FDA's Endeavors to Combat Opioids Crisis: Abuse-Deterrent Opioid and Beyond

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

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Outline

- Background on Epidemic
- FDA's guidance on evaluation and labeling for abuse-deterrent opioid
- Broader efforts on safety monitoring and risk assessment activities

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BACKGROUND

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Pain in America

- From 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%): reported a lot of 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

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Pain in America (cont.)

- Treatment options for pain: pharmacologic, physical medicine, behavioral medicine, neuromodulation, interventional, and surgical
- 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*
- Treatments have largely focused on prescription drugs because of the reimbursement structure of our healthcare system

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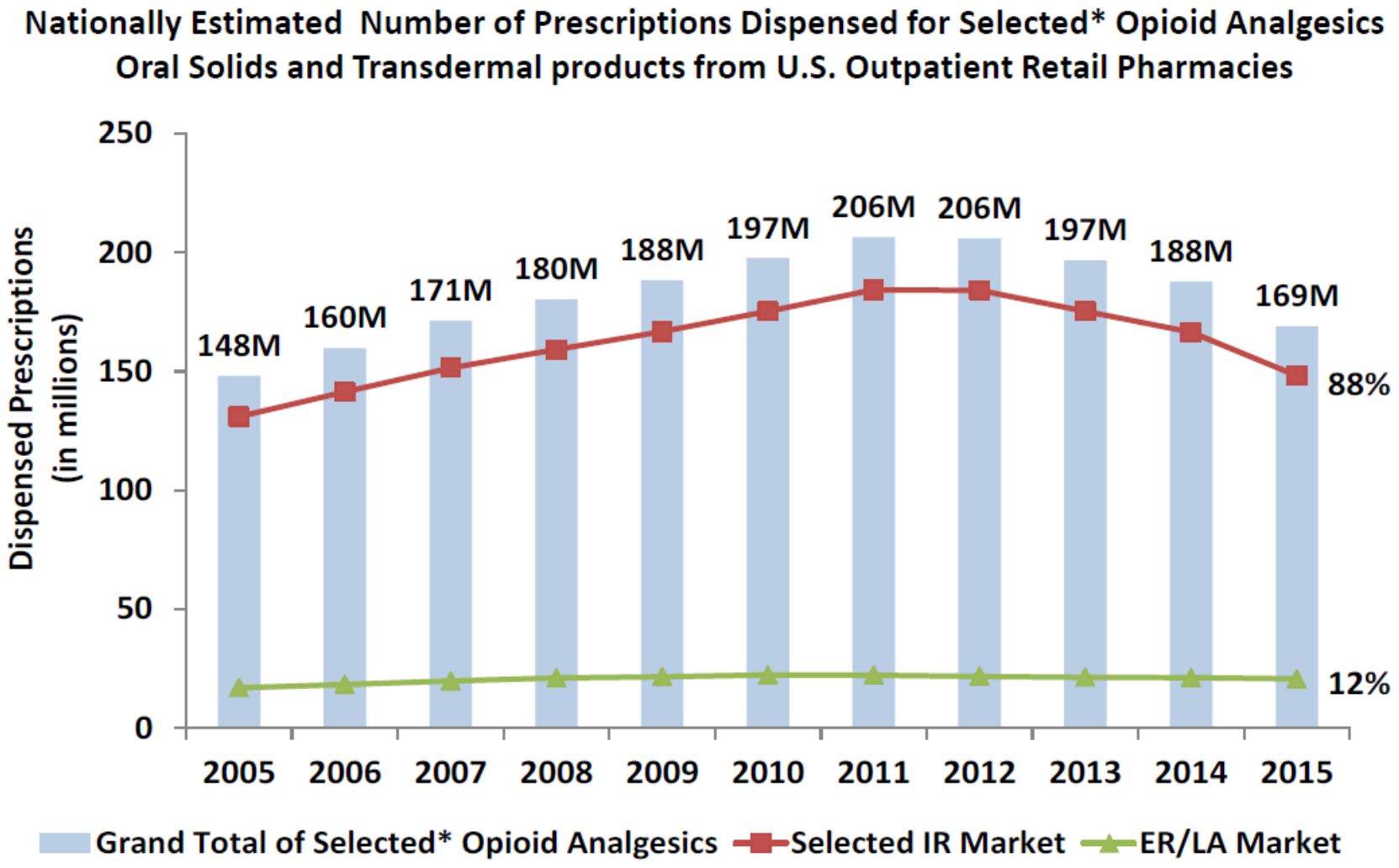
US Prescribing Rates



