of inducing life-limiting drug-drug interaction
- Active diversion of controlled substances (providing medication to someone for whom it was not prescribed)

More detail about absolute contraindications is contained in the Tool Section.

Educate patients and family/caregivers about the danger signs of respiratory depression. Everyone in the household should know to summon medical help immediately if a person demonstrates any of the following signs while on opioids:

Signs of respiratory depression:

- Snoring heavily and cannot be awakened
- Periods of ataxic (irregular) or other sleep disordered breathing
- Having trouble breathing
- Exhibiting extreme drowsiness and slow breathing
- Having slow, shallow breathing with little chest movement
- Having an increased or decreased heartbeat
- Feeling faint, very dizzy, confused or has heart palpitations

5.2 Recommendation:
The patient and, when applicable, the family or caregiver should both be involved in the educational process. *Reference Guidelines: 1*

Educational material should be provided in written form and discussed in person with the patient and, when applicable, the family or caregiver (VA/DOD, 2003). Educating the family about the signs of opioid overdose may help detect problems before they lead to a serious complication.

It is crucial to act within the constraints of the Health Insurance Portability and Accountability Act (HIPAA). HIPAA regulates the conditions under which information about the patient can be disclosed to others, such as family members, and under what conditions discussions about the patient with others are allowed.

[5] Health care professionals are responsible to "counsel their patients about how their condition affects safe driving. For example, if medication is prescribed for a patient which may cause changes in alertness or coordination, the health care professional shall advise the patient about how the medication can affect safe driving, and when it would be safe to operate a vehicle." R708-7-6(1)(b) Utah Administrative Code A health care professional or other person who becomes aware of a physical, mental, or emotional impairment that appears to present an imminent threat to driving safety and reports this information to the division in good faith has immunity from any damages claimed as a result of making the report. (§53-3-303(14)(c) Utah Code Annotated) Federal law prohibits driving a commercial motor vehicle while under the influence of a narcotic (CFR §391.15).

5.3 Recommendation:
The treatment plan, which defines the responsibilities of both patient and clinician, should be documented. *Reference Guidelines: 1, 2, 3, 4, 5*

Patient responsibilities include properly obtaining, filling, and using prescriptions, and adherence to the treatment plan. They could also include instructions to keep a pain diary, a diary or log of daily activities and accomplishments, and/or instructions on how and when to give feedback to the prescriber (VA/DOD, 2003).
The prescribing clinician may consider requiring that the treatment plan, be documented in the form of a treatment "contract" or "agreement" that is signed by the patient. Patients should be encouraged to store opioid medication in a lock box to keep the medication out of the hands of others who should not have access to them.

5.4 Recommendation:
The treatment plan should contain goals of treatment, guidelines for prescription refills, agreement to submit to urine or serum medication level screening upon request, and reasons for possible discontinuation of drug therapy. *Reference Guidelines: 1, 2, 4, 5, 6*

The treatment plan (sometimes referred to as treatment "contracts" or "agreements") should contain the items that were developed jointly by patient and clinician, such as follow-up appointments, the pharmacy and clinician to be used, as well as any non-negotiable demands or limitations the clinician wishes to make, such as the prohibition of sharing or trading the medication or getting refills early. Specific grounds for immediate termination of the agreement and cessation of prescribing may also be specified, such as forgery or selling of prescriptions or medications (VA/DOD, 2003; Trescot et al., 2008) or obtaining them from multiple providers as documented by Utah's Controlled Substance Database Program.

Optional inclusions in the agreement:

- Pill counts may be required as a means to gauge proper medication use (VA/DOD, 2003; Trescot et al., 2008).
- Prohibition on use with alcohol or certain other medications (VA/DOD, 2003)
- Documentation of counseling regarding driving or operating heavy machinery (VA/DOD, 2003 Hegmann et al., 2008)
- Specific frequencies of urine testing

Ideally, the patient should be receiving prescriptions from one prescriber only and filling those prescriptions at one pharmacy only (VA/DOD, 2003; Trescot et al., 2008; Federation of State Medical Boards, 2004).

It is not necessary to include specific consequences for specific non-compliant behaviors, but it should be documented in the treatment agreement that continuing failure by the patient to adhere to the treatment plan will result in escalating consequences, up to and including termination of the clinician-patient relationship and of opioid prescribing by that clinician.

A Sample Treatment Plan for Prescribing Opioids is included in the Tool Section.

5.5 Recommendation:
Discuss involvement of family members in the patient's care and request that the patient give written permission to talk with family members about the patient's care.

This is best done before starting to treat the patient because it can be more difficult to obtain consent after an issue occurs. Prior to initiating treatment with opioids, the physician may want to consider a family conference to help assess the patient's integrity (Trescot et al., 2008). Consultation with others, however, must be done within the constraints of HIPAA, as noted above (See Recommendation 5.2). Guidance about communications with family and others under HIPAA can be found at: **http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/provider_ffg.pdf**

Tools to accompany Recommendation 5:

- Absolute Contraindications to Opioid Prescribing
- Sample Treatment Plan for Prescribing Opioids

Initiating, Monitoring, and Discontinuing Opioid Treatment:

6. Initiate opioid therapy as a treatment trial

6.1 Recommendation:
Opioid medication should be initiated as a short-term trial to assess the effects of opioid treatment on pain intensity, function, and quality of life.

The clinician should clearly explain to the patient that initiation of opioid treatment is not a commitment to long-term opioid treatment and that treatment will be stopped if the trial is determined to be unsuccessful. The trial should be for a specific time period with pre-determined evaluation points. The decision to continue opioid medication treatment beyond the trial period should be based on the balance between benefits, including function and quality of life, and adverse effects experienced. Criteria for cessation should be considered before treatment begins. Refer to Recommendation 9 for more information on discontinuation of treatment.

6.2 Recommendation:
In most instances, the trial should begin with short-acting opioid medication.

Short-acting opioid medications are in general safer and easier to titrate to an effective dose. If the treatment trial proves successful in achieving the goals established in the treatment plan, the prescriber may consider switching the patient to a long-acting or sustained-release formulation (See the Dosing Guidelines in the Tool Section). The patient's individual situation should influence whether the patient is switched from short-acting medication. Treatment with long-acting opioid medication before a trial using a short-acting medication has been performed is an option that should be prescribed only by those with considerable expertise in chronic pain management.

6.3 Recommendation:
Parenteral[6] (intravenous, intramuscular, subcutaneous) administration of opioids for chronic pain is, in general, discouraged. *Reference Guidelines: 2*

Daily IM or SC injections should be avoided except under a highly supervised environment such as during an admission to the hospital or hospice.

Tools to accompany Recommendation 6:

- Dosing Guidelines
- COMM

7. Titration phase

7.1 Recommendation:
Regular visits with evaluation of progress against goals should be scheduled during the period when the dose of opioids is being adjusted (titration period). Reference Guidelines: 1

Follow-up face-to-face visits should occur at least every 2-4 weeks during the titration phase. More frequent follow-up visits may be advisable and caution should be used when prescribing opioid medication if the patient has a known addiction problem, suspected drug-behavior problems, or co-existing psychiatric or medical problems. Frequency of visits should also be based on risk stratification (e.g., as determined by a screening tool) and the clinician's judgment (taking into account the volume of the drug being prescribed and how likely it is to be abused) (College of Physicians and Surgeons of Ontario, 2000).

7.2 Recommendation:
When pain and function have not sufficiently improved on a current opioid dose, a trial of a slightly higher dose could be considered. *Reference Guidelines: 1, 2*

The rate at which the dosing is increased should balance the risk of leaving the patient in a painful state longer than

[6] These guidelines did not consider intrathecal administration and this recommendation was not intended to discourage trained and qualified physicians from using intrathecal opioid medications.

necessary by going too slowly with the risk of causing harm, including fatal overdose, by going too fast. Ideally, only one drug at a time should be titrated in an opioid-naïve patient (VA/DOD, 2003). Age, health, and severity of pain should be taken into consideration when deciding on increments and rates of titration. Particular caution should be used in titrating dosing of methadone.

Evidence and other guidelines are not in agreement regarding the risks and benefits of high daily doses of opioid measured in morphine equivalents. It is likely that the risk-benefit ratio is less favorable at higher doses. Clinical vigilance is needed at all dosage levels of opioids but is even more important at higher doses. Clinicians who are not experienced in prescribing high doses of opioids should consider either referring the patient or obtaining a consultation from a qualified provider for patients receiving high dosages. No clear threshold for high dose has been established based on evidence. The Washington State guideline (WSAMDG, 2007) suggested a threshold of 120 mg of morphine equivalent per day, but has been criticized for that decision. It seems reasonable to increase clinical vigilance at daily doses that exceed 120-200 mg of morphine equivalent per day.

During titration, all patients should be seen frequently until dosing requirements have stabilized. Patients should be instructed to Use Only as Directed, that is, not to change doses or frequency of administration without specific instructions from the clinician.

7.3 Recommendation:
During the titration phase, until the patient is clinically stable and is judged to be compliant with therapy, it is recommended that the clinician check the Controlled Substances Database at least quarterly.

For more information about the Controlled Substances Database, refer to Recommendation 3.3.

Tools to accompany Recommendation 7:

- Dosing Guidelines

8. Maintenance – Periodic monitoring and dose adjustments:

8.1 Recommendation:
Once a stable dose has been established (maintenance period), regular monitoring should be conducted at face-to-face visits during which treatment goals, analgesia, activity, adverse effects, and aberrant behaviors are monitored. *Reference Guidelines: 2, 4*

Assess each of the following four areas of concern at each visit: Analgesia, activity, adverse effects, and aberrant behavior. These assessments can be remembered as the "four A's" (Passik & Weinreb, 2000):

- Analgesia: inquire about level of pain (current, recent, trends, etc.)
- Activity: assess both the patient's function and overall quality of life
- Adverse events: determine whether the patient is having medication side effects
- Aberrant behavior: regularly evaluate for possible drug abuse-related behavior

A sample checklist for signs of aberrant behavior is included in the Tool Section.

8.2 Recommendation:
Providers should consider performing drug screening on randomly selected visits and any time aberrant behavior is suspected.

As discussed in recommendation 3, drug testing has been shown to identify problems that might otherwise go undetected. It may not be appropriate or necessary for all patients, but should be strongly considered by providers and may provide an opportunity to discuss the risks and problems that can occur with opioid treatment. Base the frequency of random drug screening on the assessed degree of risk of aberrant behavior for the individual patient. Pill counts may also be useful in some circumstances.

8.2 Recommendation:
During maintenance phase, Controlled Substances Database should be checked at least annually.

After the titration phase is complete and the maintenance phase is underway, the frequency of checks of the Controlled Substances Database can be based on clinical judgment, but should be done no less than annually. The Controlled Substances Database should be checked more often for high risk patients and patients exhibiting aberrant behavior. For more information about the Controlled Substances Database, refer to Recommendation 3.3.

Consider evaluating for possible drug abuse-related behavior at each visit. A sample checklist is included in the Tool Section.

Provide reinforcement for previous counseling and additional education for patients at follow-up visits (Trescot et al., 2008).

Review the pathophysiologic hypothesis (to see if the diagnosis is still valid) at each visit (Trescot et al., 2008).

8.3 Recommendation:
Continuation or modification of therapy should depend on the clinician's evaluation of progress towards stated treatment goals. *Reference Guidelines: 4*

These include reduction in a patient's pain scores and improved physical, psychological and social function. If treatment goals, including patient compliance with agreed-upon activity levels, are not being achieved despite medication adjustments, the clinician should reevaluate the appropriateness of continued treatment with the current medications (WSAMDG, 2007; Federation of State Medical Boards, 2004).

A frequent need for dose adjustments after a reasonable time interval of titration is an indication to reevaluate the underlying condition and consider the possibility the patient has developed opioid hyperalgesia, substantial tolerance, or psychological/physical dependence.

8.4 Recommendation:
Adjustments to previously stable maintenance therapy may be considered if the patient develops tolerance, a new pain-producing medical condition arises or an existing one worsens, or if a new adverse effect emerges or becomes more clinically significant. *Reference Guidelines: 1*

Options for adjustment include reducing medication or rotating opioid medication. If it is documented that the patient is compliant with agreed-upon recommendations such as exercise, working, etc., addition of supplemental short-acting medications for control of break-through pain exacerbation (e.g., as related to an increase in activity, end-of-dose pain, weather-related pain exacerbation, or specific medical conditions) can be considered as well. If patients do not achieve effective pain relief with one opioid, rotation to another frequently produces greater success (Quang-Cantagrel, Wallace, & Magnuson; 2000).

Only if the patient's situation has changed permanently and consideration has been given to increased risk of adverse events, is it reasonable to consider an ongoing increase in maintenance dosing (VA/DOD, 2003).

If rotating among different opioid medications, refer to a standard dosing equivalence table taking into account the current drug's half-life. (See the Dosing Guidelines in the Tool Section)

In general, if the patient's underlying medical condition is chronic and unchanging and if opioid-associated problems (hyperalgesia, substantial tolerance, important adverse effects) have not developed, it is recommended that the effective dose achieved through titration not be lowered once the patient has reached a plateau of adequate pain relief and functional level (VA/DOD, 2003).

8.5 Recommendation:
Dosing changes should generally be made during a clinic visit. *Reference Guidelines: 1*

If the patient's underlying pain-producing chronic medical condition improves, it is expected that the clinician will begin tapering the patient off the opioid medication (See Recommendation 10 for guidelines on discontinuation.)

Tapering opioid medication with or without the goal of discontinuation may be performed as described below (Recommendation 10) or as described in Strategies for Tapering and Weaning in the Tool Section.

Tools to accompany Recommendation 8:

- Checklist for Adverse Effects, Function, and Opioid Dependence
- Signs of Substance Misuse
- Pain Management Evaluation Tool
- Dosing Guidelines
- Strategies for Tapering and Weaning

9. Evaluate the treatment trial

9.1 Recommendation:
Continuing opioid treatment after the treatment trial should be a deliberate decision that considers the risks and benefits of chronic opioid treatment for that patient.

9.2 Recommendation:
A second opinion or consult may be useful in making the decision to continue or discontinue the opioid treatment trial.

10. Discontinuing opioid treatment

10.1 Recommendation:
An opioid treatment trial should be discontinued if the goals are not met and opioid treatment should be discontinued at any point if adverse effects outweigh benefits or if dangerous or illegal behaviors are demonstrated. *Reference Guidelines: 5*

10.2 Recommendation:
Discontinuation of opioid therapy is recommended if any of the following occurs:

- Dangerous or illegal behaviors are identified
- Patient claims or exhibits a lack of effectiveness
- Pain problem resolves
- Patient expresses a desire to discontinue therapy
- Opioid therapy appears to be causing harm to the patient, particularly if harm exceeds benefit

Reference Guidelines: 1

The decision to discontinue opioid treatment should ideally be made jointly with the patient and, if appropriate, the family/caregiver (Federation of State Medical Boards, 2004). This decision should include careful consideration of the outcomes of ongoing monitoring.

10.3 Recommendation:
When possible, offer to assist patients in safely discontinuing medications even if they have withdrawn from treatment or been discharged for agreement violations.

Reference Guidelines: 1

The goal is to taper all patients off opioid medication safely. "Strategies for Tapering and Weaning" in the Tool Section contains advice on tapering opioid medications (WSAMDG, 2007). If the patient is discharged, the clinician is obliged to offer continued monitoring for 30 days post-discharge.

Tools to accompany Recommendation 10:

- Strategies for Tapering and Weaning

Other Issues:

11. Documentation and Medical Records

11.1 Recommendation:
Clinicians treating patients with opioids for chronic pain should maintain records documenting the evaluation of the patient, treatment plan, discussion of risks and benefits, informed consent, treatments prescribed, results of treatment, and any aberrant behavior observed. *Reference Guidelines: 1, 2, 4, 5, 6*

11.2 Recommendation:
A written treatment plan should document objectives that will be used to evaluate treatment success. *Reference Guidelines: 1, 2, 4, 5, 6*

The objectives should address pain relief, improved physical and psychosocial function, including work and exercise compliance, and should indicate if additional diagnostic tests, consultations, or treatments are planned (Trescot et al., 2008). Use of validated instruments to measure pain and function is preferred. Details on establishing treatment goals and formulation of a treatment plan are covered elsewhere in these guidelines (Recommendations 4 and 5.)

11.3 Recommendation:
The prescription for opioid therapy should be written on tamper-resistant prescription paper in a manner to help reduce the likelihood of prescription fraud or misuse. *Reference Guidelines: 2*

The written prescription for opioid therapy should contain the name of the drug, the strength, the number of dosage units, (written numerically and in text), how the drug is to be taken, the full name, address, and age of the patient, the name, address, and DEA registration number of the practitioner, and the signature of the physician or other authorized practitioner. It shall be dated and signed on the day when issued. After a stable maintenance therapy dosage has been established and therapy goals have been achieved, schedule II opioid medications may be prescribed for three months by providing the patient with prescriptions for each of the three months. Each prescription for a one month supply of medication should include the date the prescription is written and the date when that prescription is to be filled.

To reduce the chance of tampering with the prescription, write legibly, and keep a copy (College of Physicians and Surgeons of Ontario, 2000). (See the Tamper Resistant Requirements in the Tool Section.)

11.4 Recommendation:
Assessment of treatment effectiveness should be documented in the medical record. *Reference Guidelines: 2, 4, 5*

Document the patient's progress toward treatment goals, including functional status, at every visit, rather than merely reporting the patient's subjective report of decreased pain. Ideally, this progress would be evaluated using validated tools (Trescot et al., 2008).

Both the underlying medical condition responsible for the pain, if known, and other medical conditions that may affect the efficacy of treatment or risks of adverse events should be evaluated and documented at every visit.

11.5 Recommendation:
Adherence to the treatment plan, including any evidence of aberrant behavior, should be documented in the medical record. *Reference Guidelines: 1*

Specific components of the treatment plan for which adherence should be assessed include:

- Use of opioid analgesics
- Follow-up referrals, tests, and other therapies

Clinicians are encouraged to make use of resources provided by the state of Utah that are designed to assist them in managing patients with aberrant behavior (See Checklist for Adverse Effects, Function, and Opioid Dependence and Signs of Substance Misuse in Tool Section). Referral to law enforcement/legal agencies may be appropriate if actions by patients are occurring that could be criminal in nature (VA/DOD, 2003). Clinicians

should consider consulting with legal counsel before contacting law enforcement (VA/DOD, 2003). Serious non-adherence issues (illegal, criminal, or dangerous behaviors, including altering of prescriptions) may also warrant immediate discontinuation of opioid therapy. See Recommendation 10.

Tools to accompany Recommendation 11:

- Tamper Resistant Requirements
- Checklist for Adverse Effects, Function, and Opioid Dependence
- Signs of Substance Misuse

12. Consultation and management of complex patients

12.1 Recommendation:
Clinicians should consider consultation for patients with complex pain conditions, patients with serious co-morbidities including mental illness, patients who have a history or evidence of current drug addiction or abuse, or when the provider is not confident of his or her abilities to manage the treatment. *Reference Guidelines: 4, 5*

Prescribers may wish to consider referring patients if any of the following conditions or situations is present or if other concerns arise during treatment:

- The patient has a complex pain condition and the clinician wishes verification of diagnosis;
- The patient has significant co-morbidities (including psychiatric illness);
- The patient is high-risk for aberrant behavior or addiction; or
- The clinician suspects development of significant tolerance, particularly at higher doses.

The main goal of a consultation is for the prescribing clinician to receive recommendations for ongoing treatment.

12.2 Recommendation:
Patients with a history of addiction or substance use disorder or who have positive drug screens indicative of a problem should be considered for referral to an addiction specialist for evaluation of recurrence risk and for assistance with treatment.
Reference Guidelines: 1, 4, 5

Although this is a desirable approach, it is recognized that following this recommendation may not be feasible in parts of Utah where there is a shortage of readily available addiction specialists. The Directory of Resources in the Tool Section includes information on available resources for these patients.

12.3 Recommendation:
Pain patients who are addicted to medications/drugs should be referred to a pain management, mental health or substance use disorder specialist if available, for recommendations on the treatment plan and possibly for assistance in management.

The clinician may consider prescribing opioid medication for pain even if the patient has a self-reported or documented previous problem with opioids, as long as monitoring is performed during titration and maintenance phase.

12.4 Recommendation:
Patients with coexisting psychiatric disorder should receive ongoing mental health support and treatment while receiving opioid medication for pain control.

Management of patients with a coexisting psychiatric condition may require extra care, monitoring, or documentation (Trescot et al., 2008; Federation of State Medical Boards, 2004). Unless the clinician treating the patient is qualified to provide the appropriate care and evaluation of the coexisting psychiatric disorder, consultation should be obtained to assist in formulating the treatment plan and establishing a plan for coordinated care of both the chronic pain and psychiatric conditions.

Tools to accompany Recommendation 12:

- Strategies for Tapering and Weaning
- Directory of Resources

13. Methadone

13.1 Recommendation:
Methadone should only be prescribed by clinicians familiar with its risks and use, and who are prepared to conduct the necessary careful monitoring.

Methadone-related death rates have been increasing in Utah and the U.S. In 2006, methadone was implicated in 30% of non-illicit drug-related deaths in Utah. Methadone was the most common drug identified by the Utah Medical Examiner as causing or contributing to accidental deaths, accounting for a disproportionate number of deaths compared to its frequency of use. Methadone was the single drug most often associated with overdose death and had the highest prescription adjusted mortality rate (PAMR) with an average of 150 deaths for every 100,000 prescriptions during 1998-2004. From 1997–2004, population-adjusted methadone prescriptions increased 727%. The increase in the methadone prescription rate was for treatment of pain and not addiction therapy.

The half-life of methadone is long and unpredictable, increasing the risk of inadvertent overdose. The peak respiratory depressant effect of methadone occurs later and lasts longer after treatment initiation or dosage change than does the peak analgesic effect.

Conversion tables that have been established to assist with converting a patient from another opioid medication to methadone are considered by many experts to be unreliable.

Methadone metabolism is complicated and varies among individuals. Methadone interacts with several other medications that can alter its metabolism changing the effects of a given dose on pain and on respiratory depression. Potential for interactions should be considered before starting methadone in a patient taking other medications and before starting any medication in a patient taking methadone.

Methadone can prolong the rate-corrected QT interval (QTc) and increase the risk of Torsades de Pointe, and sudden cardiac death. Caution should be used in prescribing methadone to any patient at risk for prolonged QTc interval, including those with structural cardiac disease, cardiac arrhythmias or cardiac conduction abnormalities and in patients taking another medication associated with QTc interval prolongation (Arizona Center for Education and Research on Therapeutics 2008). A useful on-line reference of such medications is available at: **http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm**

Clinicians should consider obtaining an electrocardiogram (ECG) to evaluate the QTc interval in patients treated with methadone, especially at higher doses. A recently published consensus guideline (Krantz 2009) recommended that an ECG be performed before prescribing methadone, within the first 30 days, and annually. Additional ECG examinations were recommended if the methadone dose exceeds 100 mg per day or if a patient on methadone has unexplained syncope or seizure. Guidance was provided for actions to be taken at two levels of QTc prolongation (450-500 ms and greater than 500 ms).

Methadone and other opioids have been associated with worsening obstructive sleep apnea and new onset of central sleep apnea. Clinicians should question patients about symptoms and signs of sleep apnea and consider obtaining a sleep study in patients treated with opioids if they develop any signs of sleep-disordered breathing or respiratory depression. This is particularly important for patients receiving higher doses of opioid medications. In one recent study, 92% of patients on opioid doses at or above 200 mg morphine equivalents had developed ataxic or irregular breathing (Walker, 2007).

Some clinicians recommend that all patients for whom higher doses of opioid medications are considered should be tested with a sleep study.

Tools to accompany Recommendation 13:

- Dosing Guidelines
- The Role of Methadone in the Management of Chronic Non-Malignant Pain

GLOSSARY

Term	Definition
Aberrant drug-related behavior	A behavior associated with drug abuse, addiction, and diversion.
Abuse	Maladaptive pattern of drug use that results in harm or places the individual at risk of harm. Often with the intent of seeking a psychotropic/ euphoric effect.
Acute pain	An episode of pain lasting six weeks or less
Addiction	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.
Breakthrough pain	An acute worsening of pain in a person with chronic pain.
Chronic pain	An episode of pain lasting more than three months
Chronic non-cancer pain	Chronic pain that is not associated with active cancer or occurs at the end of life
Diversion	The intentional transfer of a controlled substance from authorized to unauthorized possession or channels of distribution.
Hyperalgesia	Increased or heightened sensation to pain or pain stimulation.
IADL	Instrumental activities of daily living are activities related to independent living and include preparing meals, managing money, shopping for groceries or personal items, performing light or heavy housework, and using a telephone
Misuse	Use of a drug in ways other than prescribed by a health professional. Misuse usually does not include use for euphoric or psychotropic effects—that would be classified as “abuse”

Term	Definition
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.
Pseudo addiction	The development of abuse-like behaviors due to unrelieved pain, and that should be eliminated by measures that relieve the pain.
Trial Period	A period of time during which the effectiveness of using opioids is tested to see if goals of functionality and decreased pain are met. A trial should occur prior to treating someone with long-acting opioids and should include goals. If trial goals are not met, the trial should be discontinued and an alternative approach taken to treating the pain.
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.

Tools

For more tools and information visit:

http://prc.coh.org/culture.asp

http://www.PainEdu.org

The tools found in this publication can be downloaded from:

www.health.utah.gov/prescription

TOOLS

Pain Management and Evaluation Tool

Pain Management Work up and Risk Assessment

Name			ID#		Date
Pain Dxs:					DOB
					Gender M/F

Opiod Risk Tool[1]	**Mark all that apply**	**Score if Female**	**Score if Male**	**Additional Risk Assessments**		**Comments**
				Drug Screen	Y/N	
Family Hx of Substance Abuse				DOPL Screen	Y/N	
Alcohol	[ ]	1	3	Risk of Obstructive Sleep Disorder	Y/N	
Illeg Drugs	[ ]	2	3			
Prescrp	[ ]	4	4			
Personal Hx of Substance Abuse				Obesity Y/N	BMI =	
Alcohol	[ ]	3	3	Hx of Sleep Apnea	Y/N	
Illeg Drugs	[ ]	4	4			
Prescrp	[ ]	5	5			
Hx of Preadolescent Sexual abuse	[ ]	3	0	**Baseline Measures**		**Comments**
				Analgesia[2] (Pain 0-10)		
Age 16-45 yrs	[ ]	1	1	Activity[3] (Function 0-10)		
Depression	[ ]	1	1	Adverse Events	Y/N	
Psychiatric Disease				Aberrant Behavior	Identify	
ADD	[ ]	2	2			
OCD	[ ]	2	2			
Bipolar	[ ]	2	2			
Skiz	[ ]	2	2			
Total	**[ ]**					

Consultation/Referral:				**Comments**
If receiving Morphine equivalent ≥ 120 mg/day				
or Methadone ≥ 50 mg/day	**then**	Sleep Apnea Test	Y/N	
If receiving Methadone ≥ 50 mg	**then**	EKG (Qt)	Y/N	

Treatment agreement discussed and signed by patient **Date**

Patient Goals			Identify aberrant behavior which indicates discontinuation
Analgesia Pain[2] (0-10)	Activity - Function[3] (0-10)	Adverse Events - #	

[1] Opioid Risk Tool (Webster & Dove, 2007 - low risk (routine care), moderate risk (increased monitoring frequency) high risk (consider referral to Substance Abuse and/or Pain Management specialists)

[2] Pain Intensity 0 = no pain, 5 = moderate pain, 10 = worst pain imaginable

[3] Activity Function 0= no limitations, 5 = limitations (difficulty working, lifting,exercising, or conducting daily living activities) 10 = severe limitations (unable to work, conduct daily living activities, lift, or exercise)

Pain Management and Evaluation Tool

Pain Management Follow-Up

Name	ID#	Date
Pain Dxs:		DOB
		Gender M/F

Initation of Trial **Start Date** **Review Date**

Visit Frequency [1] Date	Analgesia - Pain (0-10)	Activity - Function (0-10)	Adverse Events - #	Aberrant Behavior - Identify	DOPL Check	Random Drug Screen	Comments (Date)
							Discontinuation
							Change (Date)

Titration - Visit = 2 - 4 weeks

Visit Frequency [1] Date	Analgesia - Pain (0-10)	Activity - Function (0-10)	Adverse Events - #	Aberrant Behavior - Identify	DOPL Check	Random Drug Screen	Comments (Date)
							Discontinuation
							Change (Date)

Maintenance - Visit = Quarterly

Visit Frequency [1] Date	Analgesia - Pain (0-10)	Activity - Function (0-10)	Adverse Events - #	Aberrant Behavior - Identify	DOPL Check	Random Drug Screen	Comments (Date)
							Discontinuation
							Change (Date)

[1] Webster 2008 Monitoring Frequencies
Low Risk (0-3) Routine
Mod Risk 4-7 Bi-Weekly
High Risk ≥ 8 Weekly

Produced by Utah Department of Health, Prescription Pain Medication Program, 2008

Patient Pain and Medication Tracking Chart

Patient Pain and Medication Tracking Chart

Name	ID#	Date
Pain Dxs:		DOB
		Gender M/F

Directions: At the end of each day use this log to record your function, pain, sleep and alcohol/drug use. This will be used by your provider to properly adjust your medications to obtain optimal benefit and to minimize risk to your health and safety.

Date	Medications	# Pills/day	Pain [1] (0-10)	Function [2] (0-10)	# Hours Slept	Alcohol or Drugs used

[1] Pain Scale: 0 = no pain, 5 = moderate pain, 10 = worst pain imaginable
[2] Function Scale: 0 = no limitations, 5 = limitations (difficulty working, lifting, exercising, or conducting daily living activities, 10 = severe limitations (unable to work, conduct daily living activities, lift or exercise)

Sheehan Disability Scale

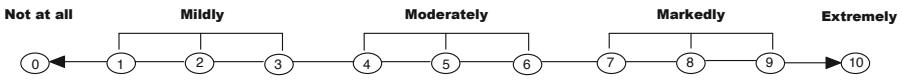
SHEEHAN DISABILITY SCALE

A BRIEF, PATIENT RATED, MEASURE OF DISABILITY AND IMPAIRMENT

Please mark ONE circle for each scale.

WORK* / SCHOOL

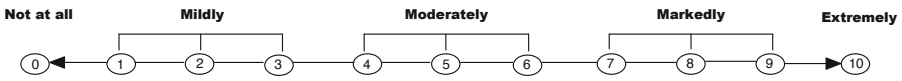
The symptoms have disrupted your work / school work:



☐ I have not worked /studied at all during the past week for reasons unrelated to the disorder.
* Work includes paid, unpaid volunteer work or training

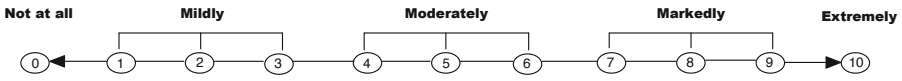
SOCIAL LIFE

The symptoms have disrupted your social life / leisure activities:



FAMILY LIFE / HOME RESPONSIBILITIES

The symptoms have disrupted your family life / home responsibilities:



DAYS LOST

On how many days in the last week did your symptoms cause you to miss school or work or leave you unable to carry out your normal daily responsibilities? _____

DAYS UNDERPRODUCTIVE

On how many days in the last week did you feel so impaired by your symptoms, that even though you went to school or work, your productivity was reduced? _____

TOOLS

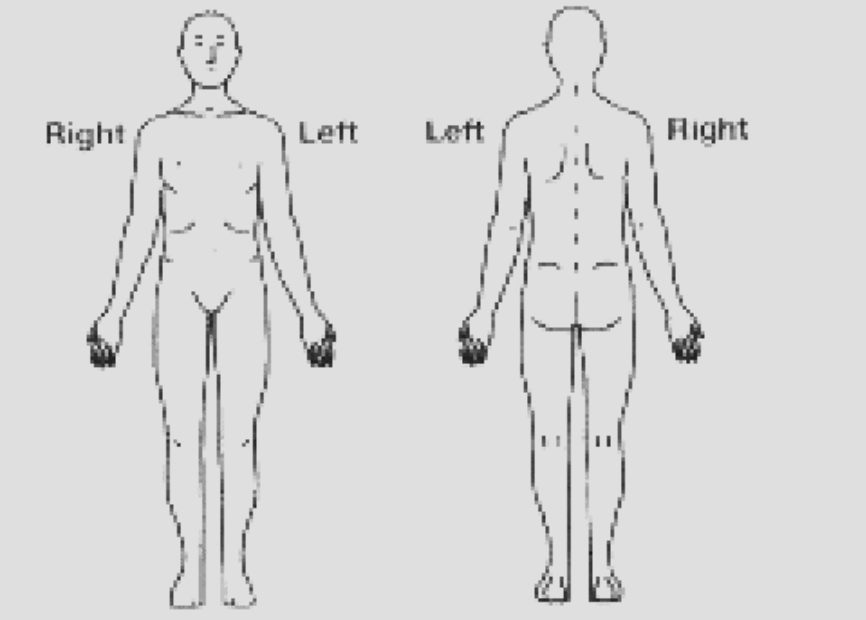
Brief Pain Inventory Form

Brief Pain Inventory (Short Form)©

Study ID#_____ Hospital#_____
Do not write above this line
Date:____/____/____
Time:_____
Name:_____
Last First Middle Initial

1) Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?
1. yes 2. no

2) On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3) Please rate your pain by circling the one number that best describes your pain at its **WORST** in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No pain — Pain as bad as you can imagine

Brief Pain Inventory Form

4) Please rate your pain by circling the one number that best describes your pain at its **LEAST** in the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

5) Please rate your pain by circling the one number that best describes your pain on the **AVERAGE.**

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

6) Please rate your pain by circling the one number that tells how much pain you have **RIGHT NOW.**

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

7) What treatments or medications are you receiving for your pain?

8) In the past 24 hours, how much **RELIEF** have pain treatments or medications provided? Please circle the one percentage that most shows how much.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No relief										Complete relief

9) Circle the one number that describes how, during the past 24 hours, **PAIN HAS INTERFERED** with your:

A. General Activity:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

Brief Pain Inventory Form

C. Walking ability

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

D. Normal work (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

Source: Dr. Charles Cleeland, Anderson Cancer Center, Pain Research Group, 1100 Holcombe, Houston, TX 77030.

Sample Treatment Plan for Prescribing Opioids

Treatment Plan Using Prescription Opioids

Patient name: _____

Prescriber name: _____

THE PURPOSE OF THIS AGREEMENT IS TO STRUCTURE OUR PLAN TO WORK TOGETHER TO TREAT YOUR CHRONIC PAIN. THIS WILL PROTECT YOUR ACCESS TO CONTROLLED SUBSTANCES AND OUR ABILITY TO PRESCRIBE THEM TO YOU.

I (patient) understand the following (initial each):

_____ Opioids have been prescribed to me on a trial basis. One of the goals of this treatment is to improve my ability to perform various functions, including return to work. If significant demonstrable improvement in my functional capabilities does not result from this trial of treatment, my prescriber may determine to end the trial.

Goal for improved function: _____

_____ Opioids are being prescribed to make my pain tolerable but may not cause it to disappear entirely. If that goal is not reached, my physician may end the trial.

Goal for reduction of pain: _____

_____ Drowsiness and slowed reflexes can be a temporary side effect of opioids, especially during dosage adjustments. If I am experiencing drowsiness while taking opioids, I agree not to drive a vehicle nor perform other tasks that could involve danger to myself or others.

_____ Using opioids to treat chronic pain will result in the development of a physical dependence on this medication, and sudden decreases or discontinuation of the medication will lead to symptoms of opioid withdrawal. These symptoms can include: runny nose, yawning, large pupils, goose bumps, abdominal pain and cramping, diarrhea, vomiting, irritability, aches and flu-like symptoms. I understand that opioid withdrawal is uncomfortable but not physically life threatening.

