

Clinical Directors Network, Inc. (CDN)

Evolution of the Opioid Epidemic

February 5, 2018
2:30 PM-4:00 PM EST

Richard C. Dart, MD, PhD
Director, Rocky Mountain Poison and Drug Center, Denver Health
Professor, University of Colorado Health Sciences Center

Competing Interest Statement

History

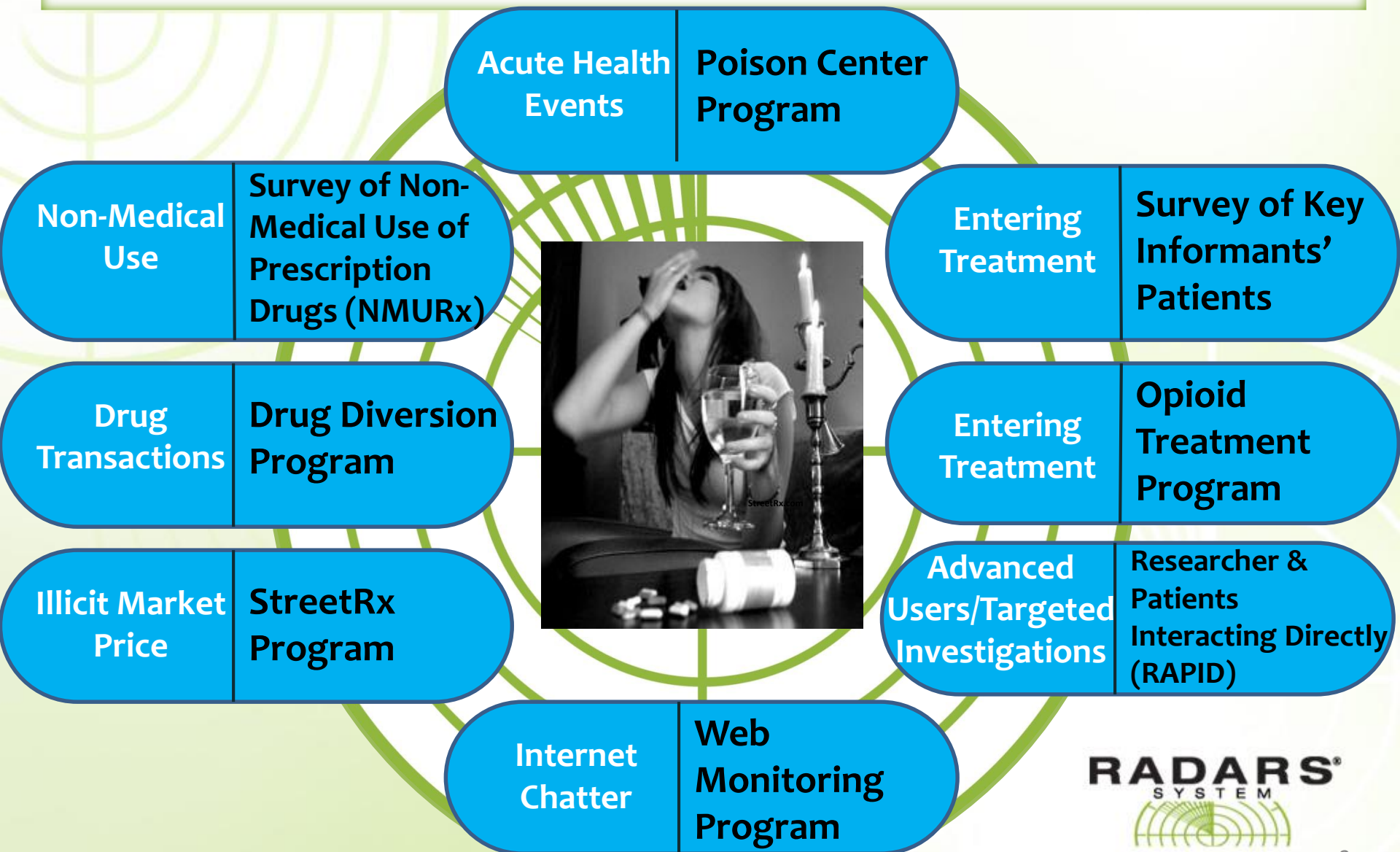
- 2002, launched by Purdue Pharma L.P.
- 2006, independent ownership by Denver Health and Hospital Authority
 - Denver Public Hospital for 150 years
 - State sanctioned independent authority



Conflict of Interest Statement

- Many manufacturers of prescription opioids or stimulants as well as federal agencies subscribe to RADARS System.
- RADARS System is the property of Denver Health and Hospital Authority, a political subdivision of the State of Colorado.
- Subscribers receive information, but do not participate in developing the System, data collection, or analysis of the data. They do not have access to the raw data.
- Employees are prohibited from personal financial relationships with any company.

Mosaic Surveillance of Prescription Drug Abuse



*Prescription opioid abuse is at
record highs and increasing*

Prescription opioid abuse is at record highs and increasing



Health » Diet + Fitness | Living Well | Parenting + Family

Live TV

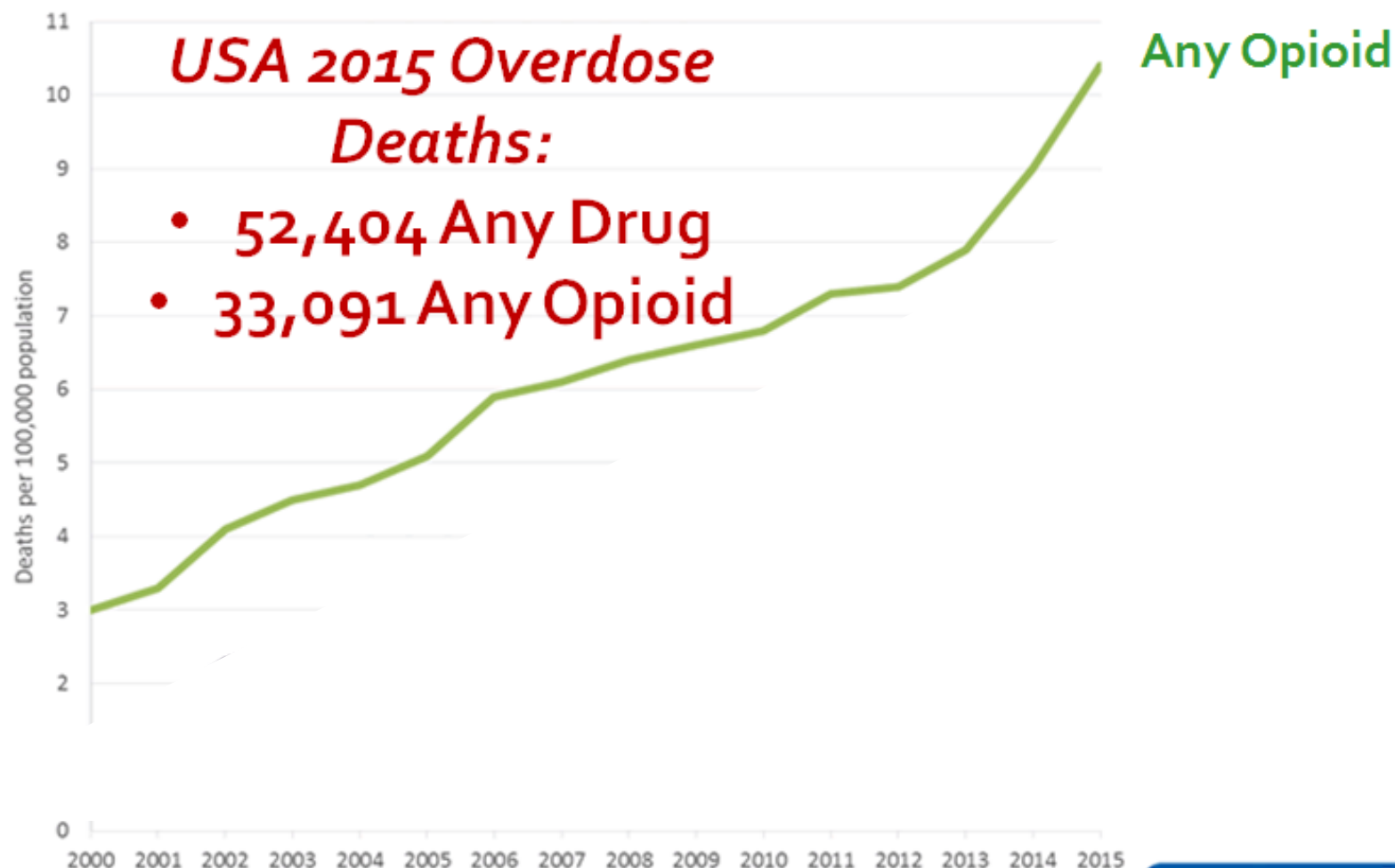
Opioid addiction rates continue to skyrocket

By Nadia Kounang

Updated 10:35 PM ET, Thu June 29, 2017

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

Overdose Deaths Involving Opioids, United States, 2000-2015

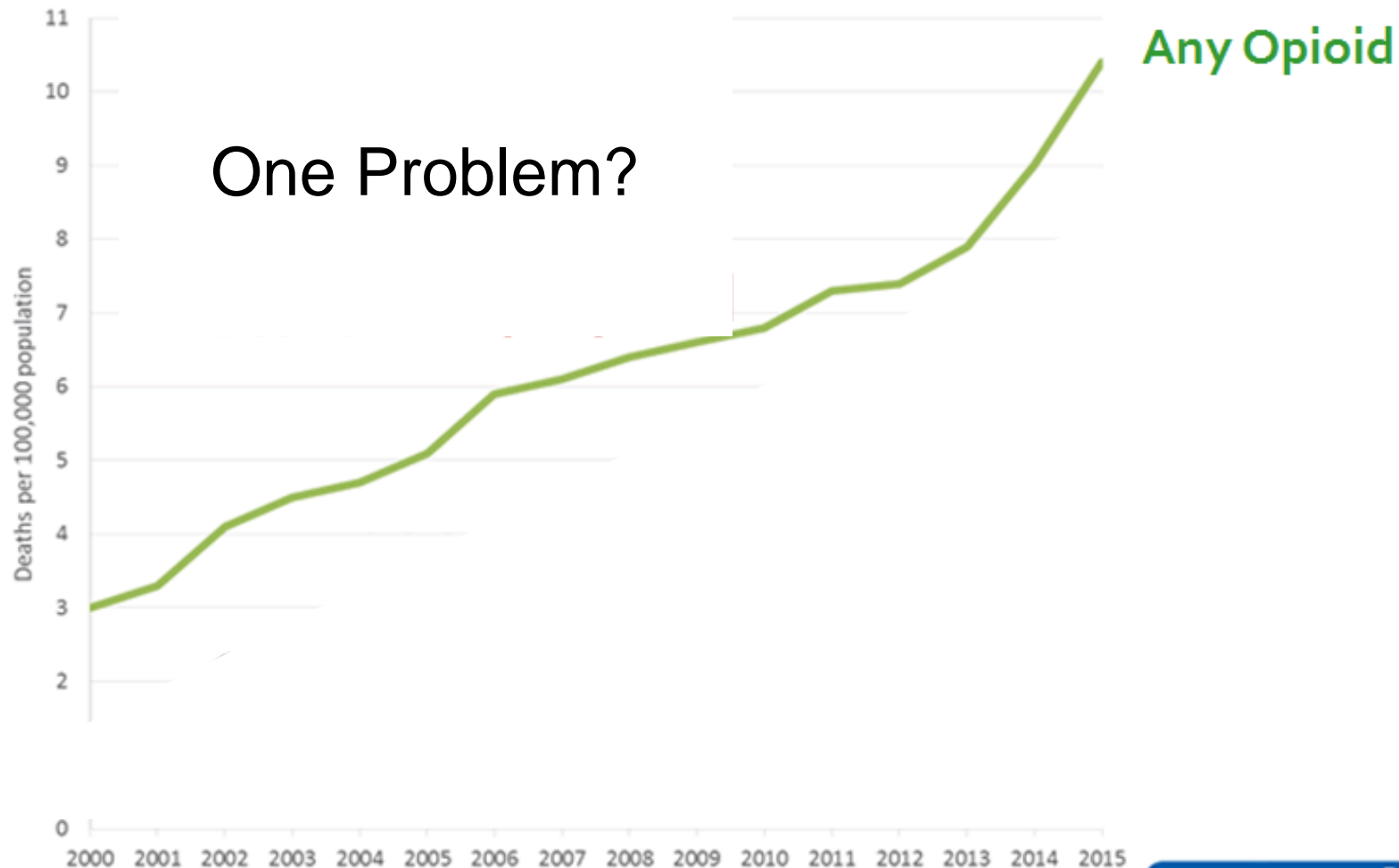


SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2016. <https://wonder.cdc.gov/>.

www.cdc.gov
Your Source for Credible Health Information

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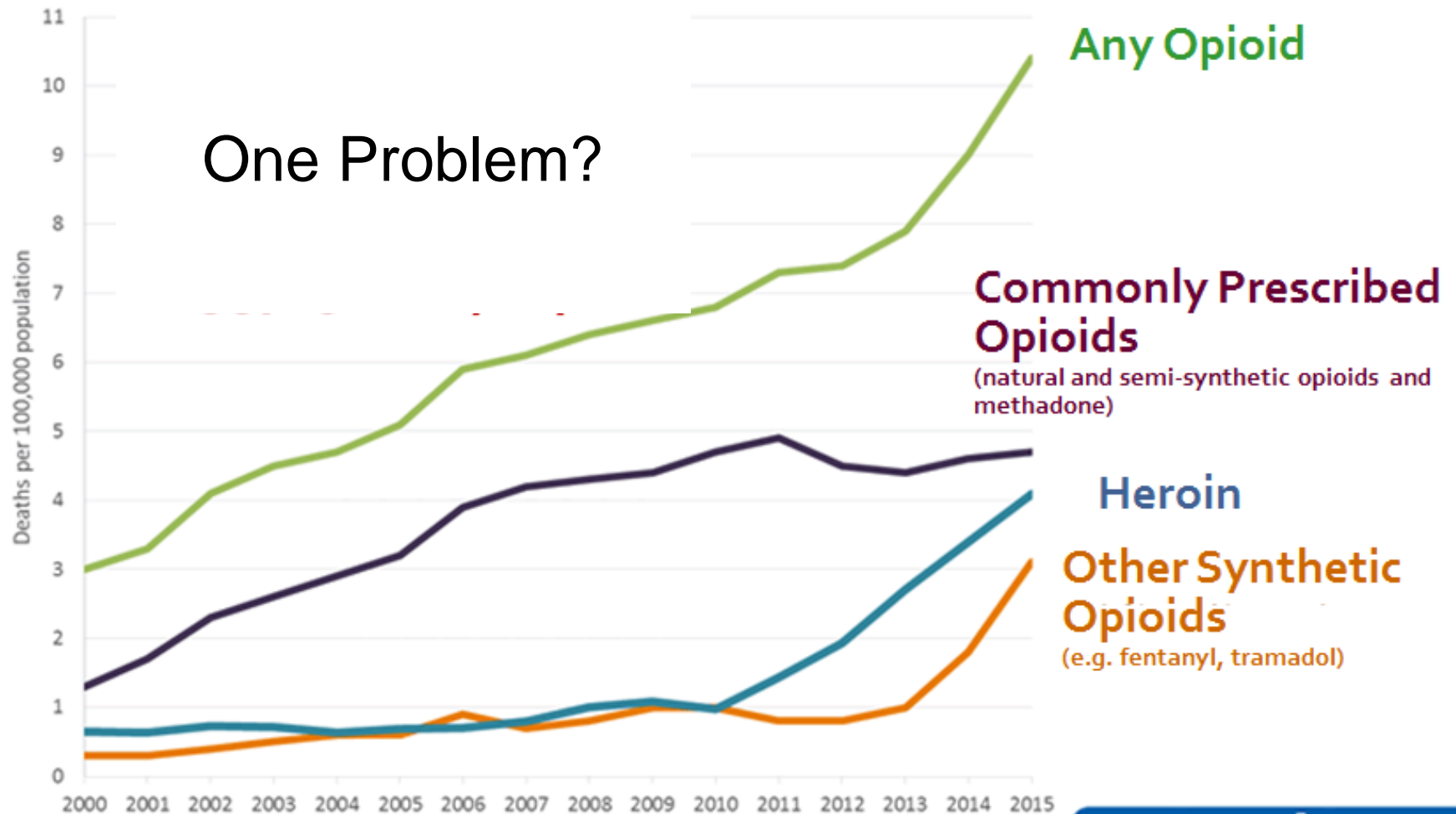


SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2016. <https://wonder.cdc.gov/>.

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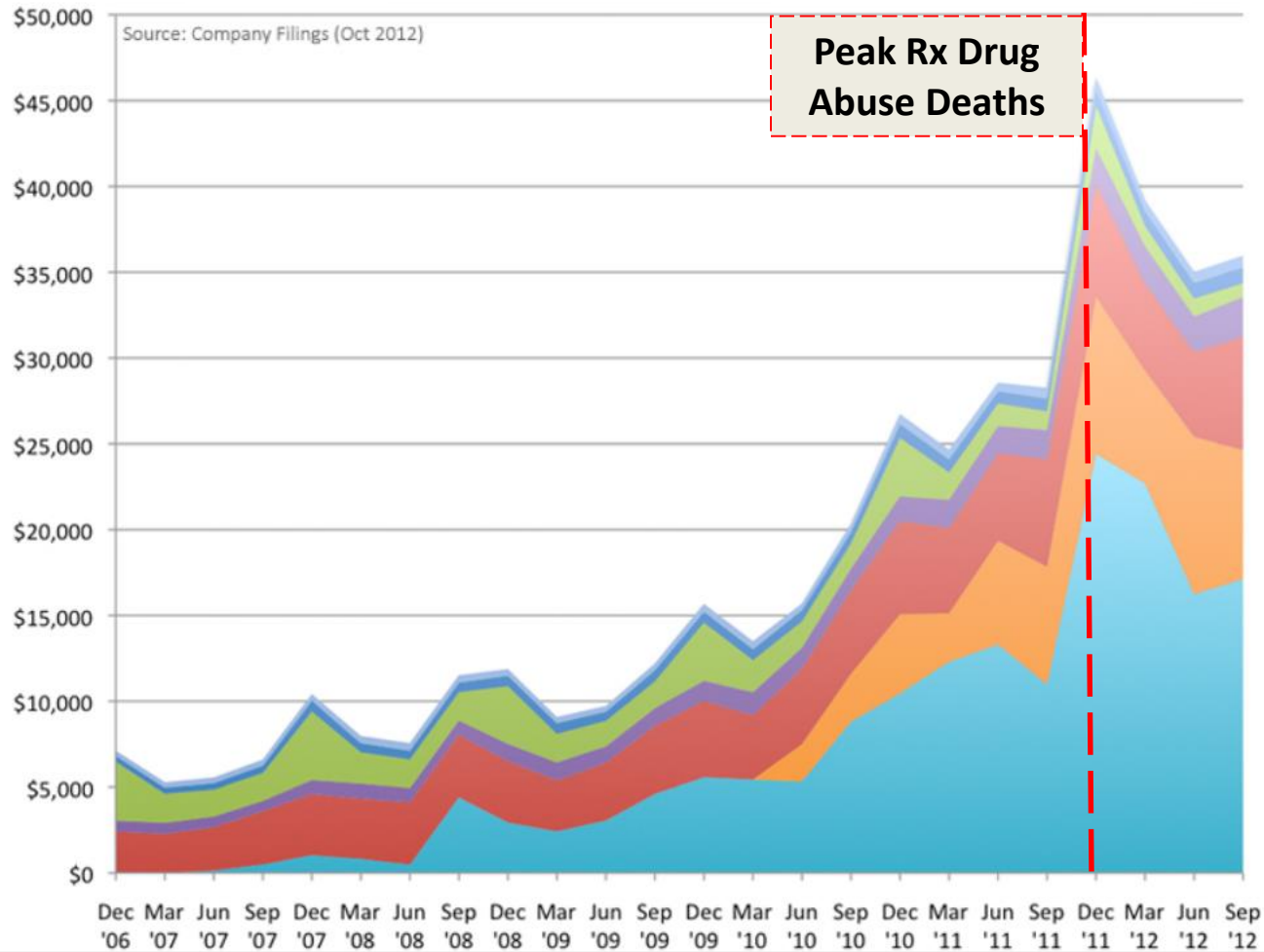


SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2016. <https://wonder.cdc.gov/>.

