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PAIN MATTERS

EVOLVING ROLES, SAME GOALS:

The Changing Landscape of Pain Management

PAIN-40149 February 2015

PLAINTIFF TRIAL EXHIBIT
P-22531_00001

Overview

- Objectives:
  - Outline some of the options for pain management, focusing on the role of opioids
    - Although efficacious, opioids are subject to misuse, abuse, and diversion
  - Consider the role of healthcare providers (HCPs), patients, and government as part of a multifaceted approach to address these issues
  - Discuss how industry may play a role in augmenting a multifaceted approach through the development of abuse-deterrent opioid formulations
    - Review FDA draft guidance on their development


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COMPLEXITIES IN PAIN MANAGEMENT

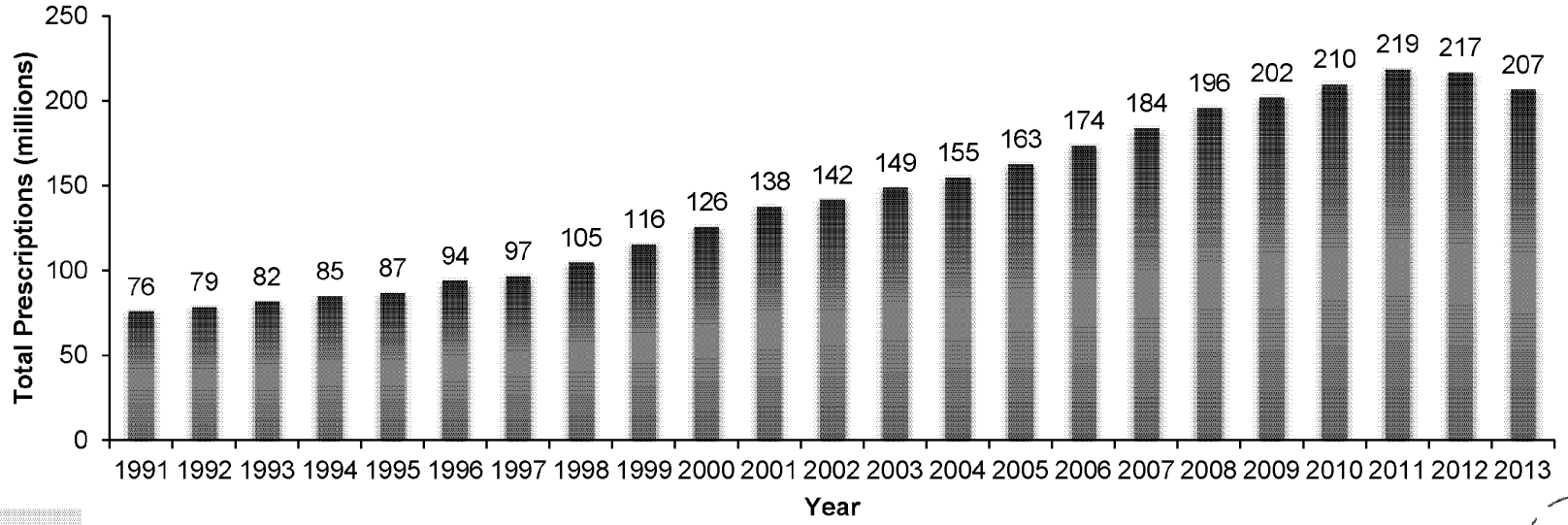
Introduction

- Chronic pain constitutes a medical need in the United States[1,2]
- Opioids represent an important part of the chronic pain armamentarium[3]
- A large and devastating problem of opioid abuse, diversion, and misuse exists and must be addressed[4]
- A multifaceted approach is needed to ensure that pain management is effectively provided to patients who need it while addressing these concerns
  - Strategies to deal with opioid abuse include educational and regulatory initiatives as well as the development of abuse-deterrent formulations
- The benefits of effective treatment must be weighed against the consequences of inadequate analgesia[5]

1. Institute of Medicine. Relieving pain in America: a blueprint for transforming prevention, care, education, and research. Washington, DC: The National Academies Press; 2011. 2. McCarberg BH, et al. *Am J Ther*. 2008;15(4):312-320. 3. Chou R, et al. *J Pain*. 2009;10(2):113-130.e22. 4. Substance Abuse and Mental Health Services Administration. http://www.samhsa.gov/data/NSDUH 2012SummNatFindDetTables/NationalFindings/NSDUHresults2012.pdf. Updated October 2, 2013. Accessed March 31, 2014. 5. American Pain Society. Pain: Current Understanding of Assessment, Management, and Treatments. http://www.americanpainsociety.org/uploads/pdfs/npc/npc.pdf. Accessed August 10, 2014.