_____ There is a risk that opioid addiction can occur. Almost always, this occurs in patients with a personal or family history of other drug or alcohol abuse. If it appears that I may be developing addiction, my physician may determine to end the trial.

Continued on other side.

Sample Treatment Plan for Prescribing Opioids

I agree to the following (initial each):

_____ I agree not to take more medication than prescribed and not to take doses more frequently than prescribed.

_____ I agree to keep the prescribed medication in a safe and secure place, and that lost, damaged, or stolen medication will not be replaced.

_____ I agree not to share, sell, or in any way provide my medication to any other person.

_____ I agree to obtain prescription medication from one designated licensed pharmacist. I understand that my doctor may check the Utah Controlled Substance Database at any time to check my compliance.

_____ I agree not to seek or obtain **ANY** mood-modifying medication, including pain relievers or tranquilizers from **ANY** other prescriber without first discussing this with my prescriber. If a situation arises in which I have no alternative but to obtain my necessary prescription from another prescriber, I will advise that prescriber of this agreement. I will then immediately advise my prescriber that I obtained a prescription from another prescriber.

_____ I agree to refrain from the use of **ALL** other mood-modifying drugs, including alcohol, unless agreed to by my prescriber. The moderate use of nicotine and caffeine are an exception to this restriction.

_____ I agree to submit to random urine, blood or saliva testing, at my prescriber's request, to verify compliance with this, and to be seen by an addiction specialist if requested.

_____ I agree to attend and participate fully in any other assessments of pain treatment programs which may be recommended by the prescriber at any time.

I understand that ANY deviation from the above agreement may be grounds for the prescriber to stop prescribing opioid therapy at any time.

_____ _____

Patient Signature Date

_____ _____

Prescriber Signature Date

Produced by Utah Department of Health, Prescription Pain Medication Program, 2008

SF-12

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
b Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3

TOOLS

SF-12

3. During the past 4 weeks, how much of the time have you had any of the result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

SF-12

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

COMM

The Current Opioid Misuse Measure (COMM)® is a brief paper and pencil self-administered patient questionnaire to help monitor chronic pain patients who are on chronic opioid therapy. The COMM helps clinicians identify whether a patient, currently on long-term opioid therapy, may be exhibiting aberrant behaviors associated with the misuse or abuse of opioid medications. Validated in 2006 and unlike other available predictive measures, the objective was to provide clinicians with an assessment tool to periodically monitor misuse of medication for patients who have been prescribed opioids for an extended period of time over the course of treatment. Additionally, the COMM serves as an ideal way to help document risk assessment over the continuum of care with opioid treatment.

The COMM tool, instructions for administration, and scoring information guide are available for download for individual clinician use at http://www.painedu.org/registration.asp?target=terms.

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.

 The Current Opioid Misuse Measure (COMM)® was developed with a grant from the National Institutes of Health and an educational grant from Endo Pharmaceuticals.

COMM

Current Opioid Misuse Measure (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?	O	O	O	O	O
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)	O	O	O	O	O
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)	O	O	O	O	O
4. In the past 30 days, how often have you taken your medications differently from how they are prescribed?	O	O	O	O	O
5. In the past 30 days, how often have you seriously thought about hurting yourself?	O	O	O	O	O
6. In the past 30 days, how much of your time was spent thinking about opioid medications (having enough, taking them, dosing schedule, etc.)?	O	O	O	O	O

COMM

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?	O	O	O	O	O
8. In the past 30 days, how often have you had trouble controlling your anger (e.g., road rage, screaming, etc.)?	O	O	O	O	O
9. In the past 30 days, how often have you needed to take pain medications belonging to someone else?	O	O	O	O	O
10. In the past 30 days, how often have you been worried about how you're handling your medications?	O	O	O	O	O
11. In the past 30 days, how often have others been worried about how you're handling your medications?	O	O	O	O	O
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?	O	O	O	O	O
13. In the past 30 days, how often have you gotten angry with people?	O	O	O	O	O
14. In the past 30 days, how often have you had to take more of your medication than prescribed?	O	O	O	O	O
15. In the past 30 days, how often have you borrowed pain medication from someone else?	O	O	O	O	O
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)?	O	O	O	O	O

COMM

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?	O	O	O	O	O

COMM

Scoring Instructions for the Current Opioid Misuse Measure (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 Ration
Score 9 or above	.77	.66	.66	.95	2.26	.35

SOAPP-R

The *Screener and Opioid Assessment for Patients with Pain- Revised Version (SOAPP®-R)* is a brief paper and pencil self-administered patient questionnaire that was developed for clinicians to help them better assess and determine how much monitoring a patient on long-term opioid therapy might require prior to prescription. The SOAPP®-R was validated in 2008, and is an updated and revised version of SOAPP V.1 originally released in 2003. The use of opioid medications sometimes includes concerns about addiction, misuse, and other aberrant medication-related behaviors, as well as liability and censure concerns. Since long-term opioid therapy may carry significant risk in certain patients, the SOAPP®-R is intended to play a role as a quick and easy-to-use tool that can help clinicians identify and mitigate that risk, document risk assessment prior to opioid prescription.

The SOAPP®-R tool, instructions for administration, and scoring information guide are available for download for individual clinician use at http://www.painedu.org/registration.asp?target=terms.
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SOAPP-R

2007 Release

Screener and Opioid Assessment for Patients with Pain- Revised (SOAPP®-R)

The Screener and Opioid Assessment for Patients with Pain- Revised (SOAPP®-R) is a tool for clinicians to help determine how much monitoring a patient on long-term opioid therapy might require. This is an updated and revised version of SOAPP V.1 released in 2003.

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-R 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. SOAPP-R 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)
- Validated with 500 chronic pain patients
- Simple to score
- 24 items
- <10 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-R is for clinician use only. The tool is not meant for commercial distribution.
- The SOAPP-R is **NOT** a lie detector. Patients determined to misrepresent themselves will still do so. Other clinical information should be used with SOAPP-R scores to decide on a particular patient's treatment.
- The SOAPP-R is **NOT** intended for all patients. The SOAPP-R 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.

TOOLS

SOAPP-R

SOAPP®-R

The following are some questions given to patients who are on or being considered for medication for their pain. Please answer each question as honestly as possible. There are no right or wrong answers.

	Never	Seldom	Sometimes	Often	Very Often
	0	1	2	3	4
1. How often do you have mood swings?	○	○	○	○	○
2. How often have you felt a need for higher doses of medication to treat your pain?	○	○	○	○	○
3. How often have you felt impatient with your doctors?	○	○	○	○	○
4. How often have you felt that things are just too overwhelming that you can't handle them?	○	○	○	○	○
5. How often is there tension in the home?	○	○	○	○	○
6. How often have you counted pain pills to see how many are remaining?	○	○	○	○	○
7. How often have you been concerned that people will judge you for taking pain medication?	○	○	○	○	○
8. How often do you feel bored?	○	○	○	○	○
9. How often have you taken more pain medication than you were supposed to?	○	○	○	○	○
10. How often have you worried about being left alone?	○	○	○	○	○
11. How often have you felt a craving for medication?	○	○	○	○	○
12. How often have others expressed concern over your use of medication?	○	○	○	○	○

SOAPP-R

	Never	Seldom	Sometimes	Often	Very Often
	0	1	2	3	4
13. How often have any of your close friends had a problem with alcohol or drugs?	○	○	○	○	○
14. How often have others told you that you had a bad temper?	○	○	○	○	○
15. How often have you felt consumed by the need to get pain medication?	○	○	○	○	○
16. How often have you run out of pain medication early?	○	○	○	○	○
17. How often have others kept you from getting what you deserve?	○	○	○	○	○
18. How often, in your lifetime, have you had legal problems or been arrested?	○	○	○	○	○
19. How often have you attended an AA or NA meeting?	○	○	○	○	○
20. How often have you been in an argument that was so out of control that someone got hurt?	○	○	○	○	○
21. How often have you been sexually abused?	○	○	○	○	○
22. How often have others suggested that you have a drug or alcohol problem?	○	○	○	○	○
23. How often have you had to borrow pain medications from your family or friends?	○	○	○	○	○
24. How often have you been treated for an alcohol or drug problem?	○	○	○	○	○

Please include any additional information you wish about the above answers.
Thank you.

SOAPP-R

Scoring Instructions for the SOAPP®-R®

All 24 questions contained in the SOAPP®-R have been empirically identified as predicting aberrant medication-related behavior six months after initial testing.

To score the SOAPP, add the ratings of all the questions. A score of 18 or higher is considered positive.

Sum of Questions	SOAPP-R Indication
> or = 18	+
< 18	-

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-R 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-R is at different cutoff values. These values suggest that the SOAPP-R is a sensitive test. This confirms that the SOAPP-R is better at identifying who is at high risk than identifying who is at low risk. Clinically, a score of 18 or higher will identify 81% of those who actually turn out to be at high risk. The Negative Predictive Values for a cutoff score of 18 is .87, which means that most people who have a negative SOAPP-R are likely at low-risk. Finally, the Positive likelihood ratio suggests that a positive SOAPP-R score (at a cutoff of 18) is nearly 4 times (3.80 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 18 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-R score suggests the patient is very likely at low-risk, while a high SOAPP-R score will contain a larger percentage of false positives (about 30%); 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-R Cutoff Score	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio	Negative Likelihood Ration
Score 17 or above	.83	.65	.56	.88	2.38	.26
Score 18 or above	.81	.68	.57	.87	3.80	.29
Score 19 or above	.77	.75	.62	.86	3.03	.31

SOAPP-R

How does the SOAPP-R help determine appropriate treatment?
The SOAPP-R should only be one step in the assessment process to determine which patients are high-risk for opioid misuse. The following discussion examines the assessment and treatment options for chronic pain patients who are at risk (high risk or medium risk) and those who are likely not at risk.

Who is at a high risk for opioid misuse? (SOAPP-R score = 22 or greater*)

Patients in this category are judged to be at a high risk for opioid misuse. These patients have indicated a history of behaviors or beliefs that are thought to place them at a higher risk for opioid misuse. Some examples of these behaviors or beliefs include a current or recent history of alcohol or drug abuse, being discharged from another physician' care because of his/her behavior, and regular noncompliance with physicians' orders. These patients may have misused other prescription medications in the past. It is a good idea to review the SOAPP-R questions with the patient, especially those items the patient endorsed. This will help flesh out the clinical picture, so the provider can be in the best position to design an effective, workable treatment plan.

Careful and thoughtful planning will be necessary for patients in this category. Some patients in this category are probably best suited for other therapies or need to exhaust other interventions prior to entering a treatment plan that includes chronic opioid therapy. Others may need to have psychological or psychiatric treatment prior to or concomitant with any treatment involving opioids. Patients in this category who receive opioid therapy should be required to follow a strict protocol, such as regular urine drug screens, opioid compliance checklists, and counseling.

Specific treatment considerations for patients in this high-risk category:

- Past medical records should be obtained and contact with previous and current providers should be maintained.
- Patients should also be told that they would be expected to initially give a urine sample for a toxicology screen during every clinic visit. They should also initially be given medication for limited periods of time (e.g., every 2-weeks).
- Ideally, family members should be interviewed and involvement with an addiction medicine specialist and/or mental health professional should be sought.
- Less abusable formulations should be considered (e.g., long-acting versus short-acting opioids, transdermal versus oral preparation, tamper-resistant medications).
- Early signs of aberrant behavior and a violation of the opioid agreement should result in a change in treatment plan. Depending on the degree of violation, one might consider more restricted monitoring, or, if resources are limited, referring the patient to a program where opioids can be prescribed under stricter conditions. If violations or aberrant behaviors persist, it may be necessary to discontinue opioid therapy.

** Note these are general ranges. Clinicians should also complement SOAPP scores with other clinical data such as urine screens and psychological evaluations.*

SOAPP-R

Who is at a moderate risk for opioid misuse? (SOAPP-R score = 10 to 21*)

Patients in this category are judged to be at a medium or moderate risk for opioid misuse. These patients have indicated a history of behaviors or beliefs that are thought to place them at some risk for misuse. Some examples of these behaviors or beliefs are family history of drug abuse, history of psychological issues such as depression or anxiety, a strong belief that medications are the only treatments that will reduce pain and a history of noncompliance with other prescription medications. It is a good idea to review the SOAPP-R items the patient endorsed with the patient present.

Some of these patients are probably best treated by concomitant psychological interventions in which they can learn to increase their pain-coping skills, decrease depression and anxiety, and have more frequent monitoring of their compliance. They may need to be closely monitored until proven reliable by not running out of their medications early and having appropriate urine drug screens.

Additional treatment considerations for patients in this category:

- Periodic urine screens are recommended.
- After a period in which no signs of aberrant behavior are observed, less frequent clinic visits may be indicated. If there are any violations of the opioid agreement, then regular urine screens and frequent clinic visits would be recommended.
- After two or more violations of the opioid agreement, an assessment by an addiction medicine specialist and/or mental health professional should be mandated.
- After repeat violations referral to a substance abuse program would be recommended. A recurrent history of violations would also be grounds for tapering and discontinuing opioid therapy

** Note these are general ranges. Clinicians should also complement SOAPP scores with other clinical data such as urine screens and psychological evaluations.*

Who is at a low risk for opioid misuse? (SOAPP-R score < 9*)

Patients in this category are judged to be at a low risk for opioid misuse. These patients have likely tried and been compliant with many other types of therapies. They should be able to handle their medication safely with minimal monitoring. They are apt to be responsible in their use of alcohol, not smoke cigarettes, and have no history of previous difficulties with alcohol, prescription drugs, or illegal substances. This patient probably reports few symptoms of affective distress, such as depression or anxiety.

As noted previously, the SOAPP-R is not a lie detector. The provider should be alert to inconsistencies in the patient report or a collateral report. Any sense that the patient's story "doesn't add up" should lead the provider to take a more cautious approach until experience suggests that the person is reliable.

Patients in this category would be likely to have no violations of the opioid treatment agreement. These patients are least likely to develop a substance abuse disorder. Additionally, they may not require special monitoring or concomitant psychological treatment.

SOAPP-R

Additional treatment considerations for patients in this category:

- Review of SOAPP-R questions is not necessary, unless the provider is aware of inconsistencies or other anomaly in patient history/report.
- Frequent urine screens are not indicated.
- Less worry is needed about the type of opioid to be prescribed and the frequency of clinic visits.
- Efficacy of opioid therapy should be re-assessed every six months, and urine toxicology screens and update of the opioid therapy agreement would be recommended annually.

** Note these are general ranges. Clinicians should also complement SOAPP scores with other clinical data such as urine screens and psychological evaluations.*

Opioid Risk Tool

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 Obsessive Compulsive Disorder Bipolar Schizophrenia	[ ]	2	2
	Depression	[ ]	1	1
TOTAL		**[ ]**		

Total Score Risk Category Low Risk 0 – 3 Moderate Risk 4 – 7 High Risk $\geq$ 8

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Opioid Risk Tool

Low-risk patients should be monitored at a level that could be described as routing. This does not mean these individuals are not monitored with vigilance and care, only that no extraordinary measures are required.

- Explain the standard treatment agreement; both provider and patient should sign it.
- Schedule regular follow-up visits (monthly at first).
- Set the frequency of medication refills (monthly for the first 6 months).
- Perform initial urine (or other) drug screening.
- Communicate with pharmacies or obtain initial reports from prescription-monitoring programs (where available) and prior medical providers.
- Document every patient and clinician interaction.
- Continually review the Four A's during return visits.
- Consultations with specialists are not required.
- Medication type: adequate analgesia, no restrictions.

Moderate risk for drug abuse calls for another layer of vigilance in addition to the routine monitoring established for low-risk patients:

- Regular follow-up visits and prescriptions refills should occur every 2 weeks initially.
- Observe patients for signs of complicating co morbid diagnoses, such as anxiety, depression, or a sleep disorder.
- Consider referring the patient for evaluation by pain management and psychiatric specialists.
- Conduct regular checks (every 6-12 months) of your state's prescription monitoring database, if available, or consult with the patient's pharmacist.
- Visit with the patient's family members or other third parties to verify the patient's accounts and for evidence of environmental influences.
- Institute random urinalysis (or another screening method) to confirm compliance with medication levels.
- Consider checking leftover medications to verify their quantity.
- Consider limiting the use of rapid-onset analgesics.

High-risk patients require the following measures of intense monitoring in addition to those required by the low-risk and moderate-risk groups:

- Schedule regular follow-up visits more frequently than usual. If problems develop, shorten the treatment interval to weekly.
- Prescribe just enough medication to last until the next appointment and ensure that prescription refills are contingent upon attendance.
- Typically, psychiatric and addiction-medicine consultations are required. Consider consultation with a pain management specialist. Coordinate treatment.
- Conduct regular urine (or other) drug screenings in addition to some unexpected screenings.
- Consider using blood screenings.
- During every visit, count the patient's leftover medication.
- Consult a prescription database (if available) more frequently.
- Strongly enforce the treatment agreement.
- Avoid prescribing rapid-onset analgesics and consider limiting short-acting analgesics.

Webster & Dove, 2007

Opioid Risk Tool

The 3 risk categories help make treatment decisions easier but should not be used to label patients. Remember that the need to monitor for aberrant behavior is ongoing, and patients can move from 1 risk group to another throughout the course of treatment. For example, a patient initially assessed as low risk may later display multiple aberrant behaviors in response to a deteriorating physical condition or life stresses.

In general, exhibiting more than 3 mildly aberrant behaviors during 1 year or exhibiting 1 egregious behavior should cause a patient to move to a higher risk category and to be monitored more closely. If patients remain in the low-risk category for 6 months, the interval between visits and refills of medication can be increased. Eventually, when patients have remained in the low-risk category for 1 year, refills that last for 3 months are common.

Webster & Dove, 2007

Urine Drug Testing Devices

Urine Drug Testing Devices

To the best of our knowledge, this is a comprehensive list of CLIA waived office drug testing devices that test for specific prescription drugs and are under $10.

Test Name	Analytes that are Tested	Approx. Price
Alfa Scientific Designs, Inc. Instant Verdict Multi-Drug of Abuse Urine Test	Methadone, Morphine-Amphetamines, Barbiturates, Benzos, Cocaine, MDMA, Methamphetamines, PCP, THC, Tricyclic Antidepressants	$8.50
American Bio Medica Rapid TOX	Buprenorphine, Methadone, Opiates, Oxycodone, Propoxyphene- Amphetamines, Barbiturates, Benzos, Cocaine, MDMA, Methamphetamines, PCP, THC, Tricyclic Antidepressants	$4.15
BTNX Inc. Know Multi-Drug One Step Screen Test Panel (Urine)	Methadone, Morphine-Amphetamines, Barbiturates, Benzos, Cocaine, MDMA, Methamphetamines, PCP, THC, Tricyclic Antidepressants	$6.80

Search for CLIA approved tests
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfClia/Search.cfm
CLIA waived tests
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfClia/testswaived.cfm
CLIA waived analytes
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfClia/analyteswaived.cfm

Signs of Substance Misuse

Features of presentation that may alert practitioner to the possibility of substance misuse

- Cutaneous signs of drug abuse - skin tracks and related scars on the neck, axilla, groin, neck, forearm, wrist, foot and ankle. Such marks are usually multiple, hyper-pigmented and linear. New lesions may be inflamed. Shows signs of “pop” scars from subcutaneous injections.
- Being assertive, aggressive or emotionally labile
- Current intoxication/withdrawal
- May show unusual knowledge of controlled substances.
- Gives medical history with textbook symptoms or gives evasive or vague answers to questions regarding medical history.
- Reluctant or unwilling to provide reference information. May have no General Practitioner.
- Will often request a specific controlled drug and is reluctant to try a different drug.
- Generally has no interest in diagnosis - fails to keep appointments for further diagnostic tests or refuses to see another practitioner for consultation.

British Pain Society, 2007

Checklist for Adverse Effects, Function, and Opioid Dependence

Checklist for adverse effects

- Constipation, sweating, nausea
- Exacerbation of sleep apnea, COPD
- Opioid bowel syndrome
- Rebound headaches
- Fatigue and confusion (particularly in the elderly)
- Reproductive effects (impotence in men and menstrual irregularities in women)
- Sensitization to pain (higher opioid doses may be required in acute pain compared to stable chronic pain)
- Neurotoxicity, seizures and hallucinations (for example with repeated administration of Demerol)

Checklist for function that should be assessed

- Sleep
- Mood
- Libido
- Time out of bed, ability to sit, ability to stand
- Activities within the house and outside (e.g., household chores, shopping, etc.)
- Activities at work (return to work, modified duties, trial employment, etc.)

Checklist for signs of opioid dependence

- On high and escalating doses of opioids
- Frequently runs out of medicine early observed to be intoxicated or in withdrawal
- Alters, borrows, steals, or sells prescriptions
- Accesses multiple sources of opioids, including from ERs, other prescribers, friends, acquaintances, or on the street *
- Injects oral medications
- Threatens or harasses staff to get immediate appointment
- Reluctant to try alternatives
- Angry, demanding, or tearful if not given drug of choice
- Deterioration of functional status while in receipt of opioid
- Concurrent abuse of alcohol or other illicit drugs
- Multiple dose escalations or other noncompliance with therapy despite warnings
- Multiple episodes of prescription loss

College of Physicians and Surgeons of Ontario, 2000

Federal Guidelines on Proper Disposal of Prescriptions

Proper Disposal of Prescription Drugs

Federal Guidelines:

- Take unused, unneeded, or expired prescription drugs out of their original containers and throw them in the trash.
- Mixing prescription drugs with an undesirable substance, such as used coffee grounds or kitty litter, and putting them in impermeable, non-descript containers, such as empty cans or sealable bags, will further ensure the drugs are not diverted.
- Flush prescription drugs down the toilet *only* if the label or accompanying patient information specifically instructs doing so (see box).
- Take advantage of community pharmaceutical take-back programs that allow the public to bring unused drugs to a central location for proper **disposal**. Some communities have pharmaceutical take-back programs or community solid-waste programs that allow the public to bring unused drugs to a central location for proper disposal. Where these exist, they are a good way to dispose of unused pharmaceuticals.

The FDA advises that the following drugs be flushed down the toilet instead of thrown in the trash:
Actiq (fentanyl citrate)
Daytrana Transdermal Patch (methylphenidate)
Duragesic Transdermal System (fentanyl)
OxyContin Tablets (oxycodone)
Avinza Capsules (morphine sulfate)
Baraclude Tablets (entecavir)
Reyataz Capsules (atazanavir sulfate)
Tequin Tablets (gatifloxacin)
Zerit for Oral Solution (stavudine)
Meperidine HCl TabletsPercocet (Oxycodone and Acetaminophen)
Xyrem (Sodium Oxybate)
Fentora (fentanyl buccal tablet)
Note: Patients should always refer to printed material accompanying their medication for specific instructions.

Office of National Drug Control Policy
ONDCP, Washington, D.C. 20503p (202) 395-6618 f (202) 395-6730

www.WhiteHouseDrugPolicy.gov

TOOLS

Non-Opioid Pain Management Tool

Area/Type of Pain	Treatment Options (Strongest Recommendations listed first)	When to Initiate	Population	Duration/Indication of Treatment	Cautions/MISC
Back Pain <4 weeks	Directed Exercise Program (1, 2, 3, 4, 5, 6)	Within 7-10 days of injury	All ages	Life long	Consider co morbidities
	Controlled Weight Loss (2)	Immediately	All ages	Life long	Consider co morbidities
	Ice/Heat (2, 4, 6, 7)	During the first 1-4 days	All ages	Most effective in first 1-3 days	Consider co morbidities
	Acetaminophen up to 4 g/day (1, 2, 4, 6, 8, 9)	Immediately	Adults	Can be long term	Consider co morbidities
	Physical therapy (4, 6, 10, 11)	After 3 weeks of conservative therapy	Adults	1-2 visits	Consider co morbidities
	NSAIDs (2, 4, 6, 9, 12)	Immediately (recommended to try Acetaminophen first)	Younger adults, without any CV, Renal or GI risk factors	Short term treatment	Consider co morbidities, no CV, renal or GI risk factors
	Muscle Relaxers (4, 9, 13)	Immediately	Adults	Short term treatment	Significant side effects profile, use cautions in prescribing
	Cox-2 Inhibitors (1, 2)	If unable to tolerate NSAIDs and failed Acetaminophen therapy	Adults , not to be used in people with any CV risk factors	Short term treatment	Consider co morbidities, no CV risk factors
	Back School (14, 15)	After 1-2 weeks of conservative therapy	Adults	For length of program	This has shown to speed return to work, but not any significance in lowering of pain scores or duration of pain.
	Tramadol/acetaminophen (2)	After failing acetaminophen for 1-2 weeks	Adults	Can be long term	Consider co morbidities
	Tramadol (2)	After initial acetaminophen trail	Adults	Can be long term	Consider co morbidities
	Manipulation (1, 4, 6, 16, 17, 18, 19)	Most effective when used for pain <6 weeks of duration without radiculopathy	Adults	3-4 weeks of treatment has been studied. Up to 8 treatments.	Consider co morbidities, not shown to be better than other therapies. Not to be used with herniated disks
Back Pain >4 weeks	Directed Exercise Program (1, 2, 3, 4, 5, 8, 18, 19)	Immediately	Adults	Life Long	Consider co morbidities
	Yoga exercises (viniyoga) (20)	Immediately	Adults	Life Long, studies for 12 weekly sessions	Has been shown to be as or more beneficial than exercise in some studies.
	Controlled Weight Loss (2)	Immediately	Adults	Life Long	Consider co morbidities
	Acetaminophen up to 4 g/day (1, 2, 4, 8)	Immediately	Adults	Can be long term	Consider co morbidities

Non-Opioid Pain Management Tool

	NSAIDs (2, 4, 12)	Immediately, recommend acetaminophen trial first. Some evidence that NSAIDs are equal with acetaminophen in chronic low back pain (21) Some evidence that it is superior at pain control. (22)	Adults with no CV, Renal or GI risk factors	Short term	Consider co morbidities, no CV, renal or GI risk factors
	Muscle Relaxers (4, 13)	Immediately	Adults	Short term treatment	Significant side effects profile, use cautions in prescribing, some studies did not show any benefit after 3-4 weeks of injury
	Cox-2 Inhibitors (1, 2)	If unable to tolerate NSAIDs and no CV risk factors	Adults with no CV risk factors	Short term	Consider co morbidities, no CV risk factors
	Back School (14, 15, 18)	After 1-2 weeks of conservative therapy	Adults	For length of program	This has shown to speed return to work, but not any significance in lowering of pain scores or duration of pain. Swedish Back School program was studied.
	Tricyclic antidepressants (9, 23)	After 3-4 weeks and failing conservative therapy, acetaminophen	Adults	As long as deemed beneficial	Have significant side effects profile, consider co morbidities
	Tramadol/acetaminophen (2)	After failing acetaminophen for 1-2 weeks	Adults	Can be long term	Consider co morbidities
	Tramadol (2)	After failing acetaminophen trial, co administration with acetaminophen has been shown to have more favorable results	Adults	Can be long term	Consider co morbidities
	Injections, epidural/facet joints (24, 25)	After failing conservative treatment	Adults	As long as beneficial, if effective often last 1-4 months in duration, can be used to help diagnosis and evaluate for additional treatment options	Choose population according to guidelines. There are conflicting opinions on efficacy
	Physical Therapy (10, 11)	Recommend starting immediately	Adults	1-2 visits	Consider co morbidities
	Message Therapy (26, 27, 28)	Recommended in conjunction exercise and education	Adults	As long as beneficial has been shown to effective for up to one year, >5 visits shows better results, most studies showed results in 6-10 treatments	Some disagreement in literature, but done by licensed therapist found to be more effective
	Neuroreflexotherapy (29)	Only in Chronic LBP	Adults	Undetermined	Preliminarily this has shown some effect.

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					Requires lengthy training of practitioner to be considered effective
Neck Pain	Directed Exercise Program (1, 2, 3, 6, 30)	Within 7-10 days of injury	All ages	Life long	Consider co morbidities, can add mechanical manipulation to an exercise program
	Acetaminophen 4g/day maximum (2, 6, 31)	Immediately	Adults	Can be long term	Consider co morbidities
	NSAIDs (6, 12, 31)	Immediately (recommended to try Acetaminophen first)	Younger adults, without any CV, Renal or GI risk factors	Short term treatment	Consider co morbidities, no CV, renal or GI risk factors
	Physical Therapy (6)	After 2 weeks of conservative treatment	Adults	1-2 visits for education, counseling of home exercise	Consider co morbidities
	Manipulation (6)	Once more conservative measures fail	Adults	Best when combined with exercise	Consider co morbidities, rare instances of CVA
	IV methylprednisolone (31)	Within 8 hours of injury for acute whiplash	Adults	One time treatment	Any contraindications to IV steroids.
	IM Lidocaine (31)	Chronic neck pain with arm symptoms	Adults	Only a few treatments indicated	Consider co morbidities
	Muscle Relaxers (31)	Immediately	Adults	Short term	Consider co morbidities
	Acupuncture (32)	After failing exercise and/or acetaminophen/NSAIDs	Adults	Ideally 6 or more treatments, effects have been shown for short-term pain relief	Consider co morbidities
Headache	Directed exercise program (33)	Immediately	Adults	When the HA is a result of a mechanical neck disorder	Consider co morbidities
	Acetaminophen 4g/day maximum (34)	Immediately	Adults	Long term, has not been shown to be effective in migraines	Consider co morbidities
	NSAIDS (12, 35, 36)	Immediately	Adults	Short term, shown to be effective in both migraine and non-migraine HAs	Consider co morbidities, not to be used with CV, renal or GI risk factors
	Triptans (36, 37)	Use if unable to control HA with NSAIDs and or acetaminophen	Adults	Beneficial for migraine headaches. IM has been shown to be more effective than oral, but both are superior to placebo. Sumatriptan most studied	Consider co morbidities
	Excedrin (36)	Immediately	Adults	Shown to be beneficial in Acute migraines	Consider co morbidities
	Amitriptyline (35)	Immediately	Adults	Best for migraine headaches, can be started immediately	Monitor for side effects and complications of medication, can cause drowsiness
	Antidepressants (other TCAs, SNRIs,	After failing conservative	Adults	Migraine, tension, and mixed.	Independent of depression,

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	SSRIs) (38, 39)	therapy		Studies lasted 4-27 weeks	SSRI least effective
	Antiemetics (36)	With migraine associated nausea	Adults	Has been shown to help with pain and nausea with migraines	Consider co morbidities
	Anticonvulsants (40)	After failing other therapies, for prevention	Adults	For prevention of migraine headache	Sodium valproate/divalproex sodium and topiramate are the best studied
	NSAIDS combined with metoclopromide (41)	After failing acetaminophen	Adults	Migraine	Consider co morbidities, metoclopromide can cause dystonia. NNT 3.5
	DHE IM/SC/IV (36)	After failing more conservative therapies	Adults	Have shown to help migraines, more effective in combination with antiemetics	Consider co morbidities
	Isometheptene (36)	After failing more conservative therapies	Adults	Found effective for mild-moderate migraine	Consider co morbidities
	Normal barometric oxygen therapy (42)	Immediately	Adults	For use in Cluster Headaches	Unknown
	TENS (35)	Immediately	Adults	Best for cervical tension headaches, mildly affective in some migraine headaches	Do not use in patients with pacemakers, cardiac conduction abnormalities, or over the carotid body or sinus
	Manipulation (35)	Immediately	Adults	Best for tension, post-traumatic headache. Can be helpful in some migraine headaches	Choose population according to literature
	Acupuncture (43)	As adjuvant treatment	Adults	Shown to be effective for both tension and migraine	Choose population according to literature, not effective for all
Osteoarthritis	Directed Exercise Program (1, 2, 3, 6, 44)	Within 7-10 days of injury	All ages	Life long	Consider co morbidities
	Controlled Weight Loss (2)	Immediately	All ages	Life long	Consider co morbidities
	Acetaminophen 4g/day maximum (2, 8)	Immediately first line	Adults	Can be long term	Consider co morbidities
	NSAIDs (2, 12)	Immediately	Younger adults, without any CV, Renal or GI risk factors	Short term	Consider co morbidities, no CV, renal or GI risk factors
	Non-acetylated salicylates (2)	Immediately	Adults	Short term	Consider co morbidities, watch for ototoxicity
	Topical capsaicin (2)	Immediately	Adults	Short term	Consider co morbidities
	Intra-articular steroid injection (2, 45)	Immediately	Adults	Can be long term, but if too long can consider joint replacement.	This should be considered first-line therapeutic intervention if OA is confined to a single joint.
	Cox-2 Inhibitors (1, 2)	If unable to tolerate NSAIDs and failed Acetaminophen	Adults , not to be used in people with any CV risk factors	Short term treatment	Consider co morbidities, no CV risk factors

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		therapy			
	Diacerein (46, 47)	After failing other therapies	Adults	Studies lasted 2 months to 3 years	Consider co morbidities, shown to have minimal pain relief
Acute Sports Injury	Ice/Heat (2)	Immediately for first 1-4 days	All ages	For first 1-4 days	Instruct on timing to not cause tissue damage
	Acetaminophen 4g/day maximum (2)	Immediately	Adults	Can be long term	Consider co morbidities
	NSAIDs (2, 12)	Immediately, recommended to try acetaminophen first	Adults	Short term	Consider co morbidities
Neuropathic Pain	Acetaminophen 4g/day maximum (48)	Immediately	Adults	Can be long term	Consider co morbidities
	Anticonvulsants (49, 50)	After failing acetaminophen	Adults	Can be long term	Have a side effect profile that must be monitored. Carbamezapine and gabapentin found to most effective, some showing crabamezapine to be more effective with lower NNT and higher NNH
	Systemic administration of local anesthetics (51)	After failing acetaminophen	Adults	Undetermined	Can be as effective as anticonvulsants. Monitor for side effects
	Antidepressants (34, 52)	After failing acetaminophen.	Adults	Can be long term, TCAs (amitriptyline) and Venlafaxine shown to be most effective. Not shown to be effective in HIV neuropathies	Monitor for side effects, follow black box warnings. Newer SSRIs have less evidence supporting their use in neuropathic pain
Post-Herpetic Pain	Anticonvulsants (49)	Immediately	Adults	While symptoms last	Can cause drowsiness
Fibromyalgia	Supervised Aerobic/Strength training exercise (53, 54, 55)	Immediately, for at least 20 minutes a day 3 times a week	All ages	Life long, most studies were conducted on average for 12 weeks, 3-24 weeks.	Consider co morbidities
	Cognitive Behavioral Therapy (54, 56)	Immediately	Adults	Data showed results from 6-30 months	Works best as a multidisciplinary approach
	Amitriptyline (54, 57, 58)	Immediately	Adults	While beneficial	Does have side effect profile, tolerance to effect can occur
	Cyclobenzaprine (54, 57)	Typically is after exercise, acetaminophen and amitriptyline	Adults	While beneficial	Significant side effects
	Acupuncture (54, 59, 60)	After exercise and	Adults	While beneficial	Mild/weak evidence

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		amitriptyline			
	Deep tissue message (54)	Immediately	Adults	While beneficial	Mild/weak evidence
	Fluoxetine (54)	Typically start with exercise, acetaminophen, and amitriptyline first	Adults	While beneficial	Secondary to amitriptyline, can be used in conjunction with tricyclics
	Dual-reuptake inhibitors (SNRIs): (54)	Immediately	Adults	While beneficial	Weaker evidence than previous medications
	Gabapentin (61)	Immediately	Adults	While beneficial, studied over a 12 week period	Consider co morbidities
	Pregabalin (54, 62, 63)	Immediately	Adults	While beneficial	Still under investigation, one study showing positive results
Dental Pain	Acetaminophen (64, 65)	Immediately	All ages	As needed	Consider co morbidities
	NSAIDs (65)	Immediately	Adults	As needed	Consider co morbidities
	Acupuncture (57, 66)	Immediately post-op	Adults	1-4 sessions	
Pelvic Pain (dysmenorrheal)	Directed exercise program (67)	Immediately	All ages	Life long	Consider co morbidities
	Acetaminophen (68)	During first 3 days of menstruation	Adults	While beneficial	Consider co morbidities
	NSAIDs (68, 69)	During first 3 days of menstruation	Adults	While beneficial	Consider co morbidities
	Oral contraceptives (70)	Immediately	Adults/Adolescents	While beneficial	Consider co morbidities, can be traditional or extended continuous cycle
	Acupuncture (71)	Immediately	Adults	10 visits over 3 months	Consider co morbidities
	Chinese herbal medication (72)	After other interventions	Adults	While beneficial	Not all interactions known with other medications
Pelvic Pain (chronic pelvic pain)	Directed exercise program (73)	Immediately	All ages	Life long	Consider co morbidities
	Medroxyprogesterone acetate (73)	Immediately	Adults	Not found to be effected after 9 months	Consider co morbidities
	Goserelin (73)	After failing more conservative therapies	Adults	As long as beneficial, cannot be taken longer than six months	Consider co morbidities, extensive side effects
Pelvic Pain (Endometriosis)	Danazol (74)	After failing conservative therapy	Adults	For up to 6 months	Consider co morbidities, extensive side effects
	OCPs (75)	Immediately	Adults	While beneficial	Consider co morbidities
	Goserelin (75)	After failing more conservative therapies	Adults	While beneficial, cannot be taken for longer than six months	Consider co morbidities, extensive side effects

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Absolute Contraindications to Opioid Prescribing

Absolute Contraindications to Opioid Prescribing: Discussion

1. Allergy to opioid agents
Morphine causes the release of histamine, frequently resulting in itching, but this is not an allergic reaction. True allergy to opioid agents (e.g. anaphylaxis) is not common but does occur. Generally, allergy to one opioid agent does not mean the patient is allergic to other opioids; also switching to an agent in another opioid drug class may be effective. For example, if a patient has a hypersensitivity to a phenanthrene, then a diphenylheptane drug may be tried. (See table below.) When patients report an "allergy" to all but one agent (such as meperidine), the presence of a substance use disorder should be considered. Consultation with an allergist may be helpful to resolve these issues.

