

Abuse Deterrent Formulations: Testing effectiveness  
from the benchtop to real world

# Do Medications with Abuse Deterrent Properties Work in the Real World?

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Judging by the size and frequency of the droppings, I'd say we've found the campaign trail.

# ADFs in the Real World

- Category 4
  - Epidemiological evaluation
  - Evaluates the performance of the product in the real world
  - No product has yet requested Category 4 designation
- Methods of deterring abuse
  - OxyContin (oxycodone) and Arymo (morphine) use a physical-chemical approach that produces a tablet that is hard to crush and forms a thick gel with water.
  - Embeda (morphine) uses naltrexone as an antagonist to reduce the desired drug effect if the product is crushed.
  - Xtampza (oxycodone) uses a proprietary waxy microsphere that is difficult to crush or solubilize.

# Hill Criteria: Do ADFs Work in the Real World?

- **Strength** (effect size)
- **Consistency** (reproducibility)
- **Specificity**
- **Temporality** (Effect has to occur after the cause)
- **Biological gradient**
- **Plausibility**
- **Coherence**
- **Experiment**
- **Analogy**
- **Confounding factors**



# Hill Criteria: *Plausibility*

- A plausible mechanism between cause and effect is helpful
  - but understanding of the mechanism is limited by current knowledge

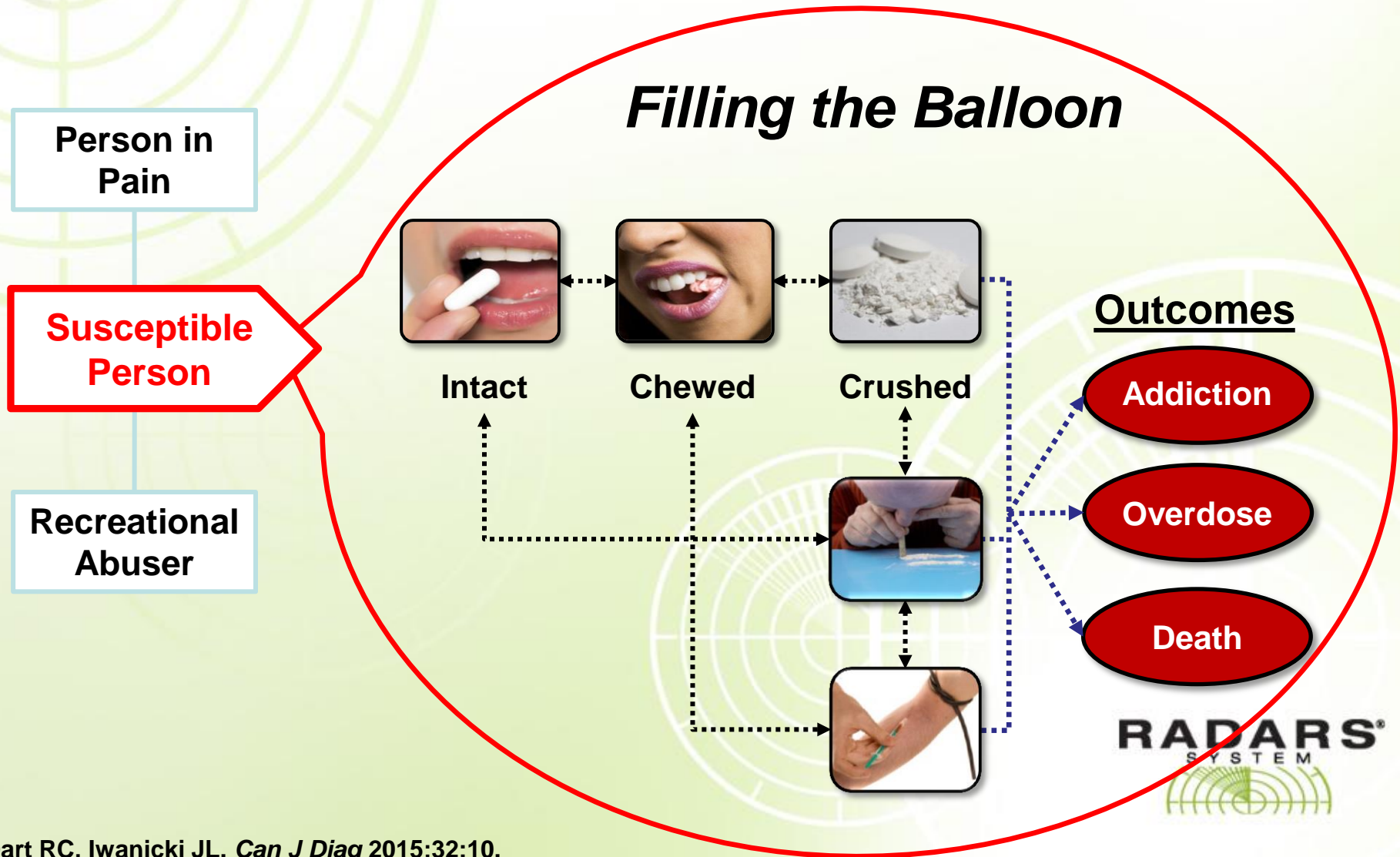


# Scientific Basis of Abuse-Deterrent Opioids

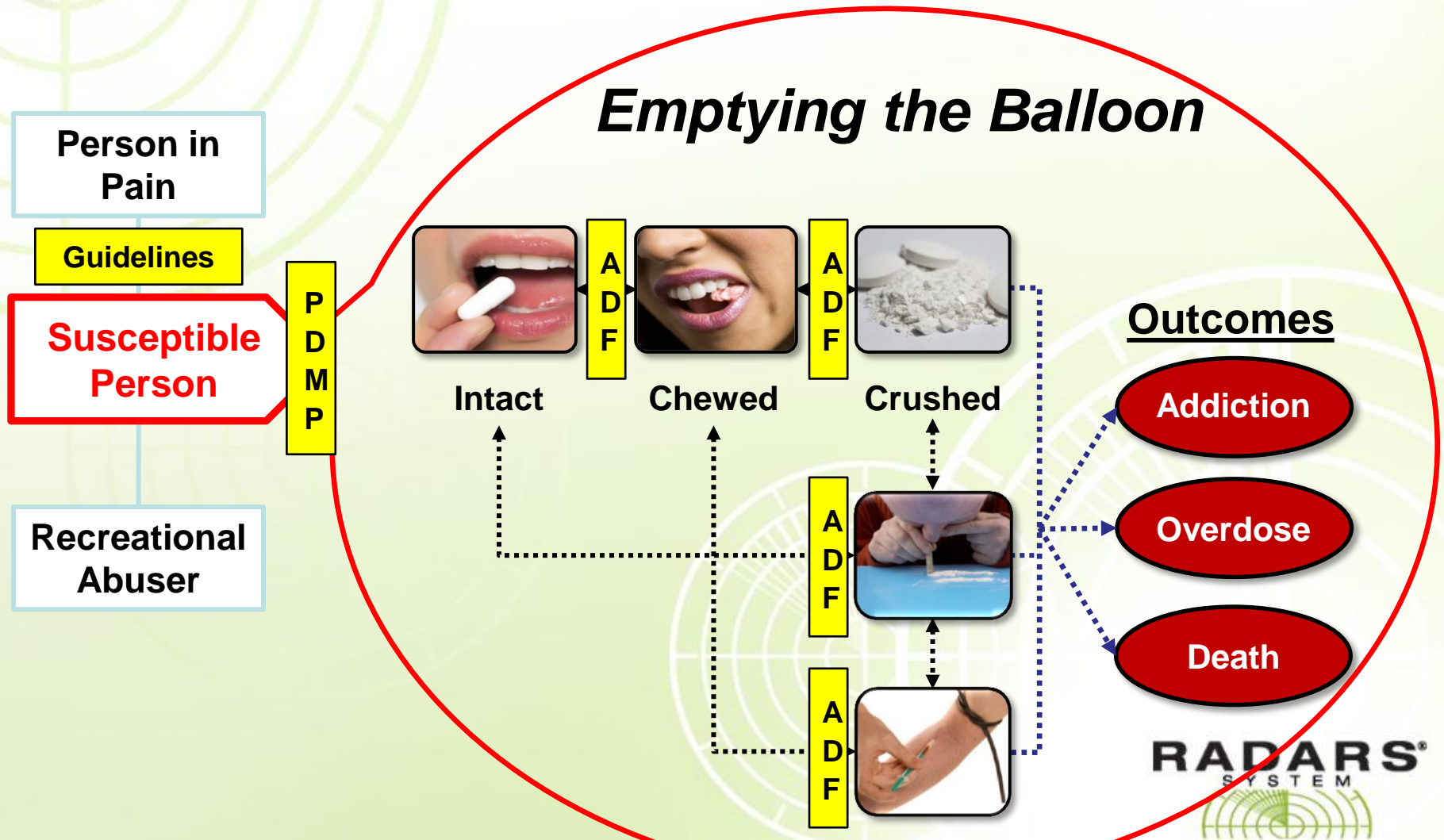
- Prescription drug abuse is like other drug abuse, except with an additional “route” of abuse:
  - Oral = intact + ***chewed or crushed***
  - Intranasal
  - Intravenous
- Importance of manipulating drug
  - Crucial transition
    - Changes perception of heroin use<sup>1</sup>
  - Risk of acute (overdose, death) and chronic events (addiction, infections, death) higher after intranasal or IV abuse than oral abuse