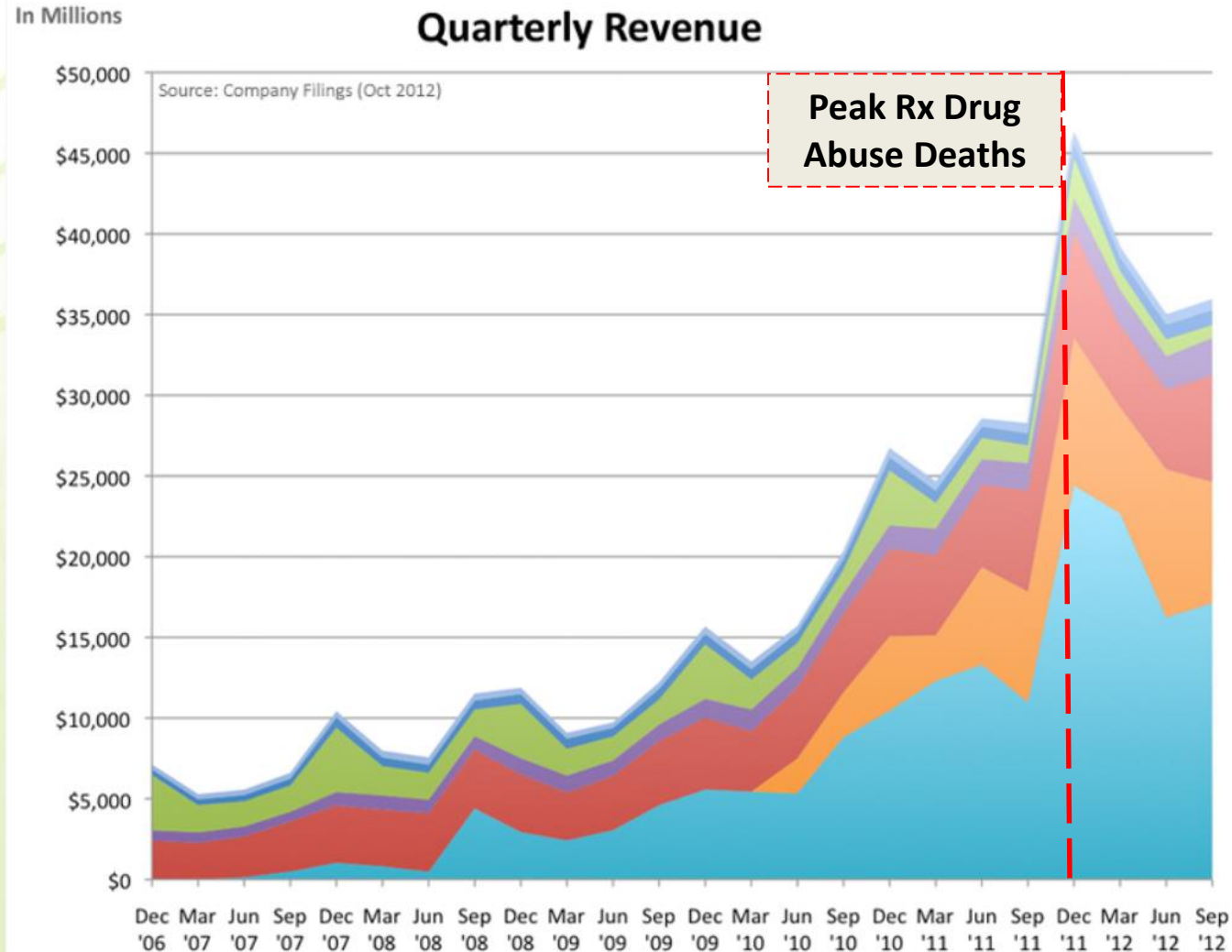
www.cdc.gov
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In Millions

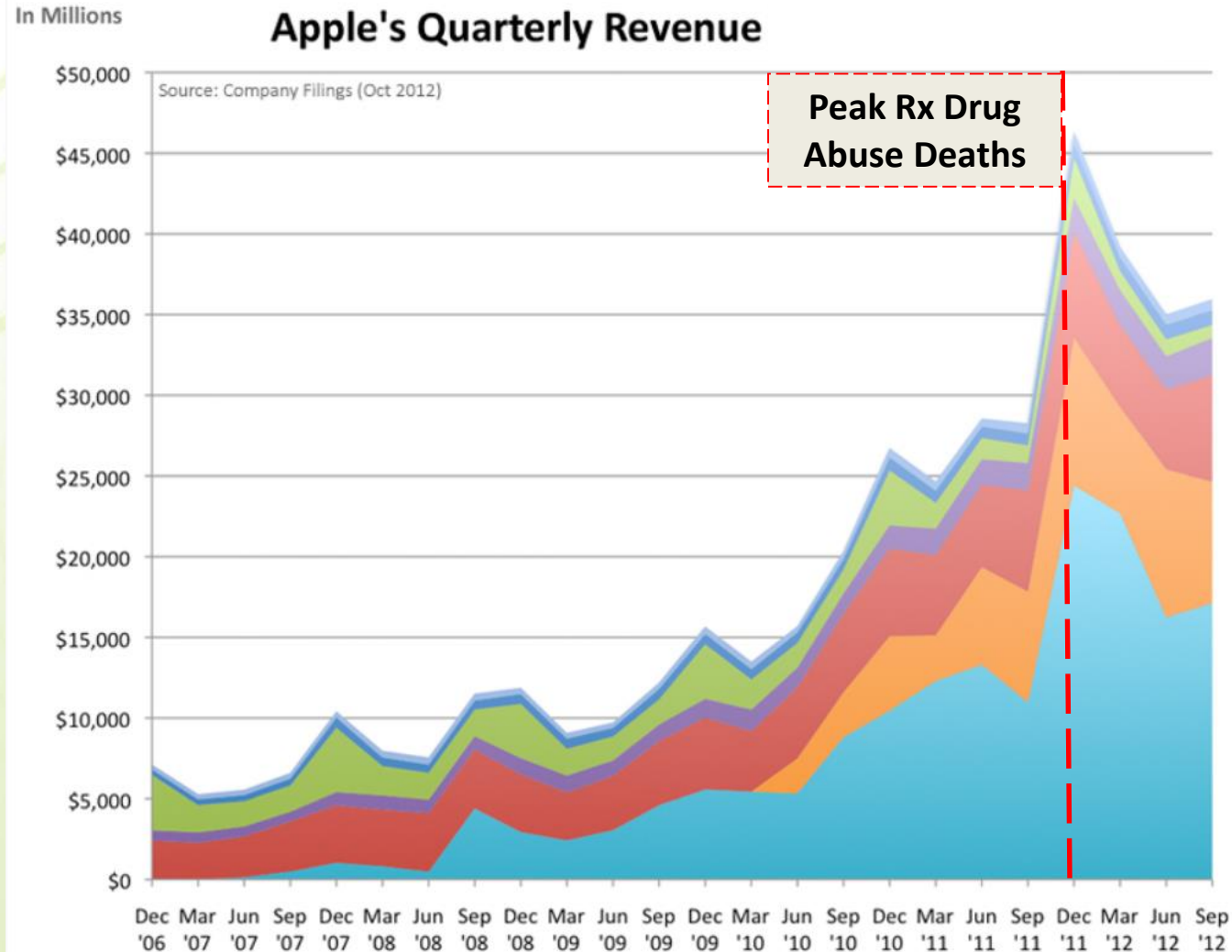
Quarterly Revenue



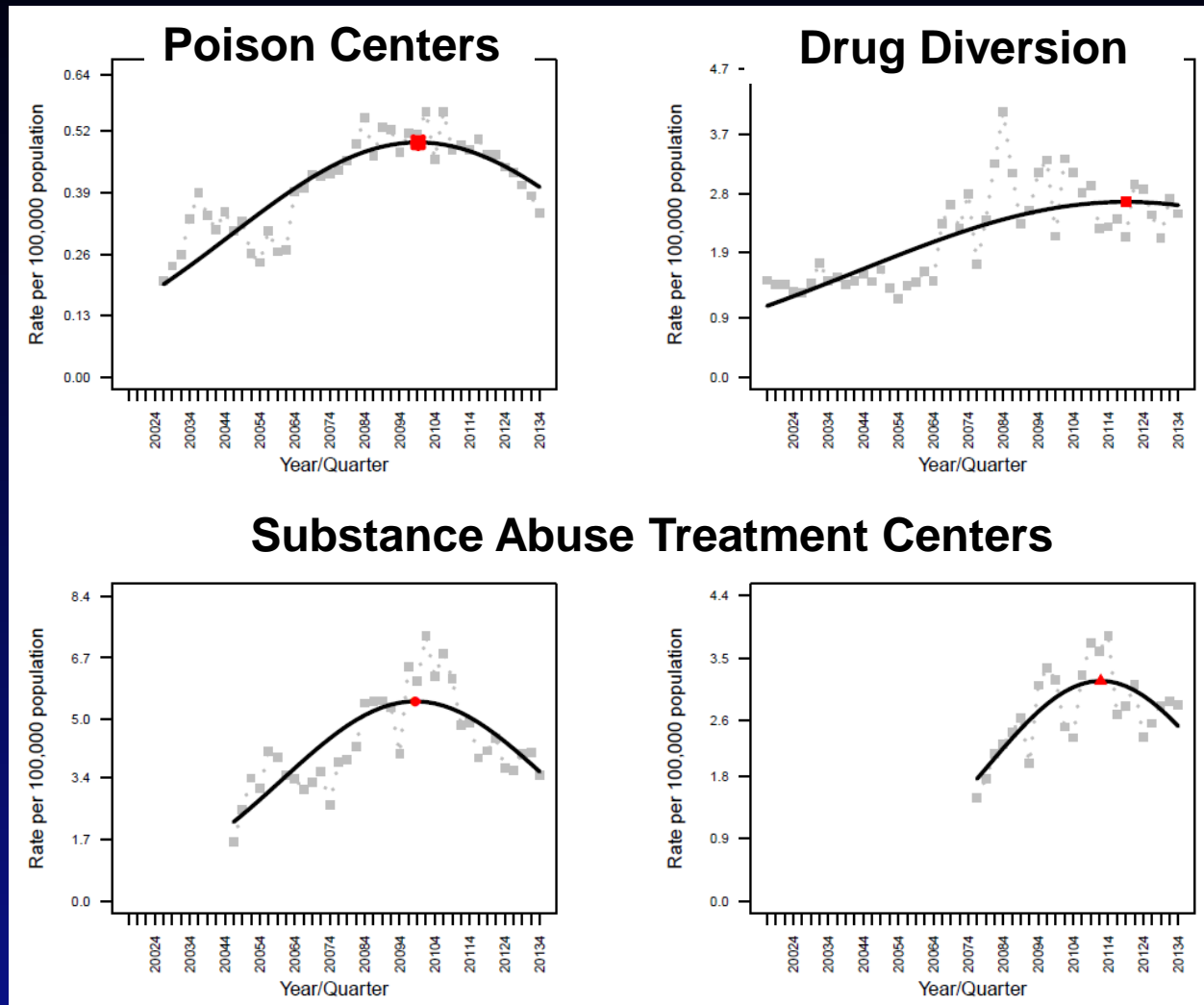
The problem is Apple!



The problem is Apple!

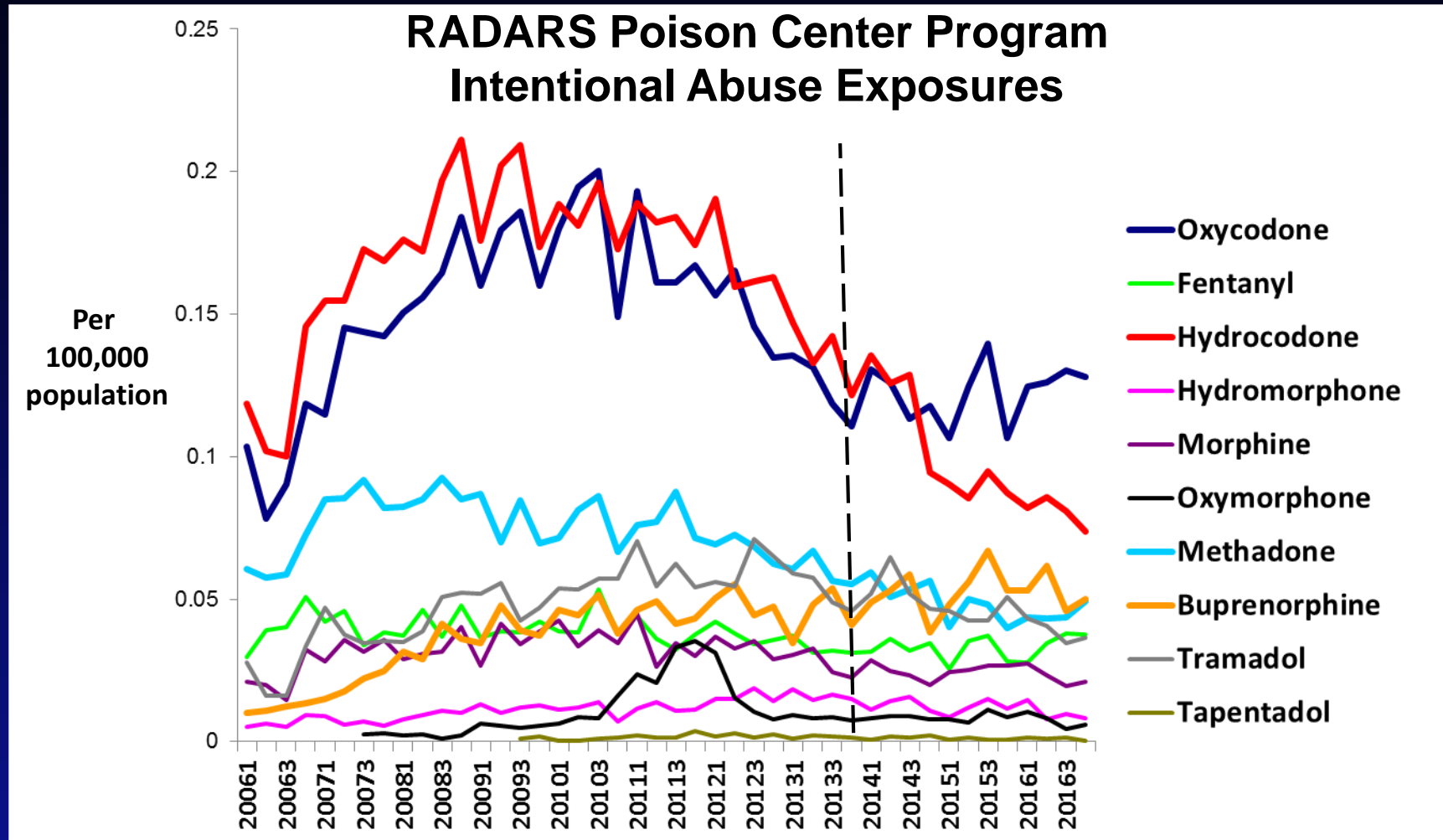


Prescription Opioid Abuse Decreasing in US

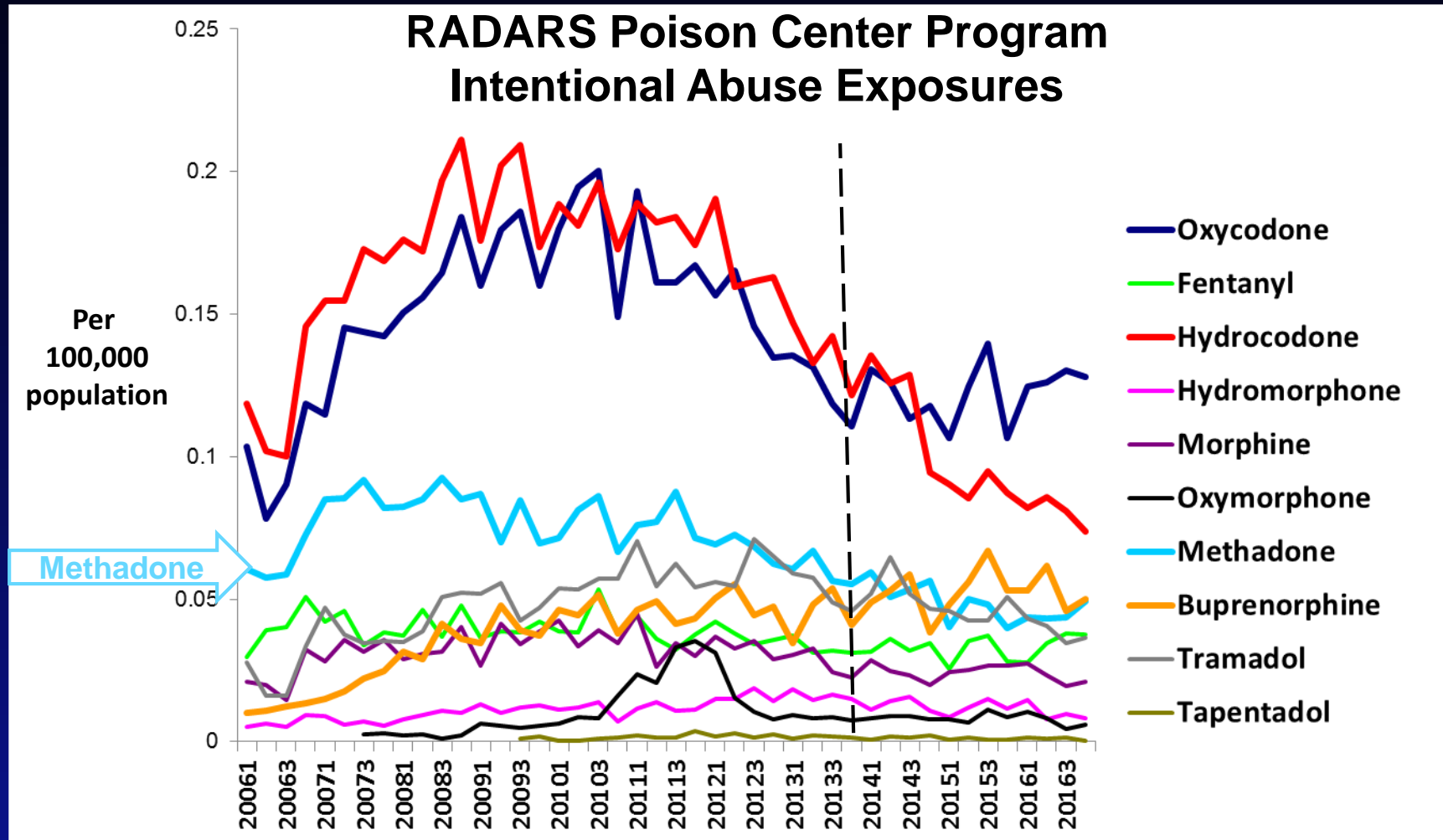


Trends in Opioid Analgesic Abuse and Mortality in the United States.
N Engl J Med 2015;372:241-8

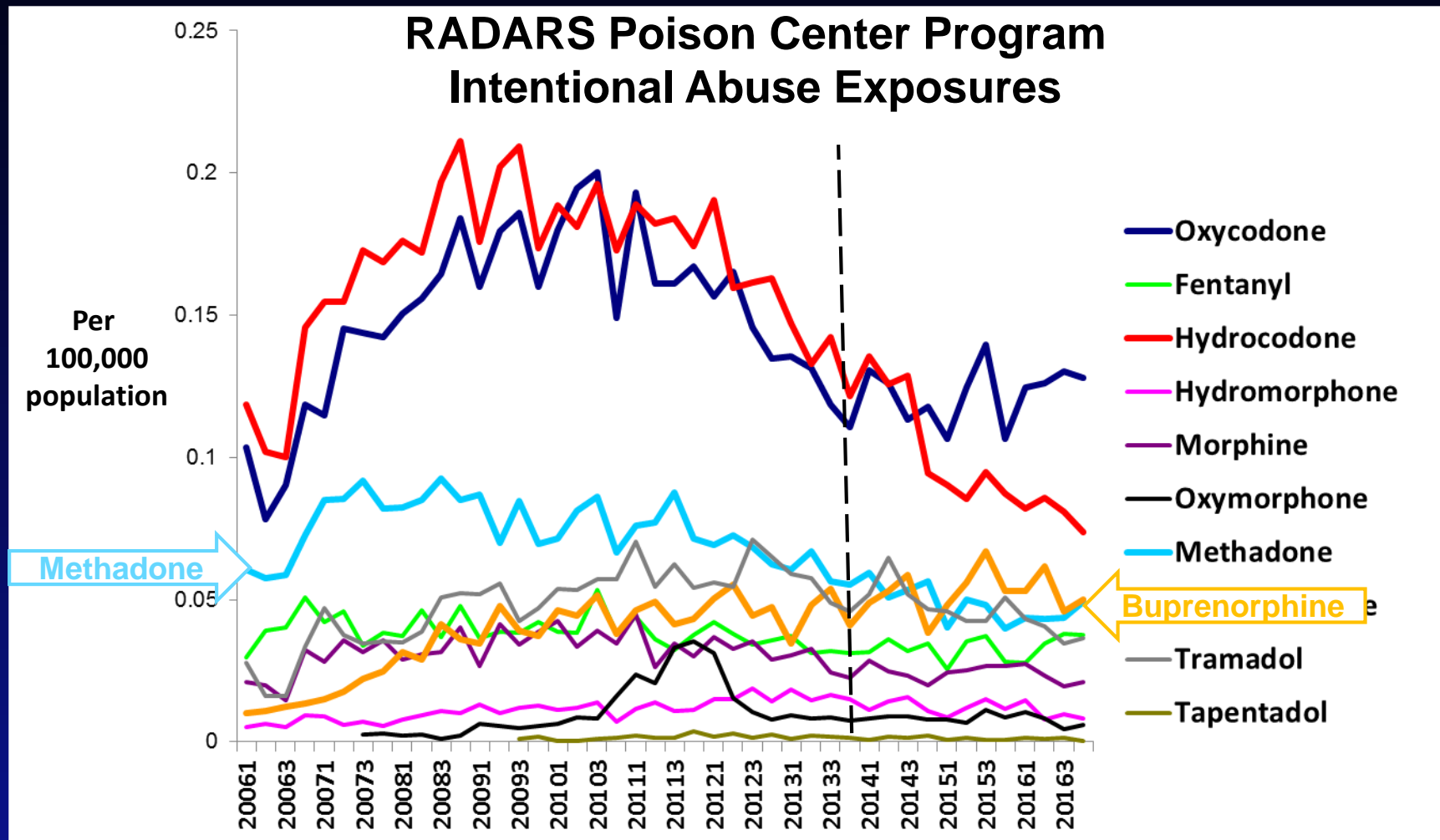
Prescription Opioid Abuse by Active Pharmaceutical Ingredient



Prescription Opioid Abuse by Active Pharmaceutical Ingredient



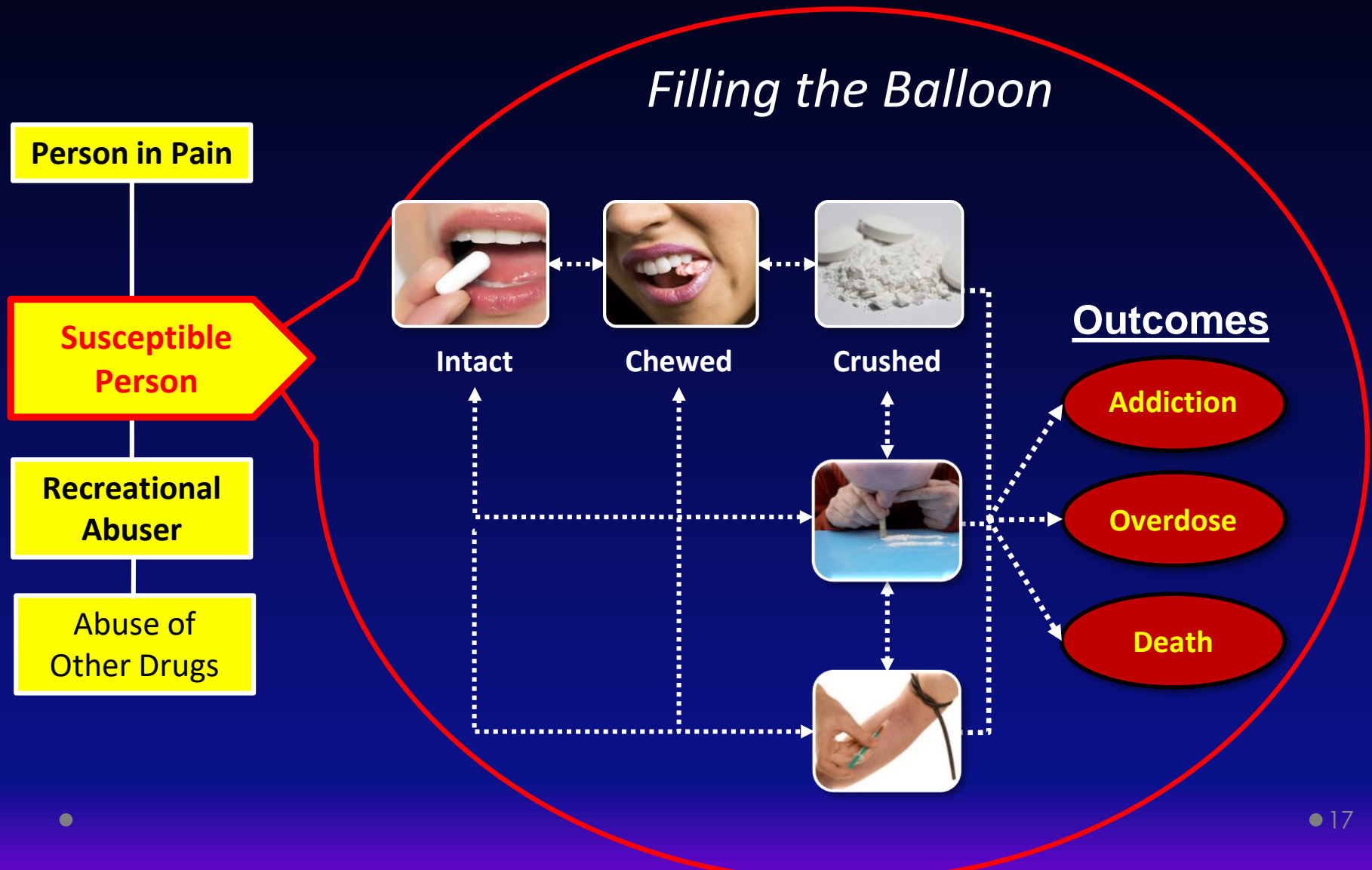
Prescription Opioid Abuse by Active Pharmaceutical Ingredient





Petty died at 66 of "multisystem organ failure due to resuscitated cardiopulmonary arrest due to mixed drug toxicity: fentanyl, oxycodone, temazepam, alprazolam, citalopram, acetylfentanyl, and despropionyl fentanyl."