Opioids: An Important Analgesic Option

Opioid Prescriptions Dispensed by Retail Pharmacies—United States, 1991–2013



Department of Health and Human Services/National Institutes of Health. Prescription Opioid and Heroin Abuse. Testimony by Nora Volkow, MD, Director, National Institute on Drug Abuse. http://democrats.energycommerce.house.gov/sites/default/files/documents/Testimony-Nora-Volkow-OI-Prescription-Drug-and-Heroin-Abuse-2014-4-29.pdf. Accessed August 2, 2014.

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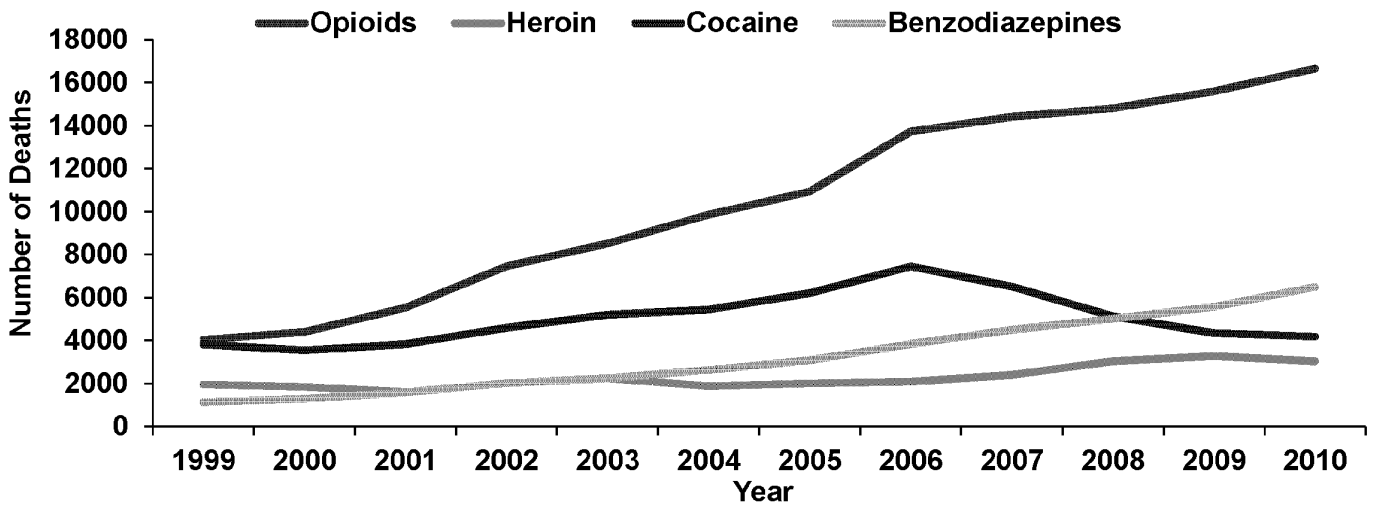
Unintended Consequences of Abuse

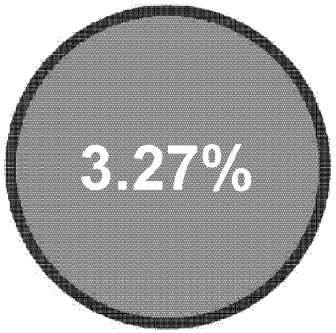
Drug Overdose Deaths by Major Drug Type— United States, 1999–2010



Centers for Disease Control. Primary Care and Public Health Initiative. Prescription Drug Abuse and Overdose: Public Health Perspective. October 24, 2012. http://www.cdc.gov/primarycare/materials/opoidabuse/. Accessed August 4, 2014.

What Is the Scope of Intended Abuse/Addiction?

- Data derived from an evidence-based review of chronic pain patients with nonmalignant pain receiving chronic opioid analgesic therapy
- 67 studies that evaluated
  - Abuse/addiction rate (24 studies, n=2507)
  - Aberrant drug-related behaviors (ADRBs) (17 studies, n=2466)
  - Urine test results (5 studies, n=1965)
- **25x lower** rate of abuse/addiction in patients without a prior history (0.19% vs 5.0%)



Percent of patients being treated with chronic opioid therapy with high likelihood of abuse/addiction

Fishbain DA, et al. *Pain Med.* 2008;9(4):444-459.