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

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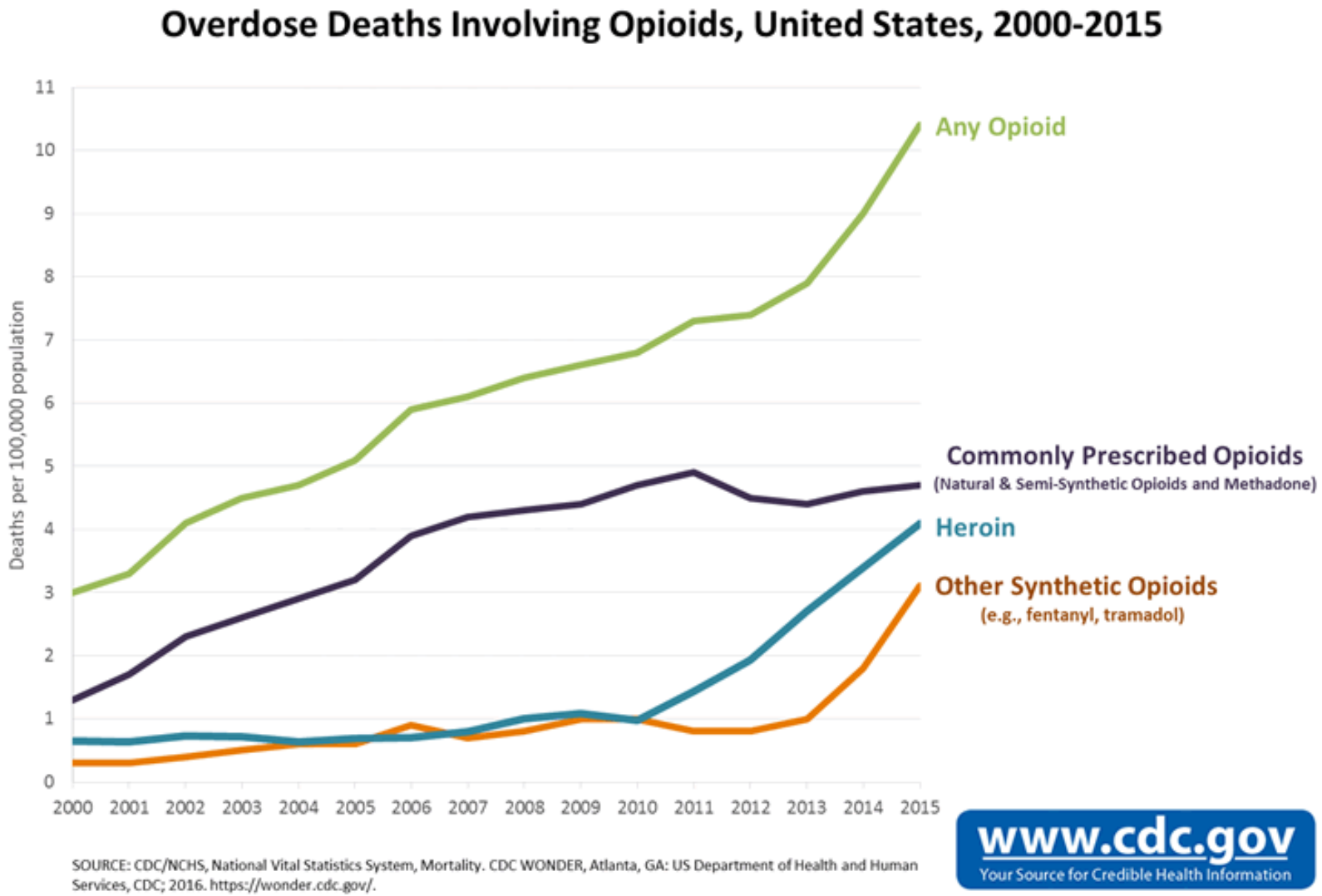
Opioid Overdose Deaths



