U.S. FOOD & DRUG ADMINISTRATION

The Epidemiology of Prescription Opioid Abuse: A Regulatory Perspective

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Office of Surveillance and Epidemiology
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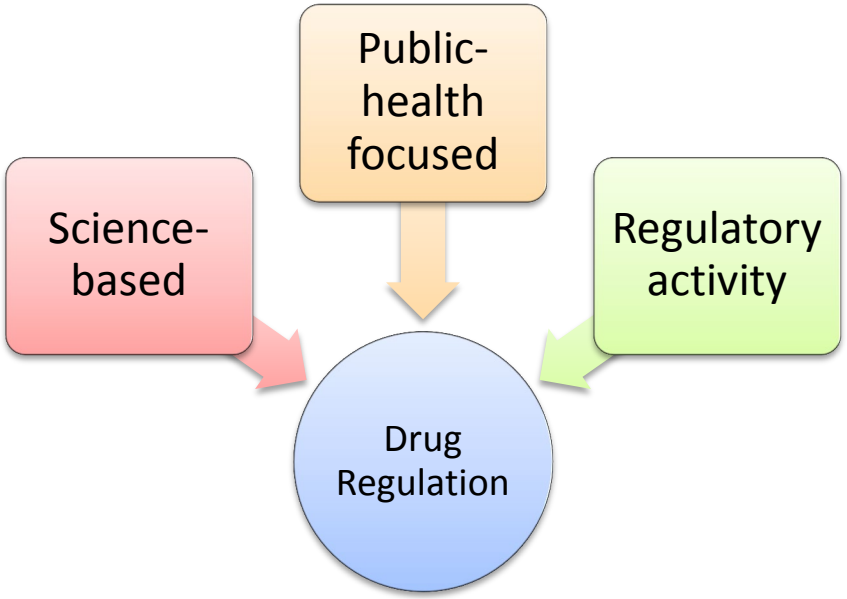
RADARS Annual Scientific Meeting
Silver Spring, MD
16 May 2019

No conflicts of interest to disclose

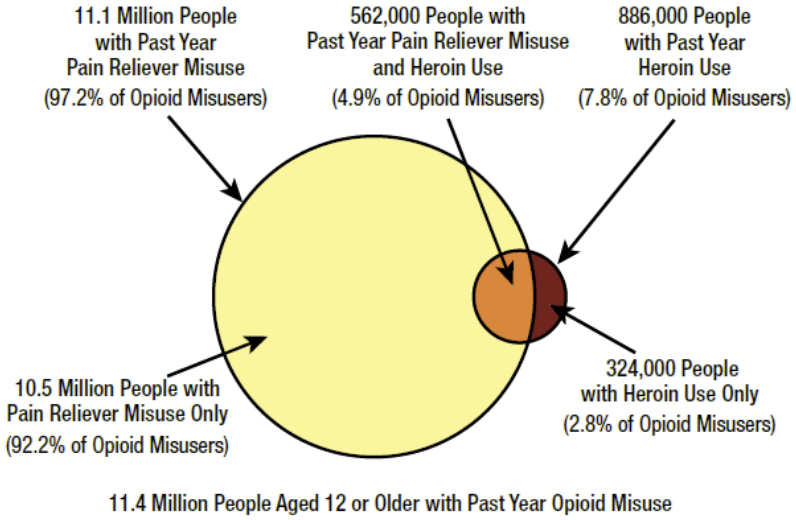
Role of the Drug Regulator

- Access to medicines
  - Assess efficacy, safety, quality
- Protection of the public
  - During clinical trials
  - Postapproval
- Information to the public



An Important Public Health Problem

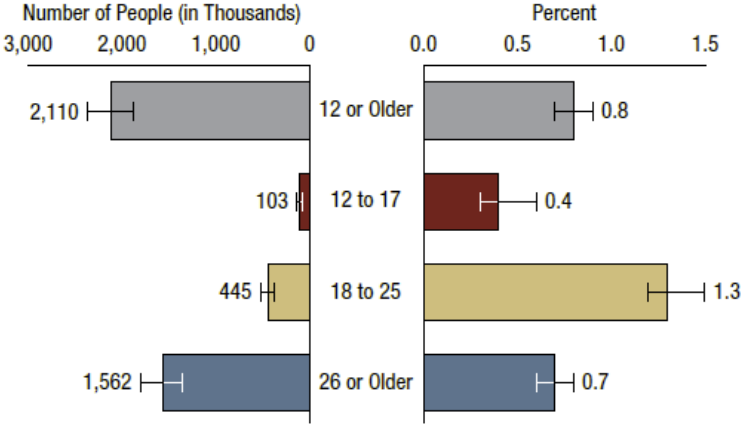
Figure 20. Past Year Opioid Misuse among People Aged 12 or Older: 2017



Note: Opioid misuse is defined as heroin use or prescription pain reliever misuse.

Note: The percentages do not add to 100 percent due to rounding.

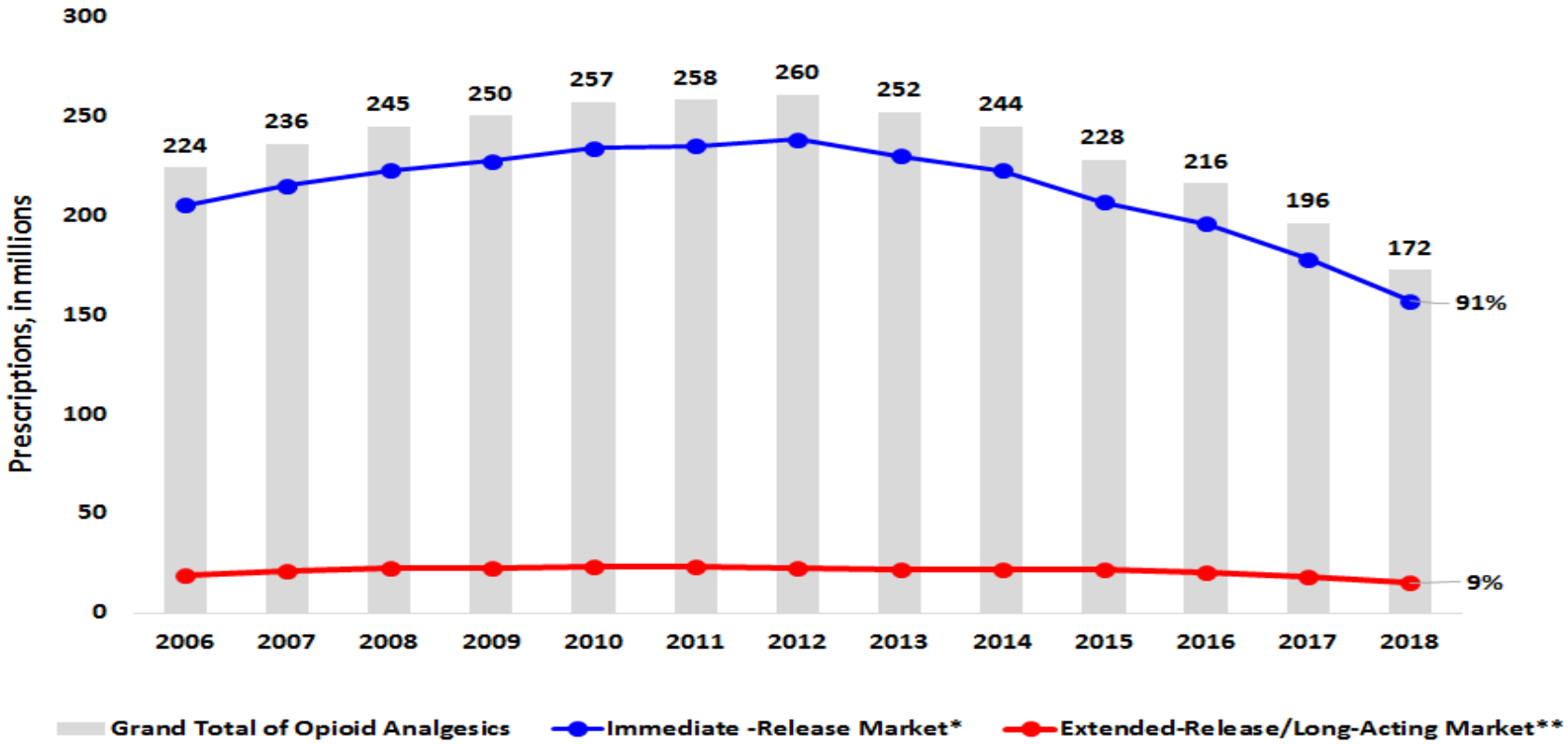
Figure 38. Opioid Use Disorder in the Past Year among People Aged 12 or Older, by Age Group: 2017