What is the Problem We Need to Solve?

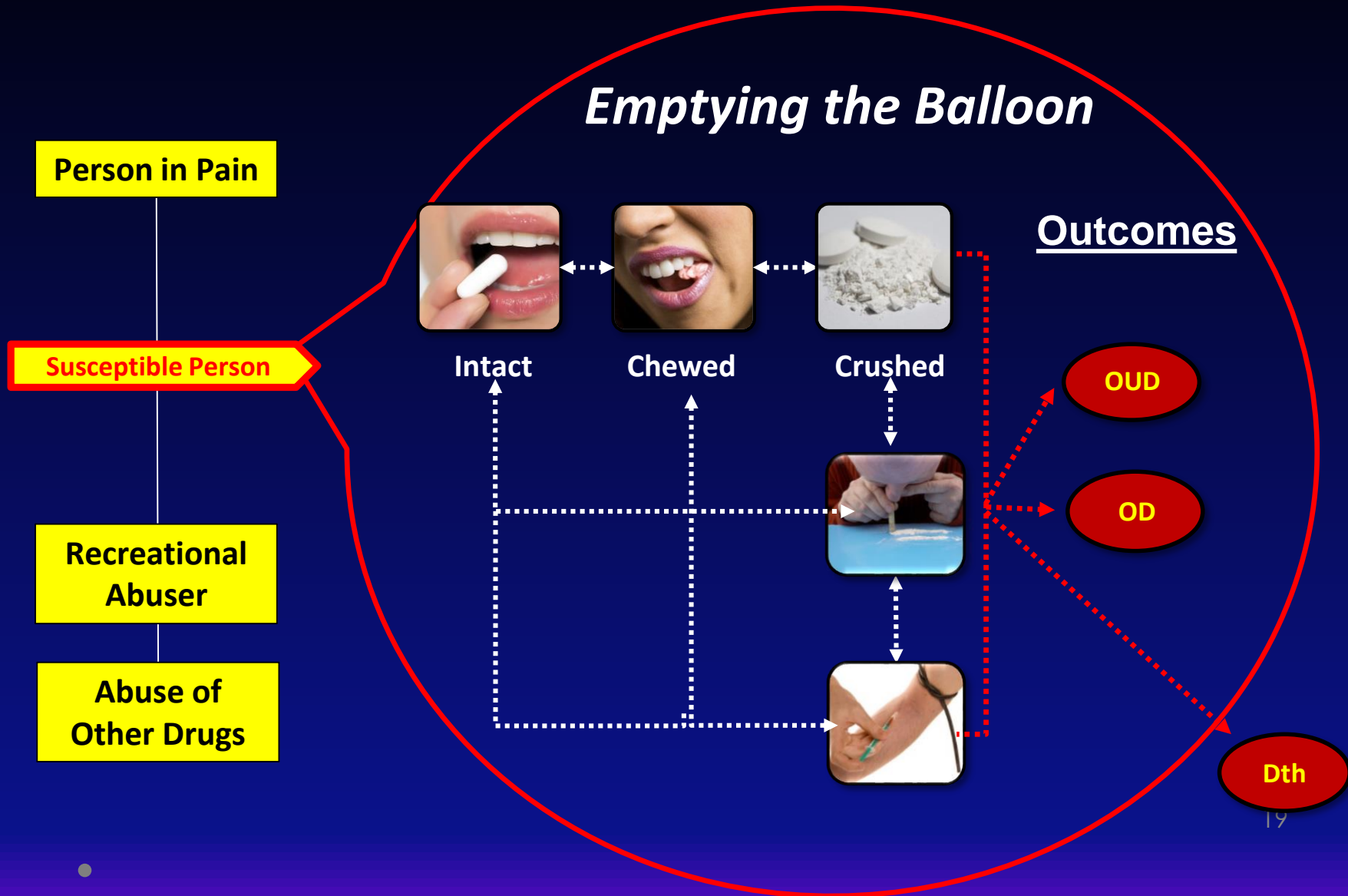


Prescription Drug Abuse

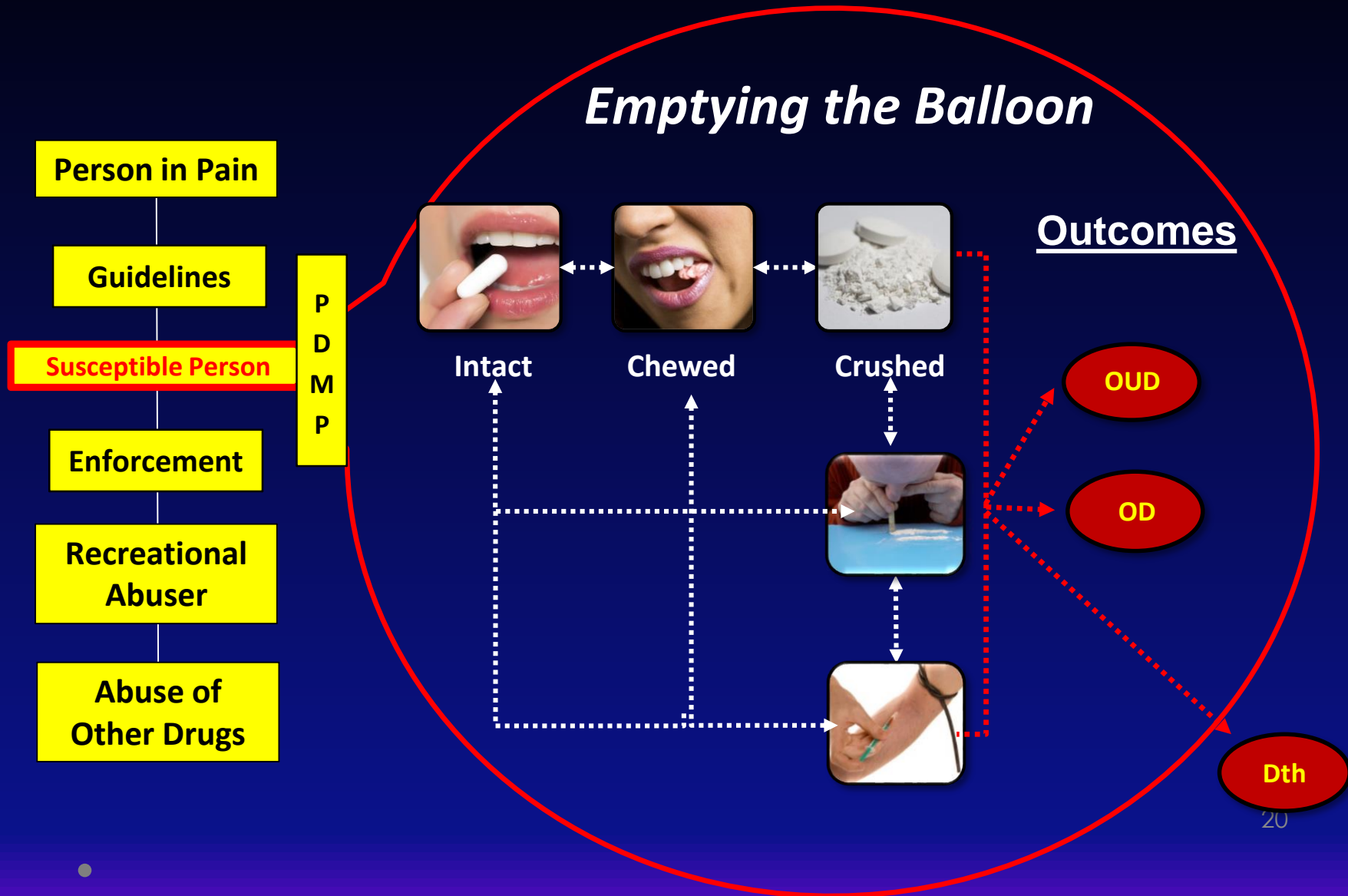
Opioid and Other

- Opioids with abuse deterrent properties (ADOs / ADFs)
- Public Health and Heroin
- The Rise of other Rx drugs abuse