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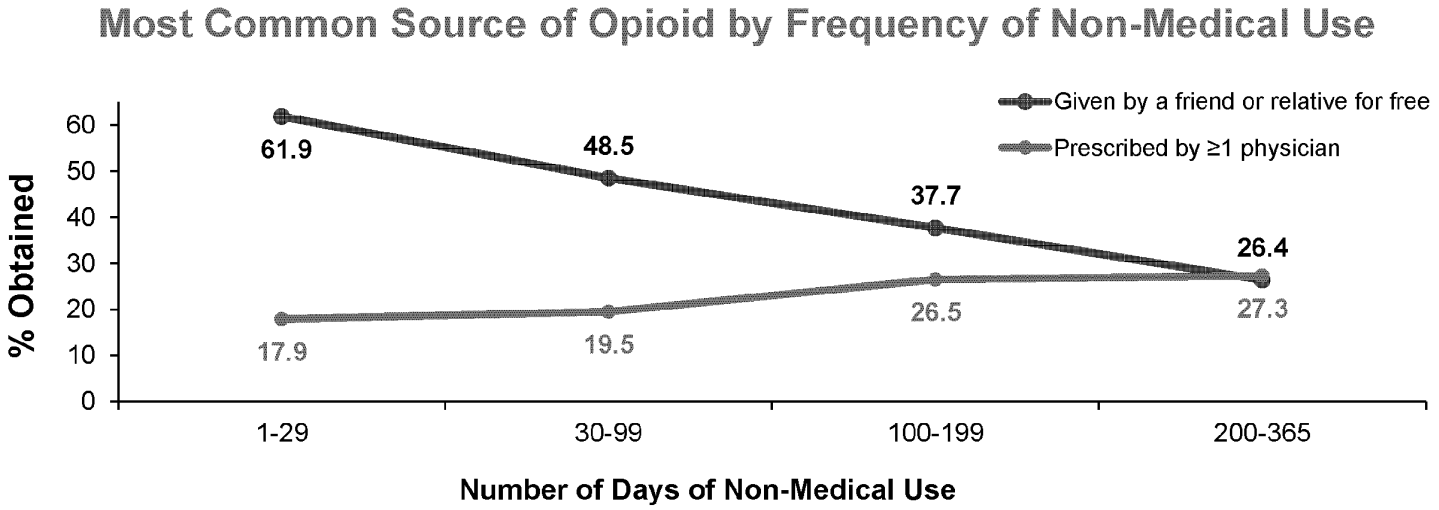
Source of Opioid Diversion with Increasing Non-Medical Use[1,2]

- Although the most common initial source of opioids for non-medical use is through friends and family,[1] the primary source changes with increased non-medical use[2]



1. Substance Abuse and Mental Health Services Administration. http://www.samhsa.gov/data/NSDUH/2012SummNatFindDetTables/NationalFindings/NSDUHresults2012.pdf. Updated October 2, 2013. Accessed March 31, 2014. 2. Jones CM, et al. *JAMA Intern Med.* 2014;174(5):802-803.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ADDRESSING OPIOID ABUSE:
A MULTIFACETED APPROACH
TEVA

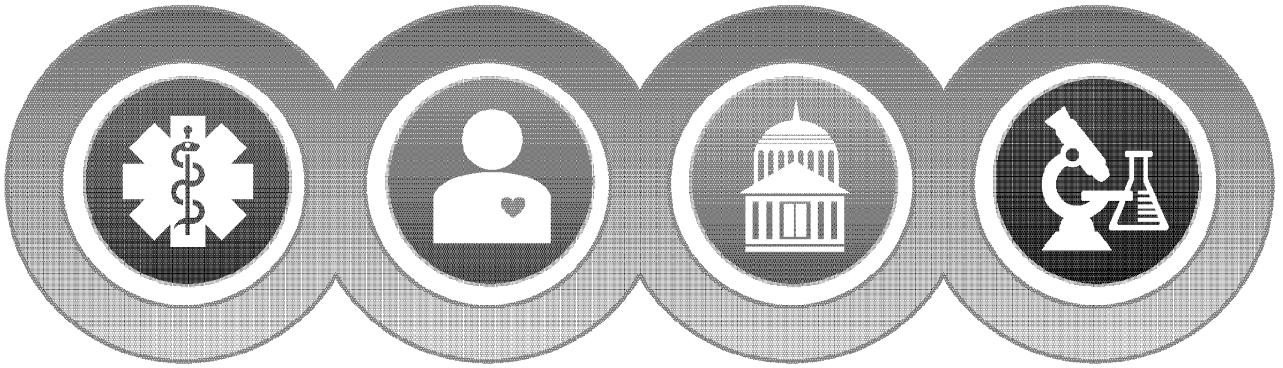
Approaches to Mitigate Opioid Abuse

- **Education**[1]
  - Clinician education on: appropriate prescribing, screening, monitoring, and patient management
  - Patient education on appropriate use, storage, and disposal
- **Guidance and tools**[1-4]
  - Prescription Drug Monitoring Programs (PDMPs)
  - Controlled substance scheduling
  - Risk Evaluation and Mitigation Strategies (REMS)
- **Developing abuse-deterrent formulations**[1,5]
  - Abuse-deterrent draft guidance from the FDA

1. U.S. Food and Drug Administration. http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm337852.htm#prescriber_education. Accessed July 28, 2014. 2. U.S. Department of Justice. http://www.deadiversion.usdoj.gov/faq/rx_monitor.htm. Accessed July 18, 2014. 3. U.S. Food and Drug Administration. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm367726.htm. Accessed July 19, 2014. 4. Federal Register: The Daily Journal of the United States Government. Schedules of Controlled Substances: Rescheduling of Hydrocodone Combination Products From Schedule III to Schedule II. http://www.gpo.gov/fdsys/pkg/FR-2014-08-22/pdf/2014-19922.pdf. Accessed August 25, 2014. 5. U.S. Food and Drug Administration. Guidance for Industry: Abuse Deterrent Opioids – Evaluation and Labeling (Draft). January 2013. http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf. Accessed July 20, 2014.