# Biological Plausibility



# Intervening in Prescription Drug Abuse





# Hill Criteria: *Temporality*

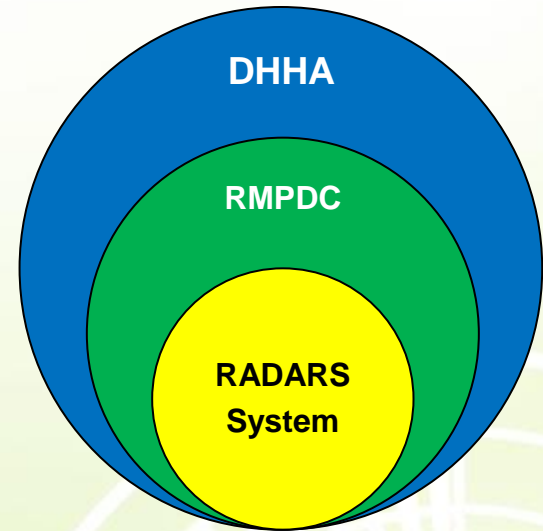
- Effect has to occur after the cause (including a delay, if expected)
- Minimal delay expected for oxycodone ER
  - All drug shipped after August 9, 2010 was reformulated version
  - Pharmacy turnover of opioids is rapid
- Only oxycodone ER has adequate data to evaluate effectiveness



# Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS System)