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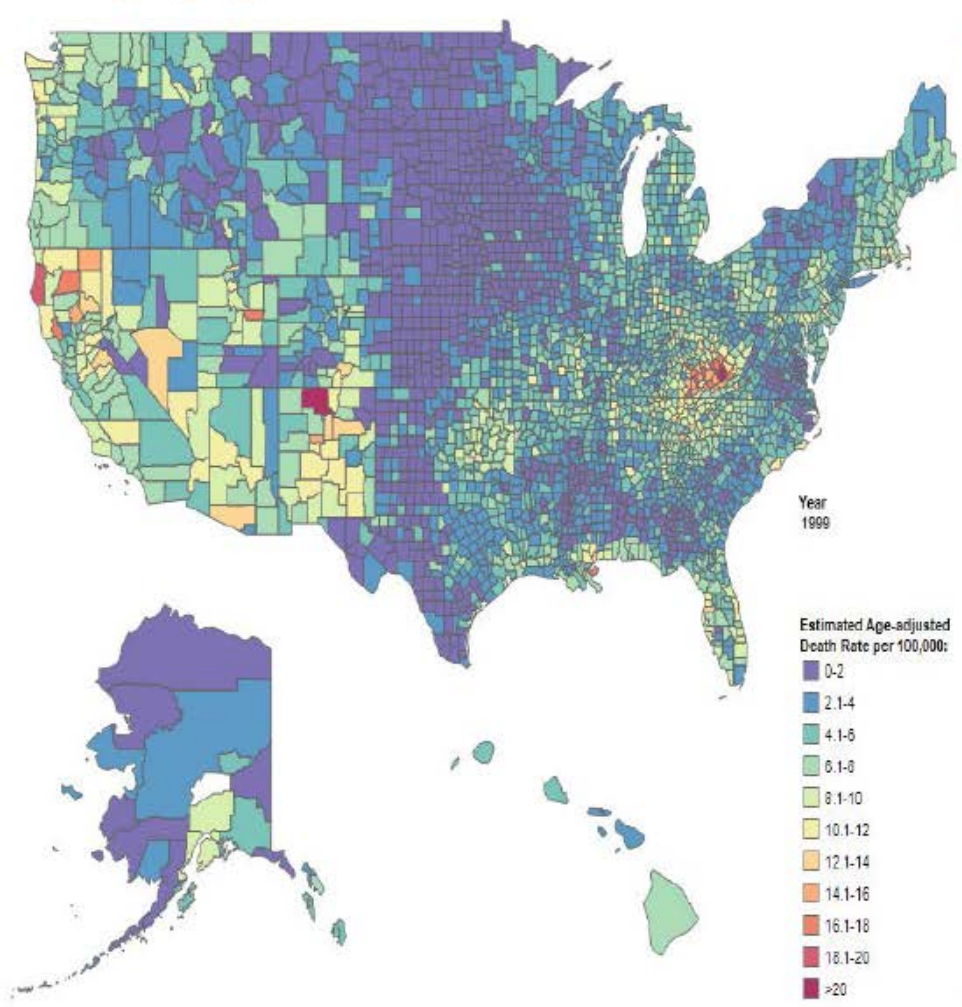
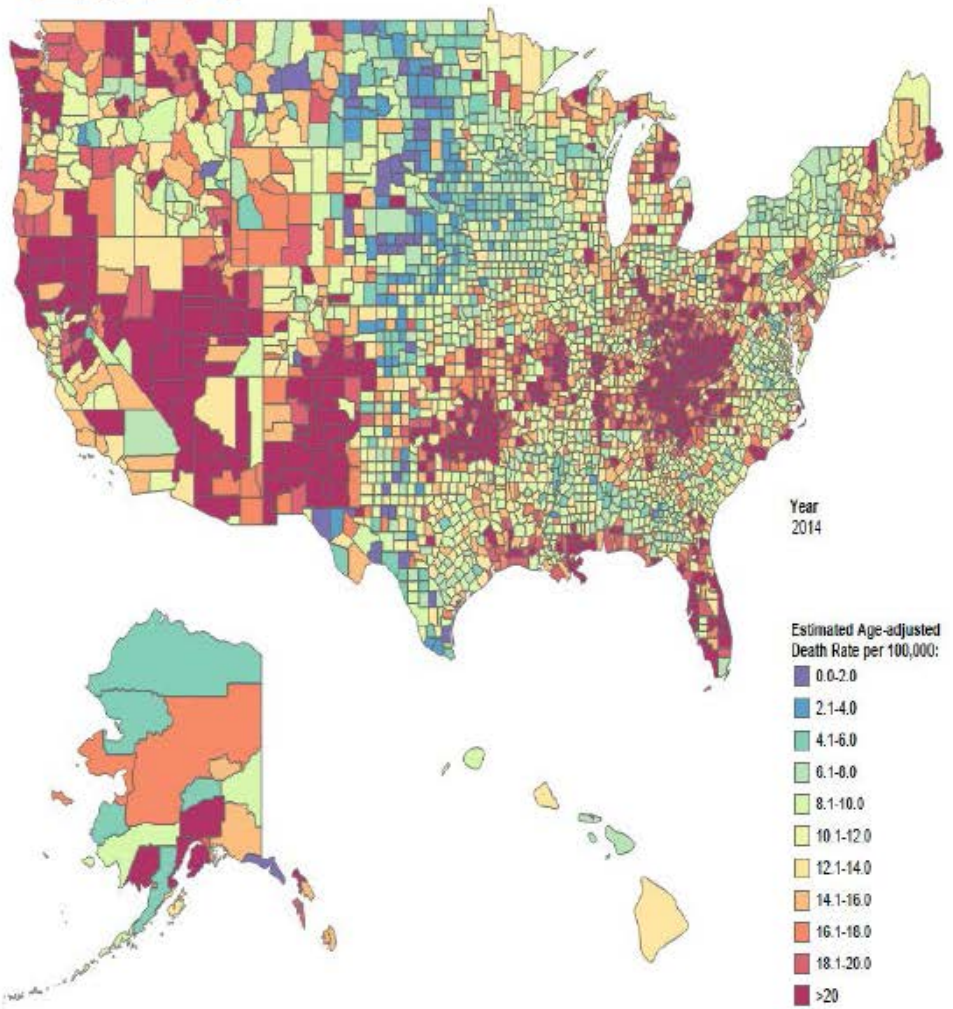
1999