Stakeholders Addressing Opioid Abuse

A collaborative approach is necessary



A multifaceted approach to mitigating risk is required to ensure safe and effective pain management

HCP Approaches to Mitigate Opioid Abuse

How often are these done in "low-risk" patients?

Universal Precautions

- Establishing diagnosis
- Treatment agreement
- Pain assessments
- Review of diagnosis
- Documentation

Screening

Various Instruments including:

- Opioid Risk Tool (ORT)
- Current Opioid Misuse Measure (COMM)
- Revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R)
- Pain Assessment & Documentation Tool (PADT)

Adherence Monitoring

- Prescription drug monitoring programs (PDMPs)
- Random drug screens
- Pill counts

HCPs are at the forefront of pain management and employ multiple methods to assess opioid risk in individual patients

Sehgal N, et al. *Pain Physician*. 2012;15(3 suppl):ES67-ES92.

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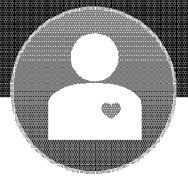
Patient Responsibilities



Safe Use[1]
- Take medications as prescribed
- Understand risks
- Awareness of inappropriate use

Safe Storage[1,2]
- Keep opioids hidden or locked to avoid access by family or friends
- Never share opioids with others

Safe Disposal[1]
- Opioids may be disposed of through community-sponsored take-back programs
- If not available, environmentally friendly disposal should be undertaken per Office of Drug Control National Policy recommendations

1. Arnstein P, St. Marie B. Managing chronic pain with opioids: a call for change. December 2010. http://www.nphealthcarefoundation.org/programs. Accessed July 20, 2014.
2. Broglio K, Cole BE. *Nurse Practitioner*. 2014:39(6):30-37.

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What is a PDMP?

Prescription Drug Monitoring Program

- Definition
  - Statewide electronic database
  - Collects data on substances dispensed in state
  - Housed by designated state agency (eg, regulatory, administrative, law enforcement)
  - Accessible to authorized personnel
- Benefits
  - Supports legitimate access to controlled substances
  - Identifies and deters drug abuse and diversion
  - Facilitates identification and treatment of those addicted to prescription drugs
  - Provides use and abuse data to inform public health efforts
  - Educates individuals on use, abuse, and diversion

U.S. Department of Justice. http://www.deadiversion.usdoj.gov/faq/rx_monitor.htm. Accessed July 18, 2014.

PDMPs State by State[1]

- PDMPs vary by state based on[2]:
  - Prescriptions tracked
  - Which prescribers must report
  - Lag time in reporting
  - Access to data
  - PDMPs may modify prescribing behavior, reduce "doctor shopping," and speed investigations

States with operational PDMPs

States with enacted PDMP legislation, but program not yet operational

States with legislation pending

The full benefit of PDMPs will not be reached until all states implement data sharing and interoperability between each other[2]

1. NAMSDL. http://www.namsdl.org/library/16666FCC-65BE-F4BB-A2BBAD44E1BC7031. Accessed July 18, 2014.
2. Finklea K, et al. Congressional Research Service. March 24, 2014. fas.org/sgp/crs/misc/R42593.pdf. Accessed August 7, 2014.