## History

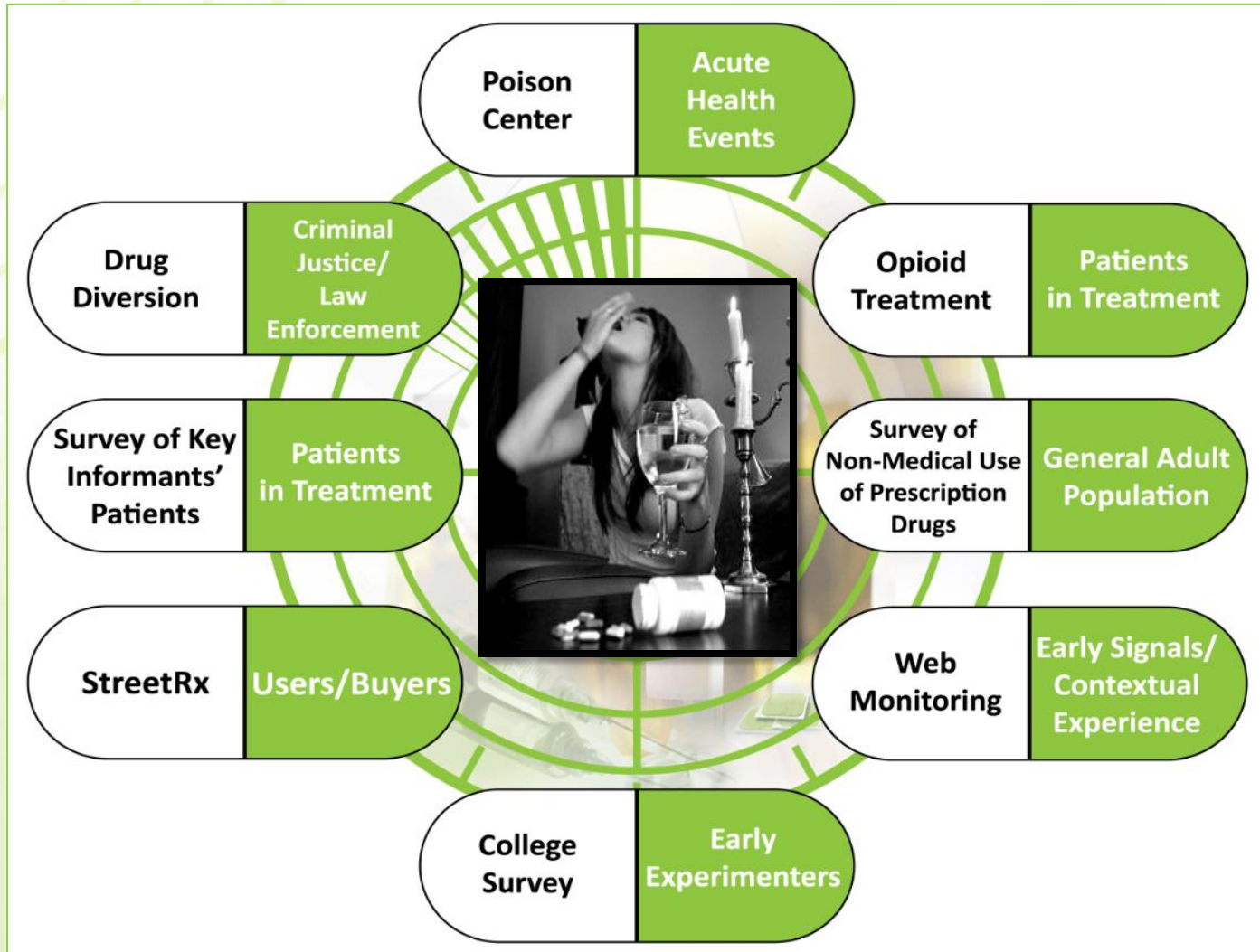
- 2002, launched by Purdue Pharma
- 2006, Denver Health and Hospital Authority takes independent ownership
  - Denver Public Hospital for 150 years
  - State sanctioned independent authority