Note: Opioid use disorder is defined as meeting DSM-IV criteria for heroin use disorder or pain reliever use disorder in the past 12 months.

Source: *Substance Abuse and Mental Health Services Administration. (2018). Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health (HHS Publication No. SMA 18-5068, NSDUH Series H-53). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from https://www. samhsa.gov/data/.*

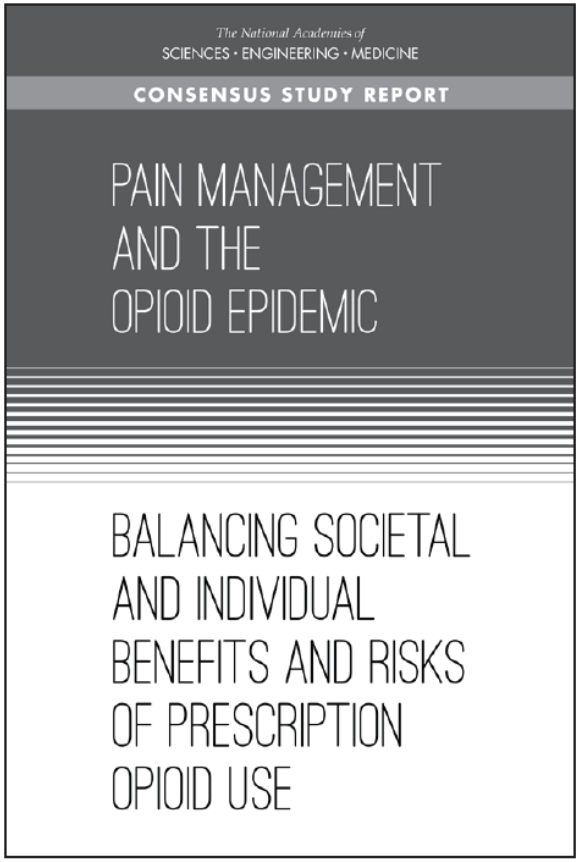
Nationally Estimated Number of Prescriptions Dispensed for Opioid Analgesics Products from U.S. Outpatient Retail Pharmacies



Source: IQVIA, National Prescription Audit (NPA) and static data 2006-2011. January 2006-December 2018.
Static data extracted March 2017, 2012-2017 data extracted February 2018, and 2018 data extracted January 2019.
*Immediate-Release formulations include oral solids, oral liquids, rectal, nasal, and transmucosal
**Extended-Release/Long-Acting formulations include oral solids and transdermal patches
Note: Include opioid analgesics only, excluding injectable formulations as well as opioid-containing cough-cold products and opioid-containing medication-assisted treatment (MAT) products

Considering public health impact in opioid drug approvals

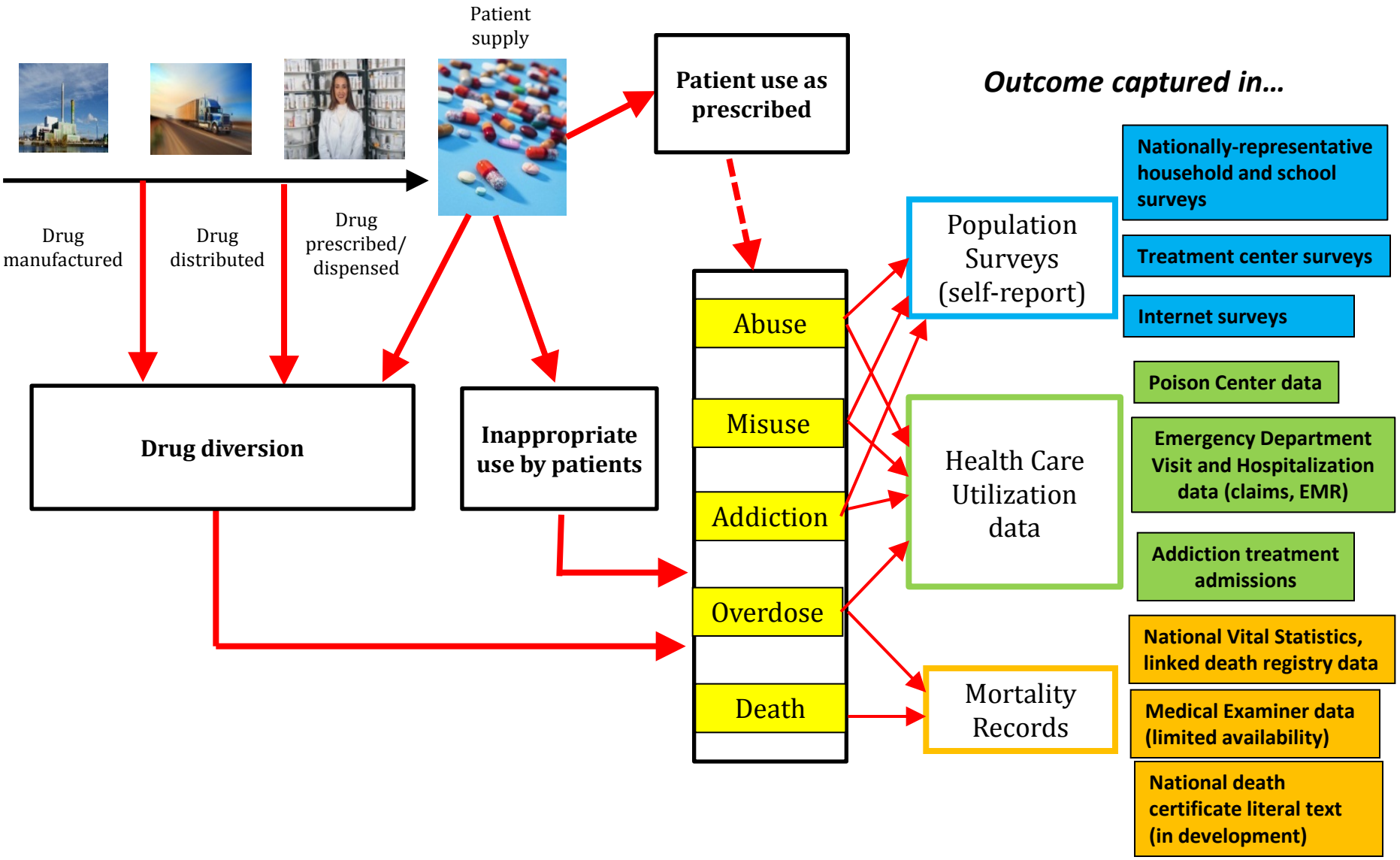
- From NASEM:
  - "Integrating public health considerations into [FDA's] regulation of opioids—including its approval decisions on new opioids—would be consistent with both its past practice and a generally accepted understanding of its statutory authority."
  - "Public health considerations may include how the availability or use of the product will affect an unintended population or the broad public health impact resulting from the aggregated effects on patients taking the drug."