Classes of Opioid Medications

Phenanthrenes	**Diphenyleptanes**	**Phenylpiperidine**
Codeine	Methadone	Fentanyl
Hydrocodone	Propoxyphene	Meperidine
Hydromorphone		
Levorphanol		
Morphine		**Other**
Oxycodone		Tramadol

[a] Meperidine is not recommended for chronic pain because of the potential for accumulation of the neurotoxic metabolite, normeperidine, and a potentially fatal drug interaction with monoamine oxidase inhibitors (MAOIs).

2. Co-administration of a drug capable of inducing life limiting drug-drug interaction
Providers should carefully evaluate potential drug interactions prior to initiating opioid therapy, (such as MAOI with concurrent meperidine use, or propoxyphene and alcohol and other CNS depressants). (Note: meperidine is not recommended for chronic pain because of this potentially fatal drug interaction and the potential for accumulation of the neurotoxic metabolite, normeperidine, with regular dosing.)

3. Active diversion of controlled substances
Diversion should be suspected when there are frequent requests for early refills, atypically large quantities are required, when purposeful misrepresentation of the pain disorder is suspected, or when a urine drug screen (UDS) is negative for the substance being prescribed, in the absence of withdrawal symptoms. Routine UDS often does not detect synthetic and semi-synthetic opioids (methadone, oxycodone, fentanyl, hydrocodone, meperidine or hydromorphone). Verified diversion is a crime and constitutes a strong contraindication to prescribing additional medications, and consultation with a pain specialist, psychiatrist, or addiction specialist may be warranted.

Strategies for Tapering & Weaning

Strategies for tapering:

From a medical standpoint, weaning from opioids can be done safely by slowly tapering the opioid dose and taking into account the following issues:

- A decrease by 10% of the original dose per week is usually well tolerated with minimal physiological adverse effects. Some patients can be tapered more rapidly without problems (over 6 to 8 weeks).
- If opioid abstinence syndrome is encountered, it is rarely medically serious although symptoms may be unpleasant.
- Symptoms of an abstinence syndrome, such as nausea, diarrhea, muscle pain and myoclonus can be managed with clonidine 0.1 – 0.2 mg orally every 6 hours or clonidine transdermal patch 0.1mg/24hrs (Catapres TTS-1™) weekly during the taper while monitoring for often significant hypotension and anticholinergic side effects. In some patients it may be necessary to slow the taper timeline to monthly, rather than weekly dosage adjustments.
- Symptoms of mild opioid withdrawal may persist for six months after opioids have been discontinued.
- Consider using adjuvant agents, such as antidepressants to manage irritability, sleep disturbance or antiepileptics for neuropathic pain.
- Do not treat withdrawal symptoms with opioids or benzodiazepines after discontinuing opioids.
- Referral for counseling or other support during this period is recommended if there are significant behavioral issues.
- Referral to a pain specialist or chemical dependency center should be made for complicated withdrawal symptoms.

Recognizing and managing behavioral issues during opioid weaning:

Opioid tapers can be done safely and do not pose significant health risks to the patient. In contrast, extremely challenging behavioral issues may emerge during an opioid taper.

Behavioral challenges frequently arise in the setting of a prescriber who is tapering the opioid dose and a patient who places great value on the opioid he/she is receiving. In this setting, some patients will use a wide range of interpersonal strategies to derail the opioid taper. These may include:

- Guilt provocation (“You are indifferent to my suffering”)
- Threats of various kinds
- Exaggeration of their actual suffering in order to disrupt the progress of a scheduled taper

There are no fool-proof methods for preventing behavioral issues during an opioid taper, but strategies implemented at the beginning of the opioid therapy are most likely to prevent later behavioral problems if an opioid taper becomes necessary.

Washington State Agency Medical Directors’ Group, 2007

Information for Patients—Opioid Analgesics for Non-Cancer Pain

Photocopy for usè by clinician

Information for Patients - Opioid (Narcotic) Analgesics for Non-Cancer Pain

FOR:

FROM: **Dr.**

DATE:

Making Pain Tolerable

The main reason for using an opioid (narcotic) analgesic for chronic non-cancer pain is to make the pain tolerable - not to eliminate it. This treatment is usually only considered after more standard treatments such as anti-inflammatory drugs have failed. If you are agreeable, your physician will prescribe an opioid analgesic for you in gradually increasing doses to minimize side effects. It is extremely important that you follow the directions exactly. Your physician will be the only one prescribing this medication to you. If you increase the dose without your physician's permission, give the medication to another person or obtain this medication from another physician without the consent of your primary physician, the physician may stop prescribing the opioid analgesic for you.

Pain medication is only part of your chronic pain treatment program. Equally important is a gradual exercise program that will increase your activity level despite ongoing pain. You and your physician should agree on specific ongoing treatment goals.

What is My Risk of Addiction?

There is increasing scientific evidence that strong painkillers can relieve some pain in selected patients without causing addiction. It is important to be careful, however, when defining what "addiction" is. Addiction, or psychological dependence, is a pattern of drug use in which the patient craves a drug for its ability to produce a "high" rather than for its pain-relieving properties. This can lead to the selling and injection of drugs and attempts to obtain drugs from multiple physicians - activities generally referred to as "drug abuse". Studies have shown that if a person has no past history of drug abuse and the pain is physical in origin, the risk of addiction is extremely low. If you are placed on an opioid analgesic for a period of weeks, however, and then are suddenly taken off the medication, it is possible to experience a short withdrawal reaction. Although this can be prevented by withdrawing the drug slowly, it does not mean that you have developed a craving for the drug or developed a drug addiction.

Information for Patients—Opioid Analgesics for Non-Cancer Pain

What are the Side Effects?

Although opioid analgesics can produce side effects (drowsiness, confusion, nausea, constipation), these can be minimized by slowly increasing the dose of the drug and by using anti-nausea drugs and bowel stimulants. Pain medication as prescribed will not depress your respiration or prevent you from breathing normally.

Remember Your Follow-up

If you seem to benefit from the pain medications, your physician will see you about every 4 to 6 weeks for the first few months and about every two to three months thereafter. During each visit, you and your physician will assess pain relief, any side effects from the pain medication and your ability to meet your established activity goals.

Other Instructions:

_____

_____

_____

The Role of Methadone in the Management of Chronic Non-Malignant Pain

The Role of Methadone in the Management of Chronic Non-Malignant Pain: Specific Considerations

Overview

Although the literature on methadone for non-malignant pain is scanty and based on case studies, the increasing use of methadone for this purpose requires recommendations to guide practice. There is extensive literature on the use of methadone as a potent analgesic agent for cancer pain and therefore recommendations for the use of methadone in the management of chronic non-malignant pain must be extrapolated from the cancer pain literature.

Methadone is a synthetic opioid analgesic with excellent oral bioavailability, a side effect profile similar to other opioid analgesics and a duration of action of at least eight hours with repetitive dosing. These qualities make it an attractive drug for outpatient pain management. Methadone also has an opioid receptor profile different from that of morphine and has N-methyl-D-aspartate (NMDA) antagonist activity that may confer advantages over morphine. However, experience in the use of methadone for cancer pain has revealed that methadone is far more potent as an analgesic agent than has been suggested by equianalgesic tables derived from single dose studies. With repetitive dosing, methadone is approximately ten times more potent than indicated in these standard tables. The main reason for this is probably the long elimination half-life of methadone (24-36 hours) which allows for much higher drug levels to be reached than could be predicted from single dose studies. This has obvious clinical implications since methadone takes 5-7 days to reach steady state at any particular dose. Therefore, the use of methadone as an analgesic agent requires the same pain assessment skills as for any other opioid drug, but even greater scrutiny in patient monitoring of analgesic and side effects.

Methadone use in the Management of Chronic Non-Malignant Pain

In Canada, methadone is available at low cost as an elixir which is usually made up at a concentration of 1 mg/ml. In opioid-naive patients or patients taking codeine preparations, methadone 2.5 mg q8h is safe and usually well-tolerated. For patients already on a major opioid analgesic like oxycodone or morphine, a reasonable starting dose of methadone is 5 mg q8h with dose increments of 5 mg q8h every 5-7 days. A general rule is to provide careful dose titration until adequate pain relief is achieved or side effects limit further dose escalation. However, one should look for a graded analgesic response to incremental dosing. The absence of a graded analgesic response may mean that the patient is not

The Role of Methadone in the Management of Chronic Non-Malignant Pain

'opioid-responsive. Patients should be seen weekly during the titration phase and every month or two during the maintenance phase.

For patients being switched from relatively large doses of an opioid analgesic (> 200 mg oral morphine or morphine equivalents daily), the table below should be used to calculate equianalgesic doses. For patients taking more than 500 mg oral morphine or morphine equivalents daily, the conversion to methadone should be staged with a third of the anticipated methadone dose being introduced every five days so that the entire conversion takes fifteen days. The dose of the previous opioid is decreased by a third every five days in inverse fashion.

Equianalgesic Doses of Common Opioid Analgesics Relative to Oral Methadone with Repetitive Dosing

Drug	Per Os (PO)	Intramuscular/Subcutaneous
Methadone	2 mg	
Morphine	30 mg	10 mg
Hydromorphone	8 mg	2 mg
Oxycodone	15 mg	

Patients and co-habitants should be warned about potential side effects (especially drowsiness and respiratory depression) and the possibility that side effects can continue to evolve for five to seven days after each dose adjustment. The spouse or significant other should be available at least twice daily to monitor for toxicity. Since drowsiness commonly precedes respiratory depression, they should be instructed to call the prescribing physician if drowsiness develops to obtain advice about further dosing. This obviously requires physician availability 24 hours a day during the titration phase. Elderly patients (over the age of 65), patients with severe lung disease and patients who cannot be adequately monitored at home should be considered for inpatient initiation of methadone treatment.

Note: *The CPSO involvement in the opioid dependence program mentioned is unrelated to the use of Methadone for analgesic purposes. If a physician wishes to obtain a permit to prescribe Methadone for analgesic purposes, he or she needs to apply to the* ***Office of Controlled Substances in Ottawa (613) 946-5139***

Dosing Guidelines

Starting Methadone Dose

Morphine Equivalent	Healthy adult <70 yrs	Adult w/ chronic illness or >70 yrs
Opioid naïve	5mg tid	2.5 mg bid
60 mg - 100 mg	5 mg tid	5 mg bid
>100mg	5 mg qid	5 mg bid

*Webster, 2005

MED for Selected Opioids

Opioid	Approximate Equianalgesic Dose (oral & transdermal)*
Morphine (reference)	30mg
Codeine	200mg
Fentanyl transdermal	12.5mcg/hr
Hydrocodone	30mg
Hydromorphone	7.5mg
Oxycodone	20mg
Oxymorphone	10mg

*Adapted from Washington 2007 Guidelines

Dosing Threshold for Selected Opioids*

Opioid	Recommended dose threshold for pain consult (not Equianalgesic)	Recommended starting dose for opioid-naïve patients	Considerations
Codeine	800mg per 24 hours	30mg q 4-6 hours	See individual product labeling for maximum dosing of combination products. Avoid concurrent use of any OTC products containing same ingredient. See acetaminophen warning, below.
Fentanyl Transdermal	50mcg/hour (q 72 hr)		Use only in opioid-tolerant patients who have been taking ≥ 60mg MED daily for a week or longer
Hydrocodone	30mg per 24 hours	5-10mg q 4-6 hours	See individual product labeling for maximum dosing of combination products. Avoid concurrent use of any OTC products containing same ingredient. See acetaminophen warning, below.
Hydromorphone	30mg per 24 hours	2mg q 4-6 hours	

*the Utah guidelines do not specifically recommend a pain consult

Produced by Utah Department of Health, 2009 adapted from Washington State Agency Medical Director's Group, 2007 and Webster, 2005

Dosing Guidelines

Opioid	Recommended dose threshold for pain consult (not Equianalgesic)	Recommended starting dose for opioid-naïve patients	Considerations
Methadone**	*See table above*		Methadone is difficult to titrate due to its half-life variability. It may take a long time to reach a stable level in the body. Methadone dose should not be increased more frequently than every 7 days. Do not use as PRN or combine with other long-acting (LA) opioids.
Morphine	120mg per 24 hours	Immediate- release: 10mg q 4 hours Sustained-release: 15mg q 12 hours	Adjust dose for renal impairment.
Oxycodone	80mg per 24 hours	Immediate-release: 5 mg q 4-6 hours Sustained-release: 10mg q 12 hours	See individual product labeling for maximum dosing of combination products. Avoid concurrent use of any OTC products containing same ingredient. See acetaminophen warning, below.
Oxymorphone	40mg per 24 hours	Immediate-release: 5-10mg q 4-6 hours	Use with extreme caution due to potential fatal interaction with alcohol or medications containing alcohol

*the Utah guidelines do not specifically recommend a pain consult

Acetaminophen warning with combination products

Hepatotoxicity can result from prolonged use or doses in excess of recommended maximum total daily dose of acetaminophen including over-the-counter products.

- Short-term use (<10 days) – 4000 mg/day
- Long-term use – 2500mg/day

Key considerations in dosing long acting opioids

- Monitoring for adequate analgesia and use of "rescue" medications (at least until the long-acting opioid dose is stabilized). All new dosage calculations should include consideration for concurrent utilization of short-acting opioids.
- If the patient is more debilitated, frail and/or has significant metabolic impairments (e.g. renal or hepatic dysfunction), consider starting at the lower end of the conversion dose range.
- Always monitor for adverse effects (nausea, constipation, over-sedation, itching, etc.)

Equianalgesic dose table for converting opioid doses

All conversions between opioids are estimates generally based on "equianalgesic dosing" or ED. Patient variability in response to these EDs can be large, due primarily to genetic factors and incomplete cross-tolerance. **It is recommended that, after calculating the appropriate conversion dose, it be reduced by 25–50% to assure patient safety.**

Directory of Resources

Utah Directory of Resources

Consultation and Referral

Identifying Pain Management, Mental Health, and Substance Abuse Providers

1) The 211 Information and Referral Bank
http://www.informationandreferral.org
The 211 Info Bank strives to ease the process of locating available and appropriate resources.

2) Utah Cares: State Online Services
https://utahcares.utah.gov/erepucpub/en/ServiceSupplier_searchPage.do?__o3rpu=ScreenReferralHomePage.do
This site allows you to do a search on providers by type and county.

3) Utah Resources Hotline: 2-1-1
Dial 2-1-1 and someone can direct you to providers by specialty in any county in Utah.

4) Utah Medicaid Pain Management Providers
http://health.utah.gov/medicaid/pharmacy/documents/chronic.php

5) Utah Mental health providers
http://mentalhealth.samhsa.gov/databases/facility-search.aspx?state=UT&fullname=Utah

6) Substance Abuse Providers
http://www.dsamh.utah.gov/locationsmap.htm
This link allows you to seek providers by location using an interactive map.

Referral Services

8) Substance Abuse Hotline: 1-866-633-HOPE (4673)

5) Utah Medicaid Restriction Program
http://health.utah.gov/medicaid/pharmacy/Restriction/restriction.php

9) University of Utah Assessment & Referral Services
Assessment & Referral Services is a University of Utah Clinic within the Department of Psychiatry that provides high-quality, objective substance abuse assessments and referrals for individuals with possible substance abuse problems.

Laws Governing Use of Controlled Substances

Federal/DEA laws – www.dea.gov

1) Practitioner Manual
http://www.deadiversion.usdoj.gov/pubs/manuals/pract/pract_manual012508.pdf
This manual has been prepared by the Drug Enforcement Administration to assist practitioners and other registrants authorized to prescribe, dispense, and

Directory of Resources

administer controlled substances. A summary of the act can be found below in Appendix C.

2) Schedules of Controlled Substances
http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr1308_01.html
Schedules of controlled substances can be found in Title 21, Chapter II.

3) Prescriptions
http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr1306_01.html
Contains the rules governing the issuance, filling and filing of prescriptions pursuant to section 309 of the Act (21 U.S.C. 829)

4) Administering and Dispensing of Controlled Substances
http://edocket.access.gpo.gov/cfr_2001/aprqtr/pdf/21cfr1306.07.pdf
Persons who are entitled to fill prescriptions are described in this document found at the link above.

State of Utah Laws – State legislation and regulations

1) Utah Medical Practice Act Rules
http://www.dopl.utah.gov/laws/R156-67.pdf

2) Utah Controlled Substance Act 58-37
http://www.dopl.utah.gov/laws/58-37.pdf

3) Utah Controlled Substance Rules R156-37
http://www.dopl.utah.gov/laws/R156-37.pdf

4) Reporting Prescription Fraud and/or Prescription Related Crime
http://www.urxnet.org/ or http://www.urxnet.org/tip/addtip.asp

5) Division of Occupational and Professional Licensure
http://dopl.utah.gov/

6) Utah Controlled Substance Database
https://csdb.utah.gov/

7) Model Policy for the Use of Controlled Substances for the Treatment of Pain—Federation of State Medical Boards
http://www.fsmb.org/pdf/2004_grpol_Controlled_Substances.pdf
The Model Policy, which was adopted by the Utah Medical Board of Examiners, is designed to communicate certain messages to licensees: that the state medical board views pain management to be important and integral to the practice of medicine; that opioid analgesics may be necessary for the relief of pain; that physicians have a responsibility to minimize the potential for the abuse and diversion of controlled substances; and that physicians will not be sanctioned solely for prescribing opioid analgesics for legitimate medical purposes. This policy is not meant to constrain or dictate medical decision making.

*If there are legal or workplace concerns, it is recommended that patients go to the industrial clinic

Utah's Tamper Resistant Requirements

Tamper Resistant Prescription Pad/Paper Mandate
Effective April 1, 2008

Effective April 1, 2008, all non-electronic prescriptions must be written on tamper-resistant pads/paper in order to be eligible for reimbursement by Medicaid. The tamper resistant prescription pads/paper requirement applies to all outpatient drugs, including over-the-counter drugs. It also applies whether DOM is the primary or secondary payer of the prescription being filled. This new provision impacts all DOM prescribers: physicians, dentists, optometrists, nurse practitioners and other providers who prescribe outpatient drugs.

The Centers for Medicare & Medicaid Services (CMS) has issued guidance to the States in implementing the new federal requirement. This guidance allows for compliance with the tamper-resistant prescription pad/paper requirement to occur in two phases. For the first phase, a prescription must contain at least one of the three features outlined below by April 1, 2008, in order to be considered "tamper-resistant." All three features are required on the prescription pads by October 1, 2008.

DOM encourages providers to implement all security features by April 1, 2008 to be in compliance with all program requirements. Note that computer generated prescriptions are not exempt from the CMS mandate.

The features listed below are recommended as best practice tamper resistant features by a national taskforce including representatives from CMS, State Medicaid agencies, and national medical and pharmacy organizations. Features listed in bold tend to be less costly and easier for prescribers to implement.

Category 1 – One or more industry-recognized features designed to prevent unauthorized copying of a completed or blank prescription form.	
Feature	**Description**
"Void" or "Illegal" Pantograph	**The word "Void" appears when the prescription is photocopied. Due to the word "Void" on faxed prescriptions, this feature requires the pharmacy to document if the prescription was faxed.**
Reverse "RX" or White Area on prescription	"Rx" symbol or white area disappears when photocopied at light setting. This feature is normally paired with the "Void" pantograph to prohibit copying on a light setting.
Coin-reactive ink	Ink that changes color when rubbed by a coin – Can be expensive and is not recommended.
Security Back print	Printed on the back of prescription form. The most popular wording for the security back print is "Security Prescription" or the security back print can include the states name.
Watermarking (forderiner)	Special paper containing "watermarking".
Diagonal lines (patented "Void")	Diagonal lines with the word "void" or "copy". Can be distracting or expensive.
Micro printing	Very small font writing, perhaps acting as a signature line. This is difficult to photocopy and difficult to implement if using computer printer. It is also difficult for a pharmacist to see.

Utah's Tamper Resistant Requirements

Category 2 - One or more industry-recognized features designed to prevent the erasure or modification of information written on the prescription by the prescriber.	
Feature	**Description**
Uniform non-white background color	**Background that consists of a solid color or consistent pattern that has been printed onto the paper. This will inhibit a forger from physically erasing written or printed information on a prescription form. If someone tries to erase or copy, the consistent background color will look altered and show the color of the underlying paper.**
Quantity check off boxes	**In addition to the written quantity on the prescription, Quantities are indicated in ranges. It is recommended that ranges be 25's with the highest being "151 and over". The range box corresponding to the quantity prescribed MUST be checked for the prescription to be valid. See illustration in Appendix 1.**
Refill Indicator (circle or check number of refills or "NR")	**Indicates the number of refills on the prescription. Refill number must be used to be a valid prescription.**
Pre-print "Rx is void if more than___ Rx's on paper" on prescription paper	**Reduces the ability to add medications to the prescription. - Line must be completed for this feature to be valid. Computer printer paper can accommodate this feature by printing "This space intentionally left blank" in an empty space or quadrant.**
Quantity Border and Fill (for computer generated prescriptions on paper only)	**Quantities are surrounded by special characters such as an asterisk to prevent alteration, e.g. QTY **50** Value may also be expressed as text, e.g. (FIFTY), (optional)**
Refill Border and Fill (for computer generated prescriptions on paper only)	**Refill quantities are surrounded by special characters such as an asterisk to prevent alteration, e.g. QTY **5** Value may also be expressed as text, e.g. (FIVE), (optional)**
Chemically reactive paper	**If exposed to chemical solvents, oxidants, acids, or alkalis to alter, the prescription paper will react and leave a mark visible to the pharmacist.**
Paper toner fuser	Special printer toner that establishes strong bond to prescription paper and is difficult to tamper.
Safety or security paper with colored pattern	White (or some other color) mark appears when erased. This is expensive paper.

Category 3 – One or more industry-recognized features designed to prevent the use of counterfeit prescription forms.	
Feature	**Description**
Security features and descriptions listed on prescriptions	**Complete list of the security features on the prescription paper for compliance purposes. This is strongly recommended to aid pharmacists in identification of features implemented on prescription.**
Encoding techniques (bar codes)	Bar codes on prescription. Serial number or Batch number is encoded in a bar code.
Logos	Sometimes used as part of the background color or pantograph.
Metal stripe security	Metal stripe on paper, difficult to counterfeit.
Heat sensing imprint	By touching the imprint or design, the imprint will disappear.
Invisible fluorescent fibers/ink	*Visible only under black light.*
Thermo chromic ink	*Ink changes color with temperature change. This is expensive paper and problematic for storage in areas not climate controlled.*
Holograms that interfere with photocopying	*May interfere with photocopying or scanning.*

Utah's Tamper Resistant Requirements

Per CMS guidance, pharmacies that are presented with a prescription on a non-tamper-resistant prescription pad/paper may satisfy the federal requirement by calling the provider's office and verbally confirming the prescription with the physician or prescriber. The pharmacy shall document through placement on the original non-compliant prescription form that such communication and confirmation has taken place.

Prescriptions that the federal requirement does not apply to:

- E-prescriptions transmitted to the pharmacy;
- Prescriptions faxed to the pharmacy;
- Prescriptions communicated to the pharmacy by telephone by a prescriber;
- Transfer of a prescription between two pharmacies, provided that the receiving pharmacy is able to confirm by facsimile or phone call the authenticity of the tamper-resistant prescription with the original pharmacy;
- Written orders prepared in an institutional setting (which include Intermediate Care Facilities and Nursing Facilities), provided that the beneficiary never has the opportunity to handle the written order and the order is given by licensed staff directly to the dispensing pharmacy;
- Drugs dispensed or administered directly to the beneficiary in the physician's office or clinic;
- Written prescriptions dispensed to MS Medicaid beneficiaries s who become retroactively eligible after April 1, 2008, provided the prescription was filled on or after April 1, 2008, and before the beneficiary became retroactively eligible for MS Medicaid;
- Emergency fills, provided that the prescriber provides a verbal, faxed, electronic or compliant written prescription within 72 hours;
- Refills of written prescriptions presented at a pharmacy before April 1, 2008;
- Written prescriptions paid for by Medicare, a Medicare Part D plan or Medicare Advantage Plan, unless MS Medicaid fee-for-service is a secondary payer. Part D excluded drugs paid for by Medicaid must be executed on tamper-resistant pad/paper[1].

[1] Prescriber may not know when Medicaid is the primary or secondary payer for MS Medicaid beneficiaries; therefore, the Division of Medicaid (DOM) recommends that prescribers use tamper-resistant prescription pads/paper for all DOM beneficiaries.

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Appendix A: Guideline Rating Scale

10/10	• Extremely explicit evidence-based guidelines The "gold standard" • Evidence has been analyzed thoroughly through an explicit rating system • Recommendations are based on the evidence with the highest rating of quality • Expert consensus creates the recommendations, • Recommendations verified through a peer review
9/10	• Very explicit evidence-based guidelines • Evidence has been analyzed thoroughly through an explicit rating system • Recommendations are based on the evidence with the highest rating of quality • Expert consensus creates the recommendations
8/1	• Explicit evidence-based guidelines • Evidence has been analyzed thoroughly through an explicit rating system • Expert consensus
7/10	• Evidence-based guidelines • No record of the evidence from which the guidelines have been created is present • No rating system of the evidence is present either
6/10	• Evidence-based guidelines • Limited details to how they were created • No record of the evidence from which the guidelines have been created is present • No rating system of the evidence is present either
5/10	• Expert consensus statement only • Very detailed explanation of how the consensus was formed • Reviewed thoroughly by pain experts
4/10	• Expert consensus statement only • Detailed explanation of how the consensus was formed
3/10	• Expert consensus statement only • Little explanation of how the consensus was reached
2/10	• Expert consensus statement only • No explanation of how the consensus was reached
1/10	• No explanation of how guidelines were created

Utah Department of Health
PO Box 142104
Salt Lake City, Utah 84114
(801) 538-6191

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EXHIBIT H

HB 137 Final Report

Prescription Pain Medication Program
Utah Department of Health

November 15, 2009

Prepared by Erin Johnson, erjohnso@utah.gov, 801-538-6542

Table of Contents

I. Introduction

During the 2007 General Session, the Utah State Legislature passed House Bill 137, Pain Medication Management and Education. The bill established a two-year program in the Utah Department of Health to reduce deaths and other harm from prescription opiates utilized for chronic pain.

The Prescription Pain Medication Program has been established in the Utah Department of Health in collaboration with the Utah Attorney General Office, the Labor Commission, and the Division of Occupational and Professional Licensure (DOPL). A Steering Committee was established to provide oversight of the program. In addition, an Advisory Committee with several active workgroups on specific issues was established to help coordinate with related initiatives and programs.

The Program goals were to:

- Reduce the number of deaths due to prescribable medications by 15% by 2009 by educating providers, patients, insurers, and the public.
- Improve understanding of occurrence of deaths related to prescription pain medications and understanding of prescribing patterns and other risk factors that increase risk of death.
- Provide recommendations regarding use of the CSD to identify risks and potentially to prevent deaths due to prescription pain medications.

The Program outcomes were:

- Saw a 12.6% reduction in the number of deaths due to prescribable medications from 317 deaths in 2008 to 277 in 2009
- Collected data to help increase our understanding of risk factors of drug overdose deaths. Analysis will take place in 2010.
- Published *Utah Guidelines on Prescribing Opioids*

Funds were contributed by the Labor Commission, University of Utah's Research Center for Excellence in Public Health Informatics, and the Worker's Compensation Fund of Utah resulting in a first year budget of $500,000. For Fiscal Year 2009, funds were contributed by Division of Substance Abuse and Mental Health, Labor Commission, and Commission of Criminal and Juvenile Justice resulting in a budget of nearly $526,000.

II. Executive Summary

Utah Clinical Guidelines on Prescribing Opioids for Treatment of Pain
Utah Clinical Guidelines on Prescribing Opioids for Treatment of Pain were published and made available to providers in March 2009. These guidelines were developed by a consensus panel after a review of existing evidence- based guidelines and common recommendations were found. The guidelines consist of a set of recommendations for acute pain and chronic pain as well as over 20 tools for providers to use in their practice.

They are available at: useonlyasdirected.org or health.utah.gov/prescription. A postcard was sent to inform all Utah control substances licensees about the guidelines and how to obtain them.

Provider Education
Our contract deliverables with HealthInsight for Provider Education were met. The contract included small group trainings, large group presentations, and mass mailings. HealthInsight will continue tracking the participants of the presentation to monitor "adoption" of the guidelines into their practice. A final report on all of their follow-up monitoring will be presented to UDOH in December 2009. Between August 2008 and June 2009, 581 medical providers and 136 additional participants attended learning sessions.

Six practices for safer opioid prescribing comprised the core educational component:
1) start low, go slow (methadone 5 mg bid for most patients); 2) obtain sleep studies for patients on >100mg/day morphine equivalent or >50mg methadone; 3) obtain EKGs for patients on methadone >50mg/day or when combining with other QT prolonging drugs; 4) avoid opioids in combination with benzodiazepines and sleep aids; 5) avoid long-acting opioid for acute pain; and 6) educate patients and families.

Session participants completed a self-reported survey querying changes in behaviors regarding the six practices at 0, 2, and 6 months. Of eligible participants, 25% completed the 6 month survey. Results are interim as data collection is ongoing.

By the 6-month survey, the percentage of respondents who had fully adopted the six practices were: 1) 52%; 2) 32%; 3) 53.3%; 4) 72%; 5) 84%; 6) 48%.

Statewide Media Campaign
A Statewide Media Campaign ran from May 2008 to May 2009 with the slogan *Use Only As Directed*. The campaign generated a total of $298,561 value in publicity from news coverage. TV and radio spots have aired throughout Utah. Collateral materials in the form of bookmarks, posters, clings (re-usable stickers), informational pamphlets, and newspaper ads have been developed and distributed throughout the state. A lot of press coverage was generated as well as many interviews with the press on the topic of prescription drug safety. The website, useonlyasdirected.org, has been an effective way to provide the general public with detailed information, receiving around 90 hits per day. A follow-up, randomized telephone survey found the following results:

- Forty-eight percent (48%) of Utah residents recall seeing the campaign's television commercial.
    - The majority (62%) who saw the commercial saw it more than 5 times.
- Fifty-one percent (51%) said that the media messages made them less likely to take Rx medications not prescribed to them.
- Fifty-two percent (52%) said that the media messages they saw made them less likely to share their Rx medications.
- Nearly one-third (29%) reported that their understanding of the dangers of prescription pain medication changed during the past year.
- Only 16% of respondents recognized the campaign slogan *Use Only As Directed*.

The website will continue and has been purchased for the next 7 years. There is a possibility of other Prescription Safety groups in Utah continuing to use the slogan *Use Only As Directed*.

Research Initiatives
Throughout FY 09, weekly meetings were held by the Prescription Pain Medication Program's IT and Research Team to identify research initiatives.

One research initiative was a study designed to identify risk factors related to unintentional overdose deaths in Utah. A questionnaire was developed to collect information on all drug overdose deaths under jurisdiction of the Utah Office of the Medical Examiner (OME) by interviewing next of kin of decedents. In 2008, 82% of drug overdose deaths in Utah involved prescription pain medications. Interviews are being conducted from October 26, 2008-October 26, 2009 and a report will be available February 2009.

Other research will include looking at emergency department visits related to overdoses of prescription medication, prescribing patterns among providers, looking at deaths by provider specialty, and investigating rates of death by opioid. In FY08, infrastructure to enable analysis of the Controlled Substance Database was established, including an agreement with Department of Commerce, a secure server, and technical approach to linkage of the database to Medical examiner and death certificate data. Initial results of those analyses are included in this report.

The number of non-illicit drug overdose deaths decreased by 12.6% in 2008 from 2007. In 2008, the average age of people who died strictly of non-illicit drugs was 40.3 yrs with 52% being male. These deaths occurred in 22 of the 29 counties across the state showing that the problem impacts both rural and urban communities.

Collaboration
Utah convened a steering committee and advisory committee with over 100 participants representing the partners and stakeholders involved in this important issue. The advisory committee was divided further into work groups that met on the topics of: patient and community education, provider behavior change, guideline recommendations, guideline tools, and data/research.

Conclusion
Utah is using a multi-pronged approach to address problems related to prescription opioid use by educating physicians, patients, and the general public in order to increase knowledge about potential dangers of Rx pain medication. By collaborating with local and state organizations, the materials have been well-accepted and dispersed throughout the state. The lessons learned as a result of this program will be useful both at the state level, as well as nationally.

III. 2007-2009 Milestones

2007

July

- Utah State Legislature passed House Bill 137 appropriating funding to the Utah Department of Health (UDOH) to establish a program to reduce deaths and other harm from prescription opiates.