2014

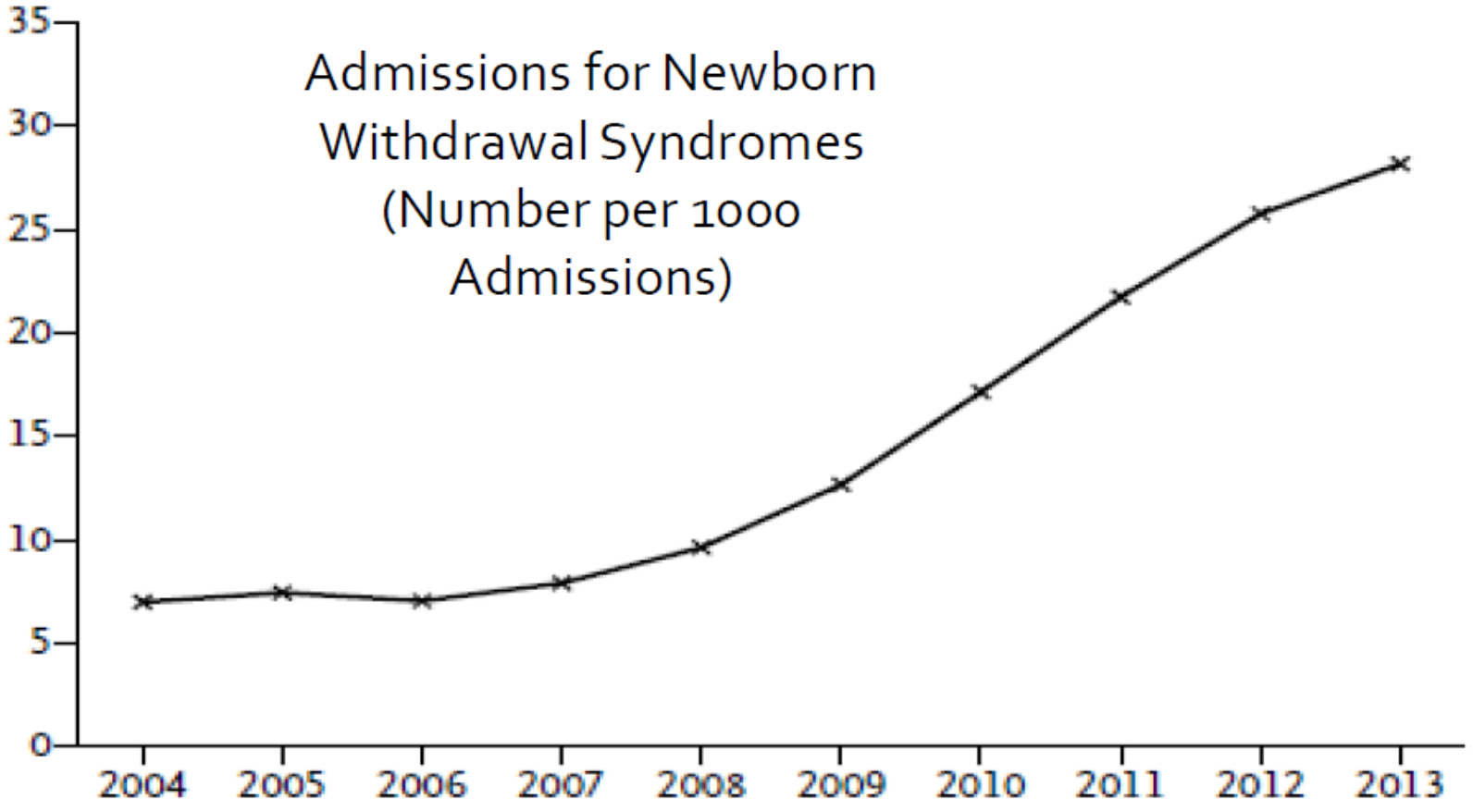




Designed by L. Rossen, B. Bastian & Y. Chong. SOURCE: CDC/NCHS, National Vital Statistics System

Science = Solutions

Increasing Prenatal Exposure



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

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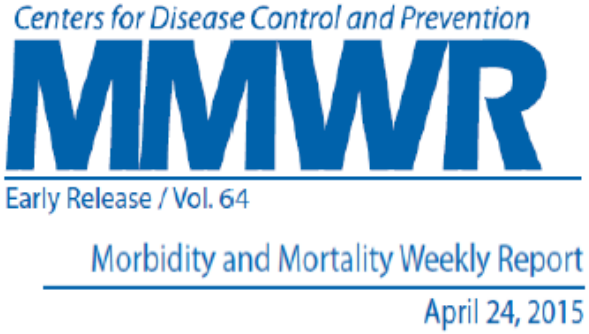
Infectious Disease Transmission

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

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FDA response to this crisis

- Abuse and misuse of prescription opioid products: serious and growing public health concern