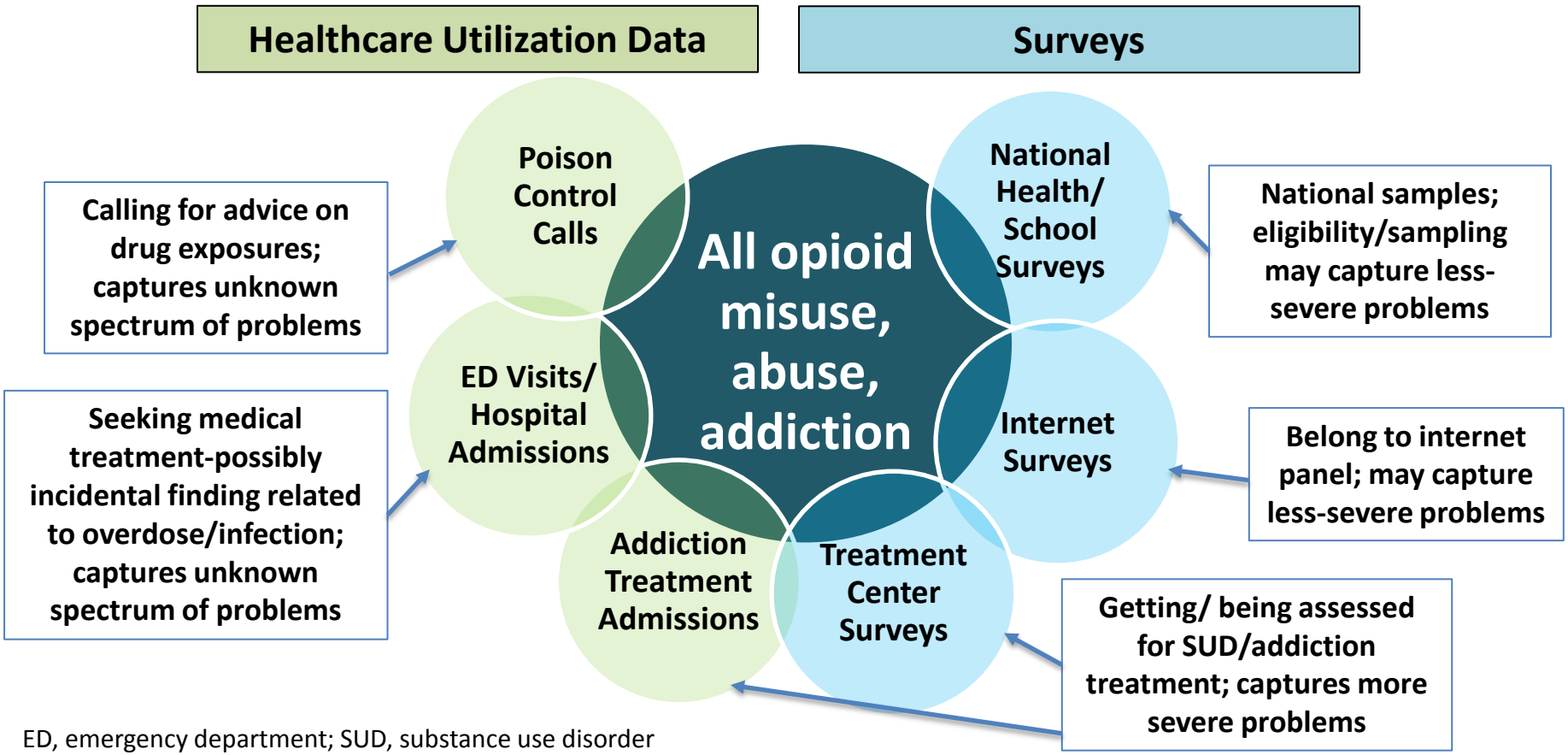
The Opioid Epidemic and Pharmacoepidemiology

- A societal problem
- Misuse, abuse, addiction, overdose and death are safety issues
- Involves both patients to whom an opioid was prescribed and non-patients
- Difficult to study and quantify

Pathways to Abuse/Misuse of Prescription Drugs and Related Adverse Outcomes



No Single Data Source Provides the Whole Picture



ED, emergency department; SUD, substance use disorder

Postmarket Safety - What We Want to Learn

- Learn about new risks
- Learn more about known risks
- Learn about medication errors
- Learn about product defects
- Learn how patterns of use may contribute to unsafe use
- Learn about the impact of our interventions

Learning about New Risks – OTC Loperamide Abuse

- Approved in 1976
- Safe and effective for diarrhea when used as directed
- Signal of cardiotoxicity detected in FDA's Adverse Event Reporting System (FAERS)
  - 48 cases of serious cardiac disorders associated with loperamide more than half since 2010
  - Cases were associated with doses much higher than recommended or with interacting medicines that resulted in high loperamide levels
  - Cases reported syncope, cardiac arrest, QT interval prolongation, ventricular tachycardia, and Torsade de Pointes
  - Ten cases resulted in death

FDA Actions on Loperamide

June 7, 2016
Risk of serious heart problems that can lead to death with higher than recommended doses

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← Home / Drugs / Drug Safety and Availability / FDA Drug Safety Communication: FDA warns about serious heart problems with high doses of the antidiarrheal medicine loperamide (Imodium), including from abuse and misuse

FDA Drug Safety Communication: FDA warns about serious heart problems with high doses of the antidiarrheal medicine loperamide (Imodium), including from abuse and misuse

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January 30, 2018
Oral solid packages sizes limited to 48 mg

U.S. FOOD & DRUG ADMINISTRATION

← Home / Drugs / Drug Safety and Availability / FDA Drug Safety Communication: FDA limits packaging for anti-diarrhea medicine loperamide (Imodium) to encourage safe use

FDA Drug Safety Communication: FDA limits packaging for anti-diarrhea medicine loperamide (Imodium) to encourage safe use