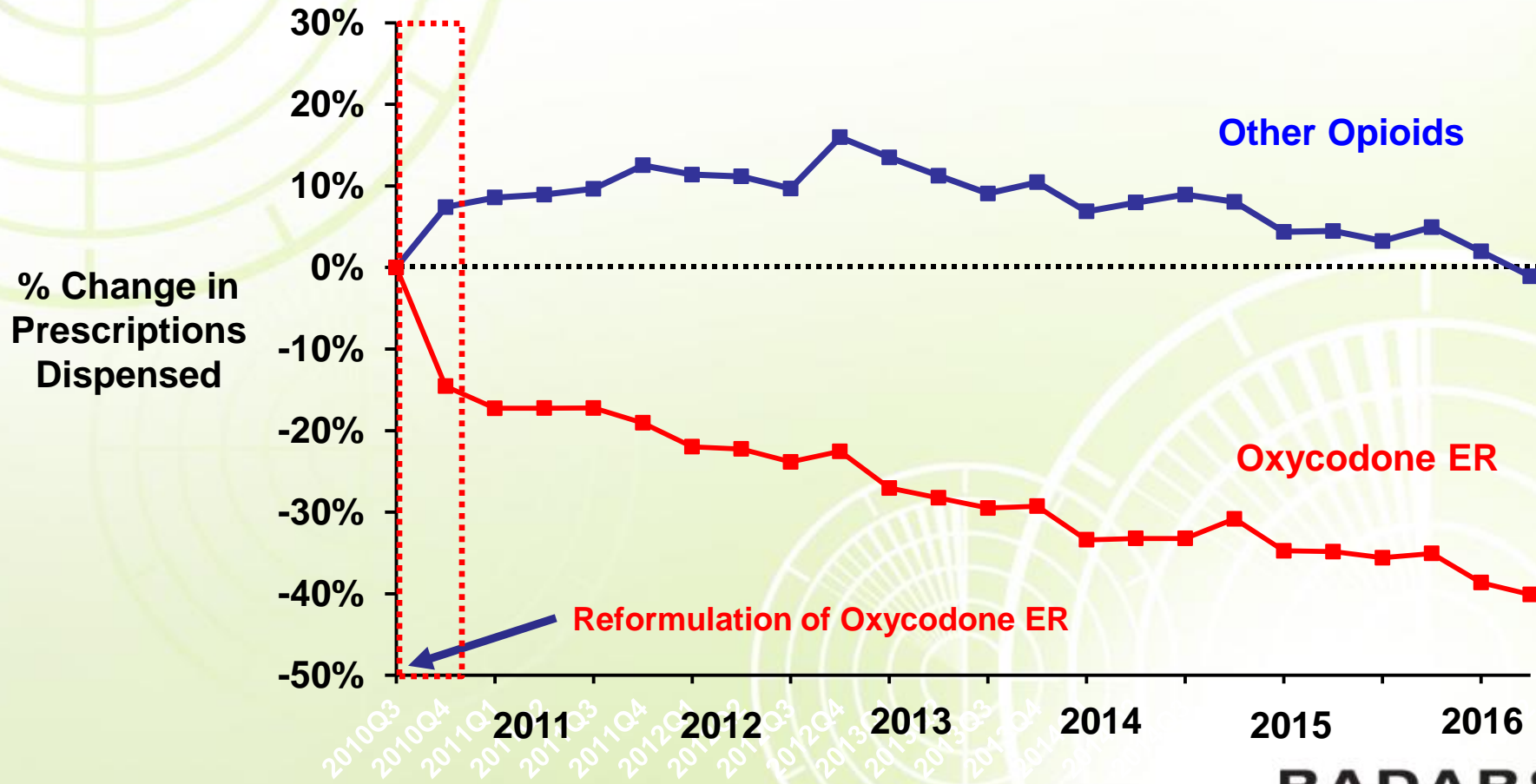
## Conflict of Interest Statement

- Most manufacturers of prescription opioids or stimulants subscribe to RADARS System.
- 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 other company.