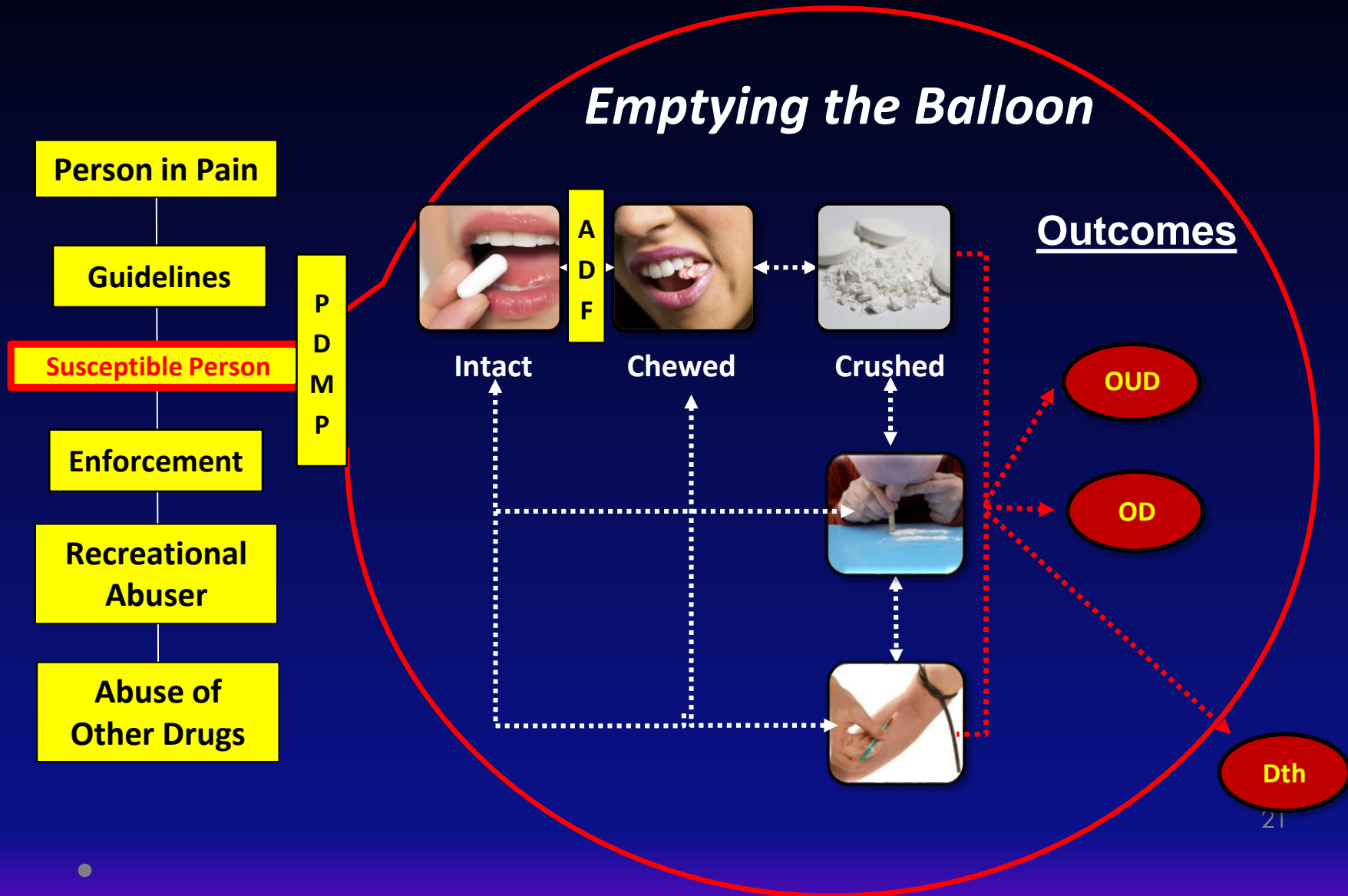
Potential Effects of Interventions



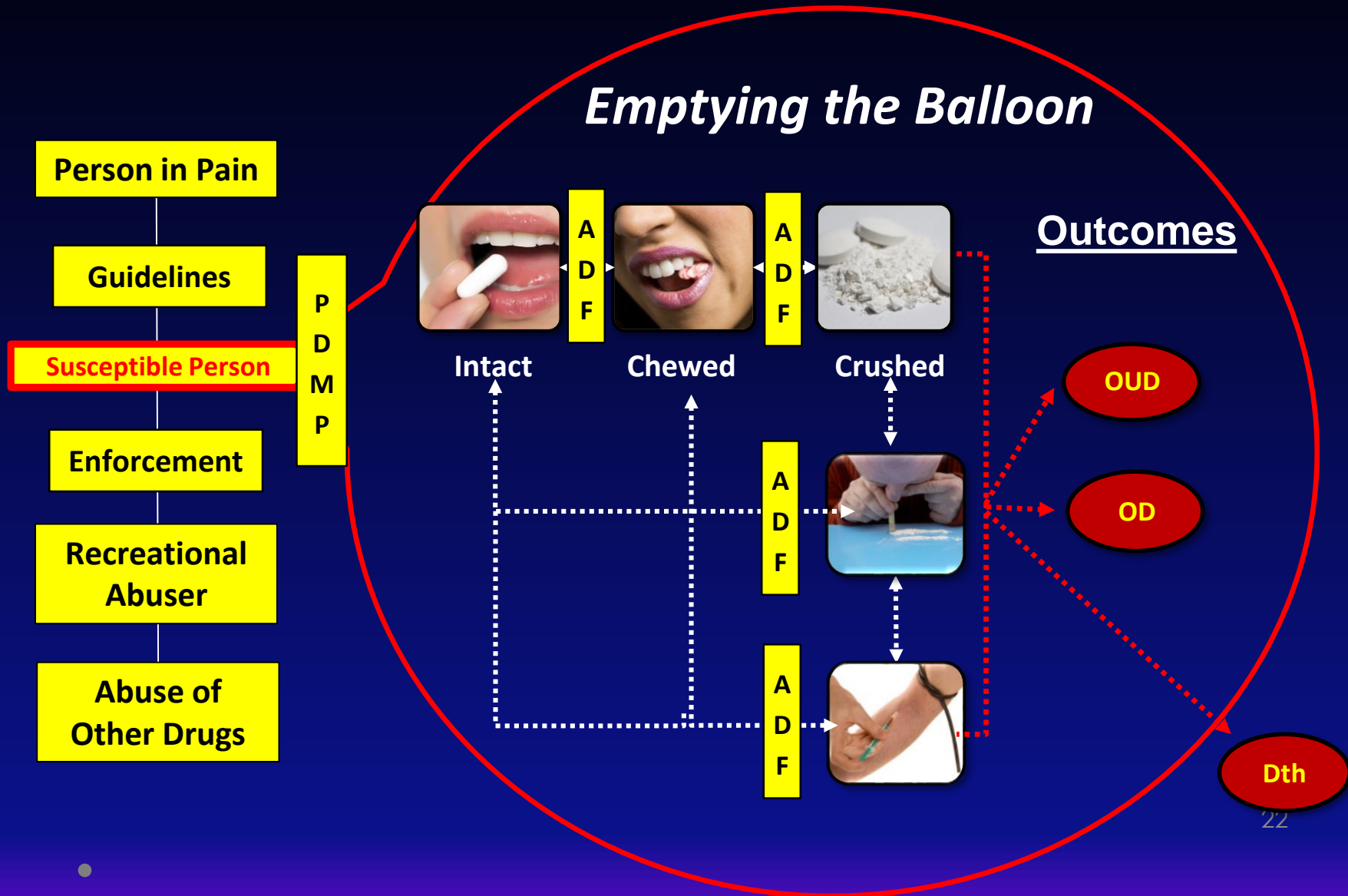
Potential Effects of Interventions



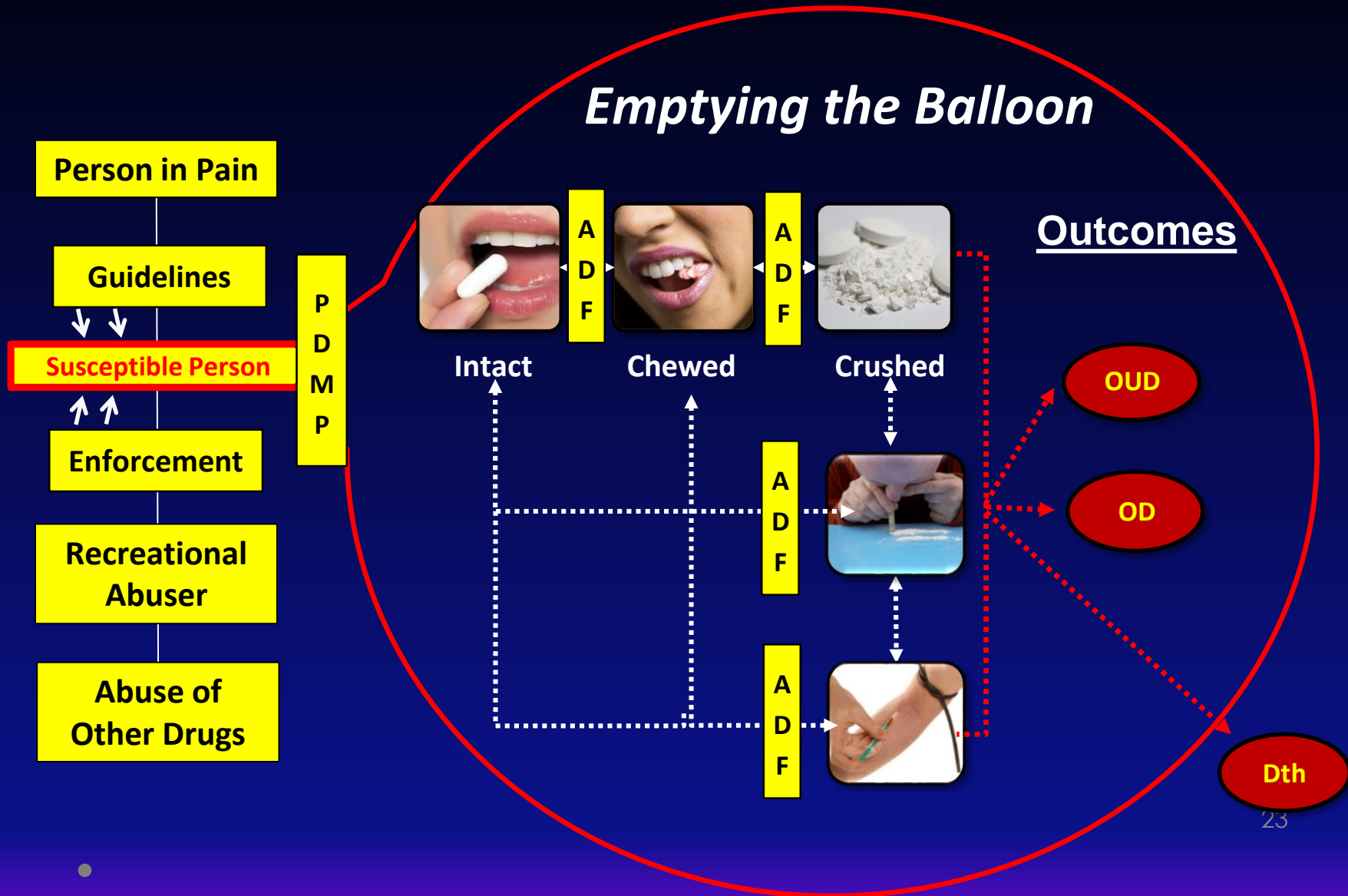
Potential Effects of Interventions



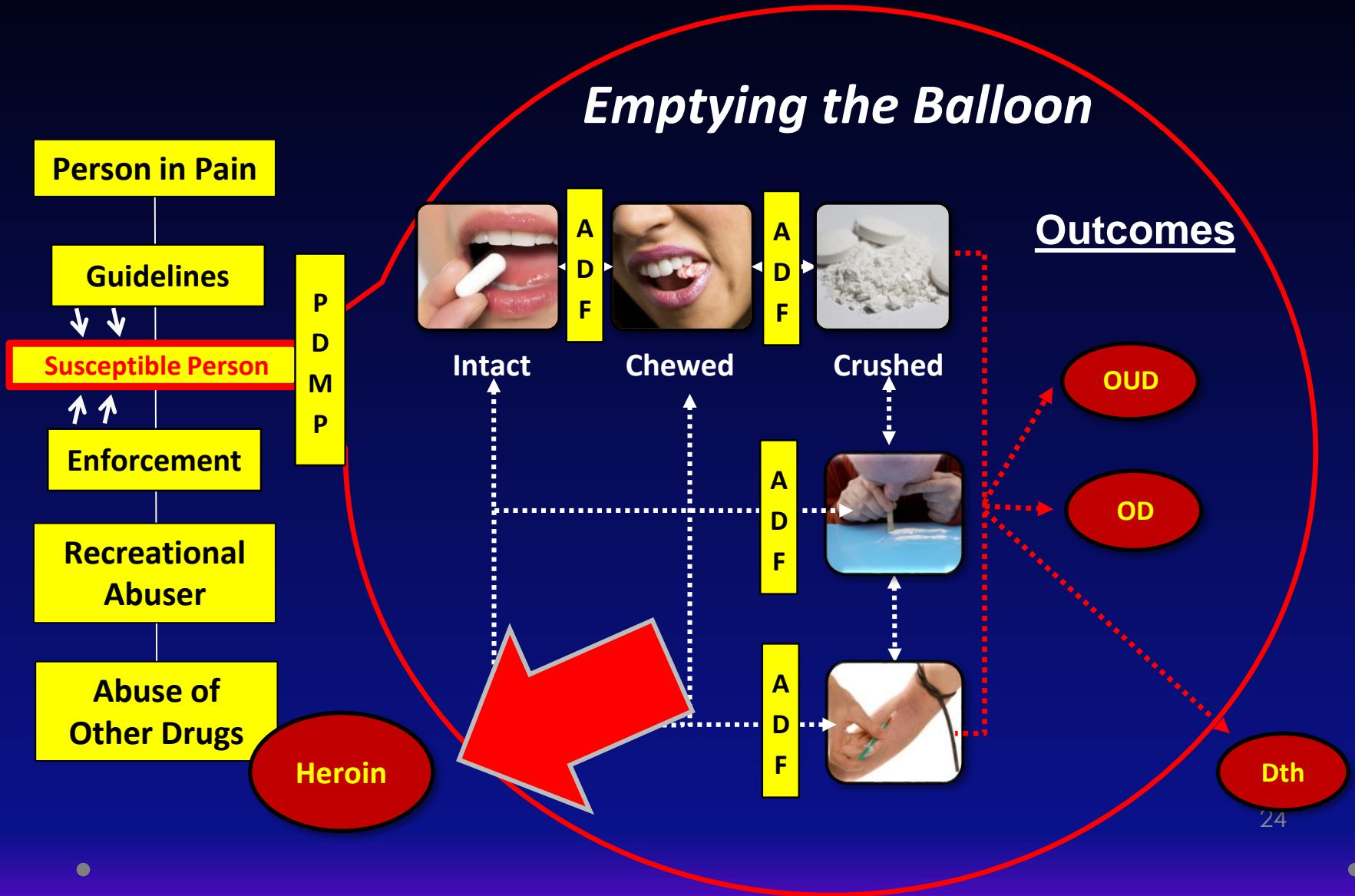
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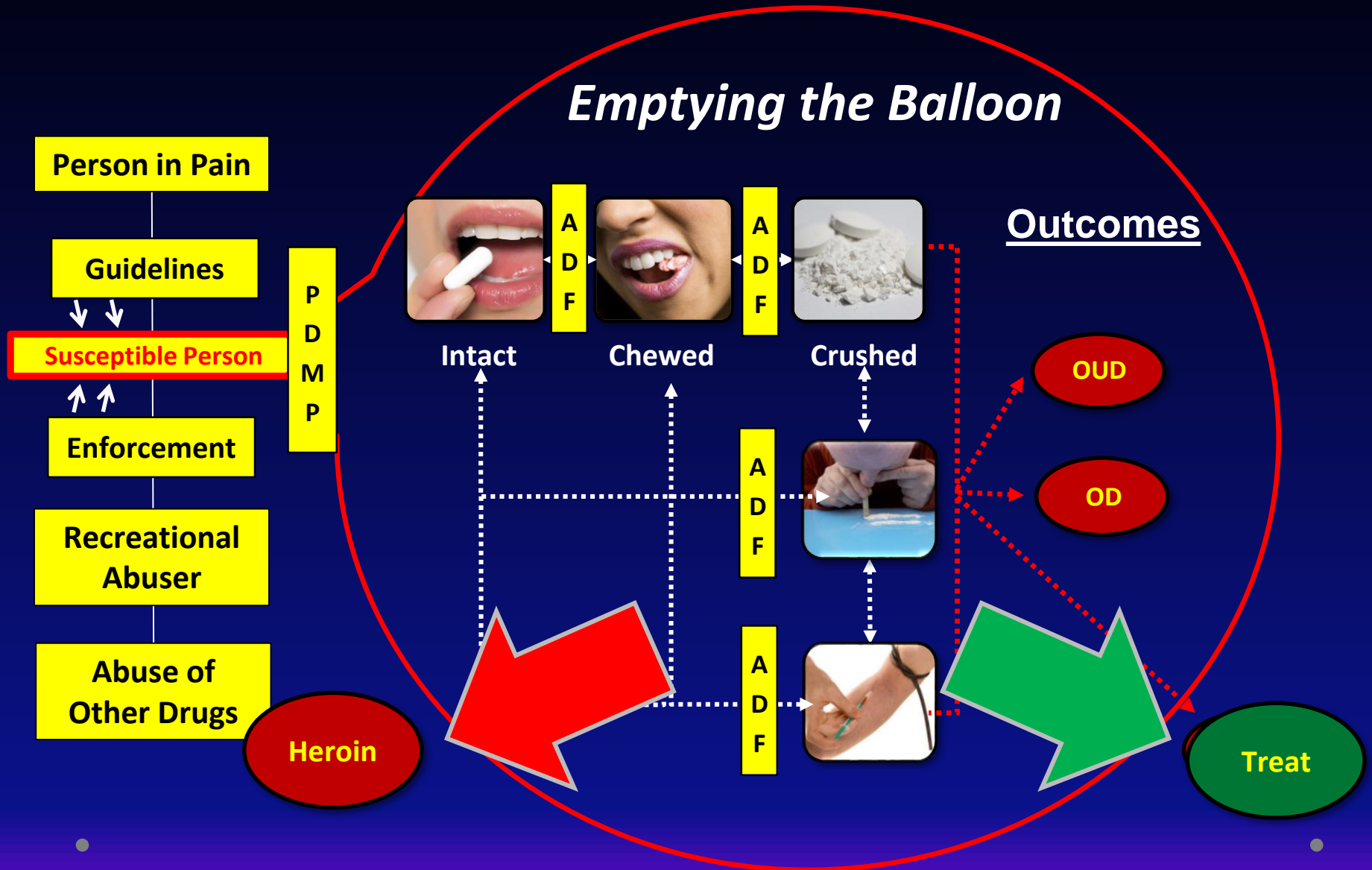
Potential Effects of Interventions



Potential Effects of Interventions



Potential Effects of Interventions



10 FDA-approved ADFs:

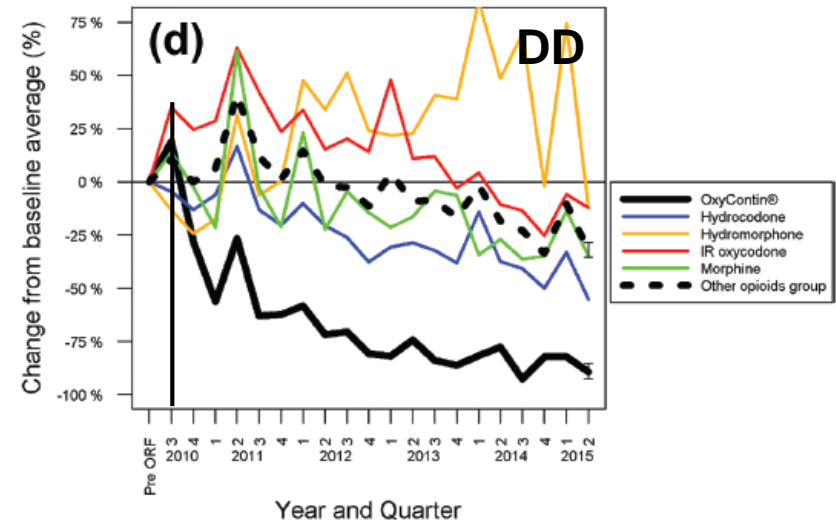
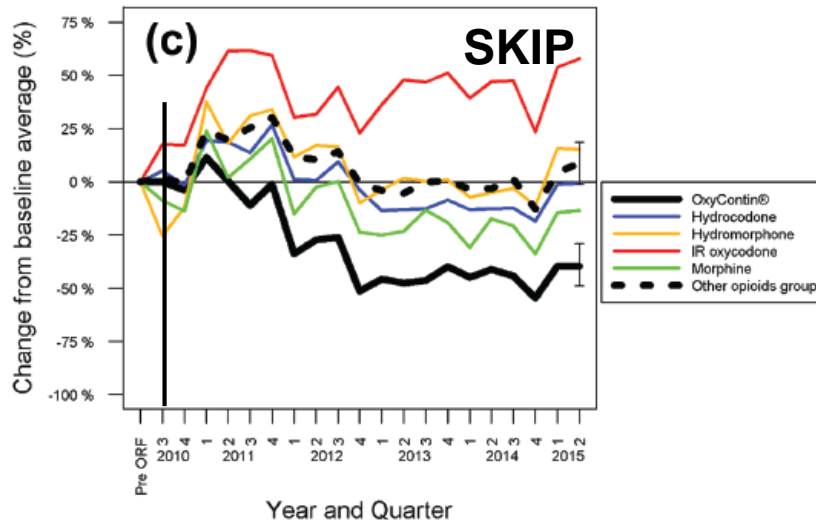
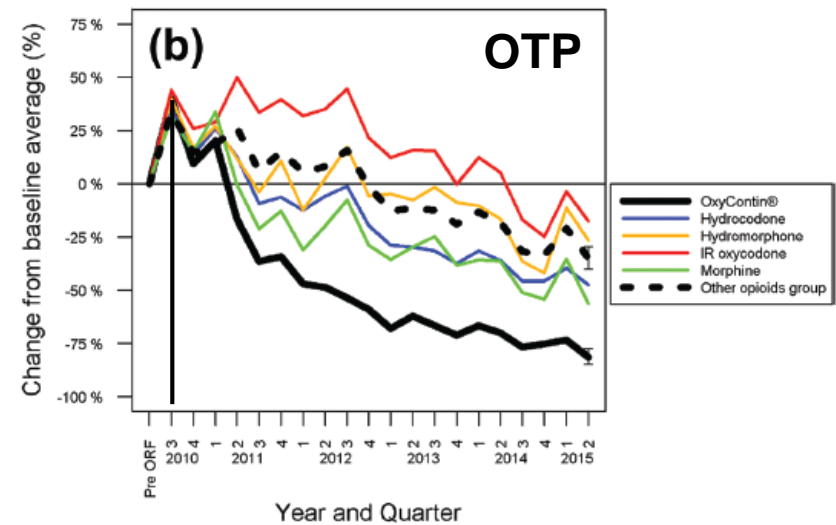
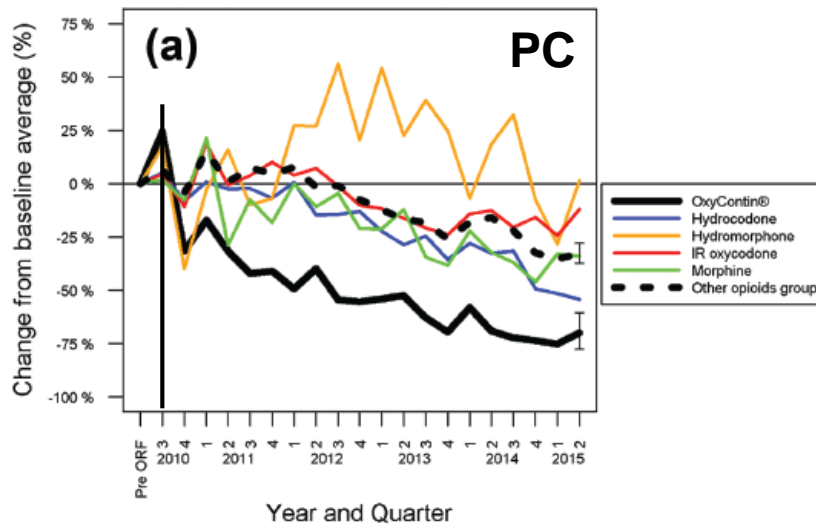
All physical/chemical or agonist/antagonist

Product	Drug Substance	Sponsor	Approval	Marketed
Oxycontin	oxycodone	Purdue	4/4/2010	YES
Targiniq ER	oxycodone + naloxone	Purdue	7/23/2014	NO
Embeda	morphine + naltrexone	Pfizer	10/17/2014	YES
Hysingla ER	hydrocodone	Purdue	11/20/2014	YES
Morphabond	morphine	Inspirion	10/2/2015	NO
Xtampza ER	oxycodone	Collegium	11/6/2015	YES
Troxyca ER	oxycodone + naltrexone	Pfizer	8/22/2016	NO
Arymo ER	morphine	Egalet	1/9/2017	Limited
Vantrela ER	hydrocodone	Teva	1/18/2017	NO
RoxyBond	oxycodone	Inspirion	4/26/2017	NO

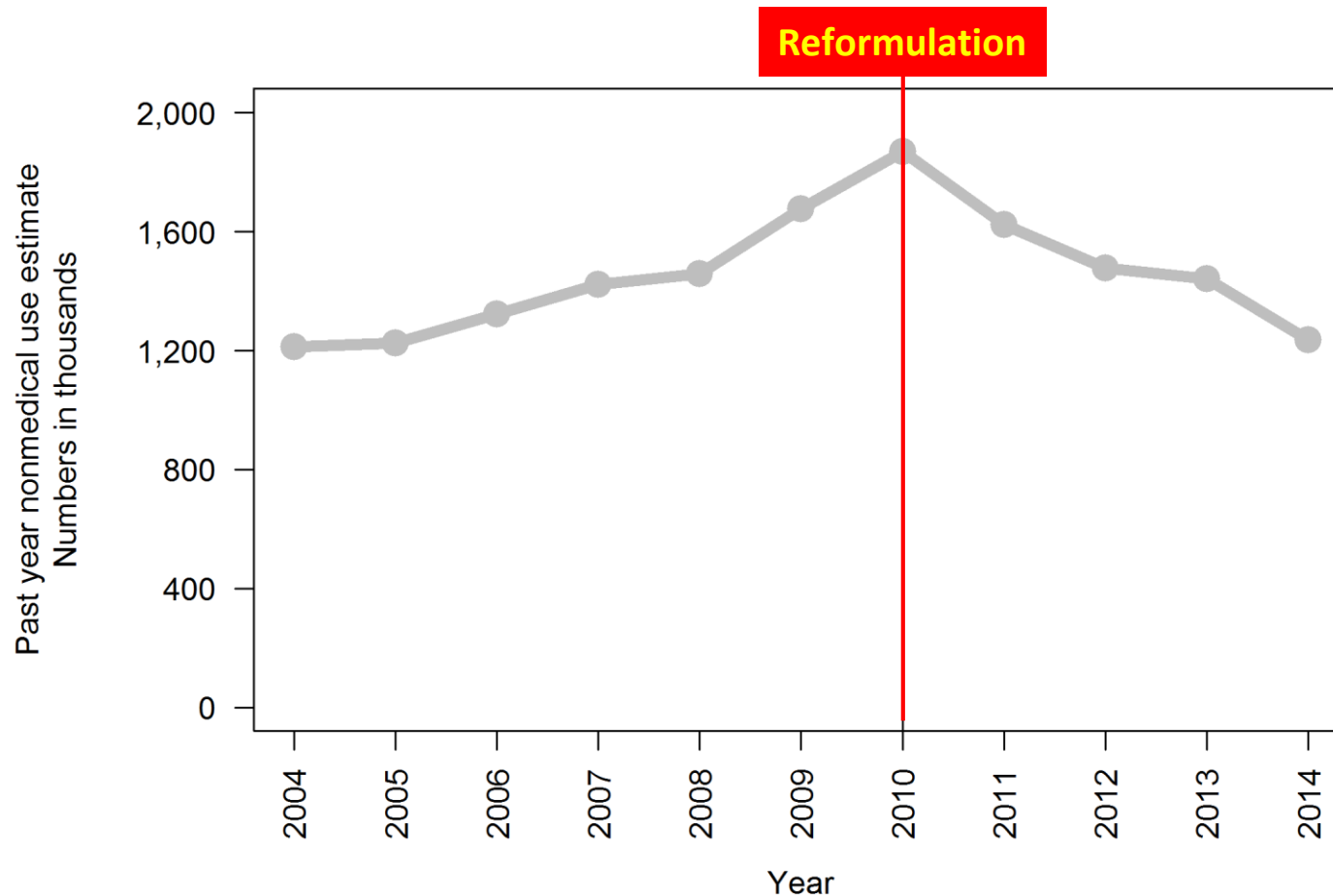
Systematic Review of Abuse Deterrent (Tamper Resistant) Formulations

- Question: What is the evidence that opioid analgesics with abuse deterrent labeling improve outcomes (abuse, misuse, overdose, death)?
- 45 reports on opioids with abuse deterrent labeling
 - Hydrocodone (n=7)
 - Morphine (n=5)
 - Oxycodone (n=32)*
- Hill Criteria
- Also assessed confounding factors and bias

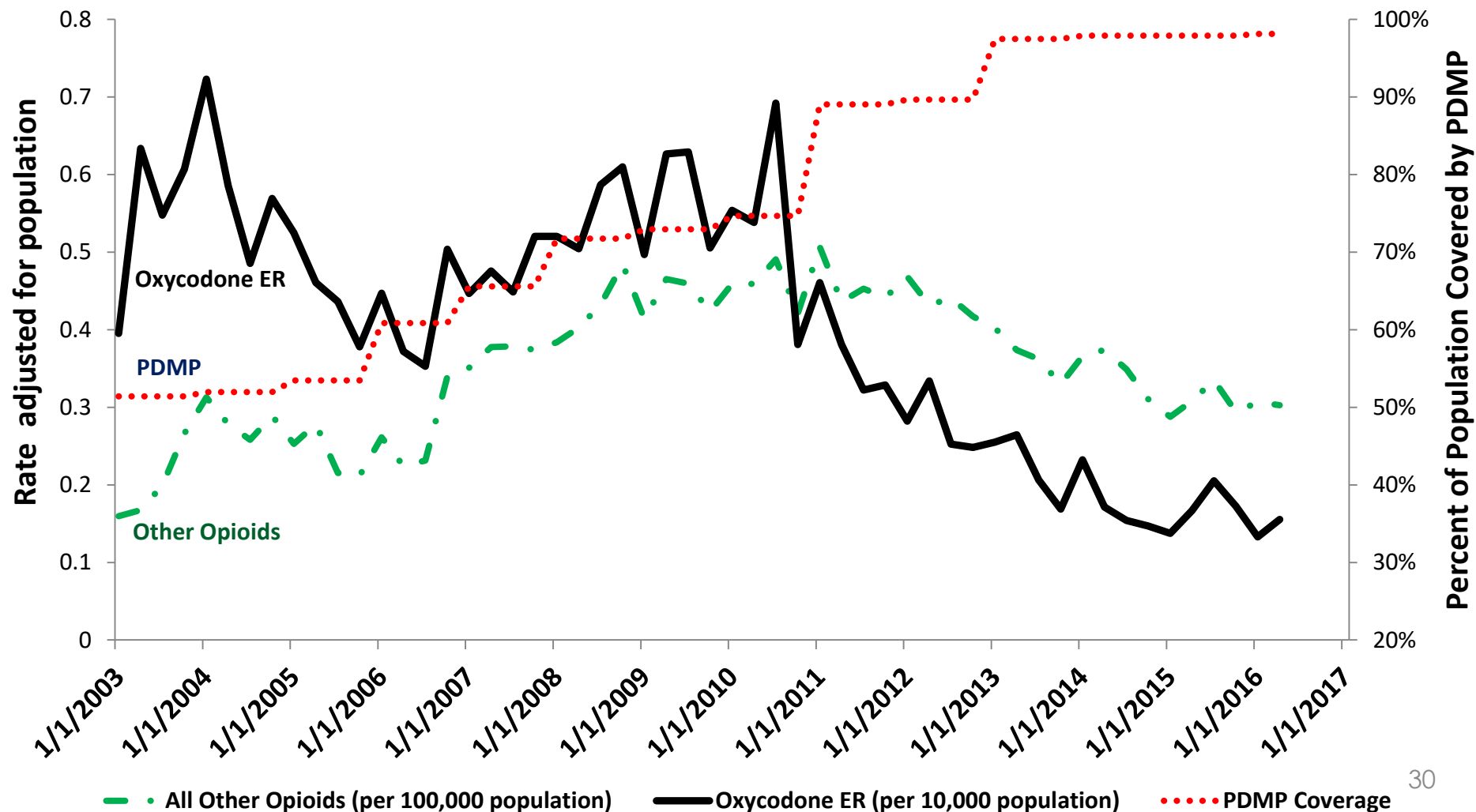
RADARS : Change in Abuse after OxyContin Reformulation