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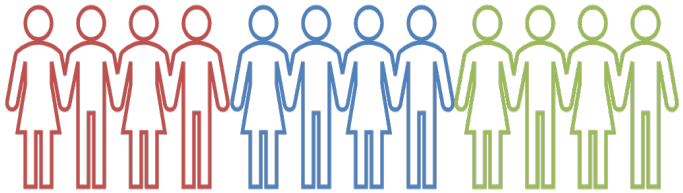
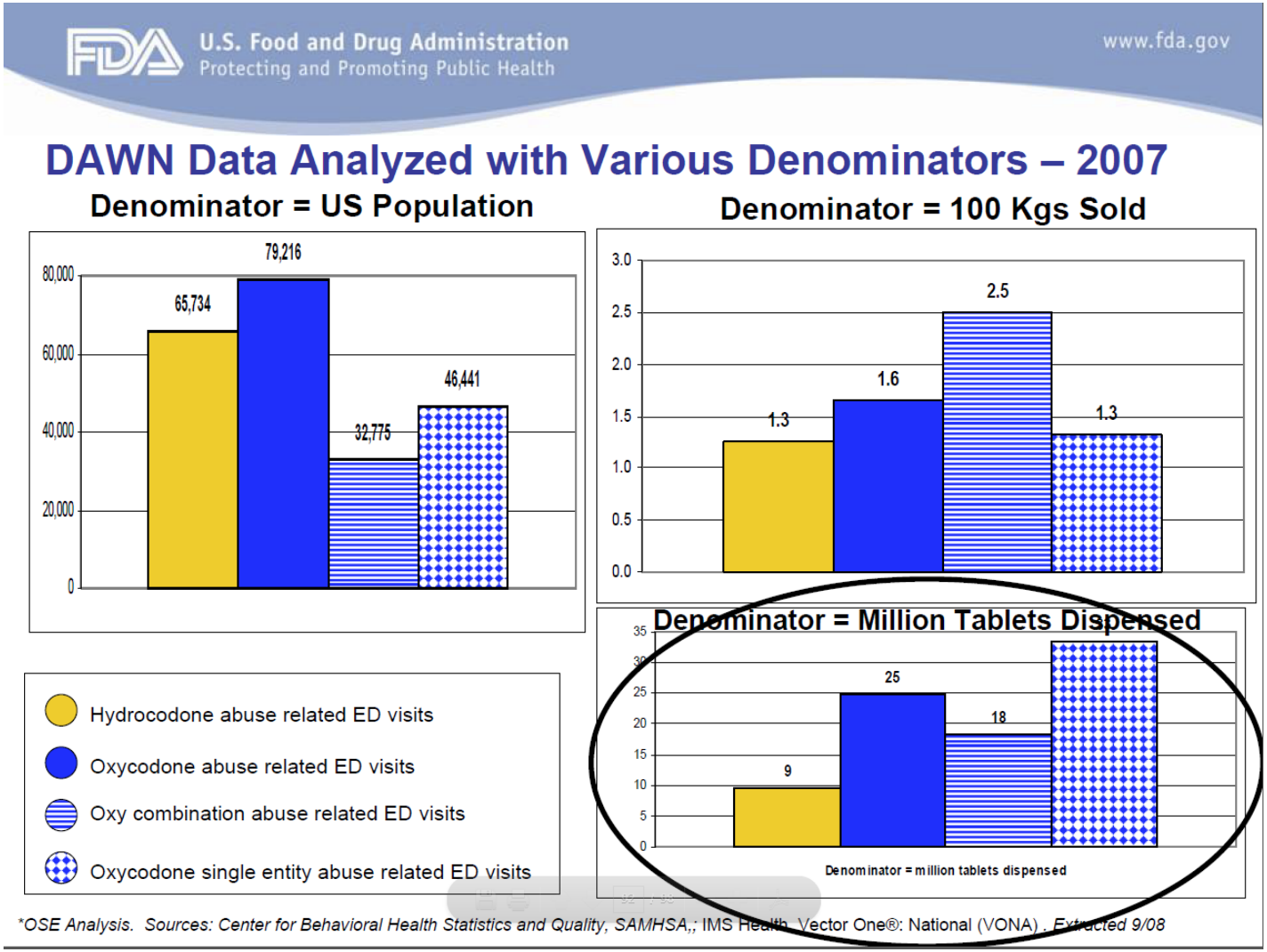
Stakeholder engagement



Learn More about Known Risks – Rescheduling of Hydrocodone

- Hydrocodone
  - Abuse potential was already known
  - Wide availability created public health problem
- Controlled Substances Act had placed hydrocodone in two different Schedules in the CSA:
  - Schedule II
    - Hydrocodone substance
  - Schedule III
    - Hydrocodone (in specified amounts) in combination with an isoquiline alkaloid of opium (specified amounts), or
    - Hydrocodone (in specified amounts) in combination with one or more therapeutically active non-narcotic ingredients

Learn More about Known Risks – Rescheduling of Hydrocodone



Source: https://wayback.archive-it.org/7993/20170405214226/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM337148.pdf

Re-scheduling of Hydrocodone

- C-III to more restrictive C-II (October 2014)
- FDA evaluation of impact on use and abuse is ongoing
- Hard to isolate effect of rescheduling, in light of all the other programs happening at same time

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA–389]

Schedules of Controlled Substances: Rescheduling of Hydrocodone Combination Products From Schedule III to Schedule II

AGENCY: Drug Enforcement Administration, Department of Justice.

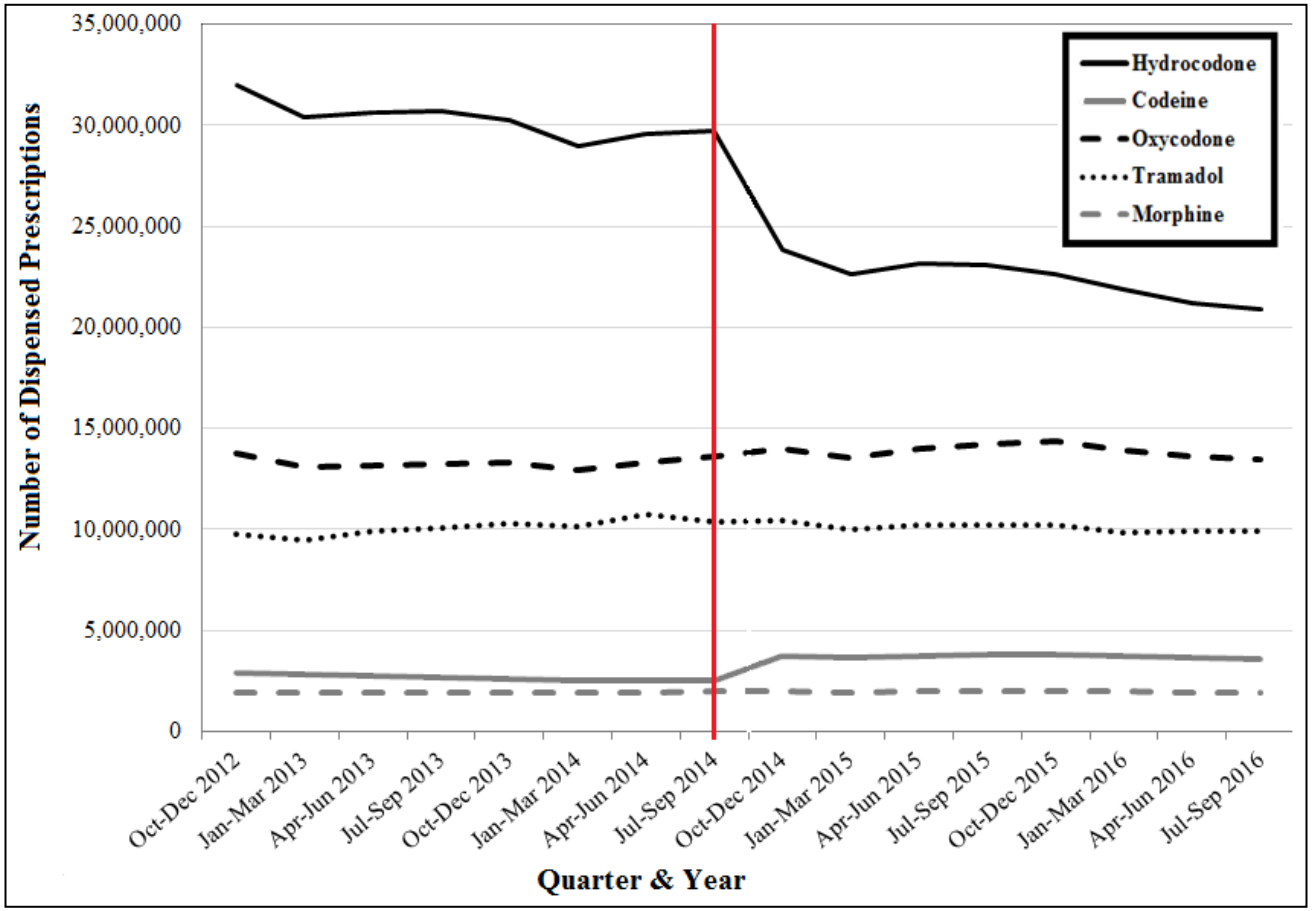
ACTION: Final rule.