# Mosaic Surveillance



# Temporality: Oxycodone ER Prescriptions Decreased Promptly After Reformulation

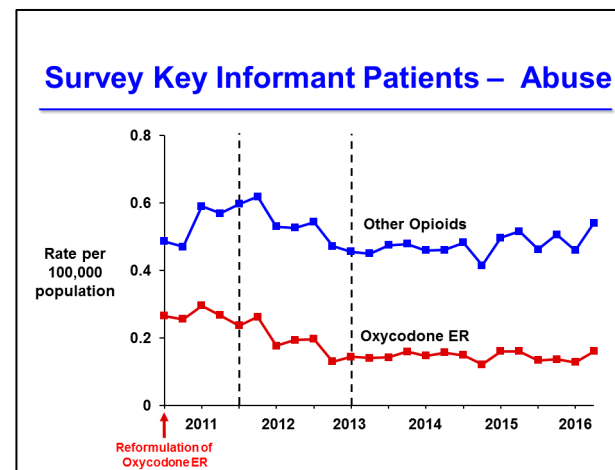
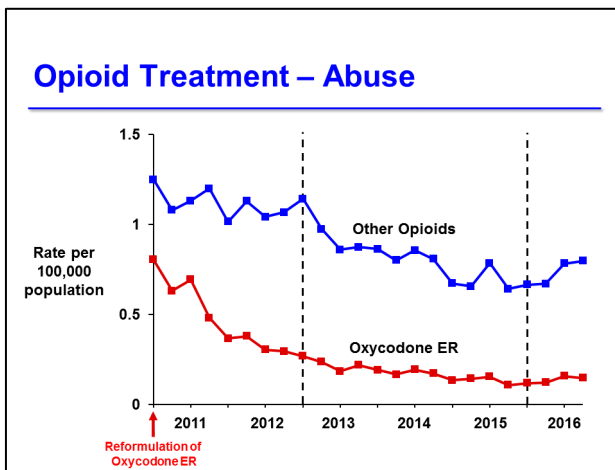
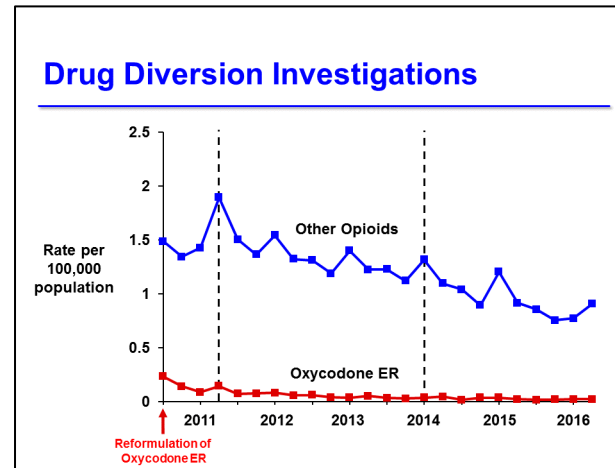
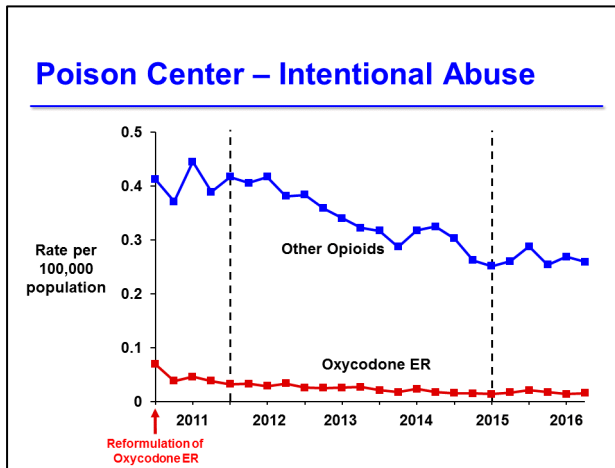


Other Opioids = Oral dosage forms of opioid analgesics: hydrocodone, hydromorphone, morphine, oxymorphone, tramadol, tapentadol, and IR oxycodone