September

- Convened Advisory Committee of over 50 individuals (meets quarterly, open to public)

October

- Convened Steering Committee of 11 individuals (meets monthly)
- Convened Patient and Community Education Work Group (meets monthly)
- Convened Policy, Insurance, Incentives Work Group (met monthly through April)

November

- Convened Data, Research, and Evaluation Work Group (meets as needed)
- Issued report on findings of analysis of Controlled Substances Database (linked with Medical Examiner and Death Certificate data).
- Memorandum of Understanding signed between DOPL and UDOH for access of Controlled Substances Database
- RFP (Request For Proposal) sent out for Media Campaign contract

December

- Media Campaign contract awarded to Vanguard Media

2008

January

- Baseline survey conducted for Media Campaign
- Applied for and received grant from Utah Commission for Criminal and Juvenile Justice for educating general public

February

- Focus groups conducted to provide feedback on Media Campaign logo and TV spots
- One-year plan for Media Campaign established
- Awarded contract for presentations to general public with producers of Happy Valley

March

- "Use Only As Directed" campaign logo created
- IRB submitted for research using CSD and ER data

April

- Radio and TV spot developed
- Completed literature review of existing guidelines
- IRB submitted for research of risk factors of those who die from prescription-related overdose (done by interviewing family members of decedents)

May

- Data from CSD sent through secure line to UDOH server

- Held “Use Only As Directed” campaign kick-off at the Capitol
- TV spot aired
- Convened Guidelines Expert Panel to develop Recommendations for guidelines

June
- Radio spot aired
- Cancelled contract with producers of Happy Valley
- Awarded contract for physician education to HealthInsight

July
- Convened Guidelines Tool Panel to select tools to include in guidelines
- Finalized guideline recommendations from Guidelines Expert Panel
- Began distributing collateral material for “Use Only As Directed” campaign

August
- Began physician education/small group presentations
- Hired research analyst for CSD data
- Hired research coordinator for risk factor study

September
- Developed questionnaire for Next of Kin to those who died of overdose

October
- Prescription Safety Awareness week declared by Governor Huntsman
- Initiated conducting interviews of Next of Kin for OME project

November
- Guidelines put out for public comment (45 days)

2009

January
- Presented Public Education Campaign and Research findings at American Academy of Pain Medicine National Conference
- Presented Guideline Development Process and Public Education Campaign at CDC STIPDA “State Strategies for Preventing Prescription Drug Overdoses”
- Submitted a grant to evaluate impact of Guidelines

February
- TV spot aired
- Advisory Committee membership exceeds 100

March
- Guidelines published (Press release)

April
- Conducted follow up survey on Use Only As Directed
- 2008 Medical Examiner data showed reduction in overdose deaths (Press release)

June
- Completed Public Education contract
- Report on preliminary results for OME project

August
- Completed Master Patient Index for the UDOH copy of Controlled Substances Database

October
- Submitted recommendations on Controlled Substances Database to legislation
- Distributed info on Utah’s program at Alliance of State Pain Initiatives Conference

December
- Completed Physician Education contract
- Published results from 2008 BRFSS in MMWR

IV. Program Progress Reports

A. Utah Clinical Guidelines on Prescribing Opioids

As part of the legislative mandate for HB 137, the Prescription Pain Medication Program was asked to create Utah guidelines on the proper prescribing of opioids.

Purpose and Target audience
The guidelines provide recommendations for the use of opioids for management of pain that are intended to balance the benefits of use against the risks to the individual and society and to be useful to practitioners. The target audience is all clinicians who prescribe opioids in their practice.

Recommendation Development Process
The guideline recommendation panel met in person on four occasions between May and July 2008. The purpose of the first meeting was to provide panel members with copies of the selected, high-scoring guidelines and to present the purpose and plan for developing the guidelines. Prior to the second meeting, panel members were asked to review the four guidelines for commonalities. The recommendations that were supported by multiple guidelines created the basis of the first draft of the recommendations used by the Guideline Recommendation Panel. Consideration was given to adopting one of the existing evidence-based guidelines outright, but the panel felt that no single guideline represented sufficiently what was desired of the Utah guidelines. The panel voted to include two (2) additional sets of guidelines that had not met the inclusion criteria for consideration while drafting the recommendations. In total, content for the Utah guidelines was drawn from six (6) guidelines. The key topics to be developed into specific recommendations were posted on a website where the guideline recommendation panelists posted comments and edited the text. The panelists' postings were the basis on which content was selected from the chosen guidelines. This content was then used to create a draft of actual recommendation statements and supporting paragraphs. At the third meeting, a straw poll was taken on the recommendation draft. Through discussion and rewording, consensus on content was achieved for all of the recommendations discussed over the course of the two meetings. Outside the meetings, non-content editing of the recommendations and supporting statements was performed, based on the panel's discussions, to create the final draft of the recommendations and supporting information.

Tool Development Process
The Guideline Implementation and Tools Panel met in person on two occasions between July and August 2008. Prior to the first meeting, a book was compiled that included all tools that were identified in the forty (40) guidelines. Sample tools were solicited from panel members as well. In total, the workbook contained forty-seven (47) tools. At the first meeting, the panel reviewed the draft recommendations and discussed whether any specific recommendations were impossible or burdensome to implement. Panel members were each given a book containing all the tools. In between the first and second meeting, panel members reviewed and graded each tool according to usefulness and whether or not it should be included in the guidelines. Votes and rating were tallied prior to the second meeting. Tools that received an average rating of below two (2) were eliminated. At the second meeting, the remaining tools were discussed and it was determined which of the remaining tools should be included, modified, or eliminated.

Completion and Distribution
Following the final panel meetings, Utah Department of Health staff formally drafted the complete guidelines document. The guidelines were published in March 2009. They were distributed through HealthInsight, who we have contracted with to conduct provider education. A postcard was sent to all controlled substances licensees in the State of Utah (~12,000 practitioners) to inform them of the guidelines and how to request a hard copy or print their own copy from the website. Not including the number of guidelines that individuals have printed off on their own, 908

copies of the complete guidelines have been distributed as well as 1,904 copies of the summary guidelines.

Summary of Recommendations

Opioid Treatment for Acute Pain
1) Opioid medications should only be used for treatment of acute pain when the severity of the pain warrants that choice and after consideration of other non-opioid pain medications.
2) When opioid medications are prescribed for treatment of acute pain, the number dispensed should be no more than the number of doses needed based on usual duration of pain for that condition.
3) When opioid medications are prescribed for treatment of acute pain, the patient should be counseled to store the medications securely, not share with others, and to dispose of properly when the pain has resolved to avoid their use for non-medical purposes.

Opioid Treatment for Chronic Pain
1) A comprehensive evaluation should be conducted before initiating opioid treatment.
2) Consideration, including adequate therapeutic trials, should be given to alternatives to opioid treatment before initiating opioid treatment.
3) The provider should consider and screen for risk of abuse or addiction prior to initiating treatment.
4) A treatment plan should be established that includes measurable goals for reduction of pain and improvement of function.
5) The patient should be informed of the risks and benefits and any conditions for continuation of opioid treatment, ideally in a written and signed treatment contract and plan.
6) Opioid treatment for chronic pain should be initiated as a treatment trial, usually using short-acting opioid medications.
7) Regular visits with evaluation of progress against goals should be scheduled during the period when the dose of opioids is being adjusted (titration period).
8) Once a stable dose has been established (maintenance period), regular monitoring should be conducted at face-to-face visits during which analgesia, activity, adverse effects, and aberrant behaviors are monitored.
9) An opioid treatment trial should be discontinued if the goals are not met and opioid treatment should be discontinued at any point if adverse effects outweigh benefits or if dangerous or illegal behaviors are demonstrated.
10) Clinicians should consider consultation for complex pain conditions, patients with serious co-morbidities including mental illness, patients who have a history or evidence of current drug addiction or abuse, or when the provider is not confident of his or her abilities to manage the treatment.
11) Methadone should only be prescribed by clinicians who are familiar with its risks and appropriate use.

B. Provider Education

HealthInsight was awarded the contract for provider education based on their extensive background in provider behavior change in Utah and their status as Utah's Quality Improvement organization. The HealthInsight Provider Education Intervention has been done through community-based meetings in both rural and urban communities to discuss safe pain medication use and prescribing habits. Meetings were conducted with primary care providers in 11 rural communities and 22 Wasatch Front communities. HealthInsight also conducted 17 presentations to larger physician audiences. HealthInsight also organized the publication of information on safe prescribing of opioids in various newsletters (see table below).

Articles	
Publication Name	Date Published
UMA Bulletin	Dec-08
UMA Bulletin	Apr-09
UMA Bulletin	Jun-09
QualityInsight	May-09
Utah Academy of Physician Assistants	Apr-09
Utah Academy of Family Practice Physicians	Jun-09
Utah Pharmacists Association	Jun-09 (WEB)

Recruitment
HealthInsight used existing relationships with primary care practices and rural hospitals to schedule presentations during regularly scheduled physician meetings. Previous experiences with physicians have shown that attendance is highest when the educational sessions are made a part of regularly scheduled physician meetings.

Large group meetings were scheduled as presentations during grand rounds, web cast grand rounds and physician conferences or large physician groups (e.g. Intermountain and University of Utah, described in more detail below).

Interaction/content delivery methods
The educational sessions were presented by a team comprising one pain expert, a primary care provider and a HealthInsight clinic facilitator.

At the educational sessions attendees were provided with:

- Comparison data available on the practice, community, state or national level; including death rates
- Guidelines and a tool box of resources including patient education forms
- Advice on how to use the DOPL Controlled Substances Database to identify problematic patients or their overall prescribing patterns, e.g.
    - Identifying patients with possible unsafe combinations of medications
    - Examining overall pattern of prescribing against “average” patterns
    - Identifying patients for whom prescribing might be altered given the guidelines presented and calling them in for visits, adjusting treatment
- Referral options for addicts, mentally ill and long term users
- Information on the how to access further assistance from HealthInsight
- Offer access to peer experts for follow-up questions via email or telephone

Immediately after the sessions, providers were asked to complete a survey. A second and third, online survey was available to them at 2 months and 6 months after the session. Completion of the surveys resulted in additional CME credits. The survey asked whether they have implemented systems changes or other improvement activities based on this topic (and the types and nature of these changes and activities); whether they have used the patient education materials and whether they have accessed and used the Controlled Substances Database.

Feedback on the education session and materials was systematically collected and reviewed to improve the product.

Data Collection system
HealthInsight utilized an online survey company to create a survey that providers could access 24/7 via the web. HealthInsight will provide UDOH with a report on presentation penetration, satisfaction with training, intent to change behavior, and engagement in implementing care process changes in December due to the fact that the final survey takes place six months after the presentation.

Data Analysis
HealthInsight will submit a final report to document the completed work including: time and extent of intervention with each provider location, feedback from providers, lessons learned to be considered for incorporation into future project phases, and any significant deviations from predicted to actual budget.

HealthInsight analytic staff will coordinate with UDOH Prescription Pain Medication Program (PPMP) to investigate changes in pain medication morbidity and mortality in the state over time. The rural intervention communities may be able to be compared to rural communities where the intervention does not take place, if there are any. Due to the limited number of annual cases in each community it is not expected that statistically significant reductions in mortality directly attributed to this arm of the PPMP project will be detectible in the first year of the project. Use of emergency department discharge data may increase the ability to detect a decrease in risk due to the increased number of events included (non-fatal overdose events)

HealthInsight met their target for setting up, scheduling, and executing the physician education sessions (see **Table 1,** below).

Results
Between August 2008 and June 2009, 581 medical providers and 136 additional participants attended learning sessions.

Six practices for safer opioid prescribing comprised the core educational component:
1) start low, go slow (methadone 5 mg bid for most patients); 2) obtain sleep studies for patients on >100mg/day morphine equivalent or >50mg methadone; 3) obtain EKGs for patients on methadone >50mg/day or when combining with other QT prolonging drugs; 4) avoid opioids in combination with benzodiazepines and sleep aids; 5) avoid long-acting opioid for acute pain; and 6) educate patients and families.

Session participants completed a self-reported survey querying changes in behaviors regarding the six practices at 0, 2, and 6 months. Of eligible participants, 25% completed the 6 month survey. Results are interim as data collection is ongoing.

By the 6-month survey, the percentage of respondents who had fully adopted the six practices were: 1) 52%; 2) 32%; 3) 53.3%; 4) 72%; 5) 84%; 6) 48%.

For a complete review of the preliminary survey results go to:
http://health.utah.gov/prescription/html/advisory_committee.html and select “HealthInsight Final Report” under “other resources: June 2009”.

The table below shows the location and the number of attendees of each presentation.

Provider Education Meeting Detail												
Rural Req= 10	Urban Req=20	Other Req= 12	Presentation Location	City	Date	# Doctors (MD, PA,NP,Psych. Etc.)	# Other (Pharm., DDS, EMT, CRNA, RN, Student, Etc.)	# Completed Survey 1	# Completed Survey 2	# Completed Survey 3	# Completed CSDB Exercise	# Adopted Guidelines
1			Sevier Valley Medical Center	Richfield	8/7/2008	7	2	7	4	3	3	4
	1		Utah Academy Family Physicians	Midvale	8/28/2008	8		3	2	2	1	2
		1	Medicaid Chronic Pain Group	Salt Lake City	9/16/2008	6	4					
	1		St. Marks Family Medicine	Salt Lake City	9/18/2008	12		12				
1			Four Corners Behavior Health	Price	9/23/2008	10	10	11	4	2	2	3
1			Gunnison Valley Hospital	Gunnison	9/25/2008	9		7	3	1	1	3
		1	Lakeview Hospital-Grand Rounds	Bountiful	10/2/2008	16		6	1			1
	1		Exodus Healthcare	West Valley	10/17/2008	11	3	14	8	5	6	7
1			Sanpete Valley Hospital	Mt. Pleasant	10/22/2008	7		7	6	2	5	5
1			Allen Memorial Hospital	Moab	10/23/2008	6	2	6	3	2	1	3
		1	UMA Women's Conference	Salt Lake City	10/23/2008	36		22			5	
	1		Health Clinics of Utah	Salt Lake City	10/30/2008	10	14	9	1	1		1
	1		Davis Hospital & Medical Center	Layton	10/31/2008	19		18	4	4	3	4
1			Mountain West Hospital	Tooele	11/4/2008	20		19	12	6	10	9
		1	Salt Lake Regional Medical Center	Salt Lake City	11/5/2008	30	27					
1			Central Valley Hospital	Nephi	11/7/2008	7		7	1	1	2	1
		1	SL County Medical Society	Ogden	11/18/2008	79		46			2	
		1	IHC Learning Day	Salt Lake City	11/21/2008	15	10					
	1		Mountainlands Clinic	Provo	12/3/2008	10	1	9	6		4	4
1			Heber Valley Medical Center	Heber	12/15/2008	8	1	8	3		1	3

Prepared by Erin Johnson, erjohnso@utah.gov, 801-538-6542

	1		Central Utah - Payson	Payson	1/21/2009	5	3	7	3		2	2
		1	U of U - Greenwood	Midvale	1/21/2009	23	6	18			5	
	1		Central Utah - Provo	Provo	1/23/2009	5	2	7	3		2	3
	1		Central Utah - Provo	Provo	1/27/2009	4	7	6	3			3
	1		Intermountain South Sandy Clinic	Sandy	2/9/2009	4	5	5	4		4	4
1			Castleview Hospital	Price	3/3/2009	5	4	7				
1			E. Carbon Medical Center	E. Carbon	3/4/2009	1	8	6				
1			Bear River Clinic	Tremonton	4/1/2009	7	9	7			1	
			IMC Central Region:			39		34	7		4	6
	1		Cottonwood FP, Internal Medicine, Medical Towers	Salt Lake City	4/23/2009	12						
	1		Taylorsville, Holladay Clinic, Holladay Pediatrics	Salt Lake City	4/23/2009	11						
	1		Salt Lake Workmed, Internal Medicine Associates, Intermountain So. Sandy, Hillcrest Clinic, Instacare, IMC OB/Gyn	Salt Lake City	4/23/2009	16						
		1	IMC Clinical Learning Day	Logan	4/24/2009	16	2	10				
	1		Salt Lake Clinic	Salt Lake City	4/28/2009	23	1	19	4		1	3
		1	IMC Clinical Learning Day	Salt Lake City	5/15/2009	41						
	1		IMC Layton	Layton	5/20/2009	8		2				
	1		BYU Health Center	Provo	5/20/2009	10	6	12			5	
	1		Intermountain Memorial Clinic	Salt Lake City	5/20/2009	7	2	6				
	1		Olympus Clinic	Salt Lake City	5/26/2009	5						
	1		U of U Neuro Psychiatric Institute	Salt Lake City	5/26/2009	9		9				
	1		Intermountain Bountiful Clinic	Bountiful	5/27/2009	4	7					

	1		Utah County Medical Associates	Payson	6/12/2009							
		1	U of U Greenwood	Midvale	6/24/2009							
		1	IHC DRMC CME Lecture Series	Cedar City	6/26/2009							
	1		Davis Family Clinic	Layton	7/14/2009							
		1	Mountain View Hospital	Payson	8/12/2009							
		1	PA Conference	Snowbird	8/14/2009							
		1	Orthopedic Society Meeting	Deer Valley	9/25/2009							
		1	IHC Northern Region Learning Session	Layton	10/9/2009							
		1	American Fork Hospital	Am. Fork	10/13/2009							
		1	Intermtn. Dept. of Medicine	SLC	10/23-24/09							
11	**22**	**17**	**Totals:**			**581**	**136**	**366**	**82**	**29**	**70**	**71**

C. Statewide Media Campaign

Vanguard Media Group was awarded the contract to develop the Prescription Pain Medication Program Media Campaign. Through bi-weekly meetings with Vanguard and the Prescription Pain Medication Program, much progress was made toward educating the general public about the dangers of prescription pain medication and how to use these medications safely. The campaign slogan that was selected was *Use Only As Directed.*

Production of Television Spot

During January and February of 2008, focus groups were conducted to determine which ad concepts would have the best impact on the general public. Vanguard Media Group identified the ad concept that was later used to produce the television spot, “Long Nap.” The script for "Long Nap" was taken and refined by Vanguard Media Group, then reviewed and approved by the Prescription Pain Medication Program. The 30 second television spot was then produced during the month of April.

2008 Television Air Schedule

In April 2008, Vanguard Media Group worked with local television stations to identify the station that would provide the strongest air schedule for the campaign. After receiving and reviewing the proposals from each television station, Vanguard Media Group recommended spending $25k with KSL-TV (Channel 5) and $20k with KSTU (Fox 13). The air schedule began on May 5, 2008 and continued through the end of May 2008. The following breakdown highlights the final elements (reach and frequency) that were delivered.

KSL-TV ($25k)

The following information outlines the results from the completion of the air schedule in May 2008. KSL fulfilled their negotiated and contracted responsibilities.

• KSL ran 66 of the 71 bonus spots as part of the added value element of the contract, which aired during the specified programming.

• KSL ran the 30 second television spot on Weather Plus during the month of May 2008

• The booth space at the KSL Family Fair was used to place a chalk outline of a body and a large sticker highlighting that prescription drugs killed more people last year than motor vehicle crashes.

• The tile ad was placed on the Web site under the KSL-TV tab and linked users to the campaign Web site. KSL reported that there were more than 62,500 views to the KSL TV web-page where the tile ad was placed.

• The rotating banner ads did run on KSL.com, totaling 52,236 impressions during the month of May, with a total of 73 click-throughs (0.14% click-through rate).

The total reach and frequency for the air schedule on KSL, without including the bonus television spots, came to 49.4% (Reach) with a frequency of 2.4 times that each person saw the spot. When the bonus spots are added in to the schedule, the numbers are 64.2% reach and a frequency of 2.8. This indicates that about 426,638 people between the ages of 35- 54 saw the television spot a total of 2.8 times during the month of May. These numbers indicate that KSL-TV fulfilled their end of the contract.

KSTU TV ($20k)
The following information outlines the results of the television air schedule that ran on KSTU (Fox 13).

• Fox 13 ran 38 bonus spots using the 15 second television commercial. There were 87 paid television spots that ran during the flight.

• A television segment on Fox 13's Good Day Utah aired on June 9, 2008 at 7 a.m. aired on a local Spanish television station.

The final report from KSTU combined the added value schedule along with the paid schedule. The numbers were reported as follows for the target audience of Adults 35- 54: Reach – 33.9%; Frequency: 6.1. Using the numbers, it is calculated that about 225,000 saw the television spot 6.1 times. These numbers indicate that KSTU fulfilled their end of the contract.

The television spot was also translated into Spanish and aired for a time on a local Spanish television station.

2009 TV Air Schedule:

In late November 2008, Vanguard Media Group reviewed proposals from local television stations, and recommended dividing out the schedule among KTVX (Channel 4), KJZZ (Channel 14) and Comcast (cable). The air schedule began on January 18, 2009 and continued through early-April 2009. The following breakdown highlights the elements promised in the contract and the final elements (reach and frequency) that were delivered.

KTVX/CW30 ($25k)

- KTVX/CW30 ran $25,000 in bonus spots as part of the added value element of the contract, which aired during the specified programming.
- The Good Things Utah segment aired on February 18, 2009.
- Tile ads were placed on both ABC4.com and CW30.com.
- Billboards ran during the scheduled flight weeks as negotiated.
- The Squeeze Plays ran on CW30 following the weekend movies as negotiated.

The total reach and frequency for the air schedule on KTVX/CW30, including the bonus television spots, came to 93.7 (Reach) with a frequency of 5.6 times. This indicates that about 646,800 people between the ages of 35-54 saw the television spot a total of 5.6 times during the flight times. These numbers indicate that KTVX/CW30 fulfilled their end of the contract.

KJZZ ($15k)

The following information outlines the results of the television air schedule and movie theater schedule that ran on KJZZ and at the Megaplex theaters respectively.

- KJZZ ran a total of 370 spots during the scheduled flight dates.
- Total value of the $10,000 air schedule was $24,585.
- Movie theater spots ran as negotiated.
- Traveling displays were rotated throughout various Megaplex Theaters in Salt Lake County.

The final report from KJZZ showed that they met their contracted obligations by running all of the spot times within the negotiated flight dates.

Comcast Cable Media Overview

A schedule was placed on Comcast to run in conjunction with the flight dates for the 2009 television air schedule. The numbers on cable are tracked differently than on broadcast television, but Comcast committed to and ran a 200% matching schedule. Therefore, the $12,000 paid air schedule was supported by a $24,000 added value schedule, meaning the investment was $12,000 and the returned value was $36,000. This included cross channel promotions with healthy living information on Comcast and the television spot made available on the "OnDemand" portion of their services.

Production of Radio Spot

Using information acquired during focus groups, the concept that best fit to the key messages and worked for a radio spot was "Poison Control Center." Following the initial development of a detailed script, the script was forwarded to Barbara Crouch, director of the Utah Poison Control Center, to assure that the spot sounded realistic. Following her review, the radio spot was produced and ready for use by the launch of the campaign on May 1, 2008. The radio spot can be listened to by accessing the useonlyasdirected.org website.

Radio Air Schedule

KSL Radio (102.7 FM and 1160 AM) $7,500

The following information outlines the results from the completion of the radio air schedule which ran in July 2008. KSL Radio fulfilled their negotiated and contracted responsibilities.

- KSL ran a 74% match in bonus spots (equal to 26 bonus spots), which is what was contracted on this portion of the added value. These spots also aired during the specified programming and within the contracted period.
- The rotating banner ads ran throughout KSL.com, totaling 35,000 impressions during the month of schedule, with a total of 92 click-throughs (0.26% click-through rate), which is more than twice the national average for click-through rates (0.1%).
- An e-mail blast was sent to 230,000 subscribers on Thursday, July 10, 2008, which provided information about the campaign and linked people to the website.
- Bookmarks were also provided to KSL Radio, who distributed them at their booth during the 24th of July Parade, as well as other KSL Radio remotes and events.

The radio spot, Poison Control Center, aired a total of 61 times. The total reach and frequency for the radio air schedule on KSL, including the bonus radio spots, came to 21% (Reach) with a frequency of 5.1 times. This indicates that about 101,000 people between the ages of 35- 54 heard the radio spot a total of 5.1 times during the two-week air schedule. These numbers indicate that KSL Radio fulfilled their end of the contract.

KSFI Radio (100.3 FM) $7,500

The following information outlines the results from the completion of the radio air schedule which ran in July and August 2008. FM100 fulfilled their negotiated and contracted responsibilities.

- FM100 ran 111 spots as part of the negotiated bonus schedule, which was contracted on this portion of the added value. These spots also aired during the specified programming and within the contracted period.
- The rotating banner ads ran throughout FM100.com, totaling 14,500 impressions during the month of schedule, however click-throughs were not able to be tracked for this.
- An e-mail blast was sent to 32,000 subscribers on Wednesday, July 23, 2008, which provided information about the campaign and linked people to the Web site.

The radio spot, Poison Control Center, aired a total of 218 times. The total reach and frequency for the radio air schedule on FM100, including the bonus radio spots, came to 19.1% (Reach) with a frequency of 9.1 times. This indicates that about 96,600 people between the ages of 35- 54 heard the radio spot a total of 9.1 times during the six-week air schedule. These numbers indicate that FM100 fulfilled their end of the contract.

Media Relations

Overall, the *Use Only As Directed* media campaign generated a total of $298,561 value in publicity based on a contract for $300,000 with Vanguard Media Group. During 2008, Vanguard Media Group generated more than $104,000 in publicity for the *Use Only As Directed* campaign. In 2009, a total of more than $194,000 in publicity for the *Use Only As Directed* campaign was generated. For 2009, the publicity value for television news coverage was $100,037.25 and print coverage was $94,561.10. (Note: The news or publicity value is calculated at three times the advertising value as it is seen as more credible than a paid advertisement.)

The campaign initially kicked off on May 1, 2008, with a press event at the State Capitol building. In attendance were the four primary television stations (KUTV, KTVX, KSL and KSTU), the two major statewide newspapers (Salt Lake Tribune and Deseret News), the Standard Examiner (Davis and Weber County), along with KCPW (Radio). Prior to the event, a press kit was developed, which resembled a prescription pain medication bottle with a label appropriate to the campaign. A backdrop banner was also produced with the new logo. Each of the television stations, except for KTVX (Channel 4) ran a news segment about the start of the campaign. The press kit was also mailed to the Spectrum (St. George), Univision (Spanish), and The Daily Herald (Provo). This generated a story in the Spanish Fork Press and the St. George Spectrum shortly thereafter.

Shortly after the kick-off press event, KSL's editorial board published an editorial about the need for such a campaign and praised UDOH for addressing the issue. Other opportunities were pursued by Vanguard Media Group to work with local media outlets to generate stories that support the campaign's efforts. This included a segment on Fox 13's Good Day Utah morning news, which featured discussion about the "Use Only As Directed" campaign, the problems that Utah is experiencing, and the need for such a campaign. Another opportunity to speak with the media occurred on June 25 with Rebecca Cressman on FM100. A television segment on Good Things Utah also took place, and footage was later used on a news story about disposing of Rx pain medications.

Two story angles account for the majority of news coverage in relation to the campaign on 2009, and included the release of the guidelines in March 2009 and the distribution of the news release about Utah seeing a decrease in prescription drug overdose deaths from 2007 to 2008. The latter story was picked up by every major television outlet in Utah, including an NBC affiliate station in Idaho (KPVI) and a Fox News affiliate in Denver, Colorado (KDVR). The major print media outlets in Utah also picked up the story along with some of the more rural papers in Utah.

Other stories that were pitched and coordinated as part of the media relations budget for 2009 included a segment on Good Things Utah, which featured a Program representative, and graduated into a news story that ran during the 5:00 p.m. news two days later. Another story was pitched and coordinated with Jed Boal at KSL relating to the Utah Poison Control Center and the numbers they were seeing in calls related to prescription pain medications. The Deseret News also ran a very large Sunday Edition story on prescription pain medications, telling the story of multiple people at various stages of recovery from their prescription pain medication addiction. Readers of the article were directed to the Program's website: www.useonlyasdirected.org.

Periodically, the Program issued news releases and media advisories related to different aspects of its work. The following is a list of news releases and media advisories issued by the Utah

Department of Health Office of Public Information for the Program during FY 2008 and 2009:

- July 31, 2007 – News Release – "New Campaign Aims at Fighting Pain Medication Abuse"
- April 30, 2008 – Media Advisory – "UDOH to Unveil Campaign to Reduce Overdose Deaths"
- May 1, 2008 – News Release – "Plain & Simple: Use Only As Directed"
- October 2, 2008 – News Release – "UDOH, Partners to Look for Clues in Rx Drug Deaths"
- October 20, 2008 – Media Advisory – "Gov. Huntsman Declares Prescription Safety Awareness Week"
- November, 19, 2008 – Media Advisory – "UDOH Seeks Input on Guidelines for Prescribing Pain Meds" March 26, 2009 – News Release – "UDOH Finalizes Guidelines for Prescribing Pain Meds"
- June 2, 2009 – News Release – "State Sees Dip in Rx Drug Deaths in 2008"

Website Development

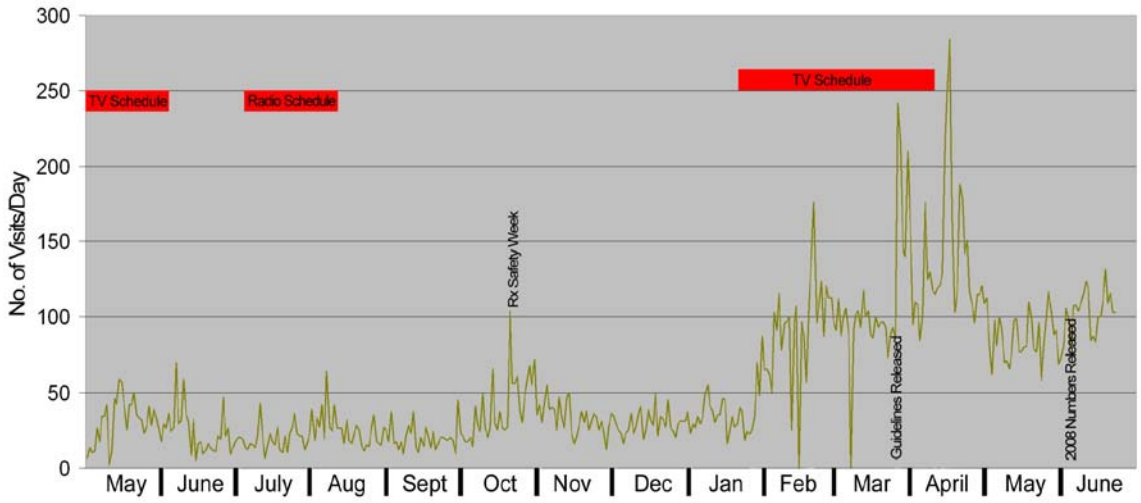
The website, www.useonlyasdirected.org, went live on May 7, 2008. During the first three weeks, we requested feedback from the Advisory Committee and the Patient and Community Education Workgroup for improvements to the website. Changes were made based on feedback received.

The website was programmed with a Web-based Content Management System that allows those with a username and password to access the control center of the site and update as needed. As needed, Vanguard Media Group made updates to design portions of the Web site not able to be completed using the CMS.

An e-mail account was established using Xmission (info@useonlyasdirected.org) to allow users of the website to submit questions or comments. Those e-mails are forwarded to the state-based email account: useonlyasdirected@utah.gov.

Visitors to the website have been tracked since the launch of the campaign. The statistics show that the majority of people entered the URL directly (www.useonlyasdirected.org), while others came from Google, Bing, Yahoo and health.utah.gov. Over the life of the website, hits per day increased in conjunction with events and media stories regarding the Program (Figure 1: Visits to www.useonlyasdirected.org from May 2008 to Sept. 2009).

Website Hits for Useonlyasdirected.org from May 2008 through June 2009



During 2009, $1,000 was allocated from the radio air schedule to add the radio spot audio to the homepage of the Web site.

The website has served as a mechanism for tracking public awareness of the campaign. At various points throughout the campaign, peaks in website visits were associated with the release of the Guidelines, media stories on various topics, and the media air schedules.

Collateral Materials

A bookmark, poster, traveling display, PowerPoint template and informational card were designed, produced, and distributed throughout the state to local county substance abuse coordinators, pharmacies, doctor's offices, provider educators, law enforcement, aging services, and others. They were made available to anyone who requested them for the purpose of educating the public, patients, or doctors on the potential dangers of prescription pain medication. A floor decal was also produced and used at the KSL Family Fair booth and the Days of '47 Parade in conjunction with a chalk outline of a body. In total, 80,000 bookmarks were printed and distributed; 30,000 informational cards were printed and distributed; 10,000 posters were printed and approximately 7900 were distributed; 5,000 window clings were printed and approximately 2500 were distributed (see Appendix – Educational Materials Tracking for a breakdown of where materials were sent, and amount of respective materials distributed; see Appendix - Traveling Display Tracking for a details of when and where the traveling display was set-up).

Other items distributed by the Program included copies of the PowerPoint template, a number of Microsoft PowerPoint presentations containing information on research and work done by the Program, CD/DVD copies of the television commercial and radio spot, and a fact sheet about prescription pain medication misuse/abuse in Utah.

Although many of the collateral materials were designed and produced as part of the 2008 contract, some of the work associated with preparing materials that were distributed to some of the health districts, namely the traveling displays, were associated with the 2009 contract budget. Additionally, Vanguard Media Group worked with the Program to layout the opioid prescribing guidelines. The layout included the full and summary versions of the guidelines, and overseeing the design, placement, and coordination for printing.

Campaign Awareness Week
Prescription Safety Week took place from October 20-October 26, 2008, and was announced by an official proclamation from Governor Jon Huntsman, declaring the week Prescription Safety Week. Traveling displays were set up in high traffic areas in Salt Lake City and educational materials were distributed at pharmacies, doctor's offices, and conferences. Editorial board visits took place in early October with KSL, Deseret News, and Salt Lake Tribune, requesting that a story be run during Prescription Safety Week. Recordings of the radio spot were sent to all major radio stations requesting PSA's during that week. In coordination with the Salt Lake City Mayor's Coalition on Alcohol, Tobacco, and Other Drugs, a public forum was held at the Salt Lake City and County Building. The forum was taped and re-played locally on Channel 17.

Campaign Impact/Effectiveness:

Follow Up Public Opinion Survey

A telephone-based public opinion survey was developed as a means of evaluating the *Use Only As Directed* public awareness campaign and obtaining additional information for future efforts. In June 2009, a public opinion survey (follow-up) was executed to evaluate changes in perceptions and opinions relating to prescription pain medications in Utah. The survey instrument was developed using questions from an initial survey implemented in February 2008 (initial survey). Some questions were eliminated, while others were added. Questions kept from the initial survey

were not changed in the follow-up to assure comparability between the question and results between the surveys. The survey was also reviewed by the Patient and Community Education Work Group, which led to the addition of several more questions to the survey.

The main objective of the post-campaign public opinion survey was to evaluate any changes in public awareness, opinions, and behaviors related to prescription pain medications in Utah over the course of the campaign. The initial survey conducted in February 2008 provided baseline data for comparison.

To achieve this objective for the follow-up survey, 410 telephone interviews were conducted with Utah residents, and sought to provide a representative sample of the population of Utah as a whole. The survey questioned respondents from 20 of the 29 Utah counties.
Specific objectives for the public opinion survey included:

- Identify the changes in level of awareness Utah residents have about the dangers, risks, and prevalence of misuse/abuse of prescription pain medications among Utah residents since the initial public opinion survey conducted in February 2008.
- Evaluate what caused changes in opinion about prescription pain medications.
- Establish an understanding of the use of prescription pain medications in Utah, where people store and dispose of their medications, and sharing of prescription pain medications for use in future efforts.
- Identify the recall ability of Utah residents in relation to elements of the public awareness campaign.

Research Methodology

Survey Design and Development

The questions from the initial public opinion survey were reviewed and pertinent questions were included in the follow-up survey; also, additional questions were drafted for the follow-up public opinion survey. Once the initial survey draft was completed, it was sent to members of the Team and discussed in the Education Workgroup. Feedback and revisions were made accordingly and the survey was then finalized and programmed for data collection.

Sampling Procedures

A comprehensive database of Utah residents was used to develop a random sample of the primary target audience for the research. The primary target audience consisted of male and female residents of Utah, age 18 and older. The number of interviews conducted allowed for an accurate extrapolation of responses to the entire population of the state, with a 95% confidence level and a +/- 4.84% margin of error. The number of respondents surveyed represents the population distribution across the state of Utah. In all likelihood, the survey samples for the initial and follow-up surveys were different. Meaning that those surveyed at follow-up were not the same people surveyed during the initial survey.