SUMMARY: With the issuance of this final rule, the Administrator of the Drug Enforcement Administration reschedules hydrocodone combination products from schedule III to schedule II of the Controlled Substances Act. This scheduling action is pursuant to the Controlled Substances Act which requires that such actions be made on the record after opportunity for a hearing through formal rulemaking. This action imposes the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule II controlled substances on persons who handle (manufacture, distribute, dispense, import, export, engage in research, conduct instructional activities with, conduct chemical analysis with, or possess) or propose to handle hydrocodone combination products.

DATES: This rule is effective October 6, 2014.

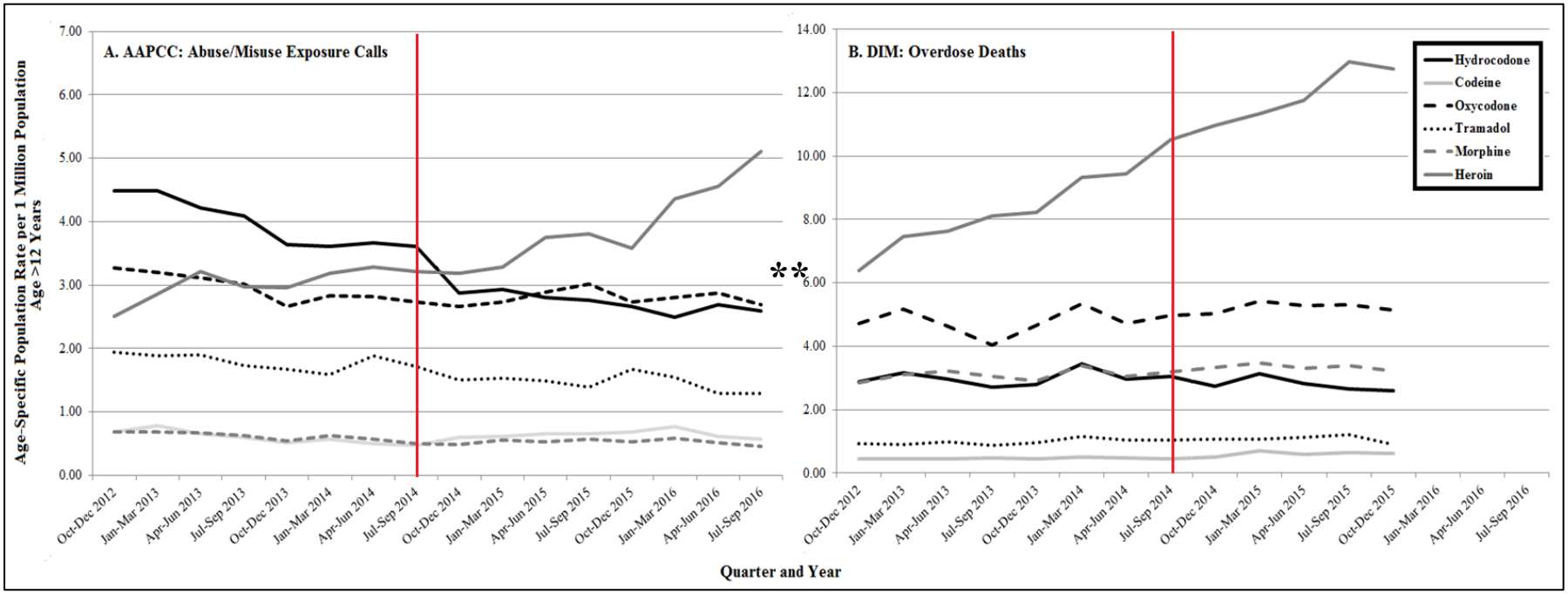
Source: https://www.govinfo.gov/content/pkg/FR-2014-08-22/pdf/2014-19922.pdf

Dispensed Prescriptions Containing Hydrocodone from U.S. Outpatient Retail Pharmacies Have declined Since Rescheduling*



*IQVIA prescription data, 2016

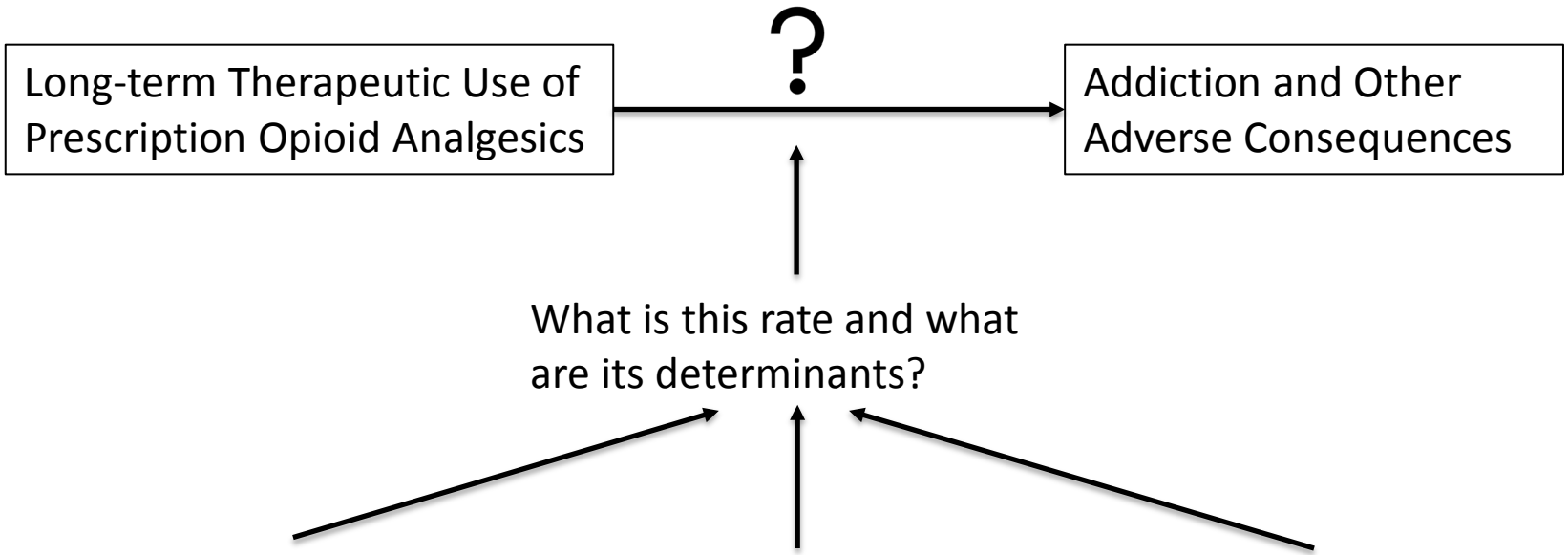
Rates of Abuse Calls* and Deaths** Involving Select Opioid Analgesics and Heroin



* American Association of Poison Control Centers data, 2016

**Drug Involved Mortality data, 2015 (National Center for Health Statistics)

Learning More About Known Risks – Postmarketing Requirements for ER/LA Opioid Analgesics



Baseline Characteristics
- Indication for use
- Pain intensity
- Prior opioid use
- Other comorbidities
- Other factors

Time-varying factors
- Disease course
- Treatment response
- Dose changes
- Other factors

Outcome Ascertainment
- What to measure
- Validity of measures
- Completeness of capture

Postmarketing Requirements for ER/LA Opioid Analgesics

- Ten observational studies
  - 8 of 10 study reports are under review
  - 2 main studies to estimate incidence of adverse effects are still underway
- One clinical trial
  - Still underway

U.S. Department of Health and Human Services

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FDA NEWS RELEASE

For Immediate Release: Sept. 10, 2013
Media Inquiries: Morgan Liscinsky, 301-796-0397, morgan.liscinsky@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

En Español

FDA announces safety labeling changes and postmarket study requirements for extended-release and long-acting opioid analgesics

New boxed warning to include neonatal opioid withdrawal syndrome

The U.S. Food and Drug Administration today announced class-wide safety labeling changes and new postmarket study requirements for all extended-release and long-acting (ER/LA) opioid analgesics intended to treat pain.