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Medicaid "Lock-In" Program

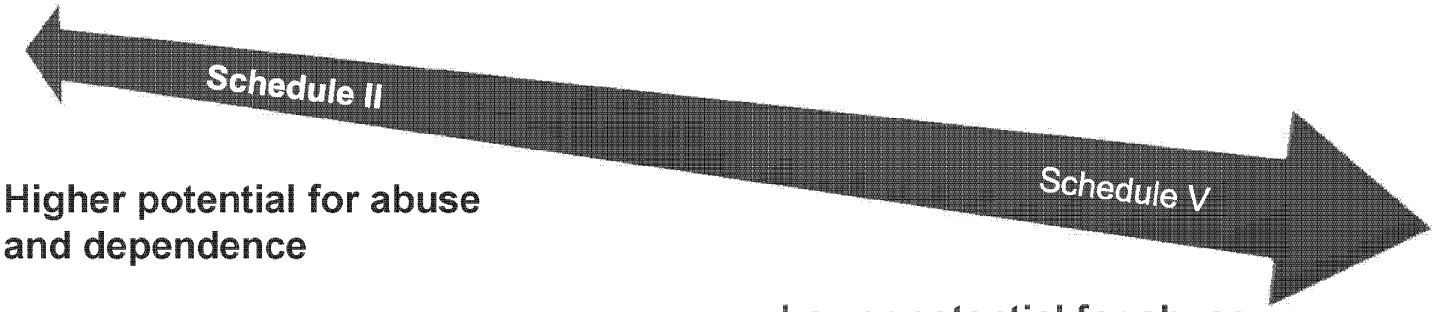
1 Patient, 1 PCP, 1 Pharmacy

- **The Law**
  - Federal law allows Medicaid to restrict patients who overutilize Medicaid services to designated providers
- **The Application**
  - High-risk opioid users can be restricted ("locked in") to receive treatment and prescriptions from a designated PCP and/or pharmacy
- **The Purpose**
  - Single provider can coordinate care
  - Reduces doctor/pharmacy shopping
  - Limits drug diversion
  - Reduces healthcare utilization and pharmacy costs
- **Future**
  - Lock-in programs might be adopted by other governmental payers and possibly private insurers as well

PCP=primary care physician.

Roberts AW, Skinner AC. *J Manag Care Pharm*. 2014;20(5):439c-446c.

DEA Changes to Opioid Scheduling



Drug Enforcement Administration. http://www.justice.gov/dea/druginfo/ds.shtml. Accessed July 19, 2014.

Opioid Risk Evaluation and Mitigation Strategies (REMS)

1. Medication Guide or Patient Package Insert[1,2]
2. Communication Plan[1*]
3. One or more elements to assure safe use[1,2]
4. Implementation System[1,2]
5. Timetable for reporting REMS assessments[1,2]

*Required for REMS specific to transmucosal immediate-release fentanyl (TIRF) drugs but not extended-release/long-acting (ER/LA) opioids REMS.[1,2]

1. U.S. Food and Drug Administration. http://www.fda.gov/downloads/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm311290.pdf. Accessed July 19, 2014.
2. U.S. Food and Drug Administration. http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm284717.htm. Accessed July 19, 2014.

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A Multifaceted Approach to Addressing Opioid Abuse

- Key stakeholders in addressing opioid abuse include HCPs, patients, and government
- HCP strategies for mitigating opioid abuse include universal precautions, screening for drug abuse and abuse risk, urine testing, and adherence monitoring
- Patients should be educated on the methods and importance of safe use, safe storage, and safe disposal of opioids
- The federal and state governments have developed and are developing programs aimed at making opioid diversion and abuse more difficult and less likely, including:
  - PDMPs
  - REMS
- Industry may also have a role by developing abuse-deterrent opioids


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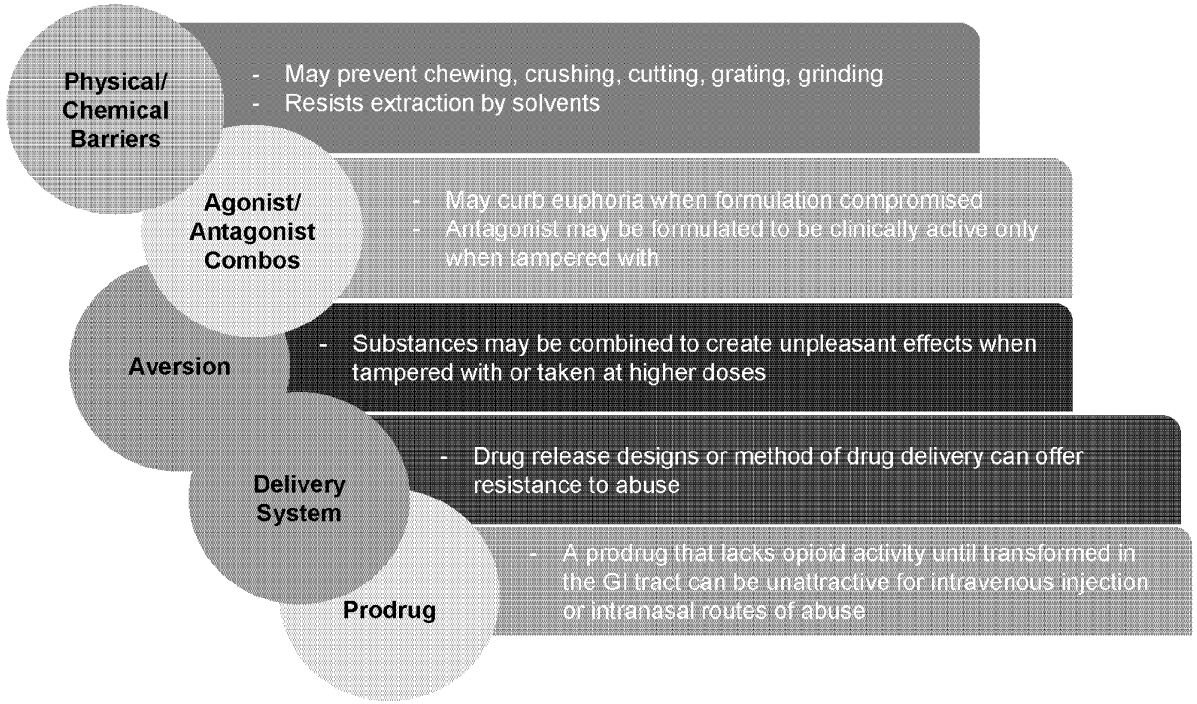
DEVELOPING ABUSE-DETERRENT OPIOIDS