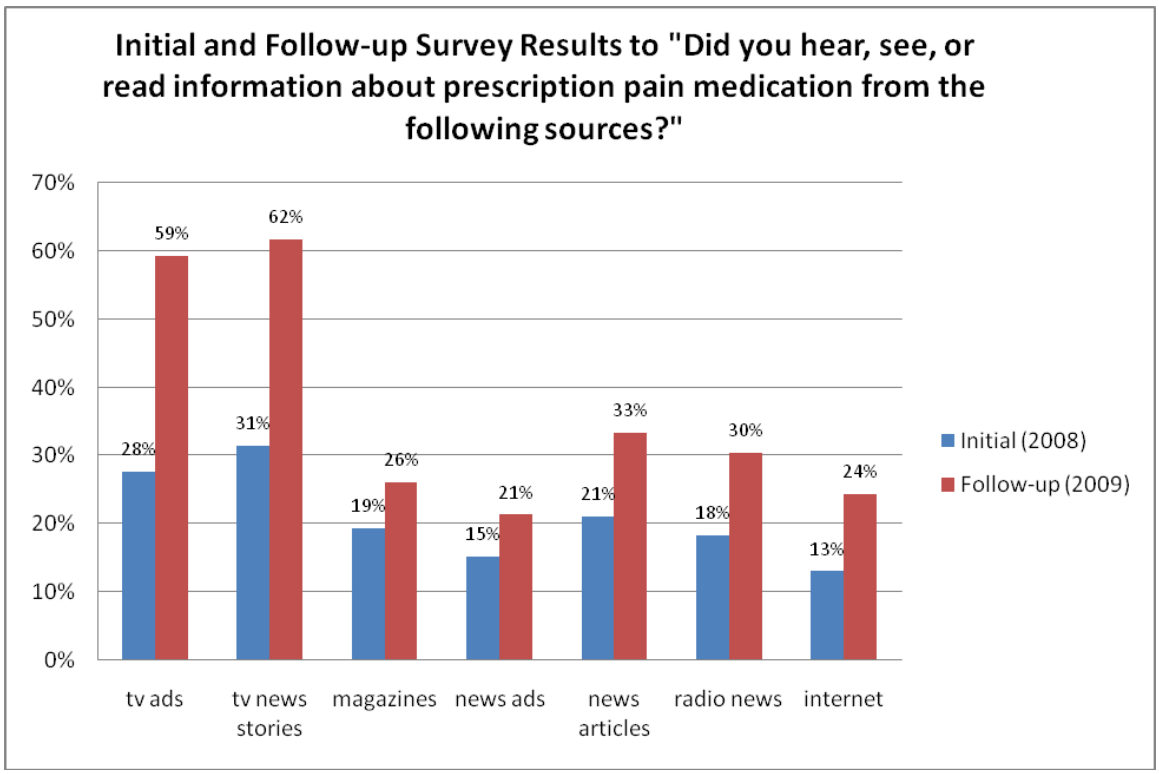
Results

From before the public awareness campaign began to its conclusion, there were several encouraging results uncovered by the survey. Highlights of the follow-up survey findings include:

- Forty-eight percent (48%) of Utah residents recall seeing the campaign's television commercial.
    - The majority (62%) who saw the commercial saw it more than 5 times.
- Fifty-one percent (51%) said that the media messages made them less likely to take Rx medications not prescribed to them.

- Fifty-two percent (52%) said that the media messages they saw made them less likely to share their Rx medications.
- Nearly one-third (29%) reported that their understanding of the dangers of prescription pain medication changed during the past year.
- Only 16% of respondents recognized the campaign slogan *Use Only As Directed*.

The Program has not been the only organization in Utah generating media messages about prescription pain medications; however it is useful to compare exposure to media messages related to safe use of prescription pain medication before and after the media campaign to find out whether there were changes during the life of the campaign. There were large increases in exposure to media messages through several sources. The sources producing the largest increases in exposure to media messages from initial to follow-up were “TV ads” and “TV news stories,” with each of those categories increasing by 31%.



*All respondents on the follow-up survey were asked specifically about seeing media messages from each of the different sources. However, on the initial survey only those who responded "Yes" to the general question, “Do you recall hearing, seeing, or reading any advertisements about safely using prescription pain medications?” were asked about the specific sources.

Just over half (51%) of respondents reported that the media messages made them less likely to take prescription pain medications not prescribed to them, and 52% reported that the media messages made them less likely to share their prescription pain medications. The majority of respondents (90%) did not feel that the media messages exaggerated the dangers of prescription pain medication misuse.

Those questions that were identical on the initial and follow-up were compared using chi-square to test whether the proportion of “Yes” and “No” responses varied from initial to follow-up. The questions with a significant association ($p<0.05$) between response and time of survey are reported below (Table 1).

Table 1. Survey variables w/significant differences from initial to follow-up (based on chi-square tests).		
	% Responding "Yes"	
Question	Initial	Follow-up
Do you consider pain medications prescribed by a doctor to be safe?	75.2	82.8
Do you feel that most Utahns take their prescription pain medications EXACTLY as prescribed by a doctor?	39.4	30.0
Have you ever taken a prescription pain medication that was not prescribed to you?	18.9	12.5
Do you feel that prescription pain medications are misused?	94.8	97.7
Do you know someone who has misused or abused a prescription pain medication?	55.1	65.8
Have you seen information about the dangers of prescription pain medication at your doctor's office?	44.4	36.6
Have you seen information about the dangers of prescription pain medication at your pharmacy?	42.4	33.2

While the results regarding exposure to media messages about safe use of prescription pain medications were encouraging, some survey results did not match with what we anticipated. Particularly, a significantly smaller proportion of respondents reported seeing information about the dangers of prescription pain medication at their doctor's office or pharmacy compared to the initial survey. Also, the fact that significantly fewer respondents reported ever having taken prescriptions not prescribed to them may indicate that fewer people are willing to admit to that behavior (which may be due to campaign messaging against that behavior).

A common source of prescription misuse in Utah, and throughout the USA, is obtaining meds from a friend or family member[1]. In the initial survey, 17% of respondents had ever shared a prescription pain medication with a friend, family member, or loved one. On the follow-up survey, 13% had ever shared a prescription pain medication. While the results are not what we would expect, the differences in proportion from pre to post test were not statistically significant.

Two questions regarding use of medications not prescribed to the person using them were added to the follow-up survey. The first was whether or not the respondent would share prescription pain medications with a family member or friend who needed them, with 19% responding "yes." However, most respondents (89%) felt it was wrong to take prescription pain medications not prescribed to them. The second question regarding sharing of medications asked whether the respondent would accept a prescription pain medication from a friend, with 18% responding in the affirmative. Additionally, 10% felt it was safe to share prescription pain medications with friends, family, or loved ones on the follow-up survey, with no significant difference from the initial survey.

Most people were aware that consumption of alcohol should be avoided when taking prescription pain medications (n=262, 78%). However, very few (n=10, 3%) were able to specifically name any of the other substances that are recommended to be avoided when taking prescription pain medications (e.g. anti-anxiety medications and sleep-aids). Avoiding alcohol, anti-anxiety medications, and sleep medications was included as part of the public education campaign.

The majority (95%) of respondents felt that prescription pain medications are misused (no significant change from the initial survey (93%)). Nearly 2/3 (65%) of respondents reported

[1] Substance Abuse and Mental Health Services Administration, Office of Applied Studies (2008). *Results from the 2007 national survey on drug use and health: national findings.* NSDUH Series H-34, DHHS Publication No. SMA 08-4343. Rockville, MD; Available at http://www.oas.samhsa.gov/NSDUH/2k7NSDUH/2k7results.cfm#2.16

knowing someone who has misused or abused prescription pain medication, a significant change compared to the initial survey responses (55%).

Over 1/7 (15.6%) of respondents reported being familiar with useonlyasdirected.org, and 2% had ever visited the website. However, this was not significantly higher than the recognition of a decoy site that we had listed to weed out those who responded "yes" to all. Of those familiar with the website, most (35%) did not remember where they learned about it, while 24% learned about it through the TV commercial.

A key message for the public education efforts of the Program was in regards to keeping prescription pain medications locked in a safe place. Therefore, respondents were asked where they kept prescription pain medications. The tables below detail the responses for this question from both the pre and post surveys (Table 2).

Table 2. Pre and Post Campaign Survey Results: Where do you keep your Rx pain medications?				
	Pre (2008)		Post (2009)	
	N	%	N	%
Medicine Cabinet	146	35%	113	28%
Don't Have Prescription Pain Medications	75	18%	106	26%
Out of Reach/Safe Place/High Up	13	3%	58	14%
Bathroom	30	7%	40	10%
Kitchen	56	14%	36	9%
Locked Cupboard	54	13%	29	7%
Bedroom	22	5%	26	6%
Drawer	22	5%	16	4%
In a Safe	7	2%	12	3%
Purse/Handbag	6	2%	8	2%
Other	9	2%	8	2%
Disposed of Them	*	*	2	1%
Don't Know	3	1%	1	0%

The number of respondents who were familiar with how to dispose of expired prescription pain medications remained unchanged from pre and post survey at less than half (43%). However, 18% of respondents reported that as a result of the media messages they disposed of their leftover medications.

Among those who had ever kept leftover prescription medication, the most common reason for keeping the medication was that the individual simply didn't bother disposing of it (32%). Table 3 provides a complete description of the responses collected on reasons for keeping leftover prescription medication. Failing to dispose properly of these medications increases the likelihood of misuse/abuse in the community, and is an issue that needs to continue to be addressed.

Table 3. June 2008 Results: Reason for keeping leftover prescription medication.		
	N	%
Simply Didn't Bother Disposing of It	65	32%
Future Need	64	31%
In Case of an Emergency	31	15%
Didn't See Need of Disposing	15	7%
Money, Save on Future Cost, Valuable	12	6%
Other	10	5%

Didn't Know How to Dispose of Them	7	3%
Don't Know	1	1%

The campaign targeted adults between the ages of 25-54, who account for the majority of prescription overdose deaths in Utah, with the average age of death being 40 years (http://health.utah.gov/prescription). However, when respondents were asked which age group had the most deaths, the group most often (45%) mentioned was young-adults (20-34 years).

Less than ¾ (65%) of respondents felt that most doctors prescribe appropriate amounts of pain medication, with the majority of those believing that doctors prescribe too much (74%), compared to those who felt that doctors prescribe too little (5%).

Due to truncated data on two open-ended questions from the follow-up survey, 100 respondents were contacted a second time and asked again about ways their understanding about prescription pain medication changed in the past year, and about what influenced the change. Tables 4 and 5 highlight the results from those questions. The most common change in understanding was in regards to being more aware of the dangers of prescription pain medication (25%), and the most common factor influencing a change in understanding of prescription pain medications was from knowing someone who had a problem with prescription pain medication (28%).

Table 5. June 2009: In what ways has your understanding about prescription pain medications changed in the past year?

	(N) %
More Aware of the Dangers of Pain Meds	(27) 25%
Understand More About Prescription Pain Meds in General	(16) 15%
More Aware of the Abuse of Pain Meds	(10) 9%
I Don't Want to Use Them / Should Get Rid of Them	(8) 7%
People Dying / Suffering from Prescription Pain Meds	(7) 7%
More Aware of the Addictive Nature	(7) 7%
The Problem is Growing	(6) 6%

Table 6. June 2009: What influenced the change?

	(N) %
Knew Someone Who Had a Problem with Pain Meds	(30) 28%
Television Commercials/News	(17) 16%
Advertisements/News [in general]	(13) 12%
Doctor/Physician Talked to Me	(6) 6%
Personal Education	(6) 6%
Guy Who Goes to Sleep and Dies Advertisement	(4) 4%
Read Article (Newspaper, Magazine, Internet)	(4) 4%

The pre and post surveys were most helpful in identifying increases in awareness of risks due to exposure to media messages, increases in exposure to media messages over the life of the campaign, exposure to the Program's TV commercial, and awareness created by media messages regarding safe use of prescription pain medications.

D. Research Progress

Progress has been made during the past year. UDOH and DOPL have worked actively to establish a partnership and technical environment to support the analyses needed to meet the legislative direction of HB 137 and provide adequate security for the sensitive data contained in the CSD. A MOU was signed November, 2007. However, it took several months to determine an adequate technical environment for transferring the sensitive data from DOPL to UDOH and several more months for the actual transfer of data to occur. We received the complete data sets in May, 2008. Once the data was transferred, a team of programmers has had to clean the data in order to make it usable. This has been a great deal of work due to the large number of records in the database and the fact that only limited quality checks are performed on the data as received in the CSD.

During 2008, we have put together a Research Team with a strong skill set. Substantial progress has been made on essential steps needed before the research results can be produced. This has included linking the prescription data across individuals (developing a master patient index) and organizing the large database for efficient analysis. Now, with a finalized master patient index for the Controlled Substance Database linked to Emergency Department data, Death Certificate data, Medical Examiner data, we are ready to analyze and get results for the following research topics:

Prescribing practices by practitioner specialty
Relationship between dose of morphine equivalence and death
Incidence rates of death by type of prescription

E. Research Initiatives

Throughout FY 08, meetings were held by the Prescription Pain Medication Program's IT and Research Team to identify research initiatives that will provide the most useful information toward addressing this problem and preventing future deaths. As noted below, a substantial proportion of decedents had received a prescription for a controlled substance that contributed to their death. However, for a substantial proportion of decedents, the source of the medications and other factors contributing to death were not known from existing data. To address that information gap a new research project was designed to examine risk factors associated with overdose deaths involving prescriptions. This research will take place at the Office of the Medical Examiner. Other research will include looking at emergency department visits related to overdoses of prescription medication. We are developing a systematic way of identifying the cases of interest through Death Certificate and Medical Examiner data. We have brought together a team of talented individuals to work on this topic.

Risk Factor Study

On October 26, 2008 we began a study to look at risk factors for prescription opioid deaths. This prospective study will collect information on all deaths under the jurisdiction of the Utah Medical Examiner for which drug poisoning (overdose) is suspected or determined as cause of death. The Office of the Medical Examiner is authorized under Section 26-4-7 of the Utah Code to investigate deaths resulting from poisoning or overdose of drugs.

Our investigation includes:

- A standard medical examiner toxicological assay on each decedent
- Review of vital statistics and medical records (available through the Utah Department of Health)
- Interviews with the decedent's next of kin conducted by trained researchers
- Review of relevant medical records during the year prior to death

A prospective case series study was designed to collect information on all deaths under the jurisdiction of the Utah Office of the Medical Examiner (OME) for which drug poisoning/toxicity (overdose) was suspected as a cause of death for a period of one year (beginning October 26, 2008). The vast majority of overdose deaths in Utah are related to prescription pain medications. Therefore, a key goal for the study is to identify risk factors related to prescription pain medication overdose death in Utah.

The Utah Department of Health (UDOH) teamed with researchers from the University of Utah to appoint and train interviewers to conduct telephone-based interviews on behalf of the OME, using a standardized questionnaire form, with next-of-kin and other close family members and/or friends of decedents to collect data for the study.

This study received approval by the Utah Department of Health Institutional Review Board. The study was patterned after a previous study of suicide using a similar methodology. While the primary focus of the study is prescription-related overdose deaths, the study was designed to collect information on all drug overdose deaths (illicit and non-illicit) as well as all deaths where suicide is suspected as the manner of death.

A preliminary analysis based on four months of data, collected on cases with dates of death from October 26, 2008 through Feb. 28, 2009, was conducted in June, 2009 and a report on the results was subsequently drafted. Interviews were conducted on 253 cases with dates of death between Oct. 26, 2008 and Feb. 28, 2009. Multiple interviews were conducted for 33 of the 253 cases, resulting in data from 286 separate interviews. In order to focus on the purposes of the Program, suicide and natural cause-of-death cases were excluded from the analysis. This resulted in 139 cases remaining for analysis.

*Note that the following highlights may include suspected suicide deaths that did not involve drugs, but were later deemed to be "undetermined" cause of death by the Medical Examiner. Also, the highlights include both illicit and nonillicit drug overdose deaths.

Highlights of the preliminary analysis include:

- Unintentional drug overdose deaths (including illicit drug overdose deaths) in Utah were slightly more common among the male population (56.1%), and among those between the ages of 25 and 54 years (75.5%), matching the profile of unintentional prescription drug overdose deaths in Utah in past years.

- More than half (51.1%) of the decedents were unemployed in the last two months of life and 1/3 (32.4%) had no health insurance at the time of death, which is higher than the general population in Utah who lack health insurance (10.7%) according to recent estimates (UDOH, 2009). Further investigation of socio-economic status and any role it may play in unintentional drug overdose in Utah is needed.

- It has been hypothesized that religion may play a role in prescription drug overdose death in Utah, in particular those of the predominant LDS faith. The preliminary results show that the proportion of LDS decedents in this study (51.8%) was less than the proportion

among the general population in Utah (approximately 60%) according to recent reports (Associated Press, 2008; Pew Forum on Religion & Public Life, 2008).

- A history of substance abuse was common among persons who died of unintentional drug overdose, with 76.6% having at least one indicator for a history of substance abuse. Additional analyses are needed, but this will be important for guiding interventions and the overall approach to this problem. Particularly telling is the fact that over 50% of accidental/undetermined (A/U) deaths had ever received treatment for substance abuse.

- A history of pain was common among the A/U deaths investigated. In the majority (n=109, 78.4%) of cases respondents reported that the decedent suffered from pain. Of those, 89 (81.7%) reported that the pain was chronic. Back pain was the most common (n=42, 30.2%) cause of pain reported. Additional analyses will explore further the interactions between pain and substance abuse, but based on these preliminary findings appropriate treatment and management of pain appears to be of particular importance in addressing this issue.

- Of 109 (78.4%) decedents who reportedly suffered from pain, 87 (79.8%) reportedly took prescription pain medication for the condition which caused pain. Further, 47 (34.1%) respondents reported that the decedent experienced inadequate pain relief in the last two months of life, with 22 (46.8%) of those reporting that inadequate pain relief was also a significant crisis for the decedent in the last two weeks of life.

- Of the 98 decedents who used prescription pain medications for pain in the past year, 78 (79.6%) had used prescription pain medications within one month prior to death. In the future these data will be compared to CSDB data to assess accuracy of reported use of medication. Also, indicators for non-medical use of prescription pain medication will be analyzed and reported.

- Symptoms related to sleep apnea experienced by decedent during the last two months of life included snoring unusually loud (n=52, 38.0%), having trouble breathing during sleep (n=43, 31.4%), and stop breathing for periods of time while asleep (n=21, 15.3%). Actual diagnosis of sleep apnea was reported in 19 (13.9%) decedents. Based on these findings it appears sleep apnea may be under-diagnosed among unintentional overdose deaths.

- As reported previously (Caravatti, Grey, Nangle, Rolfs, & Peterson-Porucznik, 2005), obesity again appeared to be a possible risk factor, with the rate of obesity found among the study population (41.7%) greater than the rate of obesity among the general population in Utah (23.1%) (Centers for Disease Control and Prevention, 2008).

A strength of this study is the high response rate among those who were contacted for interview. For cases from the first four months of the study period, there were just four cases where someone declined participating in the interview when contacted by an interviewer. Additionally, of the A/U cases identified as study candidates, interviews were conducted for 85.3% of the cases. Lack of ability to contact interviewee (e.g., no contact information available, incorrect/erroneous contact information, no answer even after multiple attempts at various times of the day) was the main reason for not completing a higher percent of interviews for cases from the first four months of the study period. As of August 19, 2009 a total of 448 interviews had been conducted for the study, with 314 of those interviews being conducted for cases deemed suspected or confirmed drug overdose.

Interviews continue to be conducted and further analysis of the data collected will be conducted to provide a more complete description of the study population, as well as provide more insight and evidence into potential risk factors related to unintentional overdose deaths in Utah.

Emergency Department Research
During FY08, the majority of our research concentrated on deaths due to overdose of prescription pain medication. We now intend to look more closely at emergency department (ED) encounters. The goal for this part of the research is to better understand the magnitude and importance of non-fatal overdoses as a consequence of prescription opioid use and abuse. Our primary research questions are:

- How many individuals visit the ED for opioid overdoses?
- What percentage of these individuals has had multiple ED visits for opioid overdoses?
- What percentage of these individuals end up dying from prescription overdose?
- How many individuals who died from prescription overdose had visited the ED for an overdose before death (potential value as warning sign and point of intervention)?
- How many individuals that visited the ED for opioid overdose had a valid prescription at the time of the encounter?

Developing a Case Definition
There is no nationwide, systematic way of measuring deaths due to opioid overdose. Some of the inherent difficulties in comparing Utah to other states are due to the differences between case definitions. Some states may differ on whether they count suicide cases that result from prescription opioid overdose. Others may differ on whether they exclude or include deaths that have prescription opioids in combination with illicit drugs. Research that UDOH has conducted up until now has been based on using a combination of the data we obtain from the Medical Examiner (ME) and from Death Certificates (DC) to determine the number of cases. We have excluded suicides as well as cases that have prescription opioids in combination with illicit drugs in the numbers that we have reported yearly. We are currently in the process of creating a way to systematically pull the cases we are interested in from the ME and DC data. This will make for a much stronger analyses since it will be automated rather than coded by hand each year.

F. Research Findings

Background information
Unintentional fatalities due to prescription medications are an increasing problem in United States and Utah. Over the past few years, the Utah Medical Examiner noted an increase in the number of deaths occurring due to overdose of prescription opioid medications that are typically used for pain management. Epidemiologic studies of data collected by the Office of the Medical Examiner, as well as from emergency department encounters and controlled substances dispensing confirmed the increases and uncovered an alarming problem.

During the years 1997–2004 deaths attributed to poisoning by drugs increased 128% in Utah from 174 to 397. Deaths of Utah residents from non-illicit drug poisoning (unintentional or intent not determined) have increased from about 50 deaths per year in 1999 to over 250 in 2006. The increase was mostly due to the higher number of deaths from prescription opiate pain medications, including methadone, oxycodone, hydrocodone, and fentanyl.

Methadone was the most common drug identified by the Utah medical examiner as causing or contributing to accidental deaths, accounting for a disproportionate number of deaths compared to its frequency of use. Methadone was the single drug most often associated with overdose death and had the highest prescription adjusted mortality rate (PAMR) with an average of 150 deaths for every 100,000 prescriptions during the study period (range: 89 deaths/100,000 prescriptions in 1998 to 224 deaths/100,000 prescriptions in 2004). From 1997–2004, population-adjusted methadone prescriptions increased 727%. This increase in the methadone prescription rate was for treatment of pain and not addiction therapy.

The numbers of prescriptions for four of the primary drugs of concern with respect to fatal drug overdose have increased at a greater rate than the growth of the Utah population. The population-adjusted relative increase in prescribing for methadone and fentanyl exceeded 700% while oxycodone nearly tripled.

For the years 1999–2003, unintentional deaths due to prescription medications were the fourth-leading cause of death in 25–54 year olds in Utah. Notably, while deaths of unintentional or undetermined intent caused by prescribable narcotics nearly tripled, cases of self-inflicted harm from narcotics remained stable from 1991–2003.

In 2006, methadone was implicated in 30% of non-illicit drug-related deaths, oxycodone in 21%, hydrocodone in 18%, and fentanyl in 9% of deaths associated with non-illicit drug overdose. The average age at death for deaths due to overdose of non-illicit drugs was 42 years old, with the ages ranging from 16 to 80 years old. Rates of death were slightly higher for males (51.3%) than females. At least one death occurred in 24 out of the 29 counties in Utah, suggesting that the problem spans both the urban and rural population.

Research combining Medical Examiner's data and data from the CSD from 1997-2004 found that 50% of individuals who died of an overdose of methadone had a valid prescription at the time of death. This is informative in showing that there are two distinct populations: individuals with a valid prescription and individuals who found prescription opioids from some other source. To prevent future deaths of individuals with a valid prescription, the approach may be teaching proper use and warning against deviating from the directions given by their doctors, whereas to prevent deaths of individuals who are getting prescription drug from other sources, the approach may be to decrease availability of these drugs (for example, by educating others to lock up or dispose of their leftover medication).

A national report found that among young adults aged 18 to 25 who used prescription pain relievers non-medically in the past year, over half (53.0 percent) reported that they obtained the medication from a friend or relative for free. (National Survey on Drug Use and Health, 2006, retrieved on October 14, 2007 from http://www.oas.samhsa.gov/2k6/getPain/getPain.htm)

Recreational use of prescription drugs is increasing. In 2003, approximately 15 million Americans reported using a prescription drug for non-medical reasons at least once during the year. Approximately 6.3 million Americans reported current non-medical use of prescription drugs. (Office of Applied Studies, Substance Abuse and Mental Health Services Administration, National Survey on Drug Use and Health, 2004)

Abuse of prescription pain killers in the last year now ranks second, following marijuana, as the nation's most prevalent illegal drug problem. Even more foreboding is the fact that the number of new abusers of prescription drugs is equal to the number of new abusers of marijuana. Much of this abuse appears to be fueled by the relative ease of access to prescription drugs. Approximately 60 percent of people who abuse prescription pain killers indicate that they got their prescription drugs from a friend or relative for free. (Office of National Drug Control Policy, 2007, retrieved on October 17, 2007 from http://www.whitehousedrugpolicy.gov/news/press07/022007.html)

Preliminary results from the linked CSD-Vital Statistics database analysis

For the years 1999-2004, the CSD includes 22,215,471 records of filled prescriptions. This represents 2,339,058 unique individuals that filled at least one controlled substance prescription. During the same time period, there were 1,920 drug poisoning deaths identified using death certificates. We analyzed the demographics of the decedents and present summary results in Table 1. Intentionality status of the decedents is determined by the medical examiner or certifying official and is captured on the death certificate. Fatal drug overdose is a problem of middle-aged adults, with an average age of 38.8 years. The majority (67%) of drug poisoning where intent was accidental or undetermined were male. The greatest number of deaths occurred in the urban

counties of the Wasatch Front where the largest proportion of the population lives, but when death rates are used to account for the population distribution (number of deaths per 100,000 population) this problem was seen to have affected frontier, rural and urban areas of the state similarly.

We linked the Medical Examiner Database to the de-duplicated CSD in order to determine what proportion of the poisoning decedents had ever filled a prescription for the implicated drug and what proportion had a valid prescription at the time of death or within certain time intervals of death. Among accidental drug poisoning deaths, 40% (101/251) of decedents had received an opioid prescription that would have lasted to within 30 days of death, and 74% (185/251) had ever received an opioid prescription. Among drug poisoning deaths of undetermined intent, 41% (393/967) of decedents had received an opioid prescription that would have lasted to within 30 days of death, and 75% (729/967) of decedents had ever received a prescription for an opioid drug. Decedents with undetermined intent, who had filled prescriptions tended to be older (38.6 years compared to 36.5 years; p=0.0059) than those for whom we found no evidence of prescription. A greater proportion of decedents of unknown intent from non-urban Utah counties had evidence of a prescription (83%) than decedents of unknown intent from urban Utah counties (73%; p=0.0181). No such differences were seen among decedents of accidental intent.

Current Findings

The number of non-illicit drug overdose deaths decreased in 2008 by 12.6% (see Figure 1.). In 2007, the number of deaths related to non-illicit drugs was 317. This was the leading cause of injury death in Utah and one of the leading causes of death for 25-54 year olds in Utah.

Figure 1.

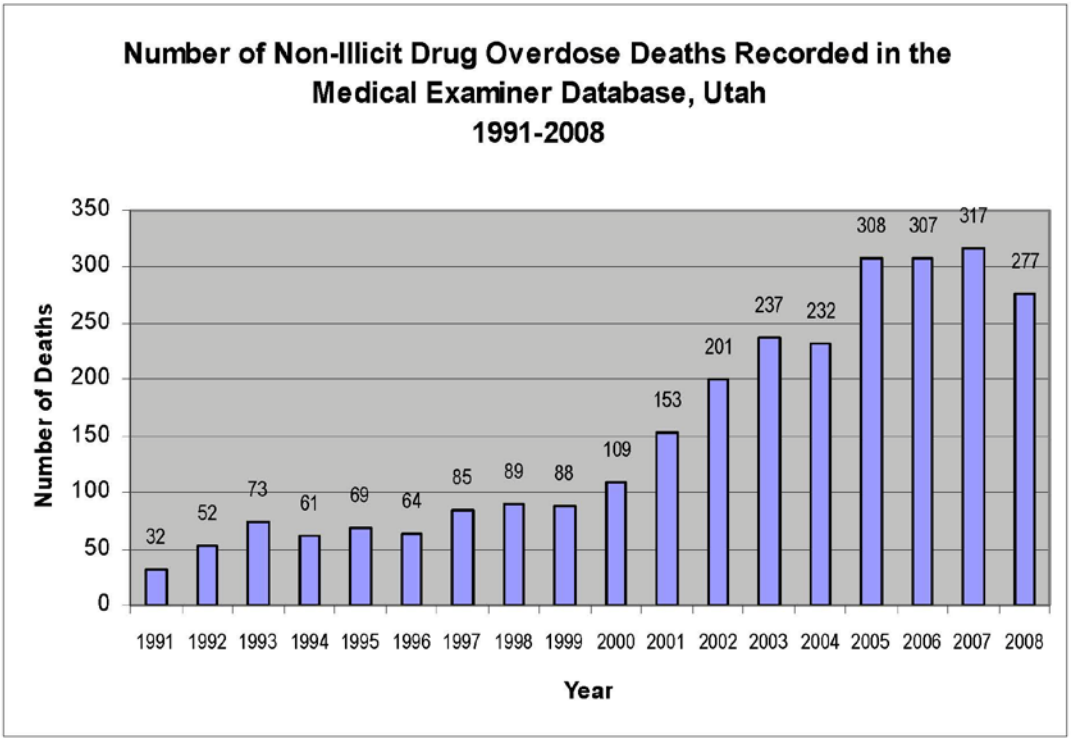


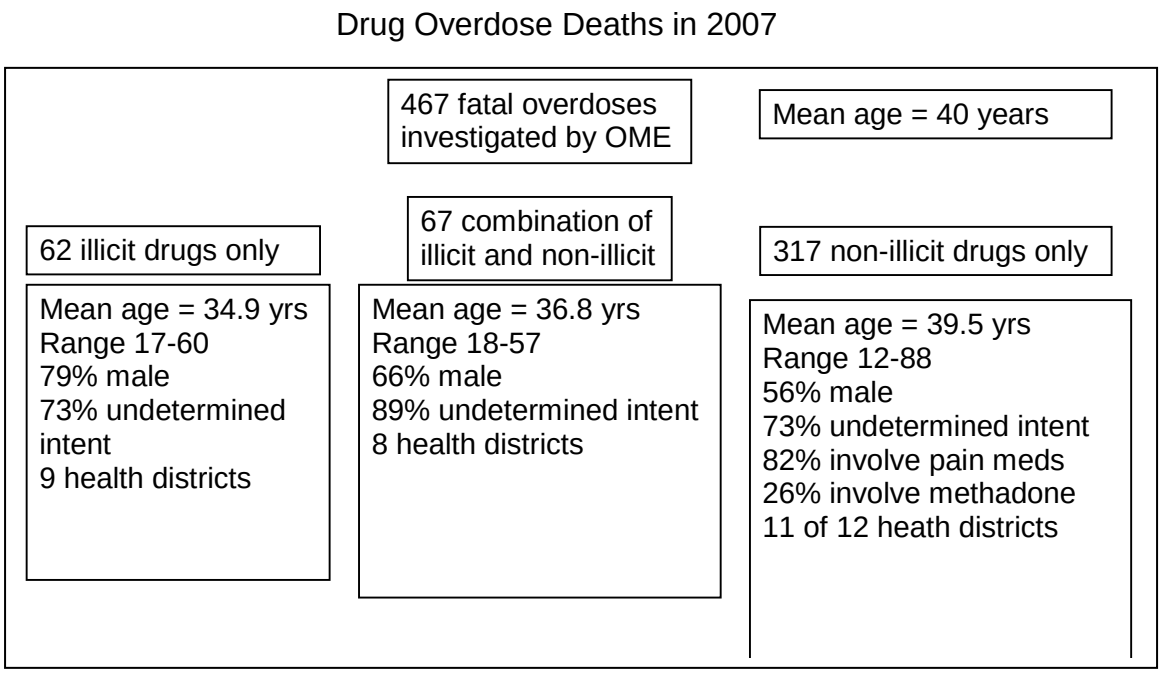
Figure 2 shows the number of deaths by type by year for 2006-2008.

Figure 2. Number of Accidental/Undetermined Drug Overdose Deaths by Year by Drug Type

Year	Illicit Overdose Deaths	Combo (both Illicit and Non-illicit)	Non-illicit Overdose Deaths
2006	96	63	307
2007	62	67	317
2008	89	41	277

In 2007, the Medical Examiner investigated 467 overdose deaths related to drugs of any type. Of these, 62 decedents had strictly illicit drugs appear on the toxicology results while 317 had strictly non-illicit drugs in the toxicology results and 67 decedents had a combination of illicit and non-illicit drugs. The mean age of people who died from a drug overdose in 2007 was 40 years old. The mean age of people who died strictly of non-illicit drugs was higher (39.5 yrs) than those who died of illicit drugs (34.9 yrs) (See Figure 3).

Figure 3.



The individuals who died of strictly illicit drugs in 2007 were more frequently male (79%) than those who died of strictly non-illicit drugs (56% male).

Unintentional fatalities due to prescription medications are an increasing problem in Utah and the United States. The annual number of prescription-related drug overdose deaths began to increase substantially in 2001 and the increase continued through 2007. In 2008, the number of deaths related to non-illicit medications (which includes both over-the-counter and prescription drugs) was 277, a 10% decrease from 317 in 2007. Prescription medication overdose deaths are the leading cause of injury death in Utah and one of the leading causes of death for 25-54 year olds in Utah.

Most of medication-related deaths are related to prescription pain medications, such as oxycodone, hydrocodone, methadone and fentanyl. In 2008, the Medical Examiner investigated 407 overdose deaths related to drugs of any type. Of these, 89 decedents had strictly illicit drugs appear on the toxicology results while 277 had strictly non-illicit drugs in the toxicology results and 41 decedents had a combination of illicit and non-illicit drugs. The mean age of people who died strictly of non-illicit drugs was higher (40.3 yrs) than those who died of illicit drugs (36.27 yrs). The individuals who died of strictly illicit drugs in 2008 were more frequently male (82%) than those who died of strictly non-illicit drugs (52% male). Deaths from only non-illicit drugs occurred in 22 of Utah's 29 counties showing that this is both an urban and rural problem and that it is impacting most counties across the state.

Deaths from non-illicit drugs only occurred in 11 of the 12 health districts showing that this is both an urban and rural problem and that it is impacting most counties across the state.

Emergency Department encounters related to opioids have also had a steady increase over the past few years (See Figures 4 and 5).

Figure 4.

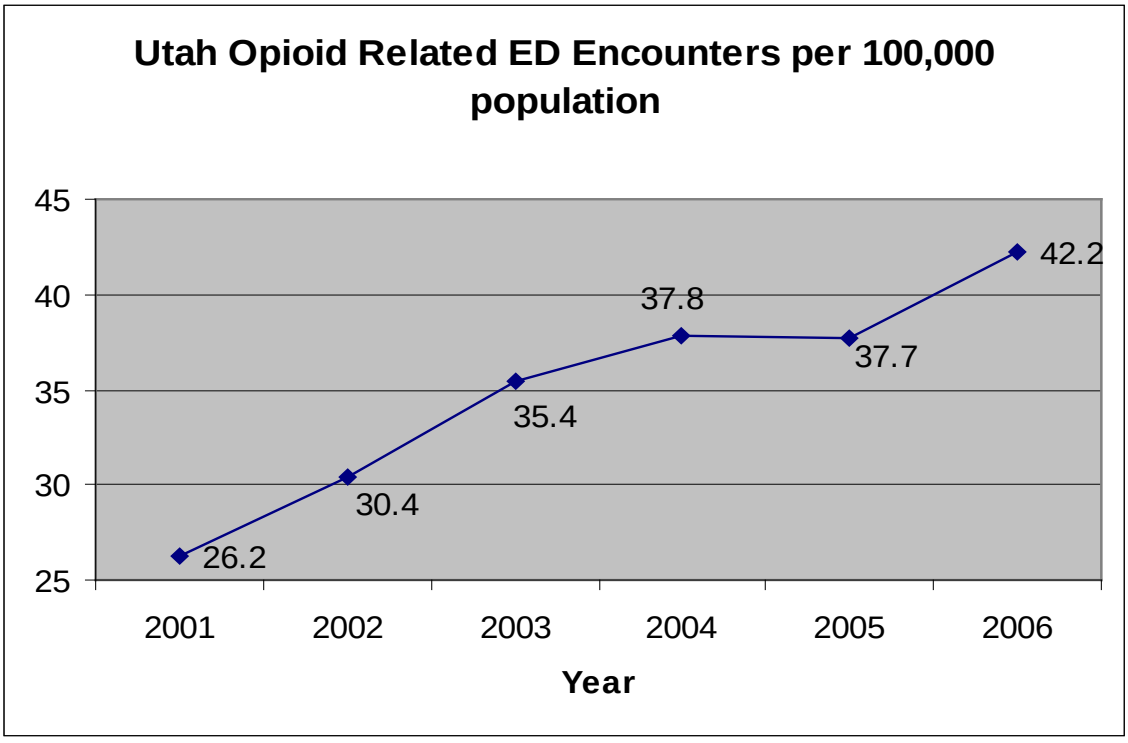


Figure 5.