# Temporality: Oxycodone ER Abuse and Diversion, Adjusted for Population, 2010–2016

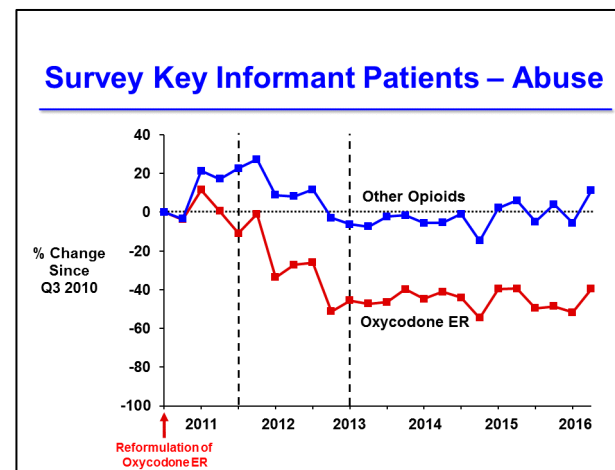
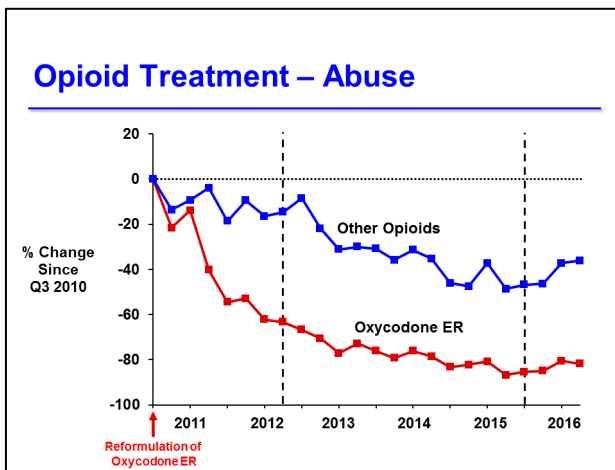
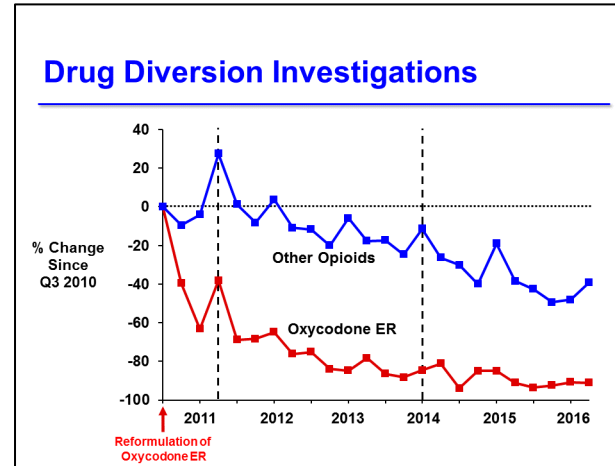
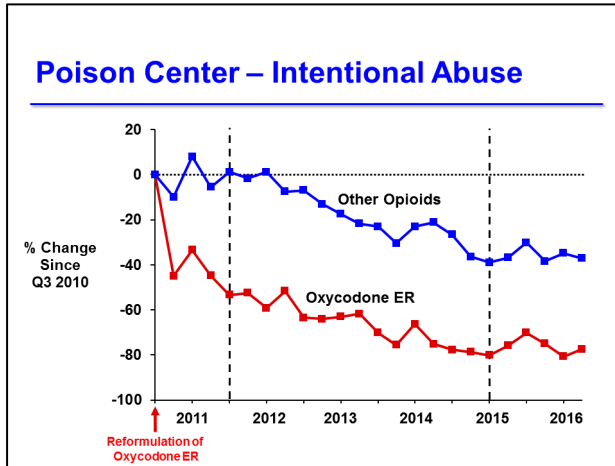


# Hill Criteria: *Effect Size*

- A small association does not mean that there is not a causal effect, though the larger the association, the more likely that it is causal.