"Recognizing that more information is needed to assess the serious risks associated with long-term use of ER/LA opioids, the FDA is requiring the drug companies that make these products to conduct further studies and clinical trials. The goals of these postmarket requirements are to further assess the known serious risks of misuse, abuse, increased sensitivity to pain (hyperalgesia), addiction, overdose, and death."

Learning About Medication Errors - Accidental Exposures of Children to Fentanyl Patches

- Thirty cases of pediatric accidental exposure identified
  - FAERS (1990-2012) + NEISS-CADES (2004-2010)
  - Serious harm
    - Death (n=10)
    - Hospitalization and medical intervention (n=16).
    - Age of the child <10 years (n=28)
      - Age 2 years or younger (n=19)

FDA Actions on Fentanyl Patches

September 23, 2012

U.S. FOOD & DRUG ADMINISTRATION

Home / For Consumers / Consumer Updates / Fentanyl Patch Can Be Deadly to Children

Fentanyl Patch Can Be Deadly to Children

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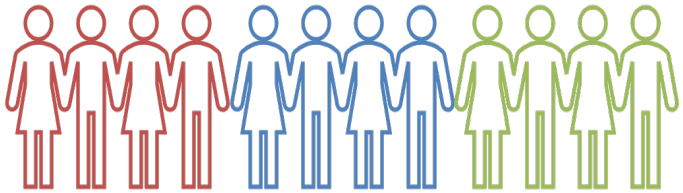
September 23, 2013
Change in color of patch

U.S. FOOD & DRUG ADMINISTRATION

Home / Drugs / Drug Safety and Availability / FDA Drug Safety Communication: FDA requiring color changes to Duragesic (fentanyl) pain patches to aid safety—emphasizing that accidental exposure to used patches can cause death

FDA Drug Safety Communication: FDA requiring color changes to Duragesic (fentanyl) pain patches to aid safety—emphasizing that accidental exposure to used patches can cause death

Communication



Learning about Product Defects - Opana ER

- Postmarketing data suggested that reformulation of Opana ER (never labeled with abuse-deterrent properties)
  - Decreased nasal abuse, BUT
  - Caused a shift among abusers to more dangerous route, from snorting to injecting—unintended consequence
    - Seen in both poison control center and treatment center data
    - Consistent with spontaneous report patterns and information from outbreak investigations
    - Geographic clustering

Opana ER

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tampering practices →

HIV Infection Linked to Injection Use of Oxymorphone in Indiana, 2014–2015

CDC Home

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SEARCH SEARCH

A-Z Index A B C D E F G H I J K L M N O P Q R S T U V W X Y Z #

Morbidity and Mortality Weekly Report (*MMWR*)

MMWR

Persons using assistive technology might not be able to fully access information in this file. For assistance, please send e-mail to: mmwrq@cdc.gov. Type 508 Accommodation and the title of the report in the subject line of e-mail.

Thrombotic Thrombocytopenic Purpura (TTP)-Like Illness Associated with Intravenous Opana ER Abuse — Tennessee, 2012

Weekly
January 11, 2013 / 62(01);1-4

← New inactive ingredient – polyethylene oxide

Source: Peters et al, N Engl J Med 2016; 375:229-39 and MMWR January 11, 2013/62(01);1-4

FDA Actions on Opana ER

March 13-14, 2017
Advisory Committee votes 8-18 that the benefits of reformulated Opana ER do not outweigh the risks

Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee Joint Meeting
March 13-14, 2017

June 8, 2017

U.S. FOOD & DRUG ADMINISTRATION

← Home / News & Events / FDA Newsroom / Press Announcements / FDA requests removal of Opana ER for risks related to abuse

FDA NEWS RELEASE

FDA requests removal of Opana ER for risks related to abuse

Learning About How Patterns of Use May Contribute to Unsafe Use – Opioid and Benzodiazepine Use

41% relative increase in co-prescribing

Table 2. Proportion of Opioid Recipients With Concomitant Benzodiazepine Use,[a] 2002–2014 (n=177 million)

Characteristic	2002[b]	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
All opioid recipients	6.8	6.6	6.8	7.3	7.6	8.2	8.6	8.5	8.5	8.6	8.7	8.5	9.6
Gender													
Male	5.5	5.2	5.4	5.8	6.1	6.7	7.0	6.9	7.0	7.0	7.0	6.8	7.7
Female	7.7	7.5	7.8	8.3	8.6	9.3	9.8	9.6	9.6	9.7	9.9	9.7	11.0
Age													
0–17 years	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.5	0.6	0.6	0.7
18–44 years	4.5	4.4	4.5	5.0	5.4	6.0	6.4	6.1	6.2	6.2	6.1	5.5	6.4
45–64 years	8.8	8.4	8.7	9.2	9.6	10.3	10.8	11.2	11.0	11.2	11.4	11.2	12.3
65+ years	11.1	10.5	10.6	10.7	9.9	10.3	10.6	11.0	11.0	11.2	11.3	11.2	12.0
Chronic users[c]	41.4	39.1	39.3	39.5	37.2	37.8	37.7	40.5	40.3	39.7	38.0	35.5	33.9
Non-chronic users[c]	3.6	3.5	3.5	3.6	3.7	4.1	4.3	4.1	4.2	4.3	4.4	4.4	5.4

Source: IMS Health Vector One®: Data Extract Tool, 2002–2014.
Note: Values are percentages.
[a]Patients were considered concomitant users if they had one or more opioid and benzodiazepine episodes that overlapped by 7 or more consecutive days.
[b]Percent of concomitant patients, out of the total number of opioid recipients during a given calendar year.
[c]Patients with at least one opioid episode ≥90 days during the study period were considered chronic opioid users. All other patients were considered non-chronic opioid users. For chronic opioid users, concomitancy proportions were based on opioid episodes ≥90 days only.

Hwang et al / Am J Prev Med 2016;51(2):151–160

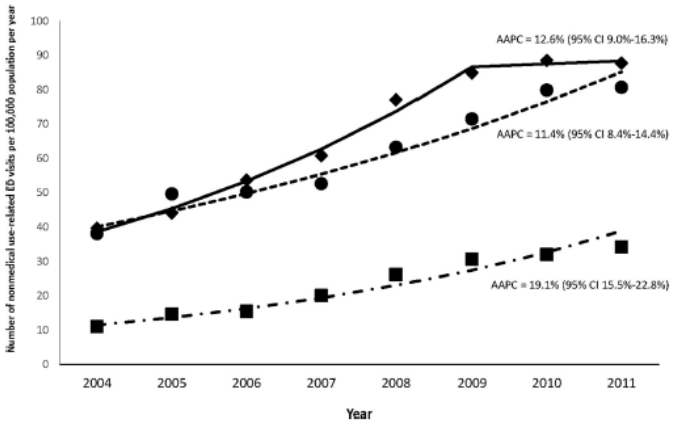


Figure 1. Trends in opioid analgesic and benzodiazepine nonmedical use-related emergency department visits, U.S., 2004–2011.