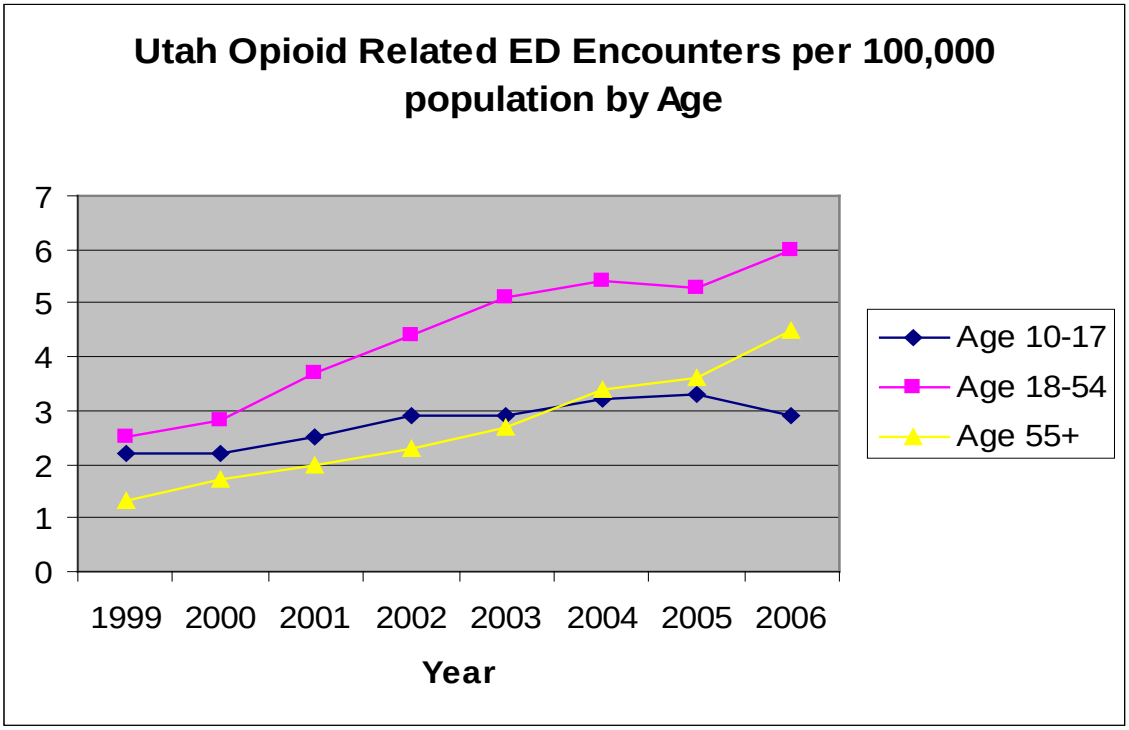


Figure 6.

Percentage of Accidental and Unknown Opioid Poisonings Deaths by Month (1999-2005)

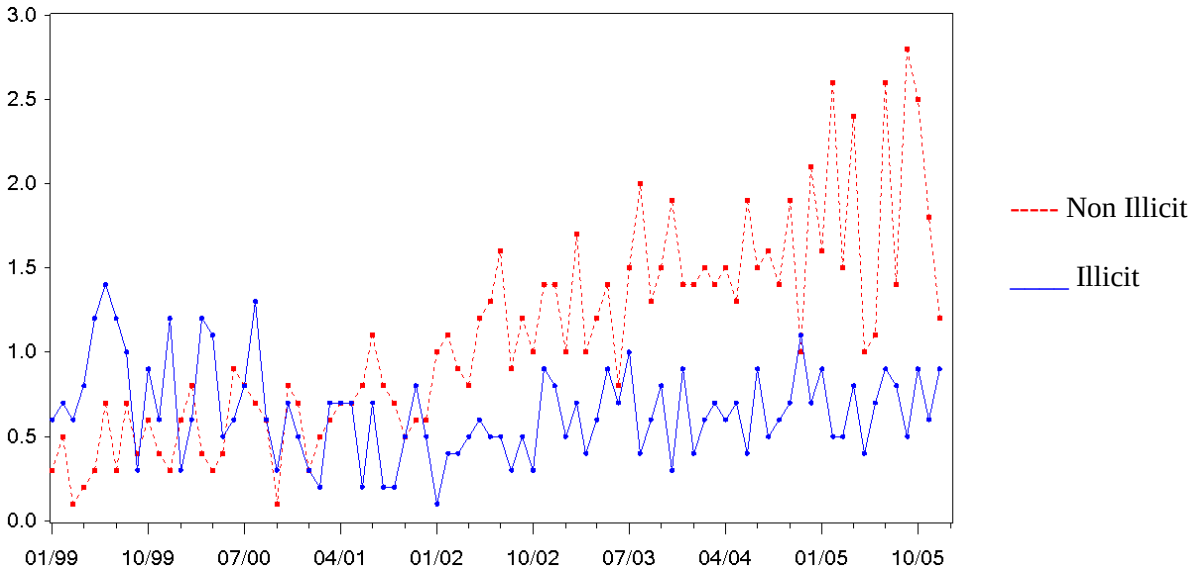
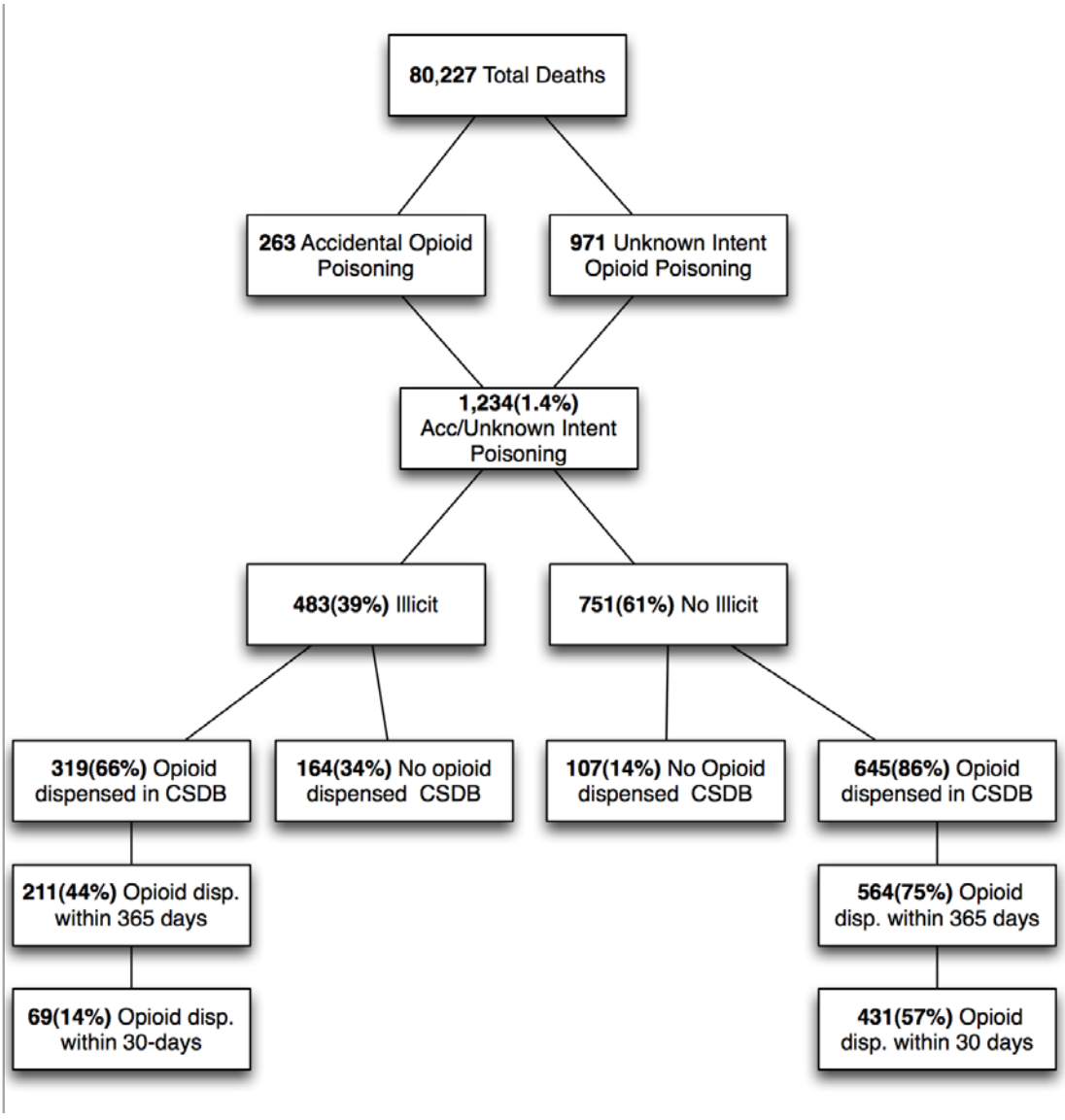


Figure 6 illustrates the percentage of total deaths identified as being opioid poisonings of accidental or unknown intent. The blue solid lines represents accidental and unknown intent poisonings where illicit drugs were found on toxicology and the red dashed line represents the same category of deaths where no illicit drugs were found on toxicology. It is easy to notice that opioid poisonings of accidental and unknown intent where illicit drugs were found on toxicology have remained relatively constant over the seven year period while the same category of poisoning deaths where no illicit drugs were found on toxicology has been steadily increasing since 2001.

Figure 7.

Breakdown of Accidental and Unknown Opioid Poisonings Deaths and Evidence of legal Access to Opioid Medications. (1999-2004)

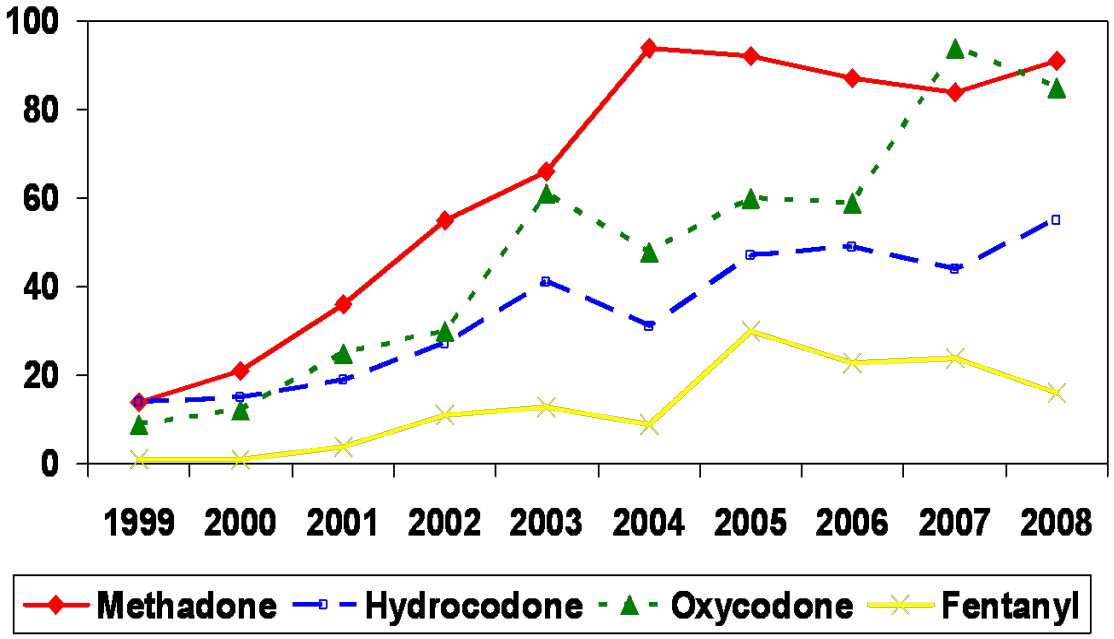


During the years of 1999 to 2004, there were a total of 80,227 deaths, of which 263 were identified as accidental opioid poisonings and 971 were identified as opioid poisoning with unknown intent resulting in 1,234 apparently non-intentional opioid poisonings. In 483 (39%) of the accidental and unknown opioid poisoning deaths illegal substances (e.g., cocaine,

methamphetamine, marijuana) were found during toxicology examination, and in 751(61%) no illegal substances were found. Sixty-nine (69) of the 483 (14%) accidental and unknown opioid deaths with illicit drug use had at least one opioid dispensed where the supply would have ended within 30-days of death if the drug was used as prescribed, while 431 of 751 (57%) of the non-illicit group had at least one opioid dispensed where the supply would have ended within 30-days of death.

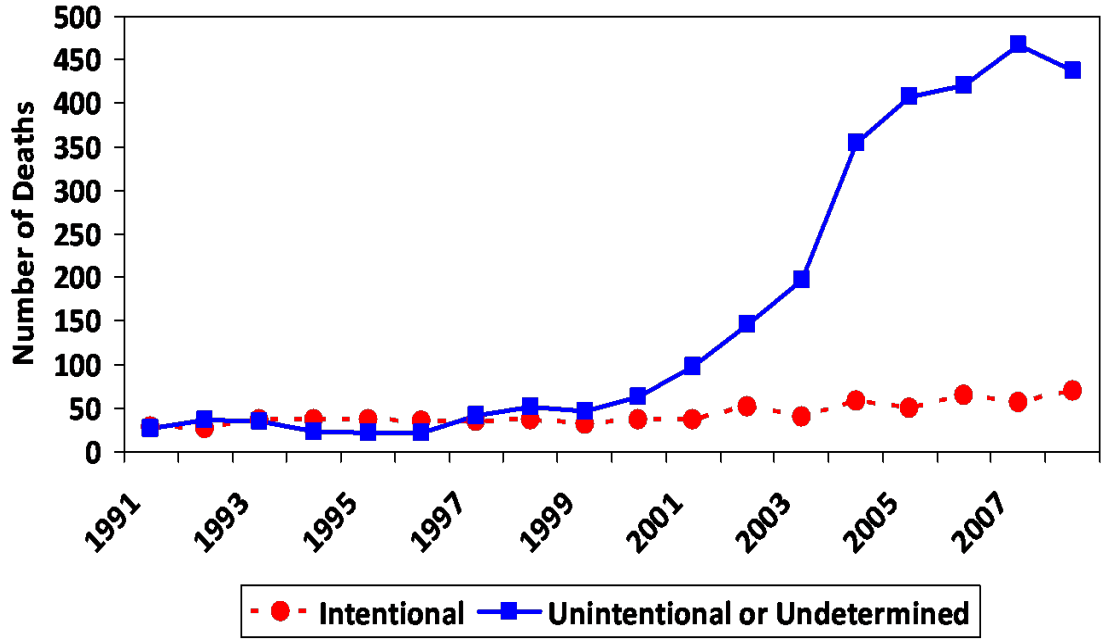
The legal drugs most often associated with overdose deaths include methadone, hydrocodone, oxycodone, and fentanyl. (See Chart 1)

Chart 1: Drug Poisoning Death by Drug and Year: Utah 1999-2008



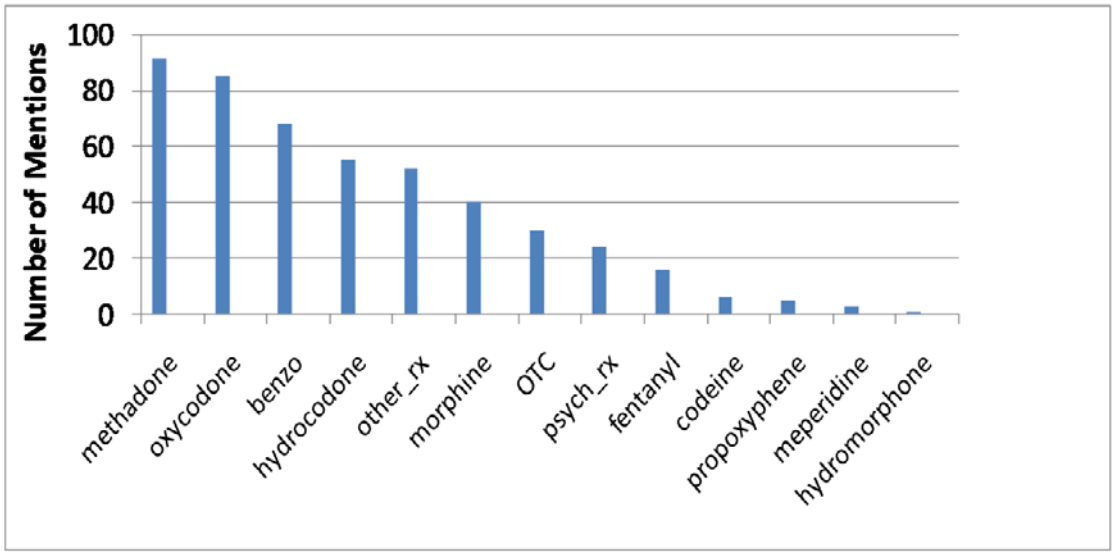
In 2008, at least one non-illicit drug overdose death occurred in 22 of Utah's 29 counties, males and females were affected about equally – with females accounting for 48 percent of deaths and males accounting for 52 percent. Pain medications remain the most common type of prescriptions involved in these overdose deaths, and were present in 82 percent of the non-illicit drug deaths. They include drugs such as oxycodone (such as Oxycontin and Percocet), hydrocodone (such as Lortab and Vicodin) and methadone. The number of deaths associated with prescription drug overdoses in the State of Utah decreased by 12.6 percent from 2007 to 2008. The decrease represents 40 fewer deaths during that timeframe. The dip is the largest decrease in non-illicit drug overdose deaths recorded in the Medical Examiner's database since 1991. Still, 277 Utahns died in 2008 of what public health officials view as a preventable epidemic. During the period from 1991-2008, intentional poisoning deaths remained fairly constant. (See Chart 2)

Chart 2. Drug Overdose Death by Manner and Year: Utah 1991-2008



Methadone was the most common drug mentioned in the Medical Examiner report as contributing to a non-illicit overdose death with a mention in 91 (32.9%) cases. Oxycodone was mentioned in 85 (30.7%) cases followed by benzodiazepines in 68 (24.6%), and hydrocodone in 55 (19.9%).

Chart 3. Substances Involved in Non-illicit Overdose Deaths of Accidental or Undetermined Intent-2008



F. Committees and Number of Participants

1. Steering Committee: 11 members; met monthly
2. Advisory Committee: 119 members; meet quarterly
3. Patient & Community Education Work Group: 43 members; met monthly

4. Policy, Insurance, & Incentives Work Group: 19 members; met monthly but was dissolved June 2008.
5. Data, Research, and Evaluation Work Group: 8 members; met as-needed.
6. Short term work groups:
    a. Guideline Expert Panel: 16 members; met throughout April-June to develop draft of guidelines
    b. Guideline Implementation Panel: 14 members; met in July to determine which tools to include in guidelines

All meeting minutes can be found at health.utah.gov/prescription

G. Recommendations on the Controlled Substances Database

Prepared by: Division of Occupational and Professional Licensing and Utah Department of Health

HB 137: "Requires the department to report to the legislative Health and Human Services Interim Committee and the legislative Business and Labor Interim Committee…to present its recommendations on: the use of the Utah Controlled Substances Database to identify and prevent the misuse of opiates; inappropriate prescribing; and adverse outcomes of prescription opiate medications."

The Utah Controlled Substance Database Program was legislatively created and put into effect on July 1, 1995. It is used to track and collect data on the dispensing of Schedule II-V drugs by all retail, institutional, and outpatient hospital pharmacies, and in-state/out-of-state mail order pharmacies. The data is disseminated to authorized individuals and used to identify potential cases of drug over-utilization, misuse, and over-prescribing of controlled substances throughout the state.

The CSD records are retained in the form that they are sent from the individual pharmacies. Some data quality weaknesses have been identified including missing or invalid data in key fields such as patient name or provider DEA number.

The Utah Department of Health has made the following recommendations on how to use the CSD to identify and prevent misuse of opiates, inappropriate prescribing and adverse outcomes of prescription opiate medication. The recommendations were sent to Department of Commerce and Division of Occupational and Professional Licensing (DOPL), who then commented on the status of the recommendation. The comments generally fall into one of the following categories:

- Great idea, warrants further consideration
- Great idea, already completed or being completed
- Great idea, project in the queue or awaiting funding
- Good idea, objective can be met with existing Database
- DOPL has concerns with the idea
- Potential idea, but other groups have expressed concerns

DOPL has worked with UDOH during the past two years to assist UDOH in accessing and understanding the Controlled Substances Database. DOPL has taken the initiative to make many beneficial changes and have plans to continue improving the Database this coming year. Since its inception in 1995, the Database has undergone many changes, both administratively and legislatively. These recommendations, along with other external recommendations and internal action points, will help DOPL to continue improving the Database.

The table below shows each recommendation by UDOH along with the response from DOPL as to the status of the recommendation and an explanation of the status.

Recommendations & Status of Controlled Substances Database

Prepared by Erin Johnson, erjohnso@utah.gov, 801-538-6542

Recommendation by UDOH	Status	Explanation from DOPL
Incorporation of a Master Patient Index. The Utah Department of Health has year creating a Master Patient Index for the CSD. A Master Patient Index will assign a specific identifying number to each individual patient by matching names with date of birth. This will make it easy and possible to view a patient's prescription history over time.	Great idea, warrants further consideration AND Potential idea, but other groups have expressed concern.	This idea highlights what is perhaps the greatest weakness of the Database, the errors created by user entry of names or dates of birth. Names and dates of birth were originally recognized as the primary identifiers since prescribers and pharmacies would not need to change prescribing or dispensing practices in order for the database to function. DOPL would have to change the Database "spine" in order to meet this recommendation. In addition, in order for the Master Patient Index to work, the prescribing practitioner and pharmacy will have to utilize the assigned index number throughout the process of prescribing and dispensing in order for the database to verify who is attached to the record. A potential IT concern is if the recommendation is intended to create another database (the Index) or just a field within the current database.
Counting of prescriptions by patient. We recommend that the Master Patient Index be linked with a counting device that would calculate a running total of the number of prescriptions for each patient. In addition to a counter for total number of controlled substance prescriptions, it would be useful to generate a running total of filled prescriptions by class of medication. These counters could be used in the future to trigger potential investigations if a patient fills more prescriptions in total or within a class than has been established as reasonable within a timeframe.	Great idea, already completed or being completed.	The Database already has the capability to count the number of prescriptions by individual in the Database, with the identifying limitations addressed under #1. Perhaps the interface functionality could be improved so the information is more easily found.
Counting of prescriptions by provider. We recommend that the database include an automated means of counting number of filled prescriptions by provider. This will allow for a means of triggering investigations if a provider writes more prescriptions within a timeframe than an established expected value.	Great idea, already completed or being completed.	The Database already has the capability to count the number of prescriptions by provider in the Database, with the identifying limitations addressed under #1. Perhaps the interface functionality could be improved so the information is more easily found.
Addition of non-human indicator field. Occasionally, controlled substances are prescribed to animals. Currently, the data from the animals' prescriptions are indecipherable from the data on prescriptions from humans (except by obvious names such as "Fluffy", comments in a name field). This causes problems in the analysis by skewing the data (at a glance, it may appear that many 2 year olds are taking controlled substances, but at a closer examination this is due to prescriptions for animals). A separate indicator field for prescriptions to non-human animals would help eliminate the problem.	Great idea, project in the queue or awaiting funding.	This is a very good idea that the Database is working on completing as resources become available.
Automated quality controls on data, such as programming legal values of fields, whenever possible. For example, the field of "sex" should only accept the answers Male or Female, and any other answer should be rejected (and perhaps automatically sent back to	Great idea, already completed or being completed	Currently, the Database creates an "exceptions report" that highlights errors in the data submissions and seeks corrections. If the exceptions report demonstrates a high level of error, the report is automatically rejected to

pharmacy for correction). Other examples include only accepting DEA IDs that follow the correct pattern of numbers and letters, and that the date of birth can not be later than the date the prescription is written or filled. Simple steps like these will increase the value of the data tremendously.	AND warrants further consideration.	the pharmacy for corrections. If the corrections are few, the Database contacts the pharmacy directly to correct the issue. Currently, 1 in 500 data records is identified as an error and requires staff coordination and correction with the submitting pharmacy. However, name variations are not caught as errors. The only time that the name field is considered an error is when it is left blank. The Database does NOT automatically reject an entire file if only a few records in the file have errors. **The Database will continue to identify additional data fields that can be highlighted for errors beyond those already identified.**
Action for incomplete reports or reports with illegal field values. For example, when entering the patient's sex, if a 9 is entered rather than an M or F, the report should not go through, but would reply that the answer is not valid. Another way to eliminate incomplete or incorrect reports would be to have an automated system that sent back these reports each time that DOPL uploaded the data and found the inconsistent fields. For example if the DEA number is 9999999999999 or if the DEA number doesn't match an entry from the Master DEA table, or the patient address is missing, the record should be rejected and returned to the sender.	Great idea, already completed or being completed.	If the exceptions report demonstrates a high level of error, the report is automatically rejected to the pharmacy for corrections. If the corrections are few, the Database contacts the pharmacy directly to correct the issue. **The Database will continue to identify additional data fields that can be highlighted for errors beyond those already identified.**
Additional indicator field for prescriptions picked up by someone other than the person for whom the prescription is written. This might assist in detecting fraud.	Great idea, project in the queue or awaiting funding.	The Database can currently provide this information. The greatest limitation has been the software used by the pharmacies, but most have the current software.
Standardization of the customer ID field. Currently, the customer ID field varies from driver's license number to social security number to written explanations about the customer. Consequently the data cannot be analyzed. Standardizing this would also require deciding whether the information would reflect the person for whom the rx is written or the person who is picking up the rx.	Great idea, warrants further consideration.	A good cost-benefit analysis could determine if the programming costs are worth the benefit.
Standardization of what goes into each field. For example, sometimes the "first name" field includes nicknames, middle names, or parenthetical comments. These could prevent the linking mechanism for "Firstname" from matching the first name if a nickname is entered.	Great idea, warrants further consideration.	A good cost-benefit analysis could determine if the programming costs are worth the benefit.
Establish a real-time link between the pharmacies and the CSD. Legislation passed in 2008 which would have established a pilot program for a real-time database. Unfortunately, due to the economic downturn, the money was retracted. The expansion of such a database statewide will result in increase of users and increase in frequency of use by each individual user. This would allow providers to learn what the patient got yesterday and last week and not just last month. This could be really important in the ER to treat someone	Great idea, warrants further consideration AND Potential idea, but other groups have expressed concern.	Real-time linking has been discussed often and supported by the Legislature. Perhaps the most significant issue here is covering the cost and truly defining "real-time." The current reporting is weekly, not monthly. The law allows more frequent reporting, but no pharmacy has elected to participate in more frequent reporting. (six pharmacies have expressed interest, but none have begun) Pharmacies have been worried that they not

safely if they aren't conscious, and to prevent acquisition of more drugs by drug seekers. Similarly it would help pharmacists know what patients had gotten from other pharmacies in the very recent past.		be burdened with the entire cost of compliance, among other concerns.
Evaluate the flags that are currently in place to trigger an intervention on the patient or providers behalf. For example, certain flags already exist that will trigger DOPL to send a letter to providers. Re-evaluating these with the expanded purpose of the database in mind can help to increase the value of each letter sent. Some things to consider are how many prescriptions are reasonable for a provider to write during a time period? How many prescriptions are reasonable for a patient to fill during a time period? If we identify high-risk drug combinations, a trigger could be set-up if a patient fills two or more prescriptions that are dangerous when combined. The provider(s) and patient could then be contacted and warned about the potentially dangerous combination. In many cases it may be that the drugs were prescribed by different providers who have no idea what else the patient is taking. This could save lives.	Great idea, already completed or being completed; Great idea, warrants further discussion; Other groups have expressed concerns AND DOPL has concerns with the idea.	Of course the purpose of the database is to protect the public from the abuse of controlled substances. The Database currently has some flags in place, such as for doctor shoppers. In addition, the Division enforcement area has used the information in bringing administrative cases against medical practitioners who, after a thorough review by medical professionals, are determined to have violated a standard of care with prescribing practices for controlled substances. Any expansion of the flags needs to be weighed very carefully against privacy rights and medical practitioner professional judgment. The system is a tool or resource for the prescribing and dispensing practitioners, but should not replace practitioner judgment. In the past, practitioners and the public have been concerned about DOPL or law enforcement or others going on “fishing expeditions.” A panel of medical providers, such as the Physician’s Licensing Board or another body would need to evaluate and establish any triggers that begin to evaluate the professional decisions of practitioners.
Procedures put in place for when flags are triggered. If DOPL reevaluates the triggers, they should also make sure that the appropriate procedures are put in place so that when the flags are triggered there is immediate and helpful action.	Great idea, already completed or being completed; Great idea, warrants further discussion; Other groups have expressed concerns AND DOPL has concerns with the idea.	Of course the purpose of the database is to protect the public from the abuse of controlled substances. The Database currently has some flags in place, such as for doctor shoppers. In addition, the Division enforcement area has used the information in bringing administrative cases against medical practitioners who, after a thorough review by medical professionals, are determined to have violated a standard of care with prescribing practices for controlled substances. Any expansion of the flags needs to be weighed very carefully against privacy rights and medical practitioner professional judgment. The system is a tool or resource for the prescribing and dispensing practitioners, but should not replace practitioner judgment. In the past, practitioners and the public have been concerned about DOPL or law enforcement or others going on “fishing expeditions.” A panel of medical providers, such as the Physician’s Licensing Board or another body would need to evaluate and establish any triggers that begin to evaluate the professional decisions of practitioners.
Market the CSD to providers and pharmacists to increase awareness of its existence and uses	Great idea, already	The Department of Commerce and DOPL are in the process of a public awareness

	completed or being completed.	campaign for the database. The current efforts include:Modifying continuing education for all medical practitioners who have access to the database so they can receive credit for DOPL taught classes about the database. All rules have been modified to permit the classes. Improving the Database interface to decrease login times and increase ease of use. Permit after hours registration with the database (by email password) so practitioners can create an account not only 44 hours per week (DOPL's hours), but 168 hours per week. Offering free classes to medical practitioners and others on how to use the database and get the most use out of the database.
Automatic logoff time should be extended. Providers are automatically logged off if the computer is left idling for a short time (5 minutes?) which requires the doc to spend time to re-login for each patient. This is very cumbersome and time-consuming in clinic. Providers suggest making it possible to stay logged in longer to help make the database more user-friendly.	Great idea, already completed or being completed.	Part of the Department of Commerce and DOPL redesign of the Database interface solves this problem. The redesign should be introduced this Fall.
The web-site needs to be accessible within no more than 3 minutes time. In order for the website to be used frequently, the 4 questions should not be asked every time, there should not be a need for both a password and a pin, and search parameters should be able to be saved with the provider's own preferences as defaults	Great idea, already completed or being completed.	Part of the Department of Commerce and DOPL redesign of the Database interface solves this problem. The redesign should be introduced this Fall.
Expand the database to include mandatory collection of data from: methadone treatment, Indian Health Services, VA & military. Currently individuals who receive prescriptions from these sources do not show up in the Controlled Substance Database	Great idea, warrants further consideration	The Database has attempted by memoranda to bring groups that are currently exempt from the Pharmacy Practice Act into cooperation with the Database in order to better protect the public. None have elected to do so.
Improve ease of registering for access to the CSD. Make it possible to receive access to CSD online (rather than phoning in). The provider should be able to change the password once it is received for security reasons.	Great idea, already completed or being completed.	Part of the Department of Commerce and DOPL redesign of the Database interface solves this problem. The redesign should be introduced this Fall.
. Make the reports sortable by date and or provider. Change the format of the results of a search from pdf to a sortable table. That way we can sort the data to make it chronological, by provider, by type of medication, by pharmacy etc. The pdf format is not chronological and so can be very cumbersome to use.	Great idea, already completed or being completed.	Part of the Department of Commerce and DOPL redesign of the Database interface solves this problem. The redesign should be introduced this Fall.
When providers run reports on themselves as providers and there is a patient who shows up on our list, the provider should be able to click on the patient and have it bring up that patients report. Currently the provider has to write down the name, exit out of the list, and then re-enter the list for the patient.	Great idea, project in the queue or awaiting funding.	Until May 2009, providers were not entitled to see this information. Now the law permits it. The Database intends to provide this functionality.
Create a way on the database to flag an issue to have it forwarded to DOPL. If a provider sees suspicious behavior on a patient that he/she is not likely to see again, then it can be forwarded to DOPL so they can alert the PCP or next provider of the possible issue.	Great idea, project in the queue or awaiting funding.	
Allow preferences to be saved on the search page. For	Great idea,	

example, one provider may always like to search with last name and date of birth, but each time he/she would have to change the search parameters.	warrants further discussion AND project in the queue or awaiting funding.	
Change the date of birth to be something the provider can type in, not scroll through. It takes too much time to scroll through it each time as it defaults on 1900	Great idea, already being completed.	Part of the DOPL redesign of the Database interface solves this problem. The redesign should be introduced this fall.

For more information please contact:

Erin Johnson
Department of Health
Prescription Pain Medication Program
erjohnso@utah.gov
801-538-6542

Mark Steinagel
Department of Commerce
Division of Occupational and Professional Licensing
msteinagel@utah.gov
801-530-674

V. Budget

A. Funding 2008

	FY 08
Labor Commission	$250,000
Legislative Appropriation	$150,000
Workers Compensation Fund of Utah	$77,000
U of U, Research Center for Excellence in Public Health Informatics	$23,000
Total	$500,000

B. Funding 2009

	FY 09
Labor Commission	$250,000
Legislative Appropriation	$150,000
Division of Substance Abuse and Mental Health	$88,954
Commission of Criminal and Juvenile Justice	$37,142
Total	$526,096

C. Itemized Budget Detail for 2008

Item	Cost
Personnel	$78,901
Office Expenses	$16,135
Contracts:	
Provider Education	$200,000
Media Campaign	$143,553
Research	$47,505
BRFSS Survey	$7,970
Total*	$494,064

D. Itemized Budget Detail for 2009

Item	Cost
Personnel	$284,124
Office Expenses	$23,000
Contracts:	
Provider Education	$50,000
Media Campaign	$119,304
Research	$36,469
Total*	$496,428

Prepared by Erin Johnson, erjohnso@utah.gov, 801-538-6542

D. Narrative of Budget Detail

Costs listed under “Personnel” include expenses for one full-time program manager, one part-time director, and one part-time intern in 2008. In FY 2009, three full-time staff and four part-time researchers and two part-time interviewers make up the “Personnel”.

Office Expenses include in and out-of-state travel, postage, phone, office supplies, cubicle space, printing, books and subscriptions, photocopies, insurance and bonds, workshops and conventions, purchase of external hard drive to store CSD data on, software for analyzing data and creating websites, and network costs.

See the Provider Education write-up for details on the provider education contract.

The media campaign contract includes costs for agency labor, public opinion survey, focus groups, tv and radio spot productions, tv and radio air time, media relations, web site development, advertising, collateral material, and communication plan.

Research costs went to pay one research consultant for work analyzing data from the Controlled Substance Database and Medical Examiner and Vital Statistics records and two programmers who worked on cleaning and merging the data.