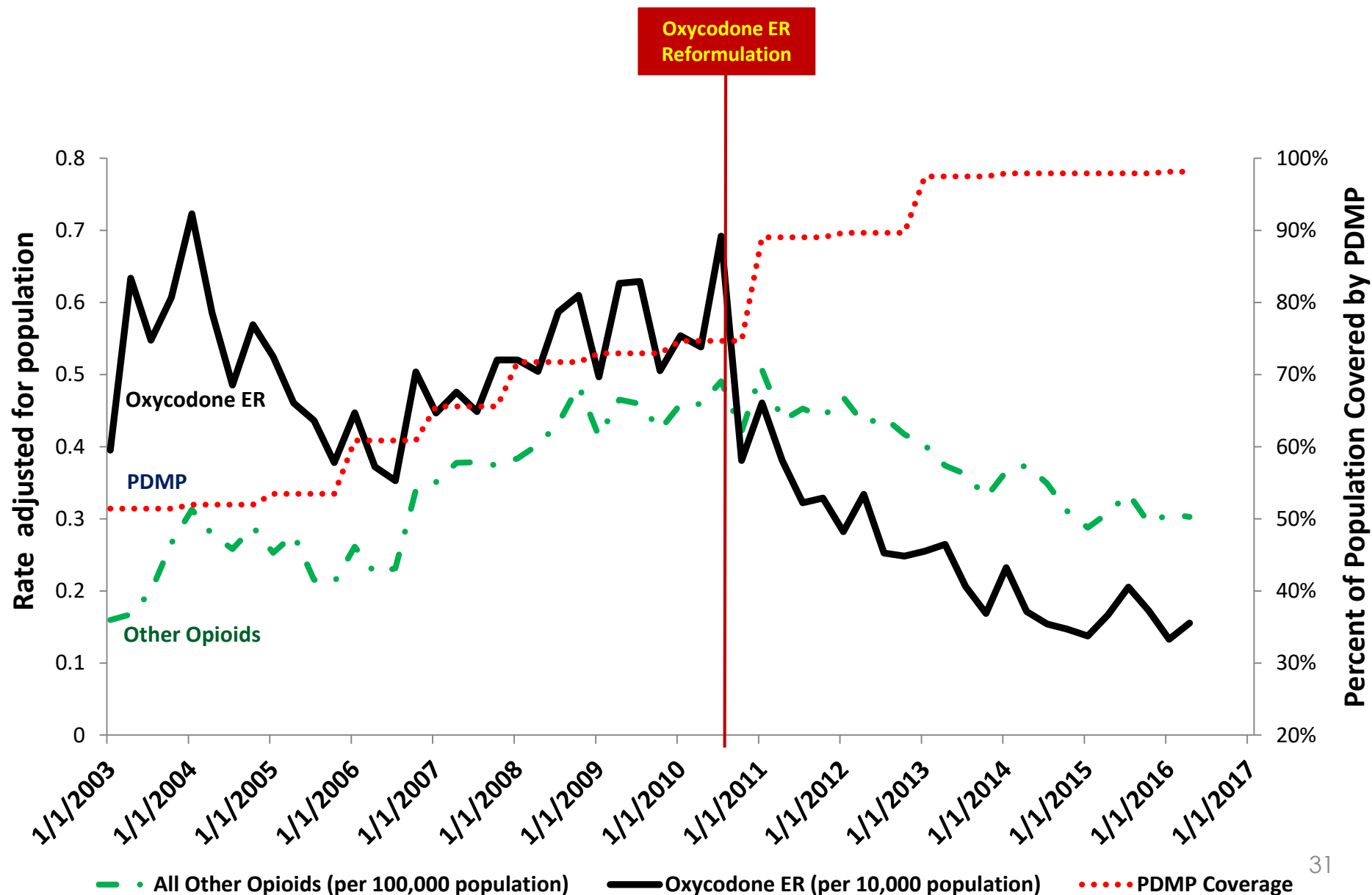
Nonmedical Use of OxyContin®, National Survey of Drug Use and Health, 2006 – 2014



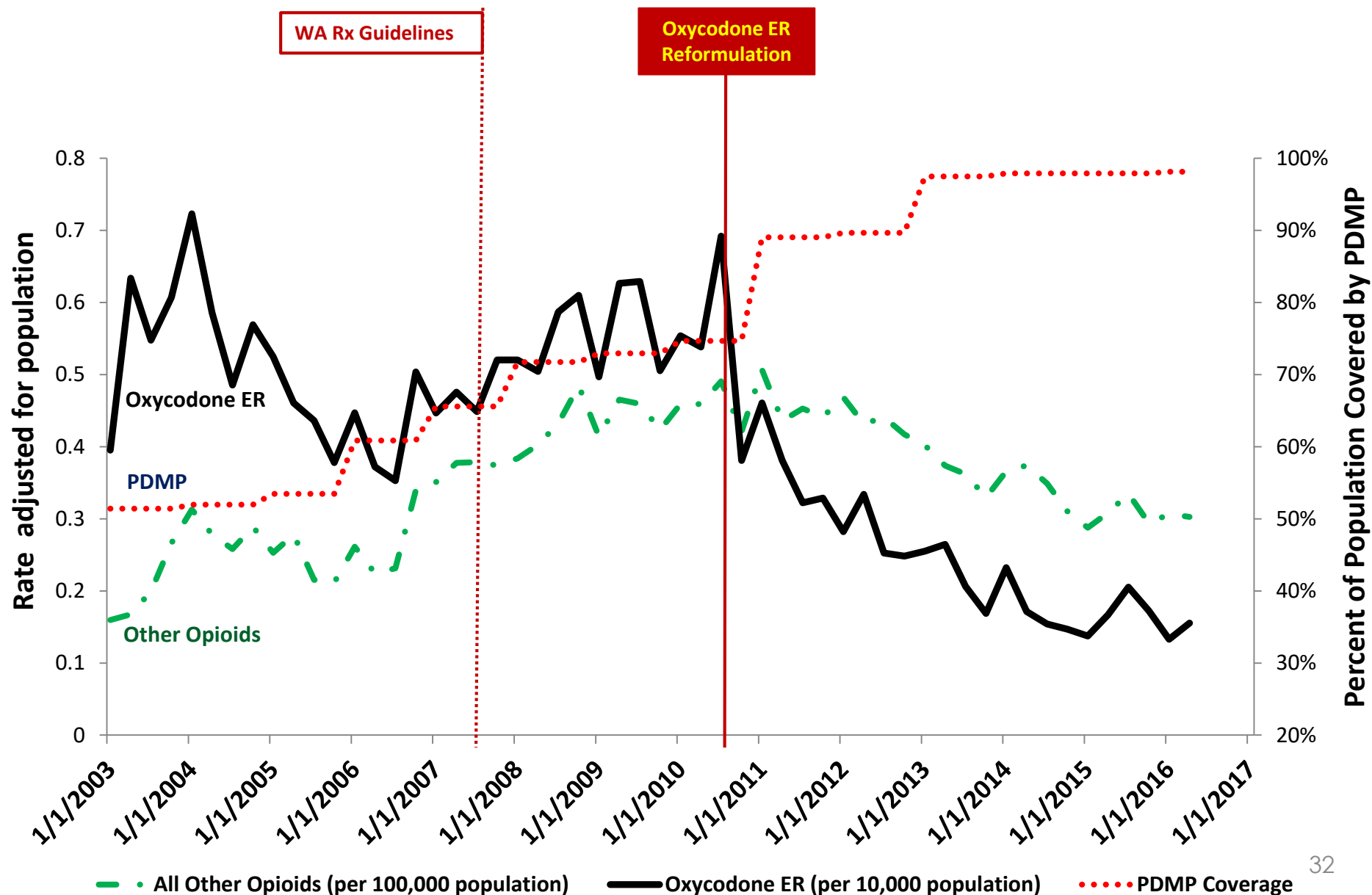
Timeline of Interventions vs. Oxycodone ER



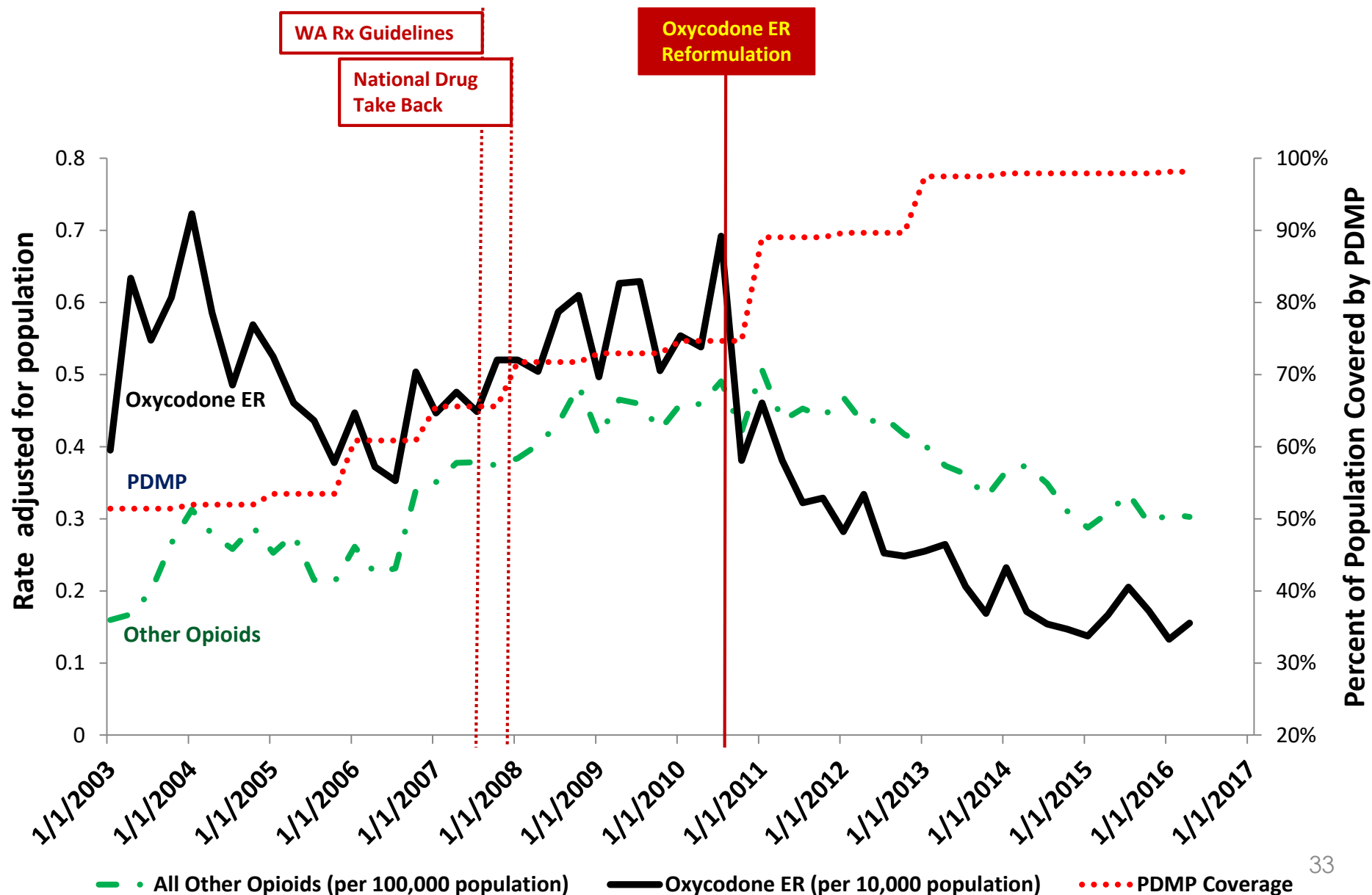
Timeline of Interventions vs. Oxycodone ER



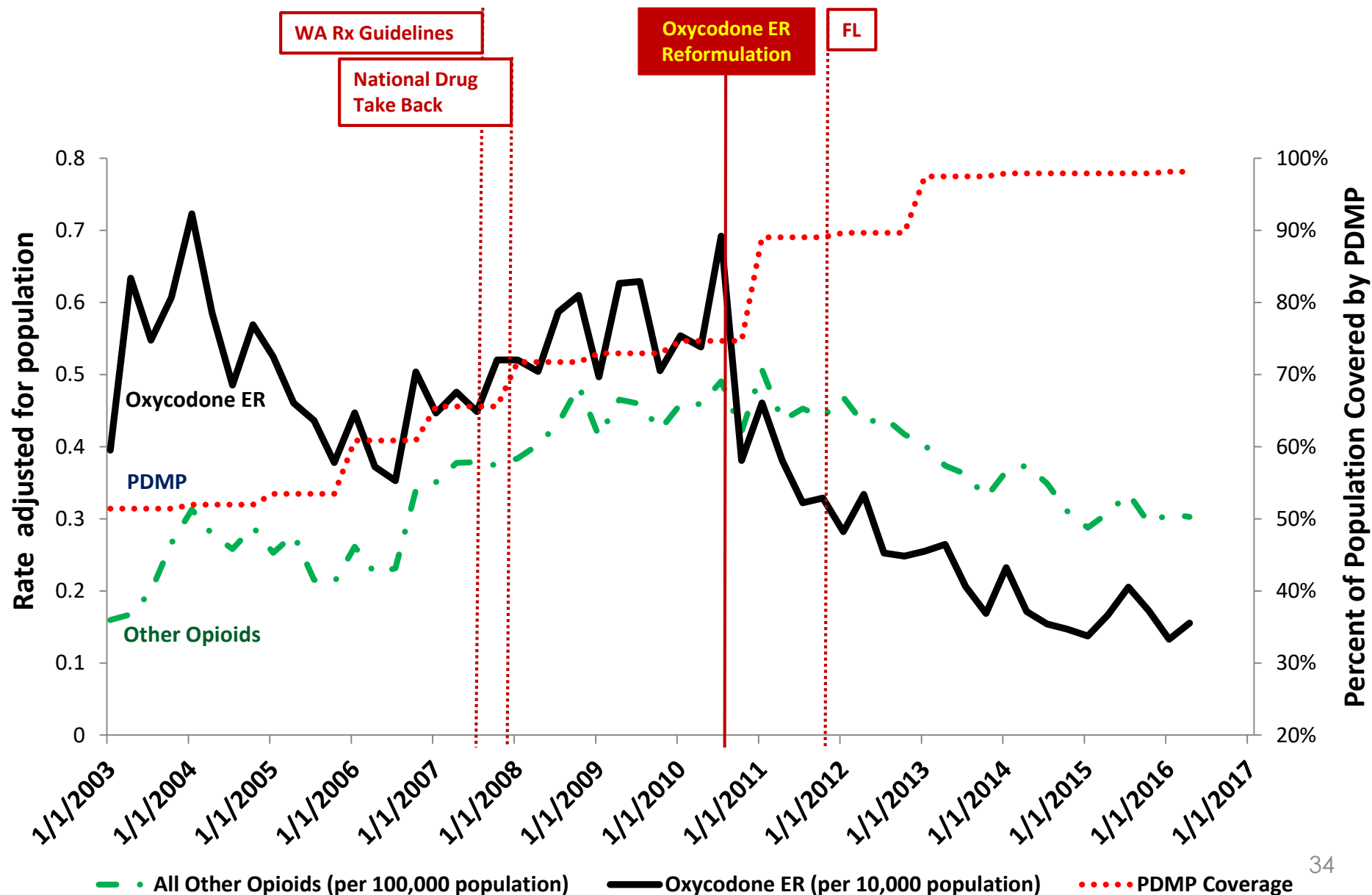
Timeline of Interventions vs. Oxycodone ER



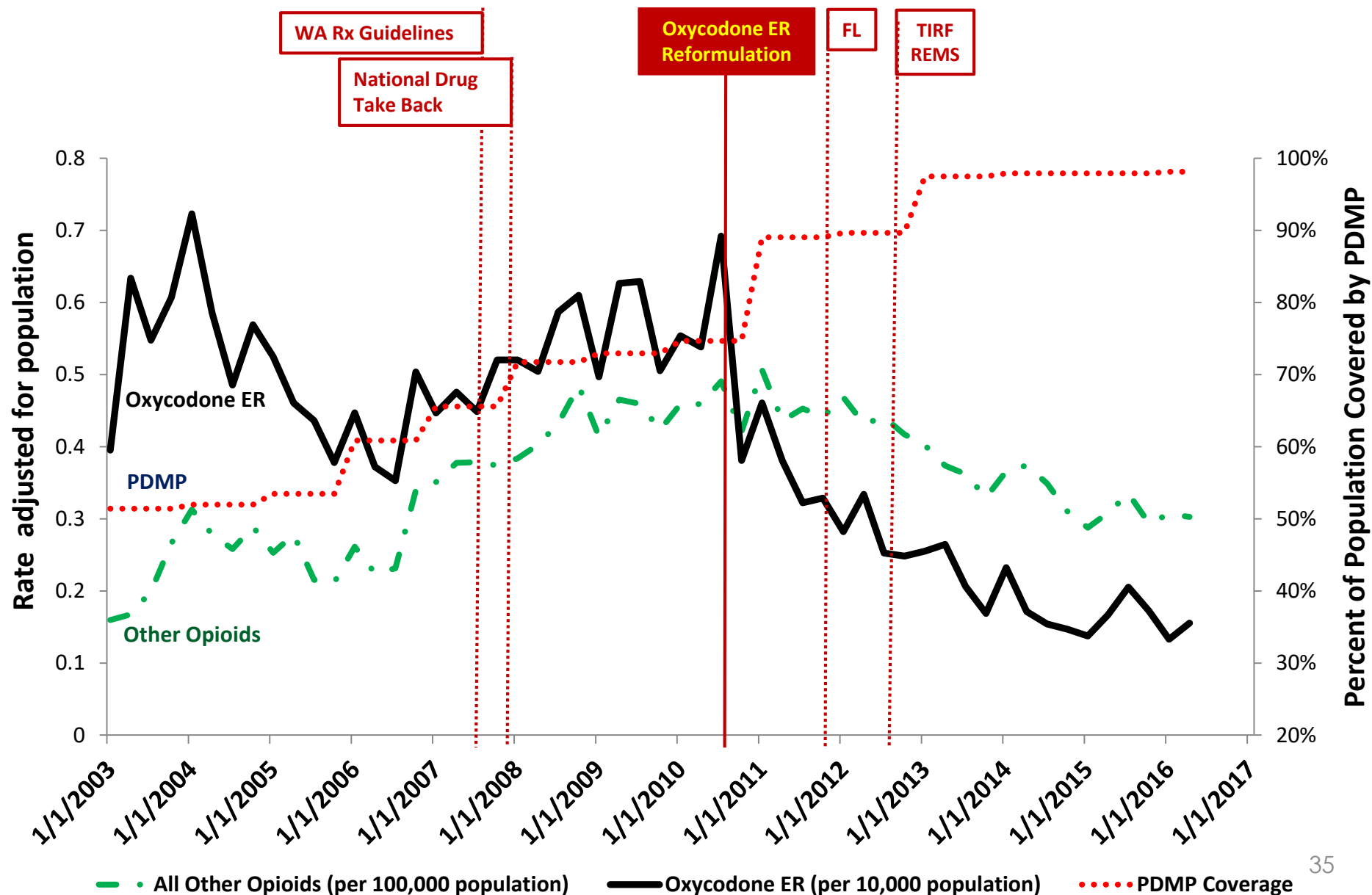
Timeline of Interventions vs. Oxycodone ER



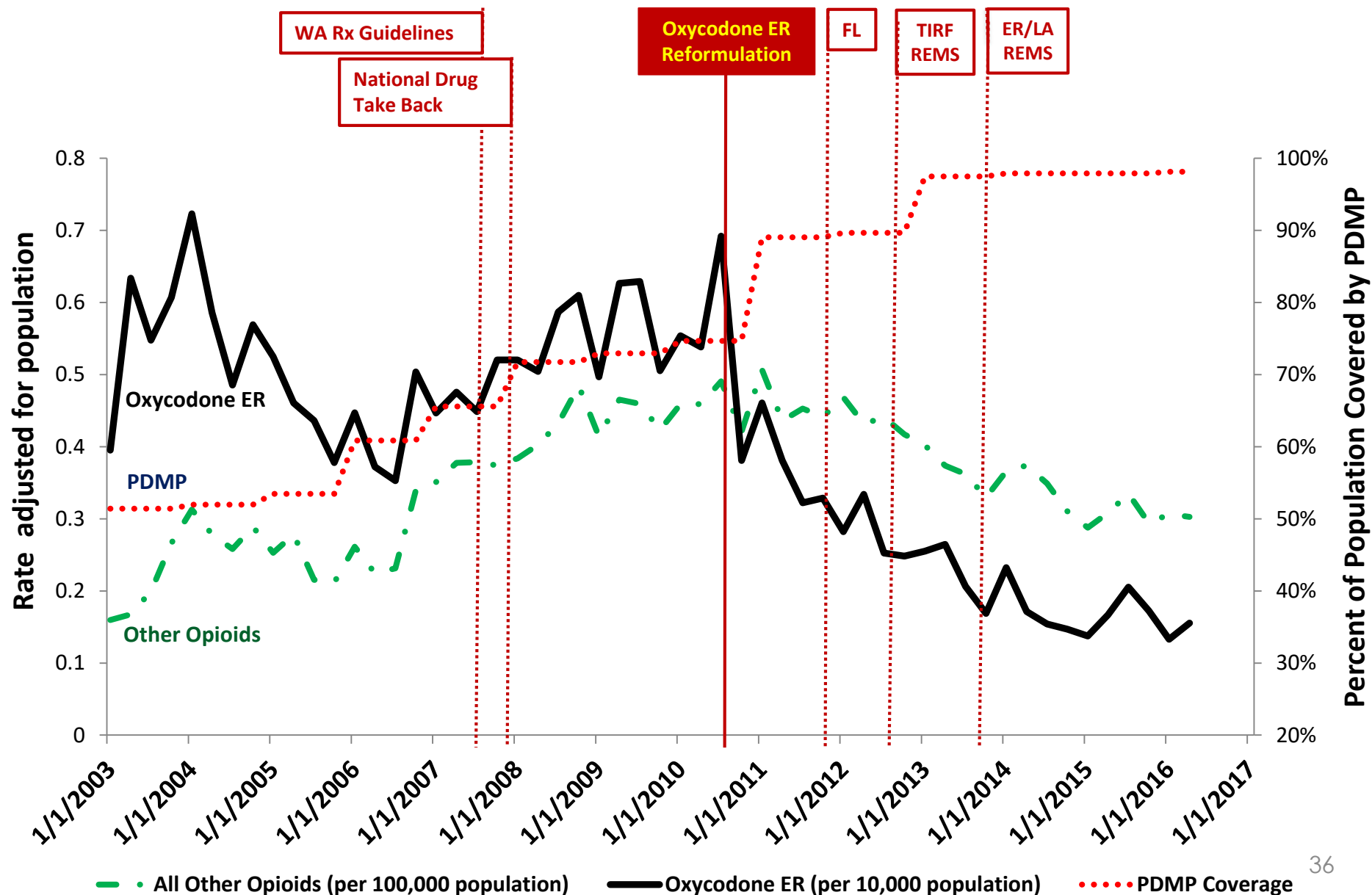
Timeline of Interventions vs. Oxycodone ER