Various Approaches to Abuse Deterrent Opioids

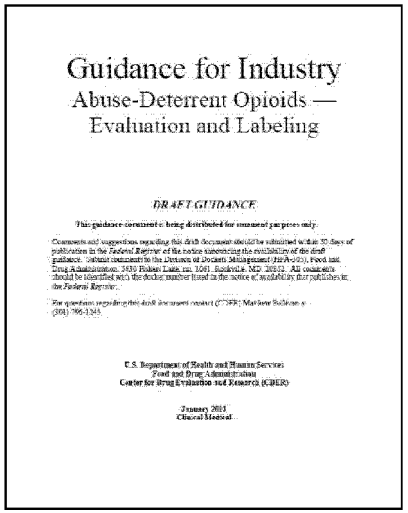


U.S. Food and Drug Administration. Guidance for Industry: Abuse Deterrent Opioids – Evaluation and Labeling (Draft). January 2013. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf. Accessed July 20, 2014.

FDA Draft Guidance on Abuse-Deterrent Opioids

Provides guidance on studies that should be conducted:

- To demonstrate that a formulation has abuse-deterrent properties
- How those studies will be evaluated
- What labeling claims may be proposed based on the results of those studies



Guidance for Industry

Abuse-Deterrent Opioids — Evaluation and Labeling

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2013
Clinical Medical

U.S. Food and Drug Administration. Guidance for Industry: Abuse Deterrent Opioids – Evaluation and Labeling (Draft). January 2013. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf. Accessed July 20, 2014.

FDA Draft Guidance for Abuse-Deterrent Opioids

FDA guidance document outlines:

- Categories of studies to evaluate abuse-deterrent properties
- Designs and goals of such studies
- Examples of labeling claims that could be proposed based on the results of these studies

Categories of Studies

1 Laboratory Manipulation and Extraction Studies
- Evaluate how easily the formulation can be manipulated

2 Pharmacokinetic (PK) Studies
- Evaluate in vivo PK profiles of manipulated and intact drug vs comparator

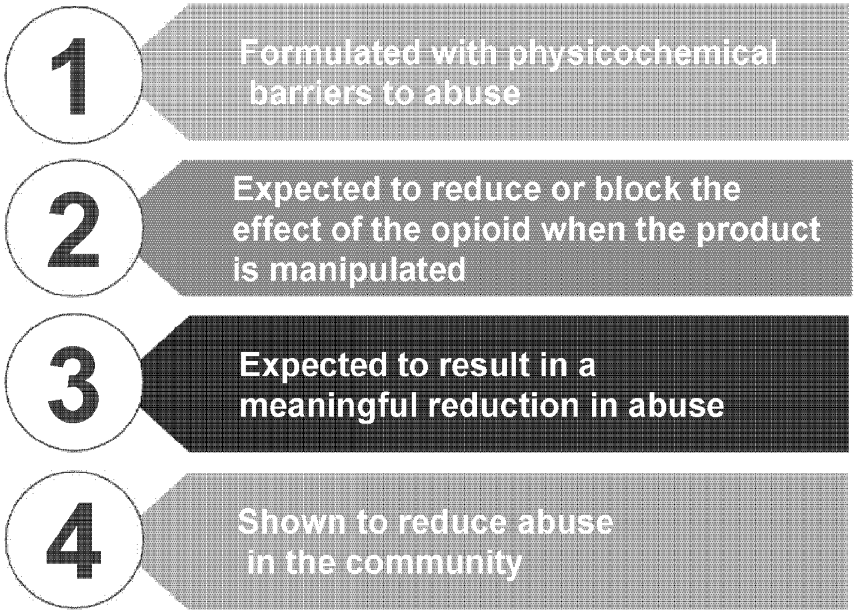
3 Clinical Abuse Potential (CAP) Studies*
- Assess impact on appeal to abusers (ie, drug liking)

4 Postmarketing Studies
- Determine if formulation results in lower levels of abuse vs non-deterrent formulations

*Also called human abuse liability (HAL) studies.

U.S. Food and Drug Administration. Guidance for Industry: Abuse Deterrent Opioids – Evaluation and Labeling (Draft). January 2013. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf. Accessed July 20, 2014.