BRFSS (Behavioral Risk Factor Surveillance System) Survey is a statewide, telephone survey. The costs went toward 9 additional questions put at the end of the standard survey that ask specifically about prescription pain medication use.

All remaining funding is being used in FY 2010 to complete the research project of interviewing next of kin of overdose decedents and continue making results of research available.

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Appendix

Appendix A: News Stories
2008-2009 Utah News Article Related to UDOH Prescription Pain Med Program Efforts

Pain pill overdose deaths dip, but health officials remain on alert

Budget cuts will end two prevention campaigns.

By Heather May

The Salt Lake Tribune, June 3, 2009

Forty fewer Utahns died of an accidental pain pill overdose last year compared to 2007, the largest drop in more than a decade.

But 277 Utahns died preventable deaths. And for the health official on the front lines of fatal drug overdoses, the decrease doesn't mean Utah has a handle on what is being called an epidemic.

"A day without a possible drug overdose around here is an extremely rare event," said chief medical examiner Todd Grey. Half of the deaths his staff was working on Monday and Tuesday -- four out of eight -- were suspected drug overdoses.

And while prescription drug deaths dropped, illicit drug deaths increased 44 percent, to 89. "This is an ongoing problem. And a year-to-year drop in one component of that problem doesn't mean we can all pack up and go home happy," Grey said.

The Utah Department of Health announced Tuesday the 12.6 percent drop in unintentional prescription drug deaths. Officials can't yet explain the dip, though they'd like to attribute it to their efforts to educate doctors and the public about proper use of pain pills. That will take further analysis.

And both prevention programs will cease at the end of the month.

Funding was set aside by the Legislature for the past two years, but the annual $150,000 allocation stops this fiscal year, which ends June 30. So does most of the program's other funding, which totaled $500,000.

The money paid for TV and radio spots called Use Only As Directed. It also funded presentations to doctors on how to use the state's Controlled Substances Database to identify patients who may be abusing drugs and ones with other prescriptions that could be harmful in combination with pain pills.

The goal of both efforts was to reduce deaths by 15 percent from 2006 to 2008. Instead, there was a 10 percent drop.

Still, "I do think the education has made a difference," said Kim Bateman, medical director of the health care improvement group HealthInsight, which had the contract to educate doctors.

While Bateman still needs to collect and analyze data to see if doctors changed their prescribing habits after the training, he believes they have.

And as one of the trainers, he said he would continue to teach fellow doctors for free. "All of our speakers are kind of on a mission," he said.

Funding will continue through December for a research project that is under way to determine risk factors for prescription pain pill deaths. The medical examiner's office is interviewing family members of the dead to determine whether they had a history of substance abuse, where their medications were obtained and other circumstances surrounding the death.

"Maybe it will give us an insight as to how best to attack the issue," said Grey. Or maybe not.

"I don't really know which thread I could pull that would make the whole tapestry of this problem go away," he said. "I don't even know if this research is going to be able to answer that question with a simple, 'Here's what we have to do.' "

Rep. Brad Daw, R-Orem, is happy with the results of the health department's efforts. He sponsored HB137, which provided the two years of funding. Over the summer, he hopes to study whether the media campaign had an effect in reducing the deaths. If so, he'd like to find more money to keep it going.

And he noted the money also helped pay for the development of guidelines on when and how doctors should prescribe pain pills.

"That's where the problem starts, is prescriptions given in a way that may be inappropriate," he said. "I'm not trying to blame doctors here."

Efforts to combat drug overdoses will continue even without state money: Daw sponsored bills in the past two sessions to change the Controlled Substance Database. Local health departments have separate funding to work on the issue.

The U.S. Drug Enforcement Administration launched the Utah Pharmaceutical Drug Crime Project to end the sale, purchase and theft of prescription drugs and continue public education efforts on the dangers of pain pills.

And the state Department of Environmental Quality set up a program to help people dispose of their pain pills at police stations and hazardous waste collection events.

"There are great efforts that will keep going," said Erin Johnson, the health department's program manager over the to-be defunct pain medication program.

Prescription Drugs
KSL Editorial
April 6th, 2009

The misuse or abuse of prescription drugs, especially narcotic medications is the number one cause of unintentional death in Utah. It has been for several years. That's why it's good to see steps being taken by state health officials to combat what they describe as an epidemic.

Their latest salvo in the battle comes in the form of recommended clinical guidelines for those authorized to prescribe Opioids for the treatment of pain. As State Health Director David Sundwall says, "health care providers bear some responsibility in combating the problem." They're the ones treating patients and writing prescriptions for medications to control acute and chronic pain. The new guidelines are intended to "help physicians better manage their patients' pain" while avoiding some of the potentially serious risks of the medications.

It is a rather unique approach. In fact, Utah is only the second state in the nation to develop such specific guidelines for more safely prescribing pain medications.

KSL encourages physicians across the state to become familiar with the new guidelines, and to view them as a helpful tool in their effort to more effectively treat their patients. When used properly, prescription narcotics can be a blessing, but they can also be tragically deadly when they are misused or abused.

New rules aim to stem prescription overdoses

By Carrie A. Moore
Deseret News
Friday, March 27, 2009

You're more likely to die of a prescription drug overdose than an auto accident in Utah.

But new guidelines released Thursday by the Utah Department of Health are designed to help reduce those drug deaths.

Prescriptions written for opioid medications such as hydrocodone, oxycodone and methadone increased six-fold from 1997 to 2002 in the Beehive State, as doctors moved forward with a nationwide trend to better control and treat pain. Dr. Robert Rolfs, state epidemiologist, said there is evidence that both acute (short-term) pain, and chronic (long-term) pain had been under-treated before the turn of the century.

Aggressive marketing by pharmaceutical companies has also contributed to the point that "the norm in terms of how (such medications) are used has dramatically shifted," he said. As the rate of usage has risen, so have the number of local deaths tied to the medications.

The health department developed the new guidelines for doctors in conjunction with two multi-disciplinary physician groups, with the goal to reduce the number of unintentional overdoses in Utah by 15 percent.

"It's important for physicians and the public to be aware that these guidelines are recommendations, they are not requirements and they are not laws," said Dr. David Sundwall, executive director of the state health department. "However, it's also important to recognize prescription pain medication overdose deaths have reached epidemic proportions in Utah and health-care providers bear some responsibility in combating the problem."

Rolfs said part of the reason more Utahns are dying is "a fairly large increase in people using them non-medically, abusing them in one way or another." While the health department doesn't have hard numbers, he said anecdotal evidence suggests that about one-third of people taking the drugs are doing so as prescribed for a real medical problem; one third are probably abusing the drugs; and another third "is probably a mix of the two."

Many people who have same-day surgical procedures or even dental work get a prescription from their physician for one of the opioids, often for a much larger number of pills than they actually need for pain. "When you get 30 and you take two, how many does that leave in the medicine cabinet where a teenager or family friend finds them" and decides either to take them personally or to sell them on the street?

Even if there is no theft, "it's not uncommon for people to just give them to someone else, and people don't realize that's technically a felony," Rolfs said. Even if physicians are prescribing more of a drug than is necessary, patients have a responsibility to "take it only if you need it, in the amount you need, store it safely and dispose of it properly," he said.

Some of the key recommendations for medical providers include:

Give alternatives to opioids before prescribing them; start with something less potent first, particularly for acute pain.

Screen for risk of abuse or addiction before initiating prescription opioids.

Use methadone rarely, if ever, to treat acute pain. Also, it should only be prescribed by those who know the risks and are prepared to carefully monitor patients who take it.

Tools for doctors to use in implementing the recommendations are included, including monitoring and screening mechanisms, sample treatment plans and dosing guidelines.

Questions still remain about whether people with chronic pain are better off a year or two after using such drugs; 5 to 10 percent of the population is prone to become addicted to them, or to have problems related to an addiction, Rolfs said. Unfortunately, "we often don't have great options when treating someone with chronic pain," particularly those dealing with terminal illness.

State officials don't now have a good handle on how many prescription drug overdose deaths are actually suicides and how many are accidental, he said, though a study is under way to learn more about "what is going on in their heads" when an overdose occurs.

He has had patients who have had non-fatal overdose episodes who describe myriad factors that play into their mental state "and it's very complicated."

More Utahns dying from prescription drug overdoses than car accidents

February 19th, 2009 @ 10:03pm
By Jed Boal

Two years ago, the number of deaths from prescription drug overdoses surpassed the number of highway fatalities in Utah. New numbers now show how quickly the problem took off.

In 2007, 269 people died in Utah traffic crashes. That same year, 317 people died from overdoses of prescription pain medication.

At the Utah Poison Control Center, the number of emergency calls for prescription drug exposures tripled over the last decade -- from 486 in 1998 to 1502 in 2008. "Definitely, our calls reflect what's going on in the community, so we certainly have seen an impact of the prescription pain medication problem," said Dr. Barbara Crouch, director of the Utah Poison Control Center.

Crouch says young children put everything in their mouths as they explore, including pills. Teens experiment to get high, and adults may commit suicide or mix drugs and have a bad reaction.
Couch says methadone, oxycodone, Loritab and Suboxone are being prescribed more and are more readily available in the home.

Another problem is that many think it is OK to share prescription medication. Not only is that dangerous, it's against the law. "A lot of people don't realize that it is a felony to share your prescription medications. These are controlled substances," explained Jonathan Anderson, with the Utah Department of Health.

The state started a campaign to target overdose by prescription drugs 9 months ago. The program, called Use Only As Directed, could reduce problems or increase the number of reported overdoses.
In 2008, the number of calls to the poison control center related to prescription pain medication leveled off, but it's still too early to tell whether the problem has leveled off as well.
"We plan on doing an evaluation later this year to get a better idea of what impact was made on the public," Anderson said.

The state health department wants to learn more about what leads to overdose, but these are key factors:

- Sharing or borrowing medications
- Mixing drugs
- Abuse
- Self-medicating or taking the wrong amount.

The Department of Health will release new overdose fatality numbers for 2008 in April.

Accidental prescription pain medication overdoses kills 300 Utahns a year

Reported by: Angie Larsen, KTVX
2/18/2009 @ 10:11 pm

SALT LAKE CITY (ABC 4 News) - Last year, more than 300 people in Utah died from accidental prescription pain medication overdoses - that number is higher than car crash deaths. To fight back, the Utah Department of Health has a campaign called "Use Only As Directed."

The new U.D.O.H. commercials depicting a father taking more than the prescribed amount of his pain medication, laying down for a nap and never waking up - is a strong message, but a crucial one. It’s a message that Sandra Kresser of Salt Lake City understands all too well.

“We've seen first hand and up close the devastating effects and our family will never be the same,” expresses Kresser.

At the age of 22, her son Josh was prescribed Oxycontin after a back injury. He got hooked and overdosed three times, before a he took a combination of three prescribed drugs that killed him -one day before his 25th birthday.

“He tried so hard to break the chains, but the addiction was too strong,” recalls Kresser.

Kresser is trying to turn her tragedy into triumph to help other families avoid the same pain. She says, “I’m doing whatever I can to raise awareness to the dangers of prescription drugs because it's a huge problem and an epidemic that's sweeping the entire country.”

The Utah Department of Health is still trying to figure out why there has been such huge increase in accidental overdoses in recent years. “Traditionally medications were for cancer pain and cancer patients and now it's more widely available. Doctors are prescribing it and it's doing a lot of good, but at the same time people are misusing and treating these medications like maybe Tylenol or aspirin when they're really controlled narcotics,” explains Jonathan Anderson with the UDOH Prescription Pain Medication Program.

And while the state focuses on awareness, Kresser is meeting with the FDA to change the way opiates are prescribed. “It seems like too often we're treating pain as a disease rather than a symptom,” she says.

Unintentional prescription pain medication overdoses have tripled in the past eight years. Before 2000, there were approximately 80 to 90 deaths a year in Utah, over 300 deaths since then.

The average age of those deaths is 41, and the percentage of men and women is equal.

Sandra Kresser will be addressing the FDA for a second time on March 6th.

If you would like more information about the "Use Only As Directed" campaign - including tips for staying safe, go to: **www.useonlyasdirected.org**.

News Stories from 2008

UDOH Launches Fight Against Prescription Drug Abuse

By Eric Ray
May 1, 2008 - KCPW

(KCPW News) Since the year 2000, Utah has experienced a four-fold increase in the amount of deaths associated with prescription pain medication. The problem has become so big that in 2006 more people in Utah died from prescription drug overdoses than from injuries received in automobile accidents.

"This is really two problems," says State Epidemiologist Robert Rolfs. "There are people abusing these medications and obtaining them illegally from a friend or some other means outside of the traditional legal channels. But there are also people dying and getting into trouble taking these medications when they are obtaining them from a physician or another health care provider.

"Rolfs says part of the reason for the increase in deaths is that doctors are prescribing more painkillers than they have in the past.
Republican Representative Brad Daw of Utah County says legislation passed last year will help inform the public of the problem, and a bill passed this year will give doctors the ability to stop so called "pill shoppers."
"Right now when a doctor goes to the prescription drug database they will see data that is about a month old or older. So if someone has begun doctor shopping in the past week or two weeks, they doctor will be completely unaware of that," says Republican Representative Brad Daw of Utah County. "Once this program is in place, the doctor will be able to query that database and see data that is up to date. No more than a day old."
Daw says he hopes the upgraded database will be available sometime next year. In addition, the Utah Department of Health launched its "Use Only As Directed" campaign today. It includes a series of television and radio ads aimed at informing the public about the dangers of prescription drugs.

Prescription Drug Overdose Deaths In Utah Higher Than Auto Deaths

By Rod Decker
May 1, 2008 – KUTV (Channel 2)

Prescription drug overdoses cause more deaths in Utah than do automobile accidents. The death toll continues to rise every year and now the Department of Health wants to launch a new campaign to prevent more deaths.

In 2006, 307 people died from prescription drug overdoses while 285 people died from automobile accidents. Only three other states have more deaths from prescription drug overdoses than Utah, according to the Center of Disease Control.

With such high numbers, many in Utah share the same tragedy that Linda Blare and her family suffered, with the loss of their son Shane.

Shane started taking pain killers after an automobile accident.

"The last night…he said, 'I love you mom and dad, you're the best parents ever, and he went up to bed," said Linda.

But Shane never woke up from that night. Linda says she'll never forget the way she discovered that Shane had died from an overdose.

"His girlfriend, who was sleeping right beside him, started screaming, 'Something's wrong with Shane!' I ran up and saw him and I knew he was dead," said Linda.

Deaths like Shane's happen almost once a day in Utah and the Health Department says that doctors are prescribing too much to patients and that those who are on medication are not educated about its dangers.

The Department of Health Doctors launched a campaign called "Use Only As Directed." They warn against taking too much of a prescription, especially of pain medicines and mixing drugs with alcohol.

They say, more education and care with drugs will mean fewer tragedies similar to Linda's.

"There are so many things you wanted to say to them or do with them, but you never had the time," said Linda.

State officials warn 'Use Only As Directed'

Jed Boal reporting
May 1, 2008 – KSL-TV

Overdoses with legal drugs now kill more people in our state each year than car crashes. The state today launched a campaign to try to tackle the problem.

This is likely the fastest growing public health problem in our state: overdose by legal drugs,

prescription or over-the-counter. The number of victims grows nearly every day.

Linda Player's son took painkillers after a car crash two years ago. He was taking them legally at first, then he started buying them illegally on the street. Within seven months he was addicted, then dead.

A friend of her son died yesterday. "That is two, two we have lost in two years," Player said. "It's important that this doesn't happen anymore. He doesn't have any friends left to lose."

Use Only As Directed: That's the message from the Utah Department of Health (UDOH) when it comes to use of any legal drugs. "In 2006, unintentional pain medication overdoses was the number one cause of injury deaths in Utah," explained Dr. David Sundwall, executive director of UDOH.

That year, the state medical examiner investigated nearly 500 drug-related deaths. More than 300 were caused by legal drugs, either prescription or over-the-counter drugs.

During that same time span, 285 people died on Utah roads. "In this area, we are not the healthiest state. In fact, we have one of the largest problems in the country, both with deaths due to pain medications and other evidence indicates the misuse and abuse that contribute to this problem," said Dr. Robert Rolfs, UDOH state epidemiologist.

Some people misused the drugs, others abused them. The most common drugs misused or abused are methadone, morphine, oxycodone, hydrocodone and fentanyl.

Rep. Bradley Daw sponsored legislation for public education and to tighten up the prescription drug database used by doctors. "We feel this will be a great tool for doctors to help stop pill shopping on their side of the fence," he said.

You'll start to hear radio spots to "Use Only As Directed."

State hopes to reduce unintentional prescription drug overdoses

By Lois M. Collins
Friday, May 1, 2008 – Deseret News

Shane Player, 26, was badly injured in a head-on car crash in 2006. His ear was torn off, he had 64 stitches on his face and he suffered extensive nerve damage.

Although his body did start to mend, his wounds, both physical and emotional, would overcome him. The pain medication that at first made life bearable, seven months later killed him.

On Dec. 17, 2006, he became a Utah statistic — one of hundreds of deaths attributed to unintentional prescription drug overdose. Unintentional over-the-counter and prescription overdoses killed more Utahns that year than motor vehicle crashes.

Player's mom, Linda Player, told the story to reporters Thursday as the Utah Department of Health kicked off an education campaign that targets those unintentional deaths. Its motto is

"RX: Use Only As Directed," and it includes radio, television and print ads, as well as a component designed to help prescribing physicians better understand the problem and help solve it, said Dr. David Sundwall, UDOH director.

"It's a growing problem affecting families, friends and communities," he said. "It is squarely on the agency as a public health policy problem we need to handle."

The Office of the Medical Examiner investigated 476 drug-related deaths in 2006 — fewer than 100 of them caused by illegal drugs. Medical examiner Dr. Todd Grey, in fact, first noted the increasing number of prescription and OTC-related deaths and called it to officials' attention. Almost two-thirds of those deaths resulted from legal drugs, either prescription, over-the-counter or a combination, and the victim's average age was 42 years. The deaths were almost evenly divided between men and women.

Sundwall said 24 of the state's 29 counties saw at least one of the drug-associated deaths. The responsible substances most often seen included methadone, morphine, hydrocodone and fentanyl. There were also deaths associated with non-narcotic drugs.

State epidemiologist Dr. Robert Rolfs said it's not really clear why Utah has such a high incidence. But he noted that the number of medications prescribed in Utah has increased "a lot in the last decade." And some of the drugs, including methadone — which stops controlling pain before it leaves the body, creating a potentially dangerous cumulative effect — are tricky to use. State health officials, he said, hope to give prescribing health-care providers "tools" to help them prescribe medications for safe use. He said the guidelines are expected out in July.

The campaign was funded by the Legislature in response to a bill sponsored by Rep. Brad Daw, R-Orem, creating the Prescription Pain Medication Management and Education Program. The program's goal is to reduce unintentional prescription pain medication overdose deaths by 15 percent in 2009.

Besides the education component, information available from pharmacists on who is getting prescriptions for the drugs also will be available in much more real-time so that physicians can spot more easily patients who might be doctor-shopping to get drugs, Daw said.

As for the ads and spots, the message is simple: Don't mix drugs with other drugs, including those sold over-the-counter, or with alcohol. And use the medication only as it was prescribed. If a pain medication doesn't provide enough relief, it's dangerous to "take a little more."

Campaign targets medication deaths

By Heather May
Sunday, May 4, 2008 – Salt Lake Tribune

Don't share pain pills. Don't take them with alcohol or other sedatives. Don't take more doses than directed.

That's the message of a new campaign launched by health officials late last week to combat Utah's high number of unintentional deaths involving pain medications: 276 Utahns in 2006, the

latest data available. That's a four-fold increase since 2000. The goal is to cut the number of deaths by about 40 next year.

The problem is a combination of abuse and misuse by patients, prescribing errors or illegal activity by doctors and the promotion of such drugs by pharmaceutical companies, according to Utah Department of Health officials.

They are starting their efforts with patients, targeted by radio and TV ads.

"If Utahns can use their medications only as directed, this will impact the deaths," said Erin Johnson, who oversees the Health Department's pain medication program.

The department found teens believe pain pills aren't harmful because they're prescribed by a doctor, leading them to view pills as a "safe high." Adults believe they can take more than prescribed, which can lead to addiction. And the elderly may double-dose because they've forgotten they've taken their pills.

Doctors are to blame, too, said Linda Player, whose son died in 2006 after being prescribed methadone. The Ogden woman said her son, Shane, became addicted after he was given pain pills for injuries suffered in a car accident. To get over his addiction, the 26-year-old went to a substance abuse clinic and was prescribed methadone, but died three days later.

"We've got to do something or we're going to lose all our kids," she said.

The Health Department also will start working with doctors, said David Sundwall, department director. Sundwall said doctors may be too eager to prescribe the drugs, compared to when he was in medical school in the 1960s. A recent survey of Utahns commissioned by the department indicates 62 percent had been prescribed Loratab, a pain medication.

By July, the department will craft guidelines for doctors about when not to prescribe the pills - if patients have prior substance abuse problems, for example - and ways to follow-up with patients to prevent abuse, said Robert Rolfs, state epidemiologist.

He said doctors will likely be advised to check a state controlled substances database - which would need to be improved to provide up-to-date information - to ensure patients aren't doctor shopping.

A Prescription for Death

Deseret Morning News Opinion Editorial
October 13, 2008

“First we seek excuse from pain,” wrote Emily Dickinson. She must have glimpsed modern America where prescription pain pills have become more plentiful than popcorn, and abuse is rampant.

In 2007, 320Utahns died from overdose or misuse of these pills. In fact, more Utahns die from unintentional prescription overdoses than in car crashes. The death toll has quadrupled since 2000, making overdosing the number one cause of injury death in the state.

The statistics roll on but don't get any better. Utah is third in the nation in prescription drug deaths. Some 24 of the state's 29 counties have the problem. And men and women are apparently dying in equal numbers.

The Utah Department of Health found those numbers chilling enough to institute a new program. In weeks to come, Utahns will be seeing posters and pronouncements and will get used to hearing the slogan "Use Only As Directed."

The new information push also lists "six tips" to help people act a little more responsibly. We note them here:

1. Never take prescription pain medications not prescribed to you.

2. Do not take more doses than prescribed.

3. Never mix with alcohol.

4. Mixing sleep aids and antidepressants with prescribed drugs can be dangerous.

5. Keep your medications in a locked, safe place.

6. Dispose of any unused medications.

The disposal issue has been a concern in the state. Flushing drugs simply sends the medicine into the water. And tossing them willy-nilly into the trash makes them targets for scavengers. The best advice is to mix old pills and medications with something undesirable (like kitty litter) and put them in the trashcan.

In a meeting with the Deseret News editorial board, the team spearheading the push said one key is for doctors, patients, pharmacists and drug companies to all work together on the problem. The more cooperation, the more success.

"We aren't proud about being a leader in this area," said David N. Sundwall, executive director of the Utah Department of Health, "but we'd like to be a leader in getting things turned around."

We urge Utahns to become familiar with the problem and help health officials deal with it.

Prescription Drug Deaths

October 17th, 2008 @ 5:30am
KSL Editorial

The Utah Department of Health is accelerating its timely campaign to reverse one of the most disturbing trends in contemporary culture: Utahns in record numbers are dying, mostly unintentionally, because they are misusing prescription pain medications.

In 2007, the number of deadly unintended prescription pain medication overdoses was 317. The number has been increasing every year recently.

These are not stereotypical drug addicts, nor are they individuals who use drugs for recreation. Mostly, they are people dealing with legitimate health issues who take larger doses of medications than prescribed, unwittingly mix prescribed medications, or self-medicate without knowing the full implications of what they're doing.

In short, these are deaths that never should occur. They are preventable. That is the message health officials are trying to get out. In KSL's view, it is a message that needs to be shouted loud and clear.

-Never take prescription pain medications that are not prescribed to you!

-Do not take more doses than prescribed by your doctor!

-Never mix with alcohol!

-Do not mix sleep aids or anti-anxiety medications together with prescription drugs!

-Keep medications locked in a safe place!

-Dispose of any unused medications!

Prescription drugs: Grim Reaper resides in your medicine cabinet

Salt Lake Tribune Editorial
October 20, 2008

We wrote this piece on Wednesday. By the time it lands in your driveway, the odds are that five Utahns will have perished, that five families will be grieving, children will be orphaned, spouses will be widowed, and parents will be preparing to bury a child, all because of prescription drugs.

These are unintended deaths resulting from abuse or improper use of legal opioids and narcotics. If child molesters or drunken drivers or cultists were killing 300 Utahns a year, imagine the clamor. But this, for the most part, has been a silent epidemic. That's about to change.

This week is Prescription Safety Awareness Week. In observance, the Utah Department of Health is intensifying its multipronged, multimedia public education campaign: "Use Only As Directed." The slogan is short, punchy, to the point and, hopefully, effective. If Utahns would simply follow that rule for their prescription medications, there would be a lot less work for the medical examiner, a lot more room at the morgue, a lot less mourning.

Methadone, fentanyl, hydrocodone and other drugs of that ilk are equal-opportunity killers. Half of the victims are male, half female. They range in age from 15 to 80. Most have, or have had, a prescription for the drug that did them in.

The incidence has grown at an alarming rate. It is now the No. 1 cause of accidental deaths in Utah. A decade ago, about 40-50 Utahns died each year from prescription drug overdoses, or deadly combinations of prescribed medications. Last year, 320 perished.

The Health Department, with $300,000 from the state Legislature that leveraged an additional $700,000 from other sources, has been studying and taking aim at the problem. It's a target-rich environment. Physicians. Pharmacists. Pharmaceutical companies. The health insurance industry. Consumers. All share in the blame.

Some doctors play it fast and loose with the prescription pad. Pharmacists sometimes fail to deliver verbal warnings or detect forged prescriptions. Drug manufacturers offer incentives for prescribing their drugs. Some insurance-company policies encourage use of inexpensive opioids instead of non-narcotic pain relievers. And consumers fail to heed that simple, sage advice: "Use Only As Directed."

Taken as directed, these powerful drugs can make life bearable for people in pain. When abused or misused, they can make life end. Learn more at www.useonlyasdirected.org.

Guv, local authorities fight against prescription drug deaths

Ace Stryker - Daily Herald

Friday, 24 October 2008

Over the past two years, prescription drugs have killed more people in Utah than car crashes. Prescription pain medication overdoses claimed 317 lives last year and 307 the year before, making it the No. 1 cause of injury death in the state. Such deaths -- whether because of abuse or accident -- more than doubled here between 1999 and 2004, according to the Centers for Disease Control and Prevention.

Utah currently leads the nation in prescription drug abuse, according to the state Health Department. About 6.5 percent of residents use prescription painkillers for nonmedical purposes, including nearly one in seven people between 18 and 25. The majority of crimes committed in Utah are linked to substance abuse, and about 70 percent of today's jail and prison inmates have substance-abuse problems.

To call attention to these problems, Gov. Jon Huntsman on Thursday night declared this week "Prescription Safety Awareness Week." As part of his formal declaration, Huntsman reiterated the state's goal to "reduce the number of unintentional prescription pain medication overdoses in Utah by 15 percent by 2009" -- a goal first set forth in the Pain Medication Management and Education Bill of 2007.

It's the latest step in a comprehensive plan prompted by last year's Legislature, which approved $300,000 in funding to combat the rising trend of prescription drug-related deaths. Two public education campaigns have also targeted the problem: "Use Only As Directed," which reinforces the importance of safe medicine use; and "Clean Out the Cabinet," a national initiative pushing the proper disposal of old drugs.

Though overdose deaths rose statewide from 2006 to 2007, Utah County seems to be faring better. During the same time, deaths linked to prescription narcotics fell here from 86 to 77 -- the lowest toll since 2004.
Health districts across the state are convening groups to address prescription drug abuse concerns on a local level. In Utah County, a diverse group of health, law enforcement, political and educational leaders called the Utah County Coalition is currently gathering data from the county's municipalities. Coordinator Kye Nordfelt said that once the coalition has the information it needs, it will draw up a comprehensive plan to be implemented over the coming years

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UDOH Trying to Reduce Prescription Drug Deaths

Oct 27, 2008
by Faroe Robinson – KCPW News

The Utah Department of Health is trying to cut the number of prescription drug related deaths. It held a prescription pain medication forum last week in conjunction with Utah's Prescription Safety Awareness Week. Prescription Pain Medication Program Manager Erin Johnson says the public needs to be aware of how to prevent prescriptions from getting into the wrong hands.

"It's pretty extreme what an addict would do. We've found people who will go to vet clinics and actually pull patches that were used on animals and suck on them to get just that little bit of juice that is left in them, but I mean, just to show you the extent to which an addict would go when they are seeking meds," Johnson said.

Utah leads the nation in painkiller abuse, according to a study by the U.S. Department of Health and Human Services, and Johnson says almost one person dies every day in Utah from a prescription drug overdose. It causes twice as many deaths as illegal drugs.

Johnson says looking for the signs of drug abuse is important.

"I think a big thing is the stigma here in Utah. People may not recognize that they need help and so being aware of those signs, and being helpful and encouraging for people to go and seek the treatment that they need, rather than stigmatizing them or making them feel like they're awkward for being an addict, help them to want to seek help and treatment," Johnson said.

Johnson advises people not to flush pills down the toilet, but to remove them from their bottles so they are unidentifiable, put them in a sealed bag and throw them away.

Shurtleff to crack down on prescription drug abuse in next term

November 5th, 2008 @ 5:10pm
By Sarah Dallof - KSL-TV

Newly re-elected Attorney General Mark Shurtleff is already laying out plans for his next term in office. One of his big goals is to crack down on prescription drug abuse in Utah -- a move inspired in part by his own personal experience.

Shurtleff tells KSL he understands more about the power of prescription drugs since seriously injuring his leg in a motorcycle accident.

The number of overdose deaths has nearly quadrupled in the past 10 years, and Shurtelff says it's time to tackle the problem of abuse from the top. "Well we've done so well with meth, but now the major problem in Utah is prescription drug abuse," Shurtleff said.

His plans include doing away with paper prescriptions and creating a electronic prescription database so pharmacists can verify prescriptions in real time and hopefully curb "doctor shopping."

Last year, 317 people died of prescription drug overdoses. A 2006 survey ranked Utah fourth in the nation for prescription drug abuse, and a 2007 survey found that abuse is on the rise among young adults. "One in six teens has used prescription drugs for non-medical reasons," said Susannah Burt grant manager for the Utah Department of Health's prescription drug study.

The state hasn't been ignoring the problem -- education and rehab programs are in place -- but the prescription drug study looks at why and how people become addicted.

Shurtleff, however, hopes to create a multi-jurisdictional task force that will share information and resources. It's something individual law enforcement agencies are looking forward to.

CLICK HERE to watch video of this story

EXHIBIT I

UTAH DEPARTMENT OF HEALTH
Violence & Injury Prevention Program

PRESCRIPTION OPIOID DEATHS

Every month in Utah, 24 individuals die from prescription opioid overdoses.