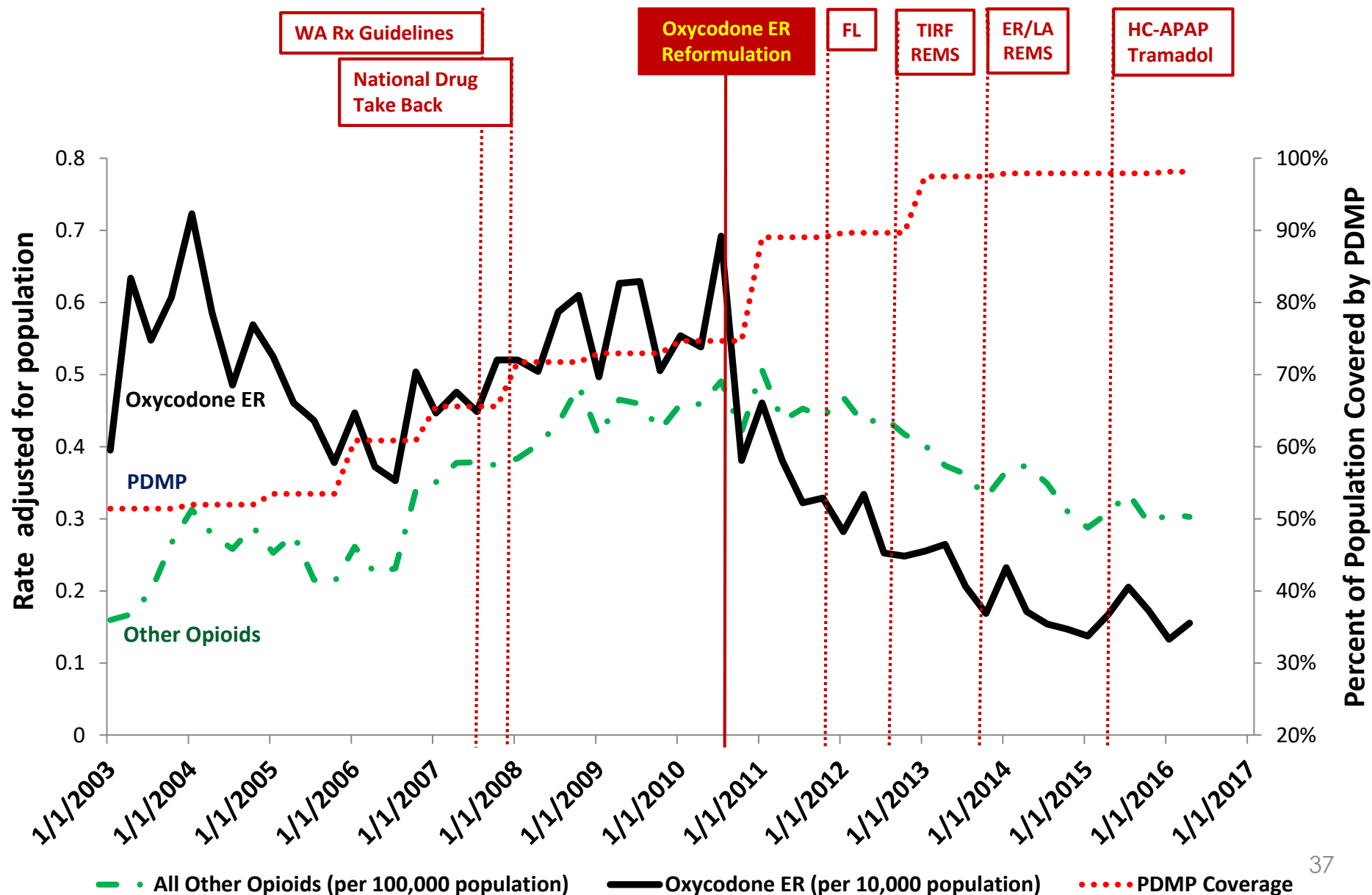
Timeline of Interventions vs. Oxycodone ER



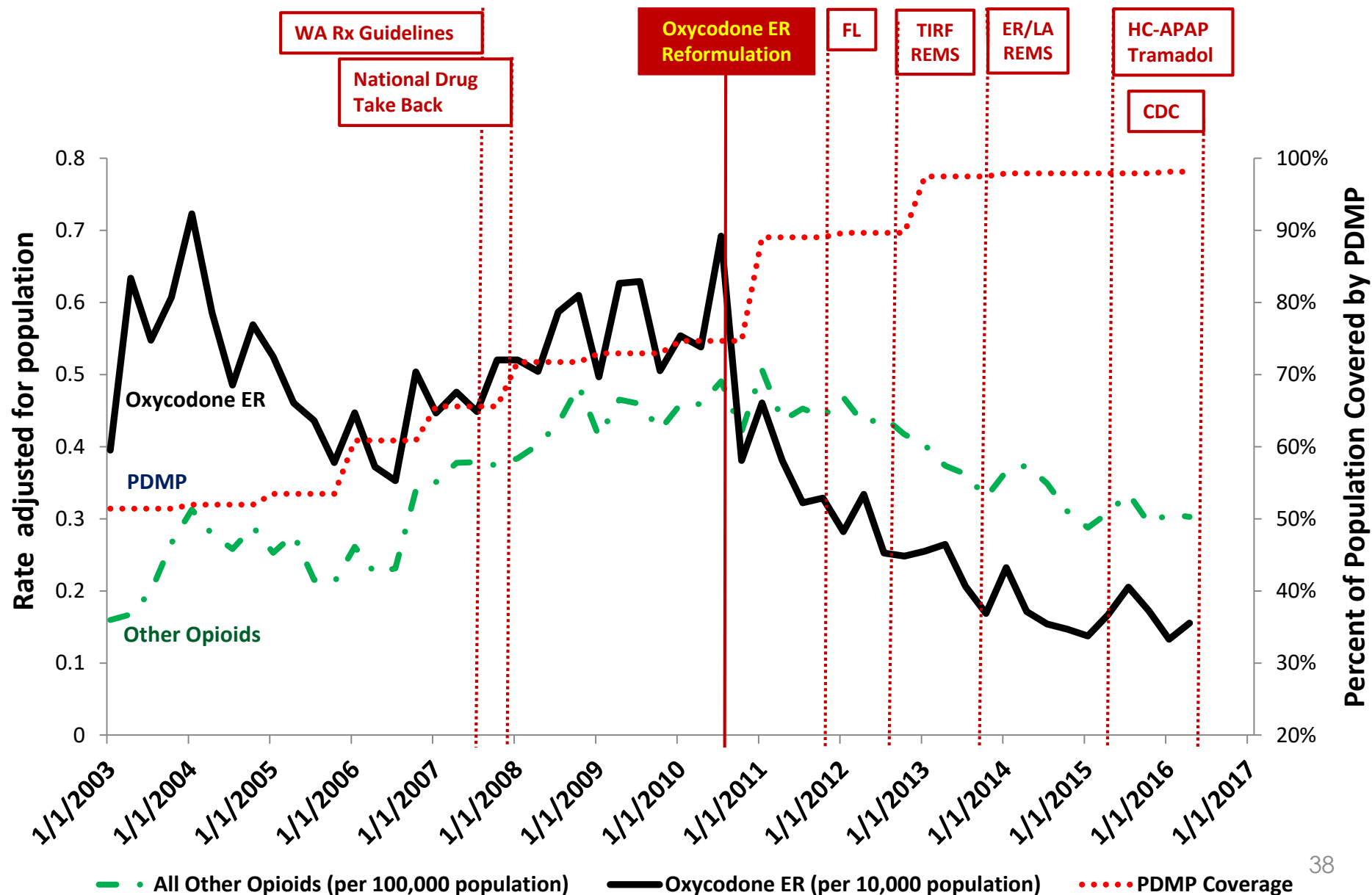
Timeline of Interventions vs. Oxycodone ER



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Timeline of Interventions vs. Oxycodone ER



Problems with a Reactionary Agenda



Problems with a Reactionary Agenda



- “OxyContin is the Problem”

Problems with a Reactionary Agenda



- “OxyContin is the Problem”
- “Drug manufacturers are the Problem”

Problems with a Reactionary Agenda



- “OxyContin is the Problem”
- “Drug manufacturers are the Problem”
- “Addicts / Drug dealers are the Problem”

Problems with a Reactionary Agenda



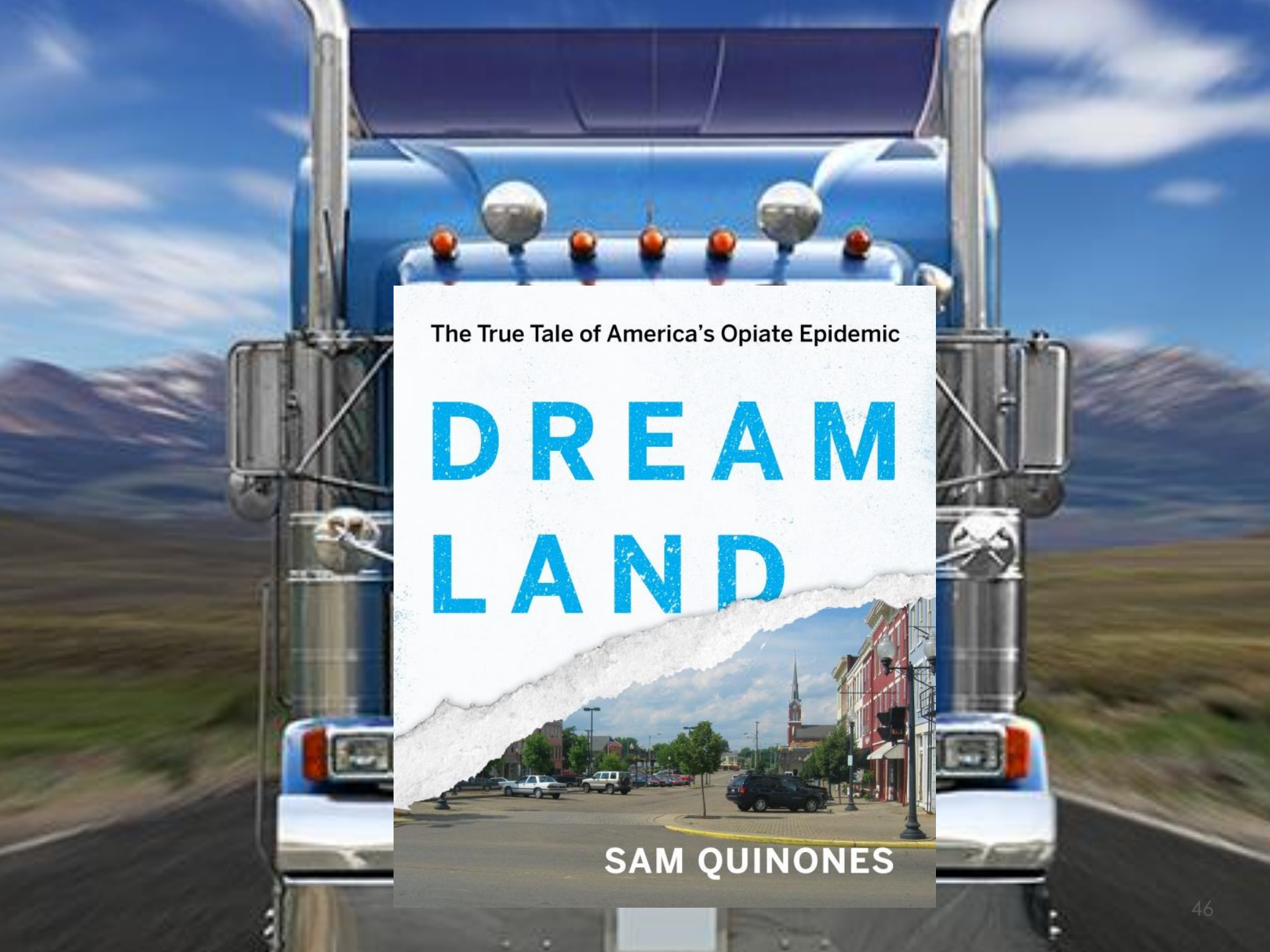
- “OxyContin is the Problem”
- “Drug manufacturers are the Problem”
- “Addicts / Drug dealers are the Problem”
- The core problem is human frailty and susceptibility to opioids (or perhaps to mind altering substances in general?)

Problems with a Reactionary Agenda



- “OxyContin is the Problem”
- “Drug manufacturers are the Problem”
- “Addicts / Drug dealers are the Problem”
- The core problem is human frailty and susceptibility to opioids (or perhaps to mind altering substances in general?)
- When we are looking back at the past...





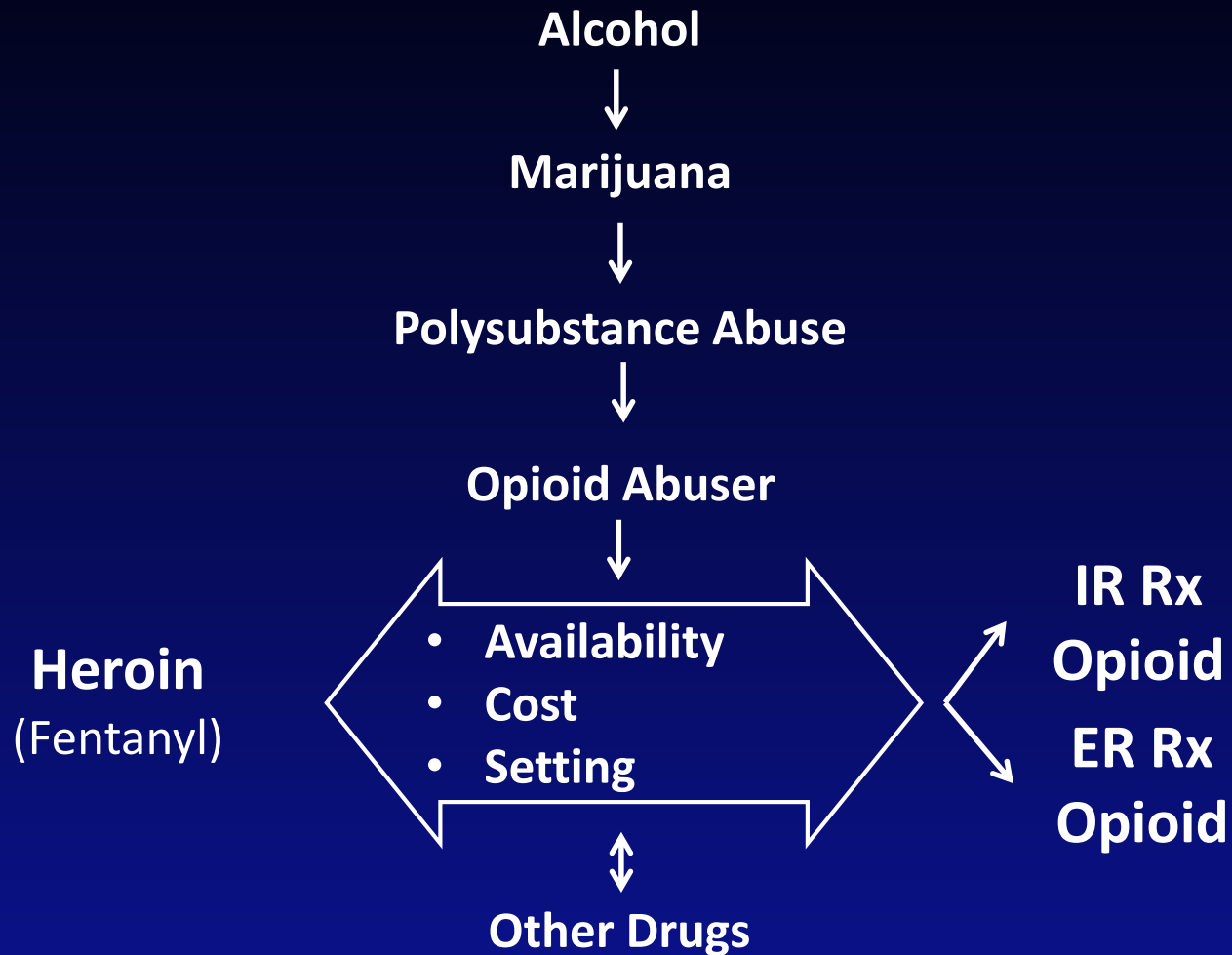
The True Tale of America's Opiate Epidemic

DREAM LAND

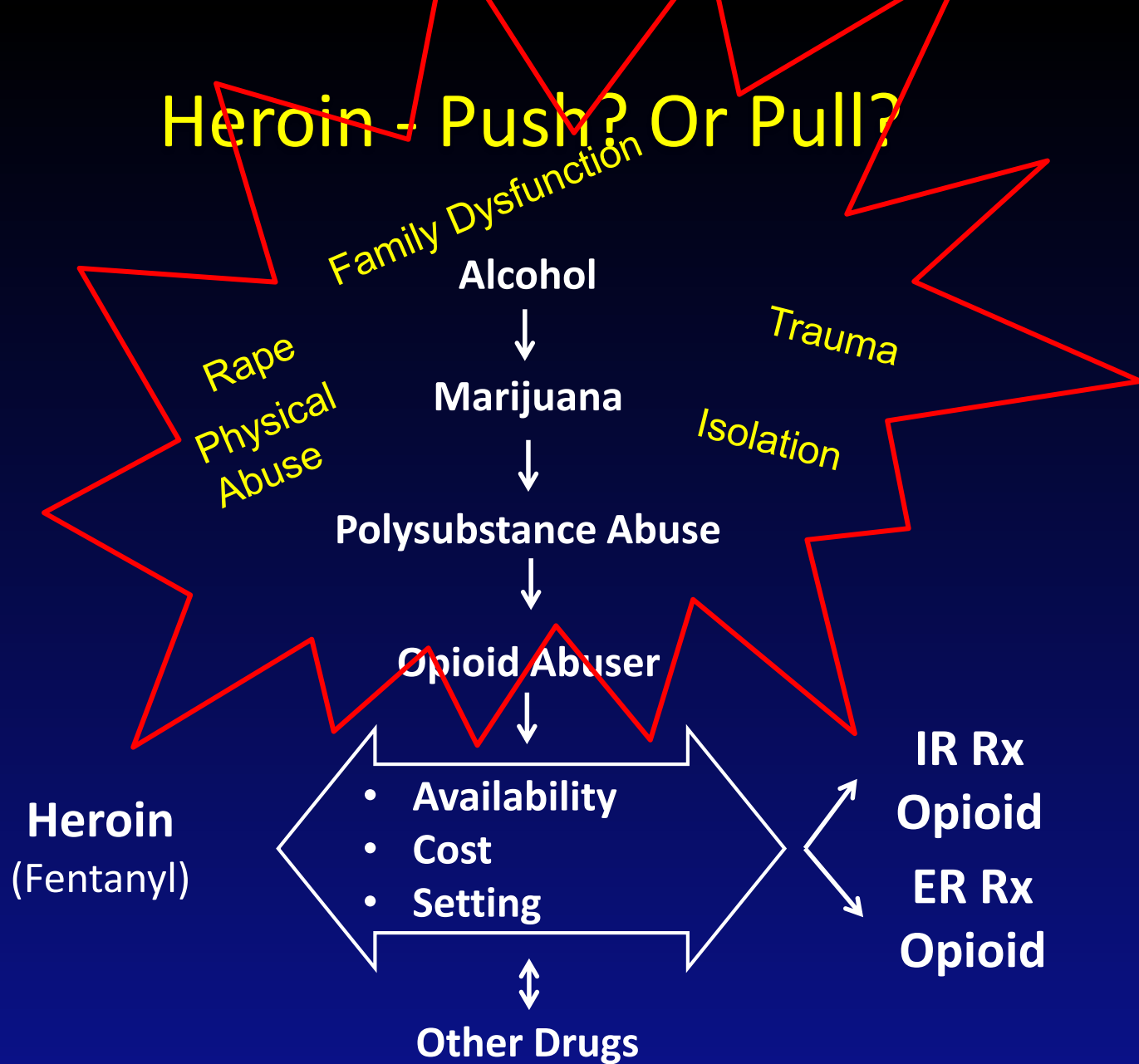


SAM QUINONES

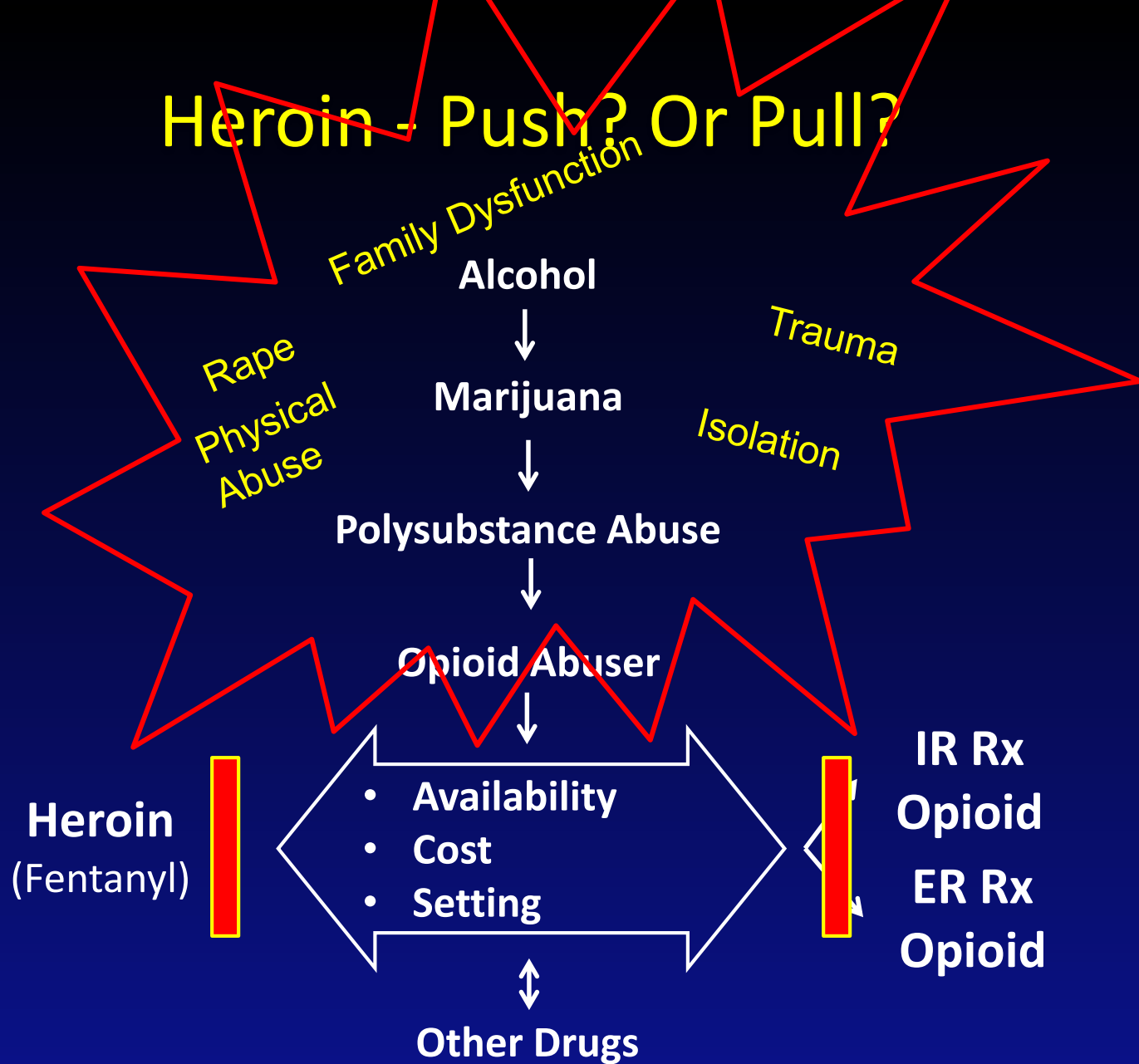
Heroin - Push? Or Pull?