Four Tiers of Label Claims



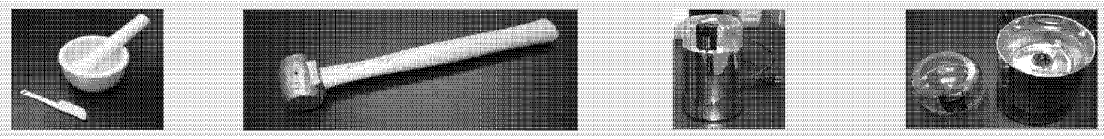
U.S. Food and Drug Administration. Guidance for Industry: Abuse Deterrent Opioids – Evaluation and Labeling (Draft). January 2013. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf. Accessed July 20, 2014.

FDA Draft Guidance for Laboratory Manipulation and Extraction Studies

Study Design

Mechanical Manipulation Studies

- Focus on **particle size**, which may influence opioid extractability
- Ordinary tools/utensils should be employed in testing; eg, spoons, cutters, and coffee grinders



- Effect of **heat** and **cold** on mechanical manipulation

Solubility Studies

- Determine ease of **solubility** with various solvents (eg, water, vinegar, ethanol, isopropanol, acetone, mineral spirits)

Route-Specific Evaluation

- ***Snorting***: particle size distribution
- ***Smoking***: vaporization temperature
- ***Injection***: opioid concentration in small injection volume and viscosity of injection fluid

U.S. Food and Drug Administration. Guidance for Industry: Abuse Deterrent Opioids – Evaluation and Labeling (Draft). January 2013. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf. Accessed July 20, 2014.

FDA Draft Guidance for PK Studies

Study Design

Pharmacokinetic Parameters

- Maximum plasma concentration (C_{max})
- Time to reach C_{max} (T_{max})
- Area under the curve (AUC)
- Relevant partial AUC (eg, $AUC_{0\text{-}30mins}$ or $AUC_{0\text{-}2hrs}$)
- Terminal elimination half-life

Areas of Special Interest Comparing Intact and Manipulated Formulations

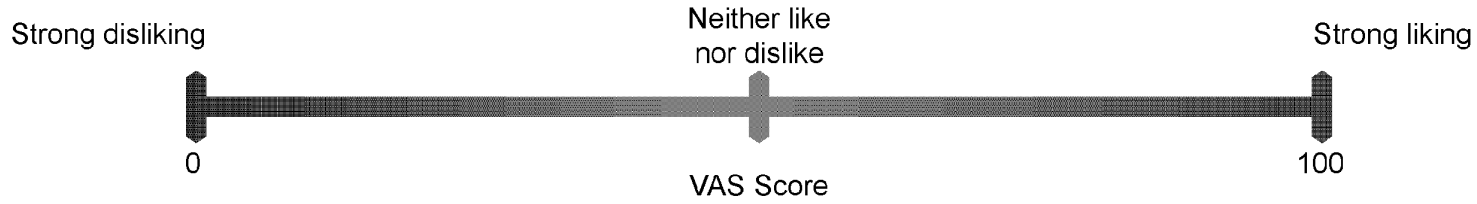
- Rate of rise of drug concentration (thought to contribute to abuse potential)
- Determination if food affects systemic exposure to formulation
- Recording of incidence and nature of adverse events (AEs)

U.S. Food and Drug Administration. Guidance for Industry: Abuse Deterrent Opioids – Evaluation and Labeling (Draft). January 2013. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf. Accessed July 20, 2014.

FDA Draft Guidance for CAP* Studies

Overview	• Controlled study in recreational drug users familiar with the effects of drug
Study Assessments	**Measurements of Interest** • Drug liking (eg, "How much did you like the drug?") • Assessment of high (eg, "How high are you?") • Good effects (eg, euphoria) • Bad effects (eg, specific AEs) • Likelihood to use drug again (eg, "How likely are you to use this drug again?")

Bipolar Scale



*Clinical abuse potential; also referred to as human abuse liability (HAL) studies.

U.S. Food and Drug Administration. Guidance for Industry: Abuse Deterrent Opioids – Evaluation and Labeling (Draft). January 2013. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf. Accessed July 20, 2014.