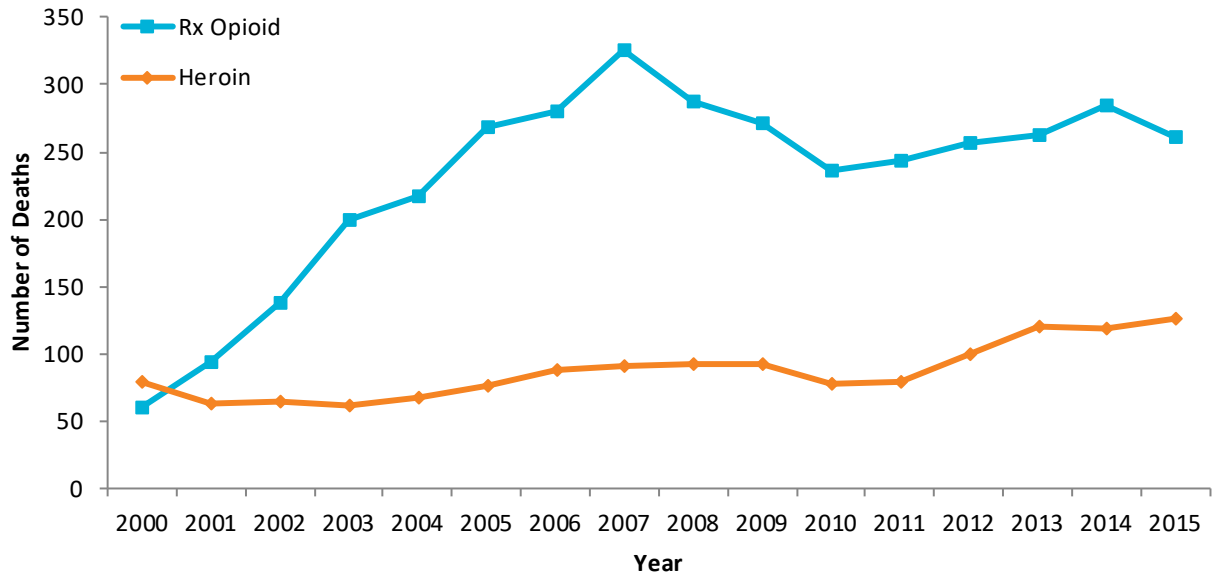
Introduction

- From 2013 to 2015, Utah ranked 7th highest in the nation for drug overdose deaths.[1]
- Drug poisoning deaths are a preventable public health problem that has outpaced deaths due to firearms, falls, and motor vehicle crashes in Utah since 2002.[2]
- In 2015, 24 individuals (residents and non-residents) died every month from a prescription opioid overdose in Utah (**Table 1**).[3]
- 2015 was the first time in six years that there was a decrease in the rate of prescription opioid deaths ages 18 years and older in 2015 (**Table 1**).
- Although Utah is seeing a decrease in the number of prescription opioid deaths since 2010, the number of heroin deaths that have increased in the same time period (**Figure 1**).[3]

Table 1. Count and rate of poisoning deaths by select categories, Utah, 2006-2015[3]

Year	Occurrent† Poisoning Deaths	Occurrent† Rx Drug Deaths	Occurrent† Rx Opioid Deaths	Rx Opioid Deaths, UT Residents 18+	Rx Opioid Death Rate per 100,000 UT Residents 18+	95% Confidence Interval
2006	416	308	280	274	15.8	(14.0 - 17.8)
2007	478	371	326	313	17.6	(15.7 - 19.6)
2008	430	321	289	278	15.2	(13.5 - 17.1)
2009	420	306	272	269	14.4	(12.7 - 16.2)
2010	369	278	236	227	11.9	(10.4 - 13.6)
2011	444	306	246	233	12.0	(10.5 - 13.7)
2012	536	327	268	257	13.1	(11.5 - 14.8)
2013	531	354	274	265	13.2	(11.7 - 14.9)
2014	531	363	301	285	14.0	(12.4 - 15.7)
2015	566	357	282	262	12.6	(11.1 - 14.2)

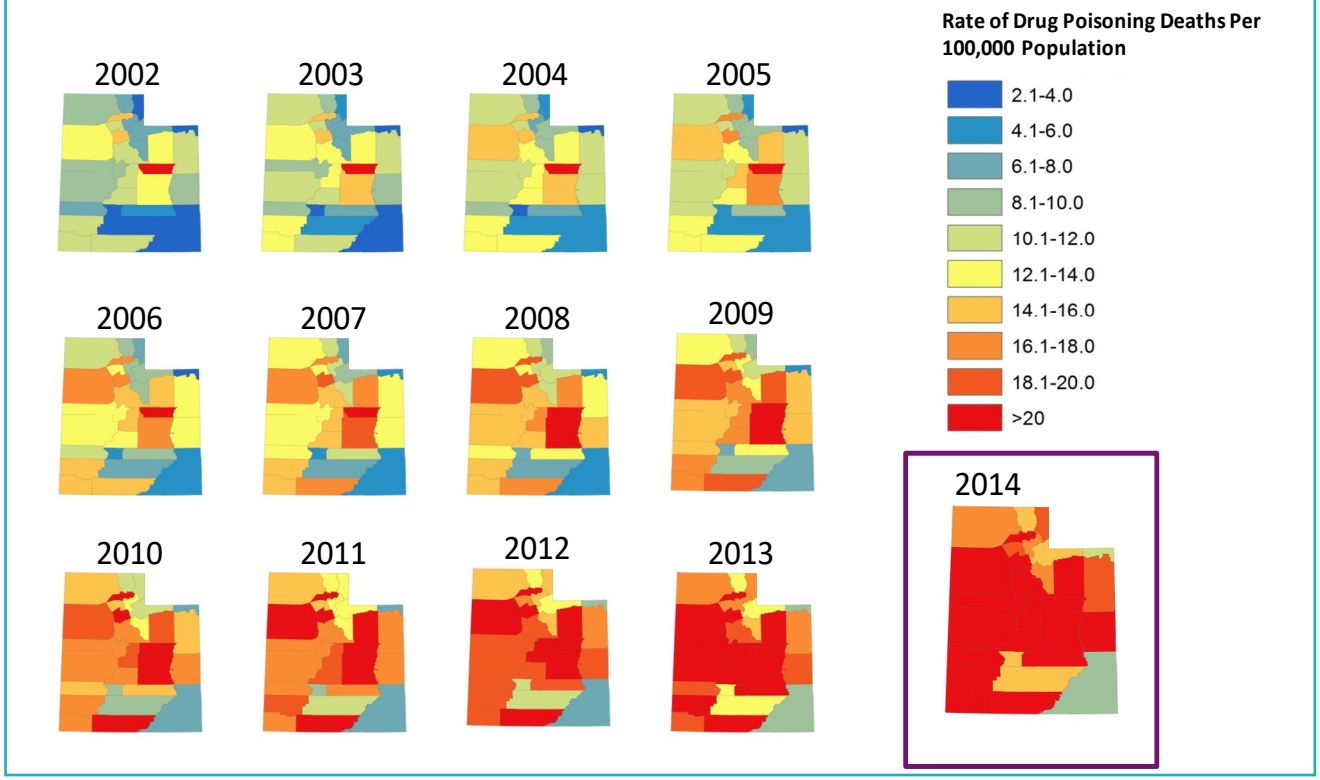
Figure 1: The number of occurrent† opioid deaths by type, Utah, 2000-2015[3]



Utah Trends

Since 2002, drug poisoning deaths per 100,000 population have increased at an alarming rate (**Figure 2**) and prescription opioids have been responsible for more drug deaths in Utah than all other drug categories, such as benzodiazepines, over-the-counter medications, or illicit drugs.[1]

Figure 2. Rate of drug poisoning deaths per 100,000 population by county, Utah, 2002-2014 (age-adjusted) [3]



Age and Sex

Overall, there was not a significant difference between the adult male and female rate of prescription opioid overdose deaths (13.0 and 13.4 per 100,000 adults) (**Figure 3**). The highest prescription opioid overdose deaths rates were observed in Utahns aged 45-54 for both males and female (**Figure 3**).[3] The highest prescription opioid overdose emergency department visits rates were observed among Utahns aged 25-34, closely followed by Utahns aged 45-54. However, for heroin overdose emergency department visits, the highest rates were observed for Utahns aged 18-24 (**Figure 4**).[2]

Figure 3: Rate of prescription opioid overdose deaths per 100,000 adult residents by sex, Utah, 2013-2015[3]

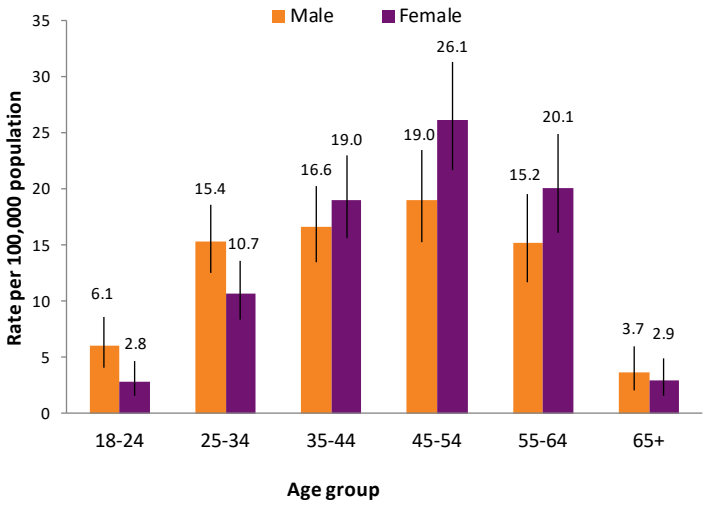
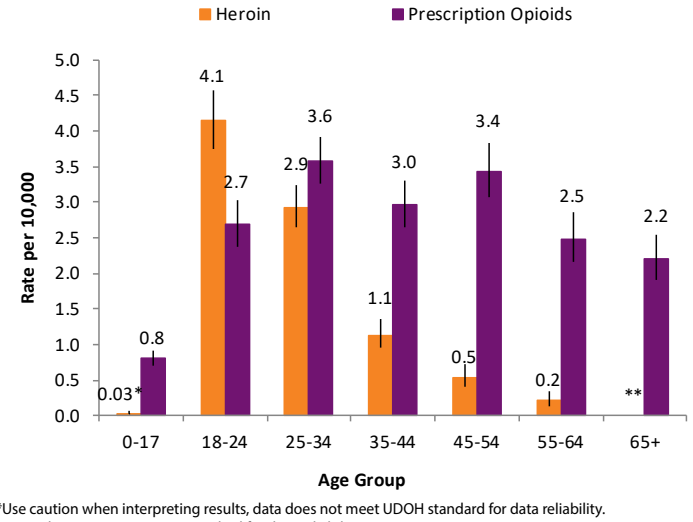


Figure 4: Rate of emergency department visits per 10,000 population by age group and opioid type, Utah, 2012-2014[2]



*Use caution when interpreting results, data does not meet UDOH standard for data reliability.
**Data does not meet UDOH standard for data reliability

Figure 5: Percent of occurrent† prescription opioid deaths by drug type, Utah, 2015[3]

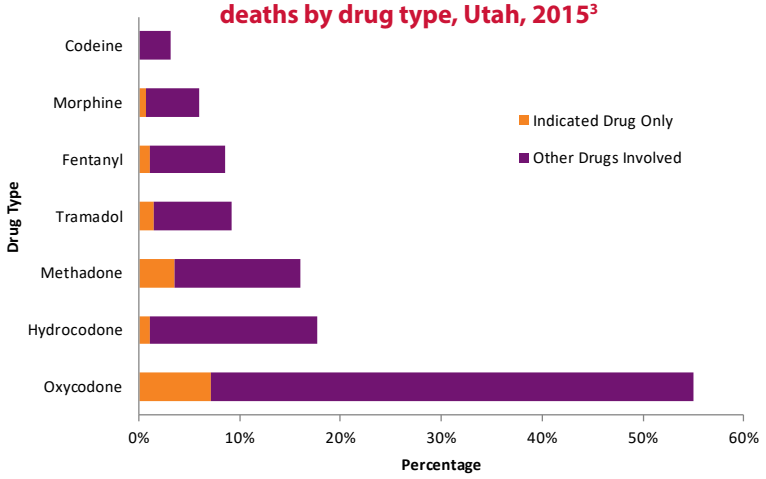


Figure 6: Rate of occurrent† deaths per 100,000 prescriptions by year and prescription type, Utah, 2004-2015[5]

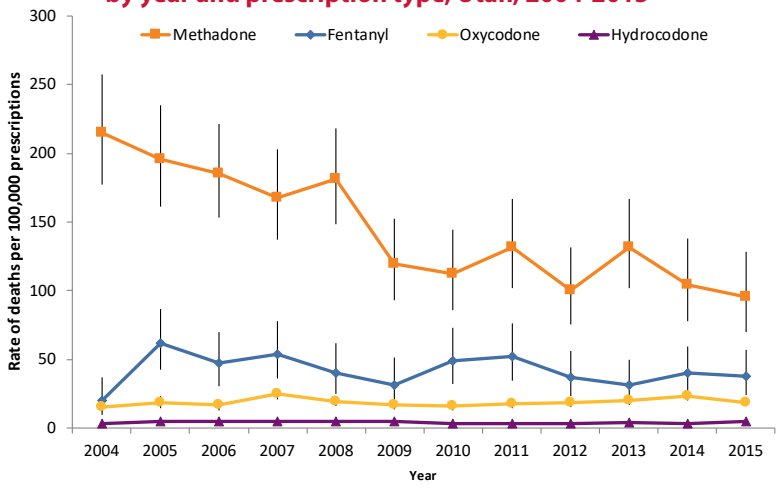
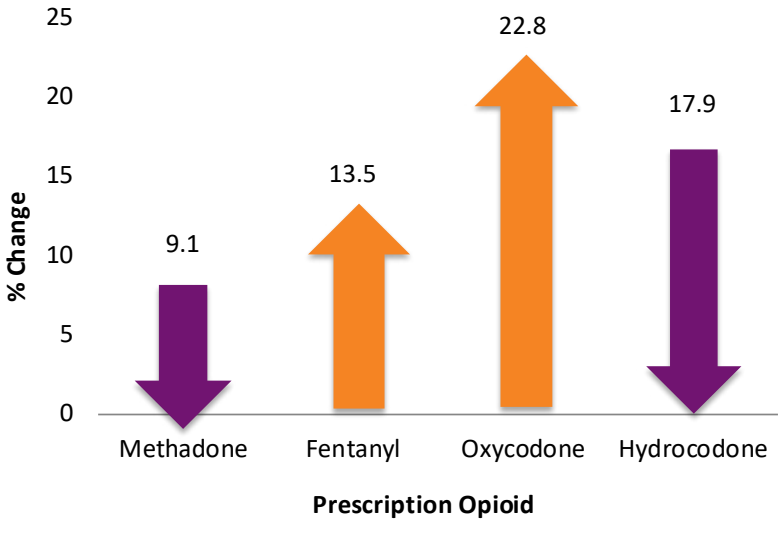


Figure 7: Percent change in number of deaths per 100,000 prescriptions, 2011-2015[5]



Prescribing Trends

Deaths from oxycodone drugs, such as oxycontin and percocet, accounted for 55.0 percent of all prescription opioid deaths in 2015. Hydrocodone was second at 17.7 percent. The majority of prescription opioid deaths involved other drugs (**Figure 5**).[3]

Although the majority of prescription opioid deaths involved oxycodone, the risk of death was significantly higher when methadone was involved compared to fentanyl, oxycodone, and hydrocodone. Fentanyl had the second highest risk of death per 100,000 prescriptions (**Figure 6**). Prescriptions dispensed for fentanyl and oxycodone increased 13.5 and 22.8 percent respectively from 2011 to 2015. Prescriptions for methadone and hydrocodone decreased 9.1 and 17.9 percent respectively during the same time period (**Figure 7**).[5]

Location of Death

The following Utah Small Areas had significantly higher prescription opioid death rates compared to the state (13.2 per 100,000 adults):[3]

- Carbon/Emery Counties (47.3 per 100,000 adults)
- Ogden (Downtown) (31.6 per 100,000 adults)

Circumstances of Death

In Utah, the top circumstances observed in prescription opioid deaths included:[4]

- 71.0% physical health problem
- 68.3% substance abuse problem‡
- 65.7% current mental health problem
- 60.4% current mental health/substance abuse treatment
- 27.4% drug involvement (not a prescription)
- 17.1% alcohol dependence/problem
- 13.7% history of suicide attempts

Prevention

- Talk to your doctor about alternatives to prescription opioids.
- Never share your prescription opioids with anyone.
- Store prescription opioids out of reach, with the label attached, and with the child-resistant cap secured.
- Dispose of all unused and expired prescription opioids properly. If possible, take your unused prescription opioids to a permanent collection site or drop-off event. If you can't find a drop-off site, dispose of your medications by following the guidelines at **www.useonlyasdirected.org**.
- For other tips on safe use, safe storage, and safe disposal, visit Use Only As Directed at **www.useonlyasdirected.org**.
- Know what the common opioids are and know their risks – dependency, addiction, or overdose.
- Know what the signs of an opioid overdose are:
  - Small, pinpoint pupils
  - Blue/purple fingernail and lips
  - Won't wake up, limp body
  - Shallow or stopped breathing
  - Faint heartbeat
  - Gurgling or choking noise
- Carry naloxone and know how to properly administer it. Visit **naloxone.utah.gov** for more information.
- For more information on the risks of opioid, signs of an opioid overdose, or the use of naloxone, visit Stop the Opidemic at **www.opidemic.org**.

Resources

- Naloxone **naloxone.utah.gov**
- Stop the Opidemic **opidemic.org**
- Use Only As Directed: **www.useonlyasdirected.org**
- Utah Department of Health: **www.health.utah.gov/vipp**
- Utah Poison Control Center: **uuhsc.utah.edu/poison** 1-800-222-1222.

Last Updated: April 2017

References

1. U.S. Centers for Disease Control and Prevention, Web-based Injury and Statistics
2. Utah Department of Health Office of Public Health Assessment, Indicator Based Information System for Public Health
3. Utah Department of Health Violence and Injury Prevention Program, Prescription Pain Medication Program Database
4. Utah Department of Health Violence and Injury Prevention Program, Utah Violent Death Reporting System
5. Utah Department of Commerce Division of Occupational and Professional Licensing, Controlled Substance Database

*Occurrent deaths include individuals who died in Utah, whether or not they were a resident of Utah.
†Utah resident status not available to report counts and rates.
‡A circumstance in which the individual was noted as using illegal drugs, abusing prescription medications, or regularly using inhalants at the time of death even if the addiction or abuse is not specifically mentioned.

Story Bank
Utah Department of Health

If your life has been affected by opioids, the Utah Department of Health wants to hear from you. Share your story with the Utah Health Story Bank at **www.health.utah.gov/bhp/sb/**.

Our Mission: VIPP is a trusted and comprehensive resource for data and technical assistance related to violence and injury. This information helps promote partnerships and programs to prevent injuries and improve public health.

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www.health.utah.gov/vipp

EXHIBIT J

Attorney General
SEAN D. REYES
UTAH OFFICE OF THE ATTORNEY GENERAL

Recent News

(https://attorneygeneral.utah.gov/the-safeut-app-2018-stats/)

The SafeUT app: together we make a difference (https://attorneygeneral.utah.gov/the-safeut-app-2018-stats/)

April 5, 2019

(https://attorneygeneral.utah.gov/ags-secure-strike-force-busts-salt-lake-drug-ring/)
AG's SECURE Strike Force busts Salt Lake drug ring (https://attorneygeneral.utah.gov/ags-secure-strike-force-busts-salt-lake-drug-ring/)
April 5, 2019

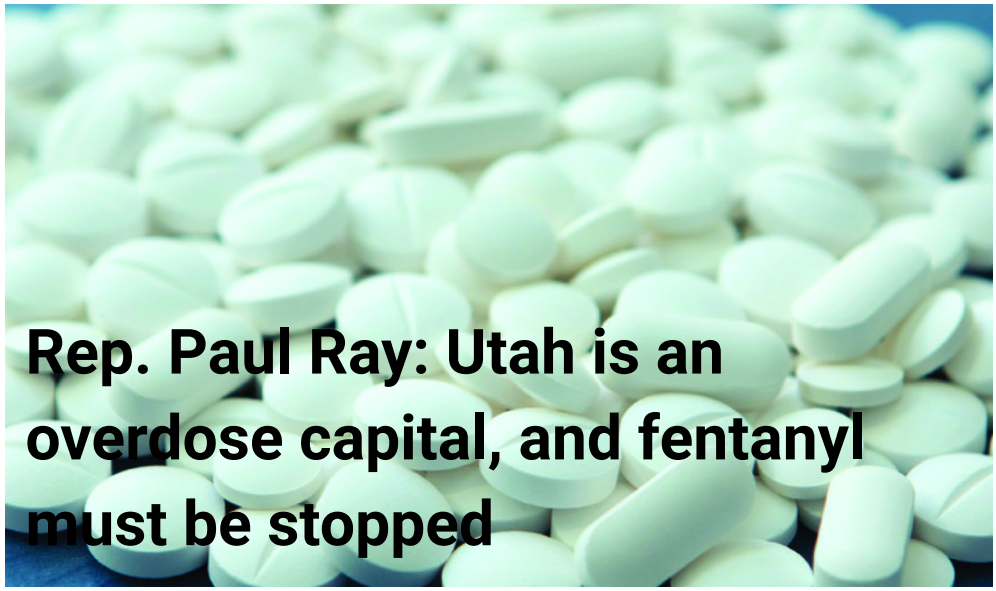
(https://attorneygeneral.utah.gov/social-media-sextortation/)
Sexting, Sextortion & the Dark Side of Social Media (https://attorneygeneral.utah.gov/social-media-sextortation/)
April 4, 2019

(https://attorneygeneral.utah.gov/hate-crimes-statute-signed-into-law/)
Hate Crimes Statute Signed into Law, Provides Protection to All Utahns (https://attorneygeneral.utah.gov/hate-crimes-statute-signed-into-law/)
April 3, 2019

(https://attorneygeneral.utah.gov/national-crime-victims-week/)
National Crime Victim's Rights Week (https://attorneygeneral.utah.gov/national-crime-victims-week/)
April 2, 2019

(https://attorneygeneral.utah.gov/national-vietnam-war-veterans-day/)
National Vietnam War Veterans Day (https://attorneygeneral.utah.gov/national-vietnam-war-veterans-day/)
March 29, 2019

(https://attorneygeneral.utah.gov/man-



Rep. Paul Ray: Utah is an overdose capital, and fentanyl must be stopped

Written by Utah Representative Paul Ray and originally posted in the Salt Lake Tribune (https://www.sltrib.com/opinion/commentary/2019/03/12/rep-paul-ray-utah-is-an/).

March 13, 2019

It may come as somewhat of a shock for most Utahns to learn that our state has one of the worst rates of opioid drug overdoses in our country. In fact, our state has been consistently ranked among the top 10 for opioid-related overdoses for the past decade. According to a study conducted by the Centers for Disease Control and Prevention (https://www.cdc.gov/drugoverdose/data/statedeaths.html), more than 600 people died from opioid-related overdoses in Utah during 2016 alone.

The data for 2016 showed a slight improvement over 2015 due to federal, state and local efforts via the Utah Opioid Task Force (https://attorneygeneral.utah.gov/utah-opioid-task-force/), as a result of its cracking down on the over-prescription and sale of legal pain-relieving medications that contain opioids. However, the rate of mortality has remained stubbornly high due to the spread of an illegally manufactured drug called fentanyl.

Fentanyl is a synthetic opioid most people had never even heard of five years ago. It is such a potent drug (https://www.businessinsider.com/what-is-fentanyl-the-drug-that-killed-prince#fentanyl-is-increasingly-showing-up-in-counterfeit-pills-seized-by-authorities-on-the-street-these-pills-which-were-labeled-hydrocodone-were-recovered-by-authorities-during-a-recent-fentanyl-investigation-in-northern-california-3) that even a few milligrams of it — equivalent to a grain of rice — can be deadly for anyone who comes into contact with it — even accidentally.

convicted-using-brothers-name/)
Man convicted using brother's name (https://attorneygeneral.utah.gov/man-convicted-using-brothers-name/)
March 28, 2019


(https://attorneygeneral.utah.gov/gold-king-lawsuit-to-proceed-against-mine-owners-for-environmental-damages/)
Gold King Lawsuit to Proceed Against Mine Owners for Environmental Damages (https://attorneygeneral.utah.gov/gold-king-lawsuit-to-proceed-against-mine-owners-for-environmental-damages/)
March 27, 2019


(https://attorneygeneral.utah.gov/epa-contractors-gold-king-spill/)
Lawsuit Against EPA Contractors Responsible for Gold King Spill to Proceed (https://attorneygeneral.utah.gov/epa-contractors-gold-king-spill/)
March 21, 2019


(https://attorneygeneral.utah.gov/utah-opioid-task-force-update/)
An Update from the Utah Opioid Task Force (https://attorneygeneral.utah.gov/utah-opioid-task-force-update/)
March 20, 2019


(https://attorneygeneral.utah.gov/sex-trafficking-victim-speaks-out/)
In the News: Sex Trafficking Victim Speaks Out (https://attorneygeneral.utah.gov/sex-trafficking-victim-speaks-out/)
March 18, 2019

China is the main source of manufacturing the illegal fentanyl finding its way across our borders. Most of the drugs are shipped to Mexican drug cartels (https://www.businessinsider.com/what-is-fentanyl-the-drug-that-killed-prince#five-of-the-six-online-fentanyl-vendors-investigated-in-a-new-senate-report-are-based-in-china-the-sellers-sent-hundreds-of-packages-to-more-than-300-sources-in-the-us-by-way-of-the-us-postal-service-usps-5) that have perfected the process of pressing fentanyl into counterfeit pills and smuggling them into the U.S. for distribution. Sometimes the fentanyl is just shipped in bulk over our borders and is turned into pills in factories on our own soil.

By now, many of us have heard the unfortunate story of Aaron Shamo (https://www.usnews.com/news/best-states/utah/articles/2018-10-19/utah-man-charged-in-death-linked-to-alleged-opioid-drug-ring), an otherwise promising young man, an Eagle Scout from a solid family. Shamo became a drug kingpin in a comfortable Salt Lake City suburb, manufacturing more than 500,000 counterfeit pills made from fentanyl to sell on the dark web.

If it can happen here, it can happen anywhere.

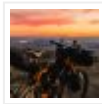
Just before the recent elections, President Donald Trump signed into law the STOP Act (https://govtrackinsider.com/stop-act-would-require-postal-service-to-scan-incoming-packages-from-overseas-for-opioids-ad5d174ad1a9), the first sweeping legislation addressing some of the problems that have given rise to this epidemic. The need for this legislation was so great, less than 10 out of 535 Members of the House of Representatives and Senate voted against it.

While this is an excellent first step, Congress needs to take further, more robust action. We desperately need more security at our borders and, like our Attorney General Sean Reyes, I urge Congress to now pass the Stopping Overdoses of Fentanyl Analogues (SOFA) Act (https://www.ronjohnson.senate.gov/public/index.cfm/2017/7/johnson-introduces-sofa-act-to-combat-opioid-epidemic), which would give prosecutors additional powers to go after the ringleaders of the production and manufacturing cartels responsible for selling these deadly drugs in our state.

Make no mistake, we cannot ease up on the pressure required to defeat the spread of this deadly drug that has invaded Utah. State leaders like myself must continue to push for legislation that will secure our communities until the death toll recedes to zero.

Paul Ray represents District 13 in the Utah House of Representatives.

Related



(https://attorneygeneral.utah.gov/wheels-of-justice/)

Wheels of Justice Rides to Make a Difference (https://attorneygeneral.utah.gov/wheels-of-justice/)

March 18, 2019

(https://attorneygeneral.utah.gov/pik2ar-empowering-positive-social-change/)

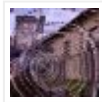
PIK2AR: Empowering Positive Social Change (https://attorneygeneral.utah.gov/pik2ar-empowering-positive-social-change/)

March 14, 2019

(https://attorneygeneral.utah.gov/a-great-victory-for-utah-hate-crime-bill-passes-utah-legislature/)

A Great Victory for Utah: Hate Crime Bill Passes Utah Legislature (https://attorneygeneral.utah.gov/a-great-victory-for-utah-hate-crime-bill-passes-utah-legislature/)

March 13, 2019



(https://attorneygeneral.utah.gov/man-sentenced-for-sex-trafficking-a-child/)

Man Sentenced to Consecutive Terms of Life in Prison for Sex Trafficking a Child (https://attorneygeneral.utah.gov/man-sentenced-for-sex-trafficking-a-child/)

March 13, 2019

(https://attorneygeneral.utah.gov/missing-in-utah-event/)

Utah Attorney General's Office Joins Law Enforcement for Missing in Utah Event (https://attorneygeneral.utah.gov/missing-in-utah-event/)

March 13, 2019

AG Reyes Updates White House Staff on Opioid Epidemic (https://attorneygeneral.utah.gov/ag-reyes-updates-white-house-staff-on-opioid-epidemic/)

October 26, 2017

In "Recent Posts"

AGO & DEA Announce Utah Take Back Program (https://attorneygeneral.utah.gov/ago-dea-announce-utah-take-back-program/)

April 26, 2018

In "Archived Posts"

An Update from the Utah Opioid Task Force (https://attorneygeneral.utah.gov/utah-opioid-task-force-update/)

March 20, 2019

In "Recent Posts"

This entry was posted in Recent Posts (https://attorneygeneral.utah.gov/category/featured-content/) and tagged Attorney General Sean Reyes (https://attorneygeneral.utah.gov/tag/attorney-general-sean-reyes/), Drug Overdose (https://attorneygeneral.utah.gov/tag/drug-overdose/), Fentanyl (https://attorneygeneral.utah.gov/tag/fentanyl/), Opioids (https://attorneygeneral.utah.gov/tag/opioids/), Rep Paul Ray (https://attorneygeneral.utah.gov/tag/rep-paul-ray/) on March 13, 2019 (https://attorneygeneral.utah.gov/utah-is-an-overdose-capital/).

EXHIBIT K

Opioid Misuse:

Options for Prevention, Identification, and Treatment

(including certain policies already implemented in Utah)

Revised 4/21/16

This is an evolving document. Suggestions for change are welcome.
The inclusion of options in this document is not any indication of their merit.

1. PHARMACEUTICAL MANUFACTURERS

a. Improve prescriber education
b. Increase production of abuse-deterrent opioids (extended-release and long-acting)

2. PRESCRIBERS

a. Engage in continuing professional education about opioid prescribing
b. Comply with opioid prescribing guidelines
    i. Utah Department of Health 2009 Guidelines
    ii. U.S. Centers for Disease Control and Prevention 2015 Guidelines
        1. Limit to acute pain for 3 – 7 days
        2. Use alternatives for chronic pain
        3. Use of lowest possible dose
        4. Use of immediate-release formulations
        5. Exceptions for active cancer, end-of-life care, and surgery
    iii. Condition-specific pain management protocols
c. Screen patients for substance misuse and refer them to treatment programs
d. Improve patient education
e. Co-prescribe naloxone with opioids
f. Use patient assessment tools and pain management contracts
g. E-prescribe controlled substances (or a subset thereof) to reduce fraud and monitor treatment compliance
h. Use secure prescription pads
i. Engage in peer review of prescribing practices
j. Abide by prescribing limits
    i. Limit the amount of first-time prescription (or other prescriptions) to a specified number of days
    ii. Limit daily supply to a morphine equivalent
    iii. Limit patient's daily morphine equivalent for all prescriptions combined
    iv. Limit emergency department prescribing/dispensing
    v. Prohibit doctor dispensing of opioids

vi. Limit the prescribing of pain medications by prescribers who are not pain specialists to a specified number of morphine equivalents per day (e.g., 50 under CDC's proposed prescribing guidelines and 120 in Washington; see 2010 Washington legislation)

vii. Refer patient to a pain specialist

k. Use the controlled substance database (prescription drug monitoring program) more effectively

i. Increase usage (check for first-time prescriptions; check periodically for each patient; check always; etc.)

ii. Develop workflow-friendly interface with electronic health records and other processes

iii. Evaluate prescribing practices in light of:

1. notices from DOPL about the prescriber's patients who have died from drug related causes;

2. notices from DOPL about the prescriber's patients who have been treated for overdose or poisoning or who have been convicted of drug related DUI

iv. Request controlled substance database notification for patients meeting specified dispensing criteria

l. Involuntarily commit a person who is an immediate danger to self or others to a drug treatment facility for up to 72 hours (proposed in Massachusetts)

m. Use pain medication treatment plans

n. Use pain medication agreements and informed consent

o. Perform a physical examination and substance use disorder assessment prior to prescribing a controlled substance

p. Obtain continuing professional education on alternatives to opioids

q. Use baseline drug testing for new patients and periodic drug testing for other patients to monitor compliance with treatment plan and detect use of other drugs

3. DISPENSERS

a. Increase use of controlled substance database

i. Check all nonresidents

ii. Check all cash transactions

iii. Check all out-of-state prescriptions

b. Integrate use of controlled substance database into pharmacy workflow (Kroger pharmacists check nearly 100% of controlled substance prescriptions)

c. Improve pharmacist response to red flags

d. Install pharmacy drop-boxes for the disposal of unused drugs

e. Require identification of those picking up prescriptions

f. Dispense at-home deactivation kits with drugs (Delaware completed a pilot program)

g. Obtain standing order for dispensing naloxone

h. Allow partial fills so that only the amount requested by a patient is dispensed, up to the amount prescribed

4. INSURERS

a. Structure coverage, prior authorization, and cost sharing parameters to incentivize compliance with CDC guidelines and other prescribing guidelines
b. Educate insureds
c. Cover abuse-deterrent opioids (extended-release and long-acting) (however, see results of 2015 PEHP study)
d. Cover naloxone
e. Cover the broad spectrum of treatment services, including medication-assisted treatment
f. Cover controlled substance database access by prescribers and dispensers
g. Use a patient review and restriction program to limit an at-risk patient to a single prescriber and a single pharmacy or pharmacy chain (e.g., BlueCross BlueShield of Massachusetts)
h. Require prior authorization for an initial prescription (e.g., BlueCross BlueShield of Massachusetts)
i. Limit initial quantities prescribed (e.g., BlueCross BlueShield of Massachusetts)
j. Work on development of more user-friendly controlled substance database interface
k. Use claims analysis to analyze dispensing patterns and notify, educate, and intervene as appropriate

5. PATIENTS

a. Securely store medications
b. Properly dispose of unused medications
c. Obtain and act on education by prescribers, dispensers, public service campaigns, etc.
d. Obtain naloxone for family and friends
e. Reduce drug sharing behaviors
f. Reduce drug seeking behaviors
g. Develop realistic expectations about pain management
h. Complete periodic education and counseling during treatment of chronic pain (proposed by Georgia 2015 H.B. 407)
i. Use a voluntary revocable non-opioid directive, where appropriate, to alert practitioners to not prescribe or administer opioids

6. TREATMENT COMMUNITY

a. Co-locate substance use and mental health treatment providers with physical healthcare providers
b. Build infrastructure for full spectrum of treatment options

7. STATE – PRESCRIPTION DRUG MONITORING PROGRAM, INCLUDING USE OF THE CONTROLLED SUBSTANCE DATABASE

a. DOPL notify prescribers of patient overdose, poisoning, drug related DUI
b. DOPL notify prescribers of patients meeting criteria established by prescriber
c. DOPL notify patient-designated third parties when a controlled substance is dispensed to a patient
d. DOPL notify prescribers with suspect prescribing patterns
e. Map controlled substance database data geographically
f. Promote third-party analysis of de-identified data
g. Batch process to screen an entire day's calendar of patients
h. Develop workflow-friendly interface (e.g., single sign-on) with electronic health record systems and other processes, and dispensers' point of sale system (see 2016 H.B. 239, Access to Opioid Prescription Information via Practitioner Data Management Systems (McKell); see also "Examining Legislative Proposals to Combat our Nation's Drug Abuse Crisis," Statement by Michael P. Botticelli, Director of National Drug Control Policy, before the United States House of Representatives Subcommittee on Health of the Committee on Energy and Commerce, Thursday, October 8, 2015)
i. Expand access to database information, as appropriate (e.g., to drug courts, treatment professionals, prisons and jails, law enforcement, prosecutors, state medical examiner, physician assistants, physician residents, licensing boards, etc.)
j. Maintain data quality
k. Monitor database use to ensure data security
l. Mandate use for patients meeting certain criteria (KY, TN, and NY mandate use of a PDMP; "As of June 2014... 22 states had laws mandating that prescribers and in some cases dispensers use the PDMP in certain circumstances")
m. Mandate use for first prescription and at least once every year thereafter
n. Notify third-party payers (see Kentucky)
o. Provide unsolicited reports to law enforcement and professional regulatory boards
p. Develop automated expert systems to expedite analyses and reports (e.g., NARxCHECK)
q. Share analytics for identifying problem patients and prescribers with prescribers, dispensers, insurers, and third-party researchers
r. Create a Controlled Substance Database Advisory Board to make recommendations to the Legislature and the Division of Occupational and Professional Licensing
s. Provide immunity to prescribers and dispensers for use of database
t. From "Prescription Drug Monitoring Programs: An Assessment of the Evidence for Best Practices," by The Prescription Drug Monitoring Program Center of Excellence, Brandeis University
    i. Collect positive ID on persons picking up prescriptions
    ii. Collect data on method of payment, including cash transactions
    iii. Integrate electronic prescribing with PDMP data collection
    iv. Improve data quality
    v. Link records to permit reliable identification of individuals
    vi. Determine valid criteria for possible questionable activity

vii. Conduct periodic analyses of questionable activity
viii. Develop expert systems to guide analyses and reports
ix. Record data on disciplinary status, patient lock--ins
x. Optimize reporting to fit user needs
xi. Integrate PDMP data with health information exchanges, electronic health records
xii. Publicize use and impact of PDMP
xiii. Proactively identify and conduct outreach to potential high--impact users
xiv. Conduct recruitment campaigns
xv. Streamline certification and enrollment processing
xvi. Mandate enrollment
xvii. Mandate utilization
xviii. Institute financial incentives
xix. Delegate access
xx. Evaluation of PDMPs
xxi. Funding of PDMPs
xxii. Adopt a uniform and latest ASAP reporting standard
xxiii. Collect data on nonscheduled drugs implicated in abuse
xxiv. Reduce data collection interval; move toward real--time data collection
xxv. Enable access to data by appropriate users; encourage innovative applications
xxvi. Enact and implement interstate data sharing among PDMPs
xxvii. Collaborate with other agencies and organizations
xxviii. Collect data on all schedules of controlled substances
xxix. Institute serialized prescription forms
xxx. Conduct epidemiological analyses
xxxi. Provide continuous online access to automated reports
xxxii. Send unsolicited reports and alerts
xxxiii. Conduct promotional campaigns
xxxiv. Improve data timeliness and access
xxxv. Conduct user education

8. STATE – OTHER

a. Update Department of Health 2009 opioid prescribing guidelines
b. Improve availability of behavioral health treatment services for incarcerated population
c. Expedite Medicaid coverage following incarceration
d. Promote the availability of "on-demand" treatment (see Baltimore)
e. Leverage medical examiner's role
f. Use patient review and restriction programs for Medicaid, Workers' Compensation, and state employees health program
g. Regulate pain clinics
h. Leverage Workers' Compensation to identify and treat misuse

i. Use Medicaid and PEHP to incentivize prescriber compliance with prescribing guidelines
j. Increase funding for treatment
k. Promote stakeholder collaboration
l. Implement syringe exchange programs (See 2016 H.B. 308, Disease Prevention and Substance Abuse Reduction (Eliason)
m. Create safe-injection sites (connection to substance use treatment and medical care for overdose victims)
n. Create adequate and sustainable funding stream for deterrence, intervention, and treatment
o. Leverage drug courts
p. Incentivize diversion to treatment by all stakeholders at all points of contact with substance users
q. Develop Medicaid as a model for identification, intervention, and treatment, including the use of claims analysis
r. Use public health model to address misuse epidemic
s. Join with other states to reduce illegal online prescribing of opioids. "According to the National Association of Boards of Pharmacy, 96 percent of entities selling drugs online are illegitimate and operating in violation of U.S. law. These illegal online drug sellers provide easy access to opioid pain relievers."
t. Promote take-back programs conducted by law enforcement in conjunction with the DEA
u. Screen elementary and secondary students for substance use disorders
v. Require Schedule II prescriptions to be filled within a specified number of days (e.g., 3, 7, 30, 60, etc.)
w. Create a pain management resource center to offer technical assistance to prescribers
x. Urge the Centers for Medicare and Medicaid Services to revise Hospital Consumer Assessment of Healthcare Providers and Systems survey measures relating to pain management

9. OTHERS

a. Report number of drug exposed infant births (hospitals)