Heroin - Push? Or Pull?



Heroin - Push? Or Pull?



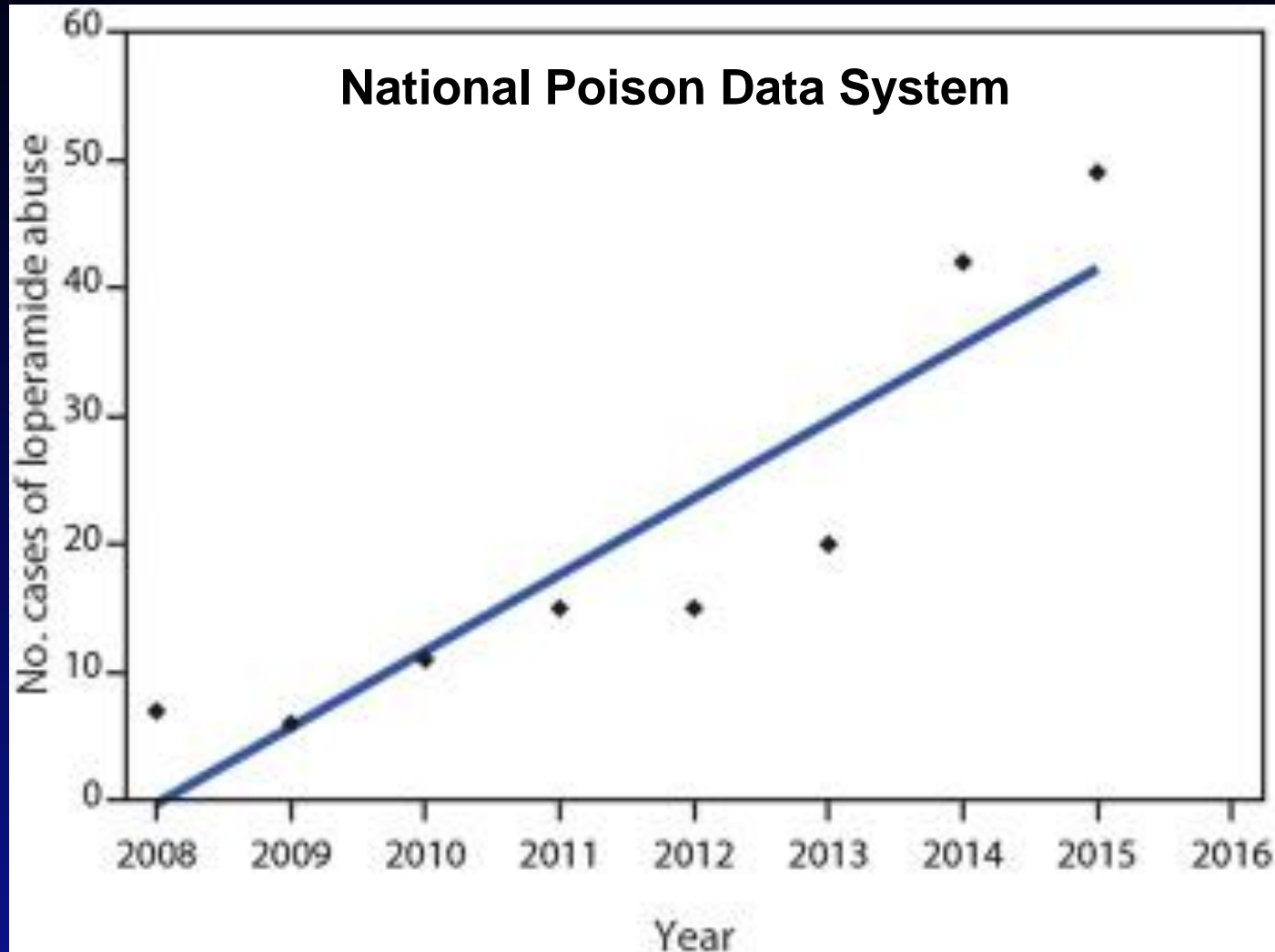
How Else Might Someone Cope?

- Opioids
- Opioids that you didn't think were opioids
- Non-opioids

Loperamide (Immodium)

- Antidiarrheal
- Prescription and OTC
- Intestinal mu agonist
- Poor systemic absorption due to p-glycoprotein
- Abused alone or in combination with opioids

Loperamide Abuse



- Miller H et al. JAPHA 2017, 57(2): S45–S50

Loperamide Abuse Associated With Cardiac Dysrhythmia and Death



William Eggleston, PharmD*; Kenneth H. Clark, MD; Jeanna M. Marraffa, PharmD, DABAT

**Corresponding Author. E-mail: williamdeggleston@gmail.com, Twitter: [@WillieDoesTox](https://twitter.com/WillieDoesTox).*

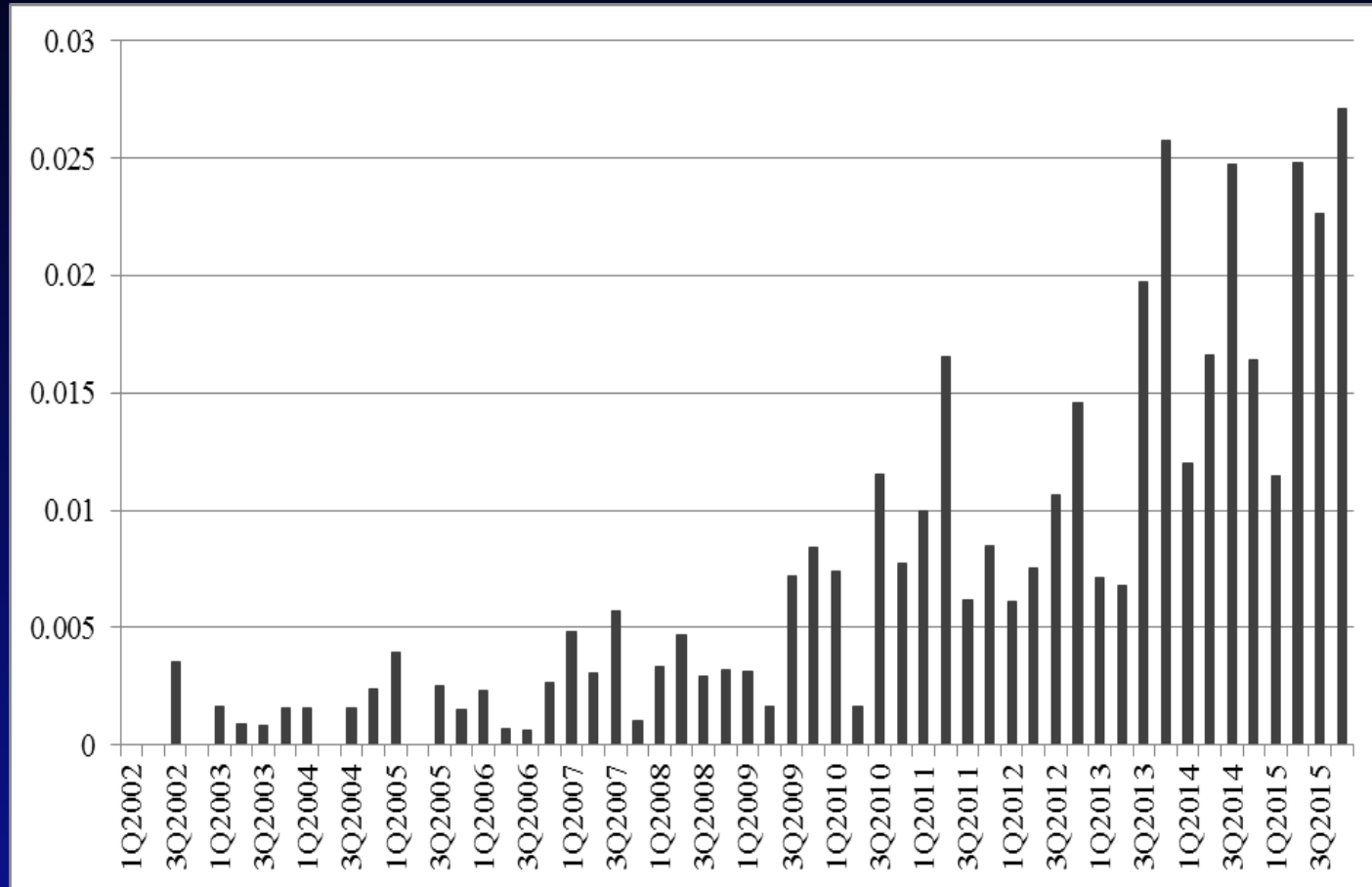
Loperamide is an over-the-counter antidiarrheal with μ -opioid agonist activity. Central nervous system opioid effects are not observed after therapeutic oral dosing because of poor bioavailability and minimal central nervous system penetration. However, central nervous system opioid effects do occur after supratherapeutic oral doses. Recently, oral loperamide abuse as an opioid substitute has been increasing among patients attempting to self-treat their opioid addiction. Ventricular dysrhythmias and prolongation of the QRS duration and QTc interval have been reported after oral loperamide abuse. We describe 2 fatalities in the setting of significantly elevated loperamide concentrations. [Ann Emerg Med. 2017;69:83-86.]

GABA Analogs

- Gabapentin, pregabalin
- 10-15% prescribed opioids also prescribed gabapentin
- Misuse common in opioid use disorders (15% - 28%)
- Increased mortality when combined with opioids
 - Likely synergistic respiratory depression

RADARS: Diversion of GABA Analogs

Rates of gabapentin diversion (per 100,000) by quarter, 2002-2015



Increasing Abuse of Gabapentin and Pregabalin as Reported to US Poison Centers 2006 through 2014

B Bucher Bartelson¹, G Bau¹, G Severtson¹, JL Green¹, RC Dart^{1,2}

¹Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority

²Department of Emergency Medicine, University of Colorado School of Medicine

Abstract

Increasing Abuse of Gabapentin and Pregabalin as Reported to US Poison Centers 2006 through 2014

B Bucher Bartelson¹, G Bau¹, G Severtson¹, JL Green¹, RC Dart^{1,2}

¹Rocky Mountain Poison and Drug Center, Denver Health and Hospital Authority

²Department of Emergency Medicine, University of Colorado School of Medicine

Abstract: To determine if abuse rates of gabapentin compared to pregabalin are changing overtime and to describe the outcomes of poison center cases involving abuse.

Methods: Data from the National Poison Data System from January 2006 to December 2014 were queried for gabapentin and pregabalin product codes and were utilized to determine if the category of intentional abuse cases were increasing in the US and if gabapentin and pregabalin abuse cases are changing at different rates. The total number of cases of intentional abuse where the exposure was to gabapentin or pregabalin was computed and divided by the estimated population of the US and scaled per 100,000 population. A Poisson regression model was used to determine the percent change per quarter in the intentional abuse population rates.

Results: Of the 3,111 intentional abuse cases exposed to gabapentin, 1,731 (55.6%) were male and the median age was 30.0 years (IQR: 21-42). Of the 1,044 intentional abuse cases exposed to pregabalin, 240 (22.9%) were male and the median age was 29.0 years (IQR: 19-42).

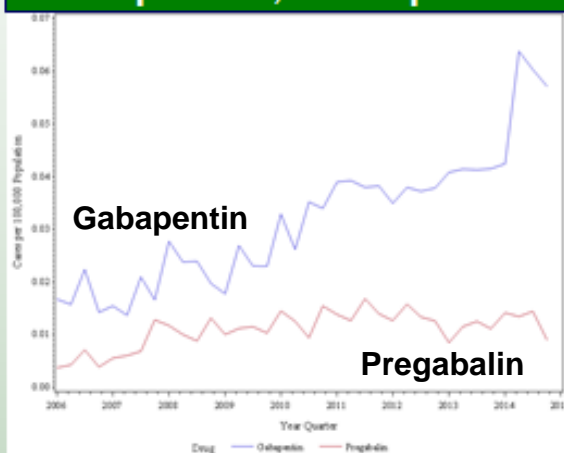
Only 1,226 (39.4%) of the exposures involved a single substance. The rate of abuse per 100,000 population in first quarter 2006 was 0.0168 and in fourth quarter 2014 was 0.0571 for gabapentin. The rate of abuse per 100,000 population in first quarter 2006 was 0.0037 and in fourth quarter 2014 was 0.0090 for pregabalin. Using Poisson regression intentional abuse population rates increased at a rate of 3.7% (95% CI: 2.5-5.0%) per quarter for gabapentin and 1.6% (95% CI: 1.0-2.3%) per quarter for pregabalin ($p < 0.0001$). The medical outcomes were similar between gabapentin and pregabalin, with 12 (0.2%) and 9 (0.9%) deaths, 162 (5.2%) and 72 (6.8%) major effects, 905 (29.1%) and 227 (21.7%) moderate effects, and 964 (31.6%) and 940 (90.0%) minor effects, respectively.

Conclusions: Population-based rates of intentional gabapentin and pregabalin abuse have increased since 2006, and abuse rates of gabapentin are increasing faster than pregabalin. Continued monitoring and increased awareness of these rates is warranted.

Financial Support: The authors are affiliated with the RUPDS system, an independent nonprofit poison-marketing surveillance system that is supported by subscription fees from pharmaceutical manufacturers. None of the authors have a direct financial, commercial, or other relationship with any of the subscribers.

Results

Yearly Gabapentin or Pregabalin Intentional Abuse Rates per 100,000 Population



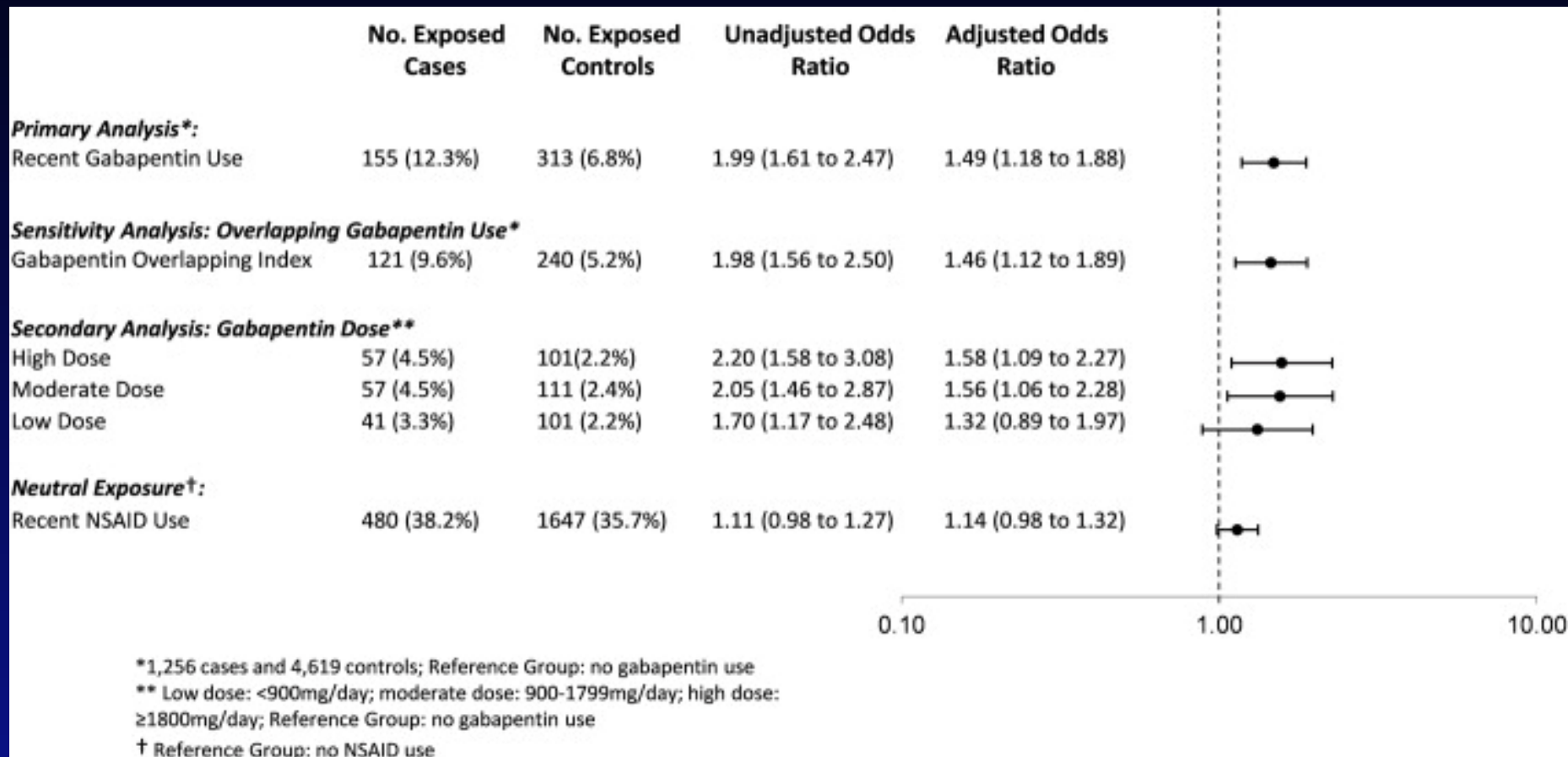
Results (continued)

- Only 1,326 (32.1%) of the intentional abuse exposures involved a single substance
- For gabapentin, the rate in first quarter 2006 was 0.0168 per 100,000 population while the rate for fourth quarter 2014 was 0.0571 per 100,000 population, a 3.4-fold increase
- For pregabalin, the rate in first quarter 2006 was 0.0037 per 100,000 population while the rate for fourth quarter 2014 was 0.0090 per 100,000 population, a 2.4-fold increase

Conclusions

- Population-based rates of gabapentin and pregabalin intentional abuse reported to US poison centers have increased since 2006, and