- 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

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FDA's Priorities

1. Decreasing Exposure & Preventing 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

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FDA's Priorities #1

1. Decreasing Exposure & Preventing New Addiction

- One potential step towards safer opioid analgesics: development of opioids that are formulated to deter abuse

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Abuse-Deterrent Opioids

- Opioid abuse: products are often manipulated by different routes of administration (e.g., crushed and snorted or smoked) or to defeat extended-release (ER) properties

- Abuse-deterrent opioid: intended to make manipulation more difficult

- Example: gel-type opioid product which is hard to crush

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FDA'S GUIDANCE ON ABUSE-DETERRENT OPIOID

https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf

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FDA's Guidance on Abuse-Deterrent Opioid

- Explains FDA's current thinking about opioid studies that aim to demonstrate abuse-deterrent properties

- Makes recommendations about
  - How studies should be performed
  - How studies should be evaluated

- Discusses how to describe implications of those studies in product labeling

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FDA's Guidance: Evaluation for Abuse-Deterrent Opioid

- Premarket studies
  - Laboratory-based in vitro manipulation and extraction studies (category 1)
  - Pharmacokinetic studies (category 2)
  - Clinical abuse potential studies (category 3)

- Postmarket studies (category 4)

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In Vitro (Category 1) Studies Evaluation

- The goal is to evaluate the ease with which the abuse-deterrent properties of a formulation can be defeated.
- Should assess various mechanical and chemical ways a drug could be manipulated:
  - defeating the controlled release of an opioid from ER formulations for purposes of abuse by different routes of administration
  - preparing an IR formulation for alternative routes of administration
  - separating the opioid antagonist, if present, from the opioid agonist
- Should be compared to comparator products

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Pharmacokinetic (Category 2) Studies Evaluation

- The goal is to understand the in vivo properties of the formulation by comparing the pharmacokinetic profiles of
  - manipulated formulation *vs.* intact formulation
  - manipulated formulation *vs.* manipulated and intact formulations of the comparator drugs

- The method of manipulation used for the pharmacokinetic studies should be based on the methods explored during in vitro testing.

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Pharmacokinetic (Category 2) Studies Evaluation (cont.)

- Traditional pharmacokinetic study designs should be employed (e.g., crossover designs), and the results should be analyzed using bioequivalence methods.

- The rate of rise of drug concentration should be assessed when possible.

- Adverse events should be collected

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Clinical Abuse Potential (Category 3) Studies Evaluation

- The preferred design is a randomized, double-blind, placebo-controlled and positive controlled crossover study.

- Generally conducted in a drug-experienced, recreational user population

- This presentation will focus on statistical analysis. Additional considerations (blinding, pre-qualification phase, assessment phase, etc) to assess potentially abuse-deterrent properties are described in the Guidance.

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Clinical Abuse Potential (Category 3) Studies Evaluation (cont.)

- The goal is to assess a number of abuse potential outcome measures in the potentially abuse-deterrent product (*T*) relative to a formulation without abuse-deterrent properties (*C*), or a newly formulated opioid product (positive control).

- Comparing the difference in means between *C* and *T* with a *margin* for abuse potential measures and comparing the difference between *C* and *T* relative to *C* in outcome measures (e.g., VAS)

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Clinical Abuse Potential (Category 3) Studies Evaluation (cont.)

- The statistical test that sponsors should use for the primary analysis of Emax on the VAS for drug liking is described in Section 8.b of the Guidance.
- An analysis of the percent reduction in drug liking for *T* relative to *C* on the individual level in subsection c is recommended as a secondary analysis, and is described in Section 8.c of the Guidance.
- Examples of some other analyses (responder analysis, analysis of the median percent reduction) are available.