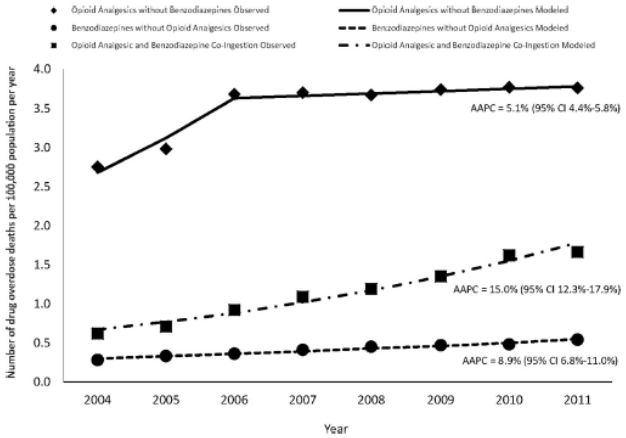
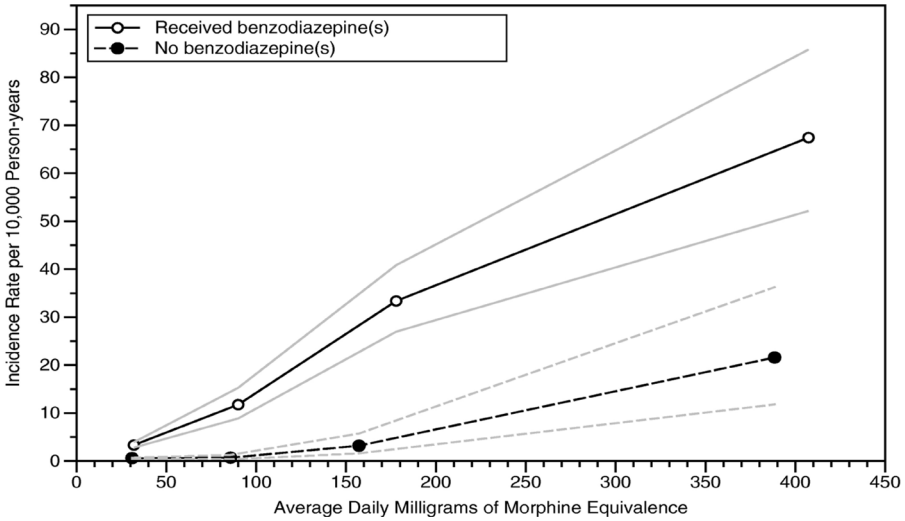


Figure 2. Trends in opioid analgesic and benzodiazepine drug overdose deaths, U.S., 2004–2011.

Source: Hwang et al, Am J Prev Med 2016;51(2):151-160 and Jones CM, Mcaninch JK, Am J Prev Med 2015;49(4):493-501.

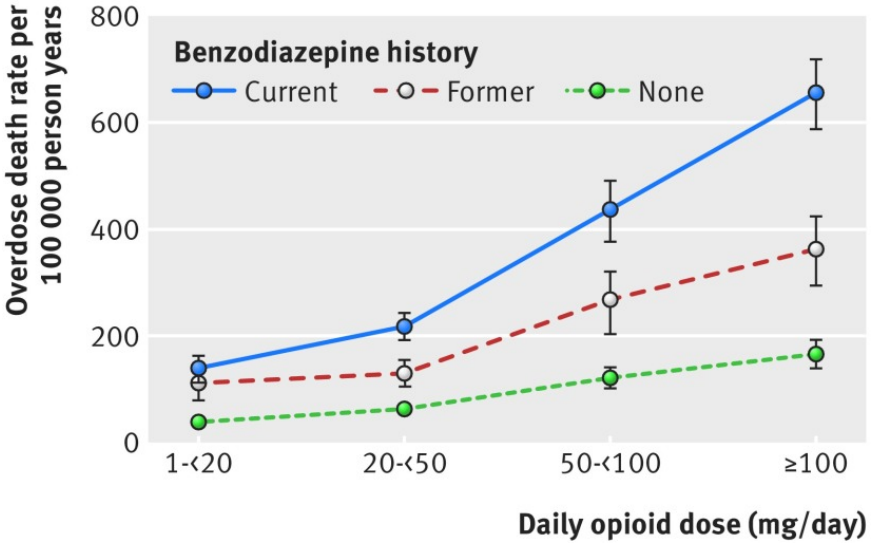
Opioids and Benzodiazepines - Overdose Deaths

Figure 5 Incidence rate ratios for overdose deaths involving opioid analgesics, by benzodiazepine prescription status. ...



Population-based cohort study of all North Carolina residents alive in 2010.

Unadjusted death rates for drug overdose by benzodiazepine prescription history and daily opioid dose. Error bars represent 95% confidence intervals. Unadjusted overdose death rates are estimates for entire source population



Case-cohort study among US veterans.

Source: Dasgupta et al, Pain Medicine 2016;17:85-98 and Park et al, BMJ 2015;350:h2698

FDA Actions on Opioid-Benzodiazepine Co-Prescribing

August 31, 2016
Announces Boxed Warning about the risks of concomitant use of opioids and benzodiazepines

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Home / Drugs / Drug Safety and Availability / FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning

FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning

September 26, 2017
Refines message regarding buprenorphine and methadone

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Home / Drugs / Drug Safety and Availability / FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks

FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks

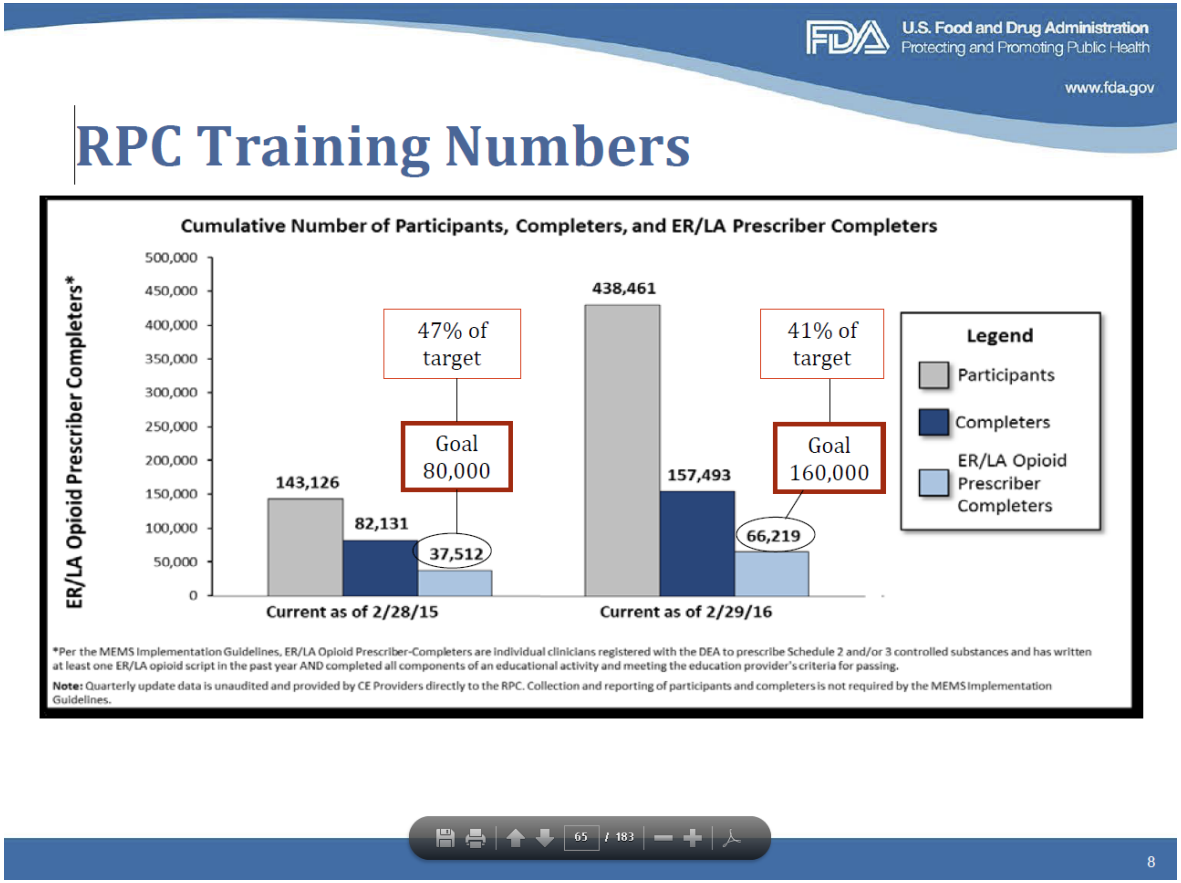
Learning About the Impact of Our Interventions – ER/LA Opioid Analgesic REMS