Gabapentin and Mortality



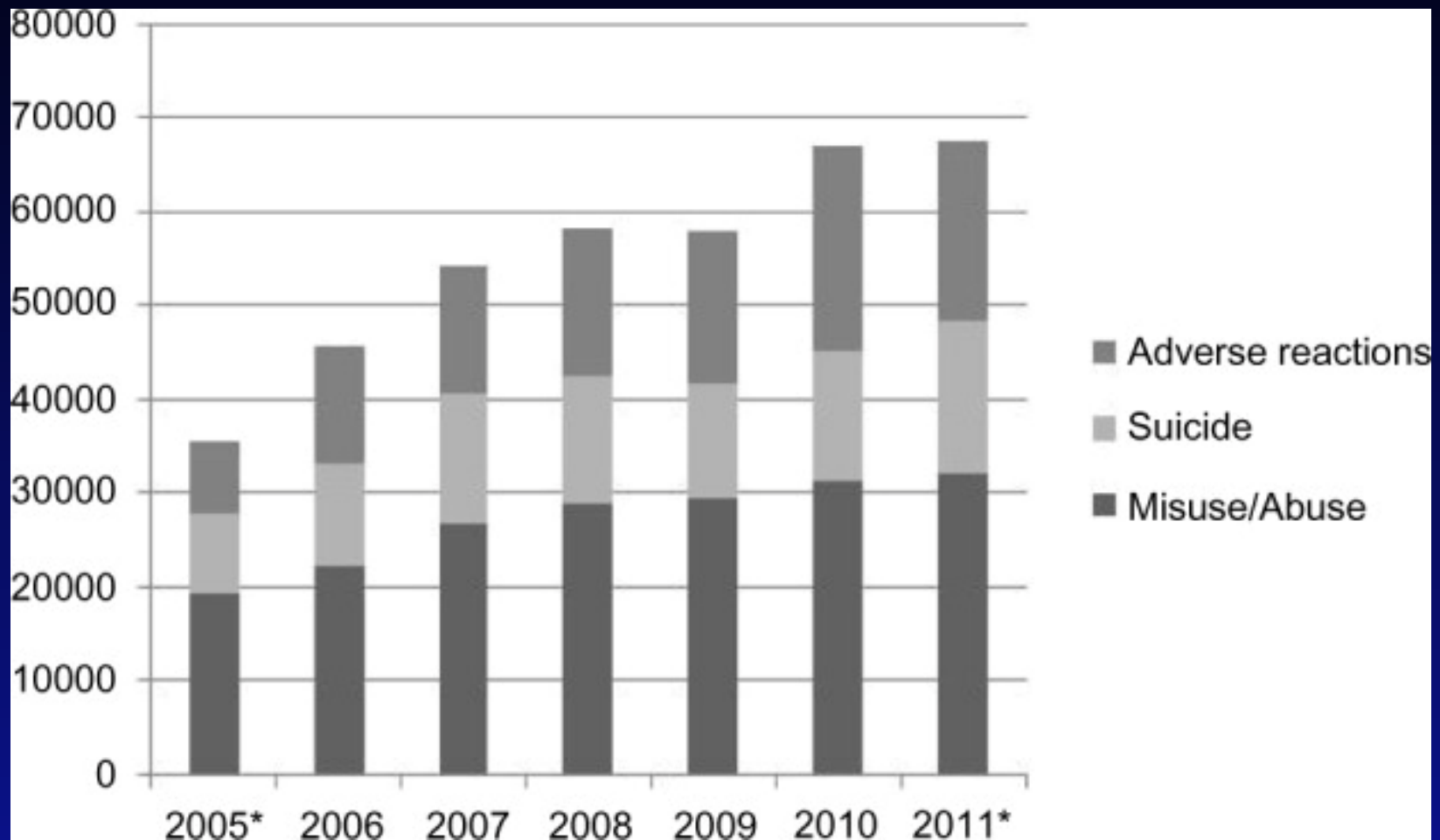
Antipsychotic Medications

- Atypical antipsychotics commonly abused both alone and in combination with other drugs
- Especially popular in incarcerated population
- Quetiapine (Seroquel) often drug of choice

Antipsychotic Abuse

- 429 patients from detox and rehab units
- 73 (17%) abuse atypical antipsychotics with alcohol, opioids, cocaine/crack, methamphetamine, and/or cannabis
- Quetiapine most common (84.9%)
- Other antipsychotics - olanzapine (17.8%), risperidone (24.7%), aripiprazole (20.5%), ziprasidone (8.1%), and asenapine (2.9%)
- Goals: "getting mellow", "slowing down", or enhancing effects of other drugs

Quetiapine DAWN ED visits



Antidepressants

- Reports of abuse of all classes
- May have higher rates with SNRI
 - Stimulant effects due to norepinephrine reuptake inhibition
 - When used with opioids, pharmaceutical “speedball” effect
 - Adverse effects include seizures and dysrhythmias

Cyclobenzaprine

- National Poison Data System (NPDS)
- Few studies of misuse/abuse
- Anticholinergic effects
- Structural similarity to tricyclic antidepressants
- Anticipate synergistic CNS and respiratory depression with opioids

Other Anticonvulsants



- Nearly all have been reported both in single substance and polysubstance abuse cases
- Levitiracetam may be on the horizon
- Synergistic CNS depression with opioids
- Cardiac effects also possible

The image features a close-up of an orange plastic pill bottle on the left, partially filled with yellow capsules. The bottle has a white label with red and black text, including '800 BU' and 'INDICA'. To the right of the bottle are several dried cannabis buds, which are green and brown, resting on a dark, textured surface. The entire scene is set against a solid blue background.

News Science

Medical Cannabis Use Leads To Decrease In Opioid Abuse

The opioid crisis is hitting large cities and small towns indiscriminately and included in this is prescription drugs

By **Alexandra Hicks** - August 21, 2017  313  1

U.S.

CAN LEGAL MARIJUANA SOLVE THE OPIOID CRISIS? MEDICAL POT STATES SEE DECREASE IN PAINKILLER ABUSE

Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States

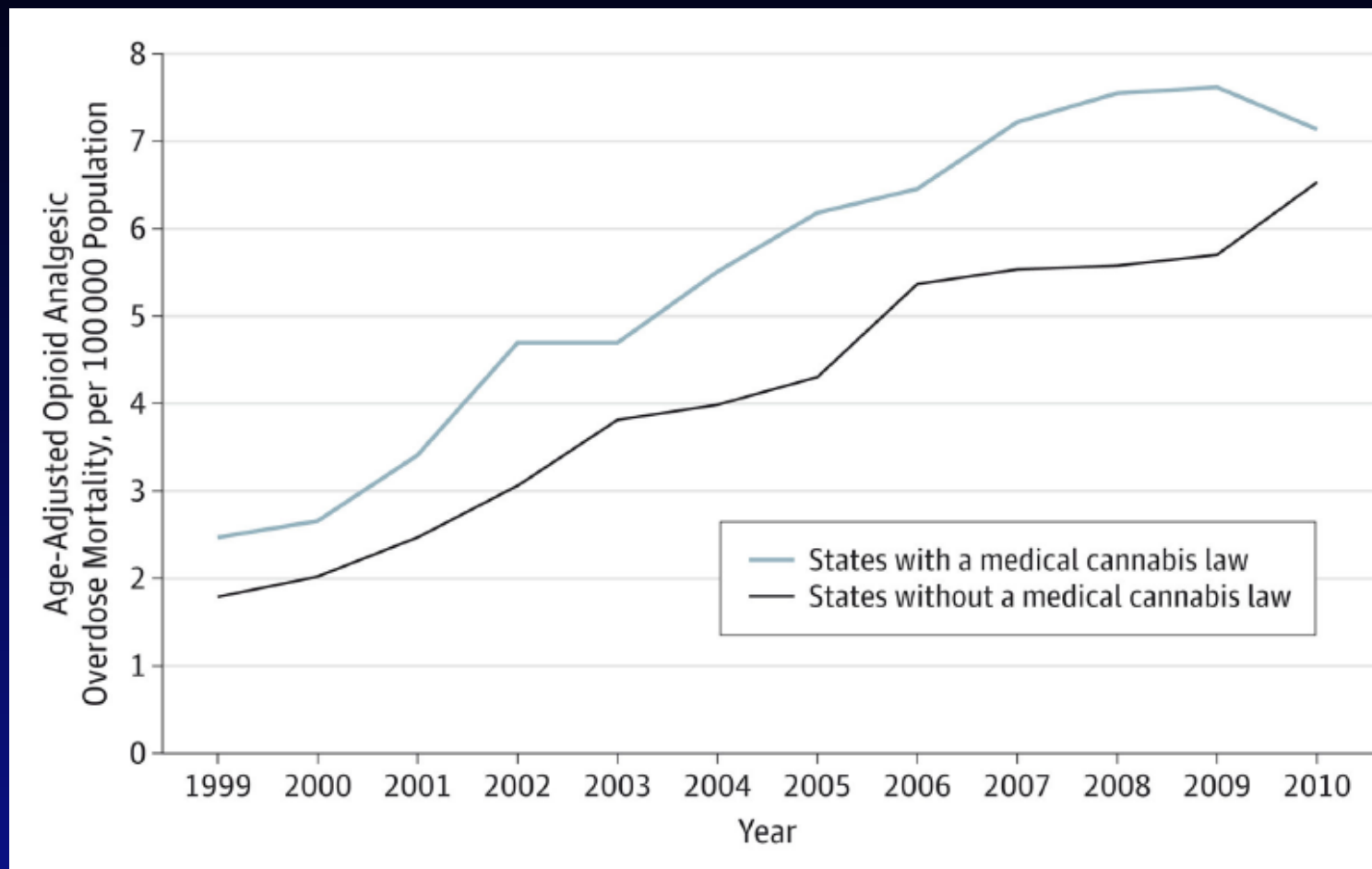
- **OBJECTIVE**

State medical cannabis laws related to opioid analgesic overdose mortality?

- **DESIGN, SETTING, AND PARTICIPANTS**

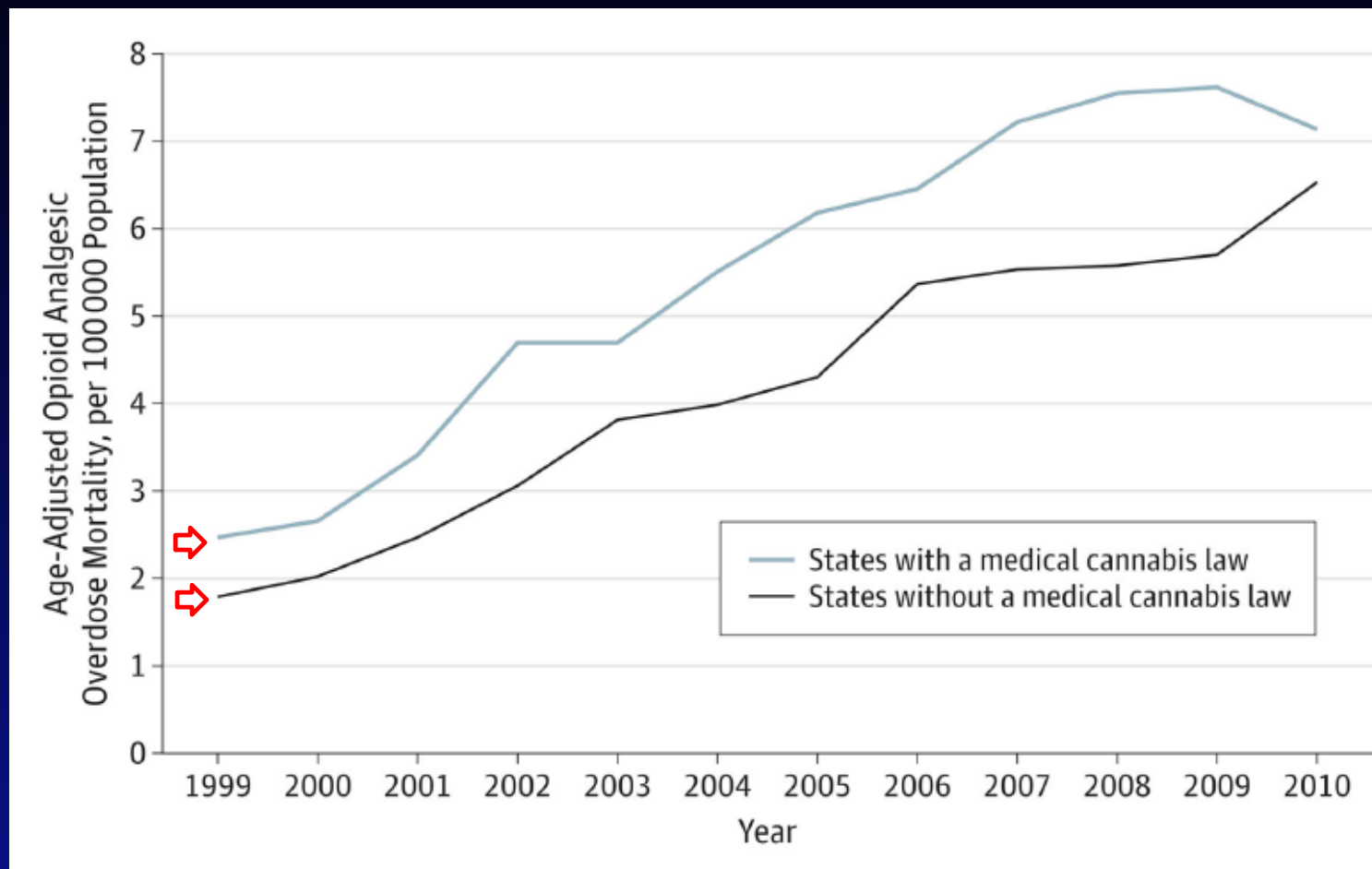
Time-series analysis of medical cannabis laws and state-level death certificate data in the United States from 1999 to 2010; all 50 states were included.

Deaths from Opioid Analgesic



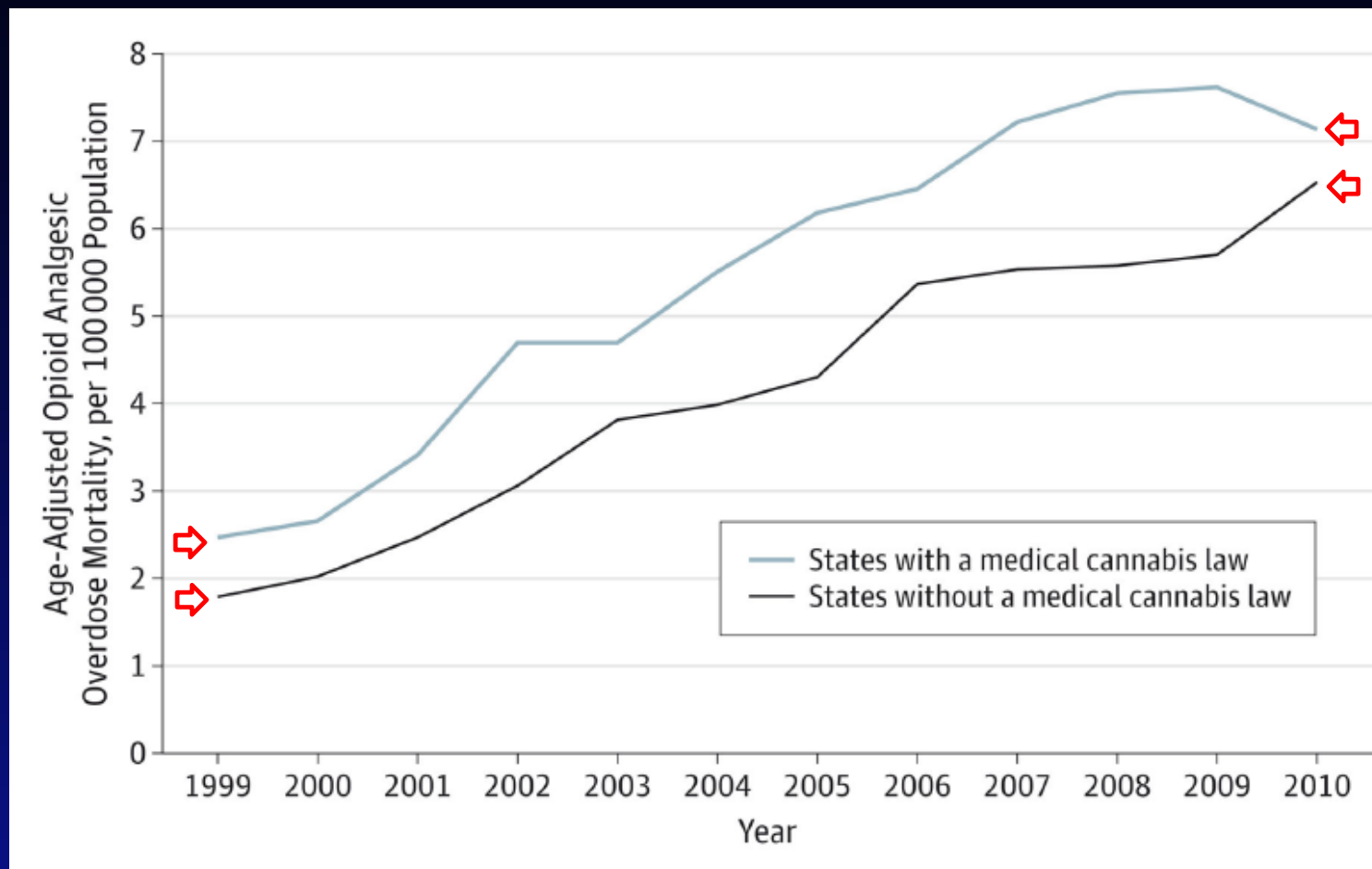
Bachhuber MA, et al. *JAMA Intern Med.* 2014; 174(10): 1668–1673

Deaths from Opioid Analgesic



Bachhuber MA, et al. *JAMA Intern Med.* 2014; 174(10): 1668–1673

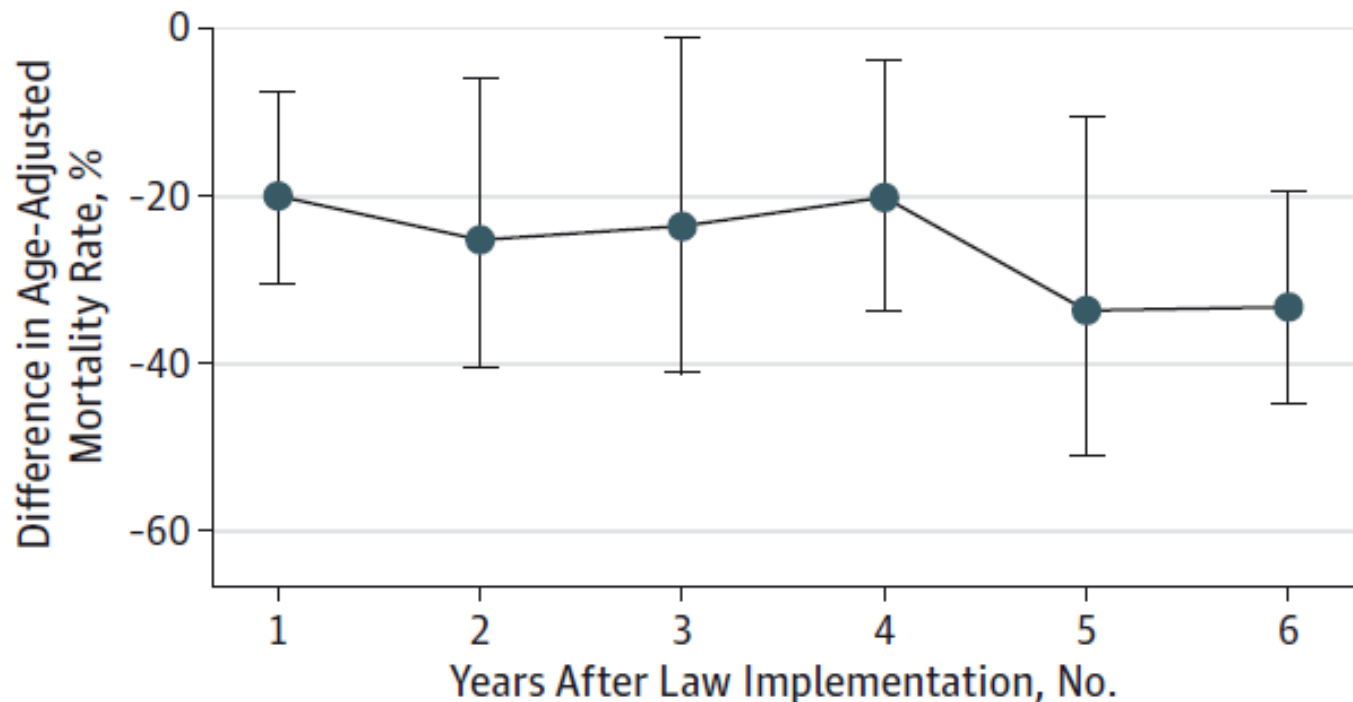
Deaths from Opioid Analgesic



Bachhuber MA, et al. *JAMA Intern Med.* 2014; 174(10): 1668–1673

Deaths from Opioid Analgesic

Figure 2. Association Between Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in Each Year After Implementation of Laws in the United States, 1999-2010



National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)

- Methods
 - Associations between cannabis use at wave 1 (2001–2002) and nonmedical prescription opioid use and prescription opioid use disorder at wave 2 (2004–2005) of NESARC.
 - Cannabis and prescription opioid use by structured interview.
 - Other covariates included age, sex, race/ethnicity, anxiety or mood disorders, family history of drug, alcohol, and behavioral problems, and nonmedical opioid use.

<https://doi.org/10.1176/appi.ajp.2017.17040413>

NESARC: Cannabis Use Associated with Increased Opioid Use

- Cannabis use at wave 1 associated with
 - Increased incident nonmedical prescription opioid use (odds ratio=**5.78**, 95% CI=4.23–7.90)
 - Increased opioid use disorder (odds ratio=**7.76**, 95% CI=4.95–12.16) at wave 2

NESARC: Cannabis Use Associated with Increased Opioid Use

- Cannabis use at wave 1 associated with
 - Increased incident nonmedical prescription opioid use (odds ratio=**5.78**, 95% CI=4.23–7.90)
 - Increased opioid use disorder (odds ratio=**7.76**, 95% CI=4.95–12.16) at wave 2
- Associations remained significant after adjustment for background characteristics.

NESARC: Cannabis Use Associated with Increased Opioid Use

- Cannabis use at wave 1 associated with
 - Increased incident nonmedical prescription opioid use (odds ratio=**5.78**, 95% CI=4.23–7.90)
 - Increased opioid use disorder (odds ratio=**7.76**, 95% CI=4.95–12.16) at wave 2
- Associations remained significant after adjustment for background characteristics.
- Among adults with pain at wave 1, cannabis use was also associated
 - Increased incident nonmedical opioid use (adjusted odds ratio=**2.99**, 95% CI=1.63–5.47) at wave 2

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- Dramatic changes in heroin distribution has rapidly changing the opioid abuse environment
 - Just call 1-800-Givememyfix
- “Squeezing the Balloon” may also affect non-opioids
- Cannabis may or may not affect opioid use
 - Studies intriguing, but stronger analytic designs needed

Questions?

Richard.Dart@rmpdc.org