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Postmarket (Category 4) Studies Evaluation

- The goal is to determine whether a product with abuse-deterrent properties results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes in a post-market (i.e., real-world) setting.
- Currently, data on the impact of an abuse-deterrent product on drug abuse in the U.S. population are limited.
  - the optimal data sources, study variables, design features, analytical techniques, and outcomes of interest of postmarket studies are not fully established
- Postmarket evaluations fall into two categories: formal studies and supportive information

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Postmarket (Category 4) Studies Evaluation (cont.)

- Formal studies:
  - hypothesis-driven, population-based, observational evaluations
  - capture one or more outcomes that can be used to assess meaningful reductions in misuse, abuse, addiction, overdose, and death
  - produce estimates of abuse and related clinical outcomes that are nationally representative, or are based on data from multiple large geographic regions that can reasonably be generalized to the national level
  - assess overall and route-specific changes in abuse
  - sufficiently powered statistically to assess meaningful changes in drug abuse and are of sufficient duration to examine trends in abuse following the marketing of the abuse-deterrent product

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Postmarket (Category 4) Studies Evaluation (cont.)

- Supportive information:
  - if it can be used to provide additional context on societal, behavioral, and clinical aspects
  - may rely on sources that capture drug utilization or prescribing patterns, diversion events, attitudes and practices of abusers and other information that may not directly be considered abuse
  - may also include investigations that are conducted in smaller populations or subgroups, and perhaps not broadly generalizable
  - may contribute to the totality of the evidence relating to abuse deterrence

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Labeling

- Several important concepts:
  - abuse-deterrent does not mean abuse-proof
  - Premarket studies: demonstrate properties that are predictive of a meaningful abuse-deterrent effect for a particular route of administration
  - The same evidence from postmarket studies are not available at the time of initial product approval
  - Labeling should reflect the predictive quality of premarket studies and include results of relevant completed postmarket studies

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FDA-Approved Products w/ ADF Labeling

- OxyContin
- Targiniq ER
- Embeda
- Hysingla ER
- MorphaBond ER
- Xtampza ER
- Arymo ER
- RoxyBond

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

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Statistical Challenges in Determining the Real-World Impact of Abuse-Deterrent Opioid

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Limitations: Data sources

1. Poison control center call data
2. Data collected from individuals entering/being assessed for substance use disorder treatment (e.g., NAVIPPRO, ASI-MV)
3. Electronic health care data including claims data
4. Population-based survey (e.g., NSDUH)
5. Others
   - The FDA Adverse Event Reporting System (FAERS)
   - Drug Diversion Data
   - Web Monitoring Programs

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Limitations: Outcomes

- The Guidance states that "*the goal of postmarket studies . . . is to determine whether the marketing of a product with abuse-deterrent properties results in meaningful reductions in* ***abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death*** *properties results in meaningful reductions in in the post-approval setting*"
- Every data source does not define these outcomes the same way

- ADF: Focused primarily on deterring non-oral abuse, most commonly via the nasal and injection routes: must consider route-specific abuse outcome

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Limitations: Metrics and Denominators

- Typically used metrics:
  - Route of abuse profile: proportion of those indicating abuse via specific routes
  - Prevalence of abuse
  - Utilization-adjusted abuse rate

- Uncertainties remain regarding the utilization-based measures:
  - Different utilization denominators (e.g., number of dosage units dispensed, prescription dispensed, individuals receiving a prescription) may be appropriate for different types of products/study questions

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Some Other Limitations

- Misclassification/Ascertainment of products
- Sampling and selection bias: concerns with non-probability samples
- Confounding and secular trends

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Broader Efforts on Safety Monitoring and Risk Assessment Activities

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Safety Monitoring & Risk Assessment Activities

- Post-marketing requirement (PMR) and post-marketing commitment (PMC) studies
- Risk evaluation and mitigation strategies (REMS)
- Interagency collaboration on substance control
- Sentinel
- FDA funded projects (task orders)
- Many others…..

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Safety Monitoring & Risk Assessment Activities

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PMR Study Example: ER/LA PMR

- Prescription opioid safety questions
  - How often do patients become addicted to prescription opioids, or have other adverse outcomes?
  - What is the impact of potential confounders such as pain measures, indications for treatment, comorbidities, or prior opioid use?
  - Can time-varying dose measurements and data-driven thresholds be used in measuring abuse-related outcomes?
  - What are valid outcome measures for abuse-related events?