July 9, 2012
Approval of
ER/LA Opioid
REMS

- Central component
  - Education component for prescribers
  - Required content in a “Blueprint” created by FDA
- Metrics to be used to determine success include:
  - Numbers of providers who successfully complete the CE
  - Changes in patterns of opioid use/abuse
  - Knowledge surveys
- Advisory committee – May 2016 discussed impact

Reach of the REMS Intervention

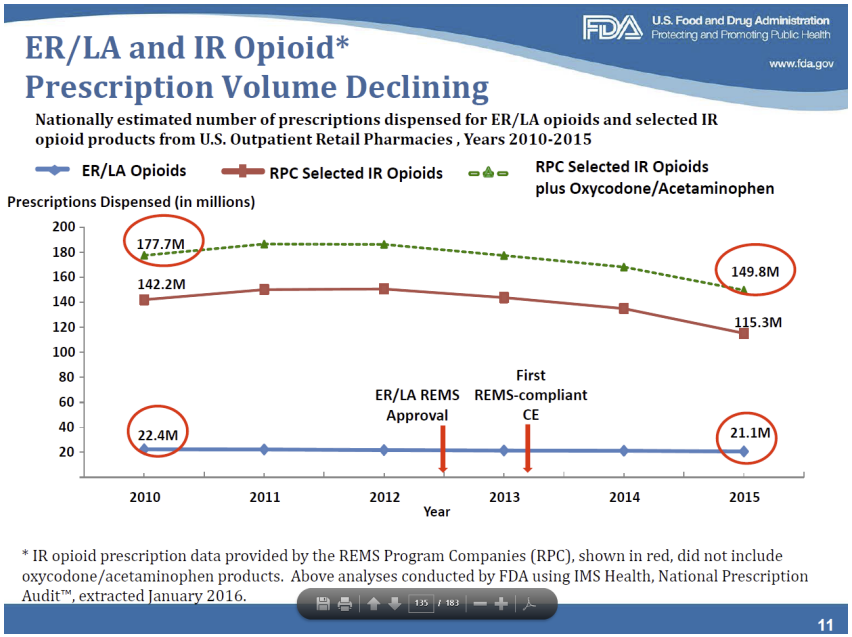
- Large absolute number trained
- Small proportion of ER/LA prescribers had completed training
- Direct linkages to prescribing practices were not available
- What population-based impact could we expect based on these findings?

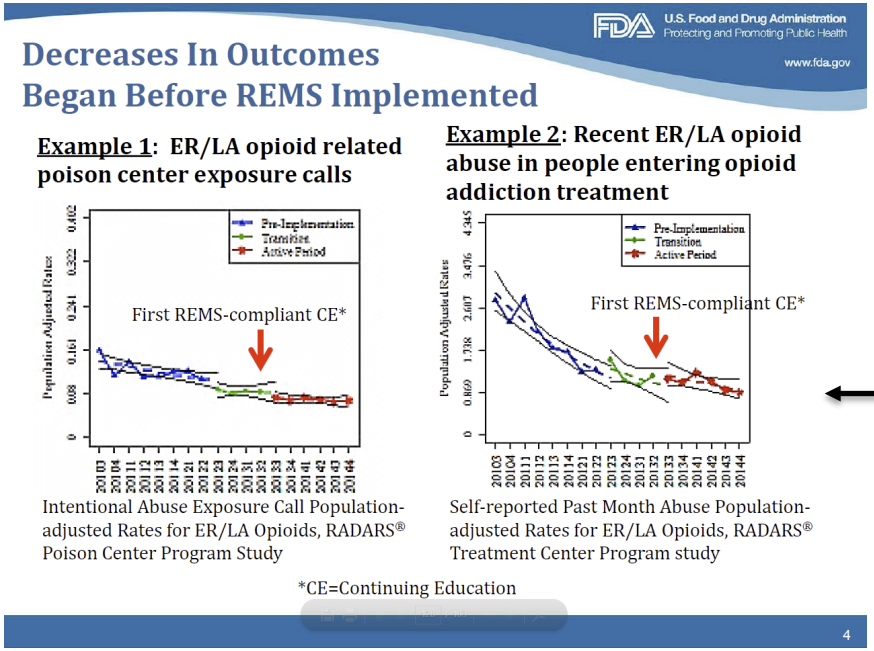


Summary of Assessment Findings

Prescription volume declining

- Does not address appropriateness of prescribing





Decreases in adverse outcomes

- Began before REMS was implemented

Source: https://www.fda.gov/media/97531/download

Complicated path from intervention to measured outcomes

- Even desirable changes in prescriber and patient behavior may have mixed effects on population outcome measures

Desired effects on prescriber/patient behavior		Possible effects on surveillance measures
Safer opioid storage and disposal— Fewer available for abuse	→ ↓	treatment center abuse rates
Improved recognition of abuse/addiction— more referrals to treatment	? → ↑	treatment center abuse rates
Safer opioid dosing and use	→ ↓	ED visit and poison center call rates?
Earlier recognition of overdose symptoms	? → ↑	ED visits and poison center call rates?

REMS Assessment to Date: Scope of the REMS Education

- FDA determined that two things were needed to modify the REMS and informed industry:
  - **Expand the REMS to include IR opioid analgesics**
    - Approved September 2018
  - **Expand the education** to include additional healthcare workers and to provide info about pain management and non-pharmacologic treatment of pain
    - FDA modified the REMS 'Blueprint' to guide the educational content

Challenges

- Better data!
  - Difficult area to study because behaviors are covert and often hidden from the health care system
  - Have pockets of data – not nationally representative
  - Better insights into behaviors all along continuum of behaviors
- Data linked to connect exposures with outcomes
  - Often collected in different systems (pharmacies vs medical examiners vs hospitals)
  - HHS working on this with national level data; FDA funding work in state of CT
- Improved methods
  - What is appropriate denominator for measuring and comparing abuse rates?

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Questions?

Thank you

FDA U.S. FOOD & DRUG ADMINISTRATION