FDA Draft Guidance for Postmarketing Studies

Study Characteristics

- Use outcomes that provide meaningful measures of abuse deterrence
- Produce estimates of abuse deterrence that are nationally representative, or are based on data from a large geographic region
- Assess overall and route-specific abuse and abuse deterrence
- Are sufficiently powered to assess meaningful changes in drug abuse

Study Population

- Should be carefully selected (ie, relevant to real-world abuse)
- At least one study should include high-risk subjects (eg, drug abusers)

Use of a Comparator

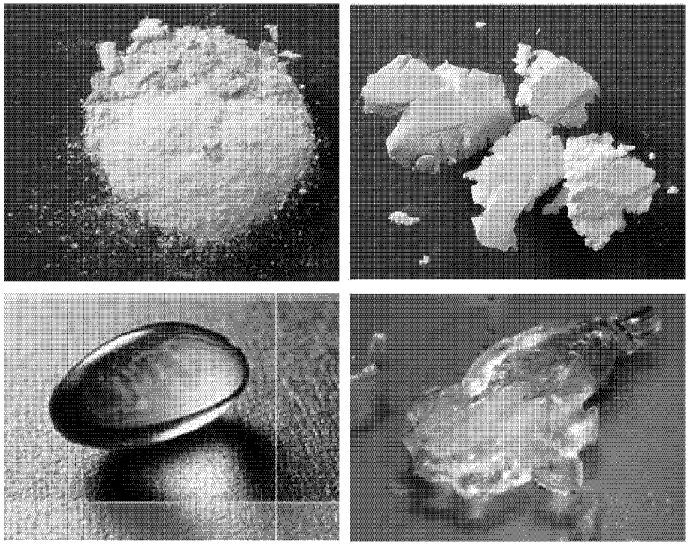
- Comparator is critical to rule out other factors (eg, educational interventions, law enforcement changes)
- Other opioids as comparator is encouraged

U.S. Food and Drug Administration. Guidance for Industry. Abuse Deterrent Opioids – Evaluation and Labeling (Draft). January 2013. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf. Accessed July 20, 2014.

Abuse-Deterrent Formulations: Crush-Resistant Pills and Capsules

How abuse-deterrent is it?

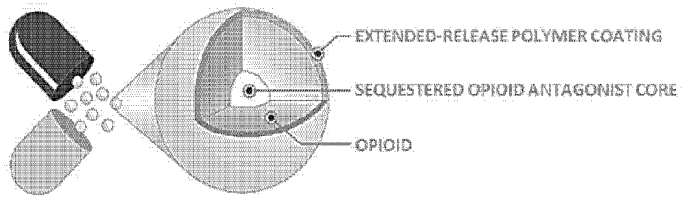
- Recent formulations seek to make crushing pills unusable for abuse
- In this form, drug may be challenging to break, snort, chew, inject
- Crush-resistant pill currently available
- Gelatin capsule rejected by FDA in 2011
- Labeling differentiates between formulations that *prevent* abuse and those that make it *more difficult*



Abuse-Deterrent Formulations: Agonist-Antagonist

Blocking the Effect

- Capsule containing many pellets of opioid
- Sequestered core contains an opioid antagonist
- No notable antagonist effect if taken orally or if pellets are sprinkled on food
- If crushed or chewed, antagonist is released, causing withdrawal symptoms

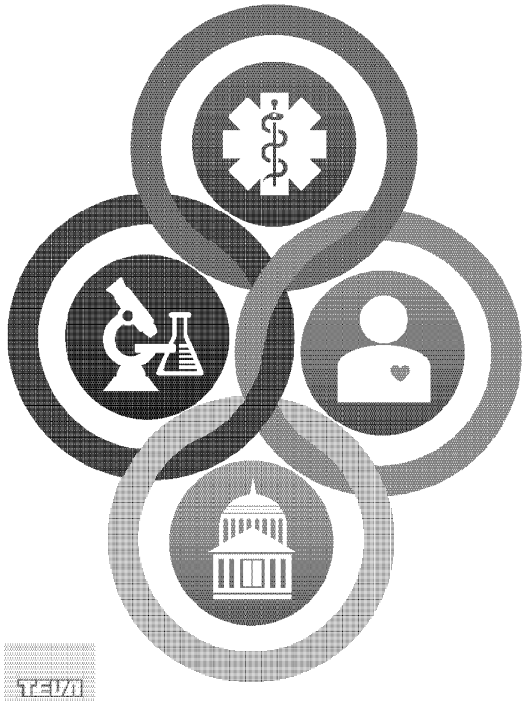


Moorman-Li R. et al. *P & T.* 2012;37(7):412-418.

The Continuing Evolution of Abuse-Deterrent Opioids

- Numerous approaches to deter abuse have been, and are being, developed to decrease the likelihood of opioid misuse, abuse, and diversion
- The FDA has provided industry with draft guidance for the development and testing of new abuse-deterrent formulations
- The draft guidance also includes levels of claims manufacturers may propose in labeling to describe the potential abuse-deterrent properties of a product based on study results

Conclusions



- Pain is a major reason patients seek medical care, and opioids remain an important treatment option for adequate analgesia
- Addressing issues surrounding opioid misuse, abuse, and diversion requires a multifaceted approach that encompasses HCPs, patients, government, and industry
- While no abuse-deterrent opioid formulations prevent all types of abuse, they may be designed to provide an additional barrier to opioid abuse
  - Education, guidance, and tools continue to be the most important impediments to abuse
  - Continued development and availability of abuse-deterrent opioids may further diminish the likelihood of abuse

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