- Risks associated with long-term use of extended-release/long-acting (ER/LA) Opioids for analgesia: ER/LA PMR

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PMR Study Example: ER/LA PMR

- The FDA determined that
  - more data are needed regarding the serious risks of misuse, abuse, addiction, overdose, and death associated with the long-term use of ER/LA opioids
  - the incidence of these serious risks is not well quantified

- Thirteen companies formed the Opioid Postmarketing Requirement Consortium (OPC) to design and implement the study program.

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PMR Study Example: ER/LA PMR

- The program is designed to address
  - 1) risks of abuse, addiction, overdose, death, and misuse
  - 2) predictors of the risks in 1)
  - 3) validate proxies/surrogates for opioid abuse and diversion, such as doctor/pharmacy shopping measures
  - 4) a randomized, controlled clinical trial to assess the risk of hyperalgesia and risk relative to analgesic efficacy with long-term use of ER/LA opioid analgesics to treat chronic pain

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ER/LA Study Overview

- Study 1 and 2: Quantitative estimate of misuse, abuse, addiction, overdose, and death associated with long-term analgesic opioid use based on prospective and retrospective studies
- Study 3 and 4: Developed and validated questionnaire to measure opioid misuse and abuse
- Study 5: Developed and validated questionnaire to measure prescription opioid addiction among chronic pain patients
- Study 6 and 7: Developed and validated algorithms to identify opioid overdose, abuse/addiction in claims and medical records databases
- Studies 8-10: Defined and validated doctor/pharmacy shopping as outcomes suggestive of misuse, abuse, addiction and/or diversion based on claims databases, patient self-reported outcomes, and information described in EMRs.

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Status of PMR

- Seven studies have been completed
- Results, findings, lessons learned from the ER/LA PMRs are forthcoming
  - The results from one study (doctor/pharmacy shopping) were published soon after study completion*
  - Results from the remainder studies will be published on completion

*Cepeda et al. Doctor shopping for medications used in the treatment of attention deficit hyperactivity disorder: shoppers often pay in cash and cross state lines. *Am J Drug Alcohol Abuse.* 2015;41(3):226-229.

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Risk Evaluation and Mitigation Strategy (REMS)

- REMS: A drug safety program that FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks

- REMS are designed to reinforce medication use behaviors and actions that support the safe use of that medication.

- While all medications have labeling that informs medication risks, only a few medications require a REMS.

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REMS in Action: Zyprexa Relprevv REMS

- Zyprexa Relprevv: A long-acting injectable anti-psychotic medication used to treat schizophrenia in adults.
- Zyprexa Relprevv can cause serious reactions following injection called post-injection delirium sedation syndrome.
- Symptoms: feeling sleepier than usual (sedation), coma, and feeling confused or disoriented (delirium)
- The risk of post-injection delirium sedation syndrome is present with every injection, although it is a small risk - less than 1 percent.

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REMS in Action: Zyprexa Relprevv REMS

- To reduce the risk of post-injection delirium sedation syndrome, FDA required the manufacturer of Zyprexa Relprevv to develop a REMS.

- The purpose of the REMS is to ensure that the drug is administered only in certified health care facilities that can observe patients for at least three hours and provide the medical care necessary in case of an adverse event.

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Interagency Collaboration on Substance Control

- DEA-FDA interagency collaboration:
  - The Drug Enforcement Administration (DEA) requests FDA forecast amounts of schedule I/II controlled substances and list I chemicals that might be sufficient to meet the legitimate medical, scientific, and stock needs of the US.
  - Forecasts are obtained by applying time-series smoothing methods to past annual sales (in Kg) data from IQVIA.

- The DEA uses the estimates provided by FDA to establish and revise production quotas of the controlled substance for the coming years.

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