# Effect Size: Oxycodone ER Abuse and Diversion, Adjusted for Population, 2010-2016

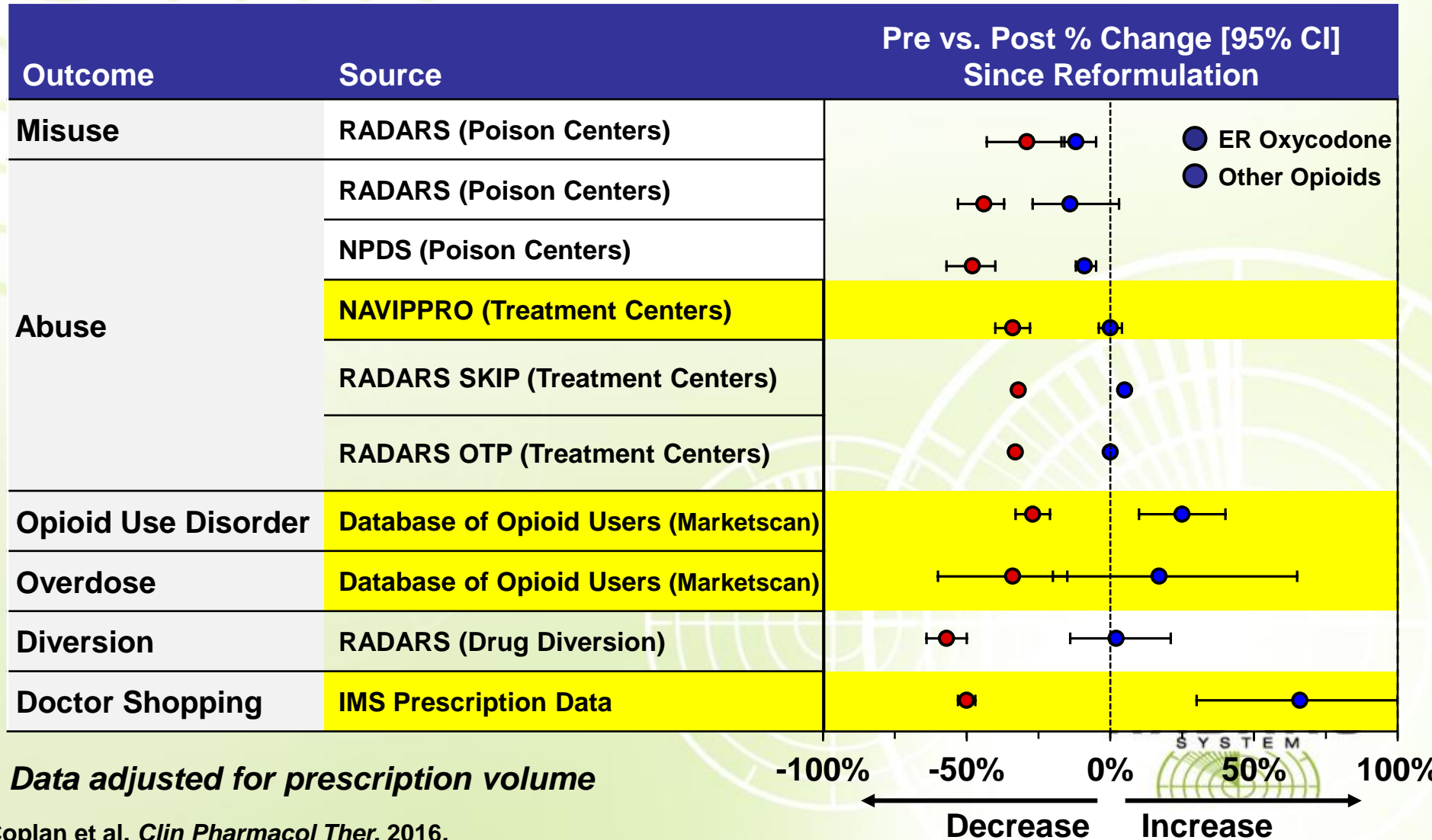


# Hill Criteria: *Consistency*

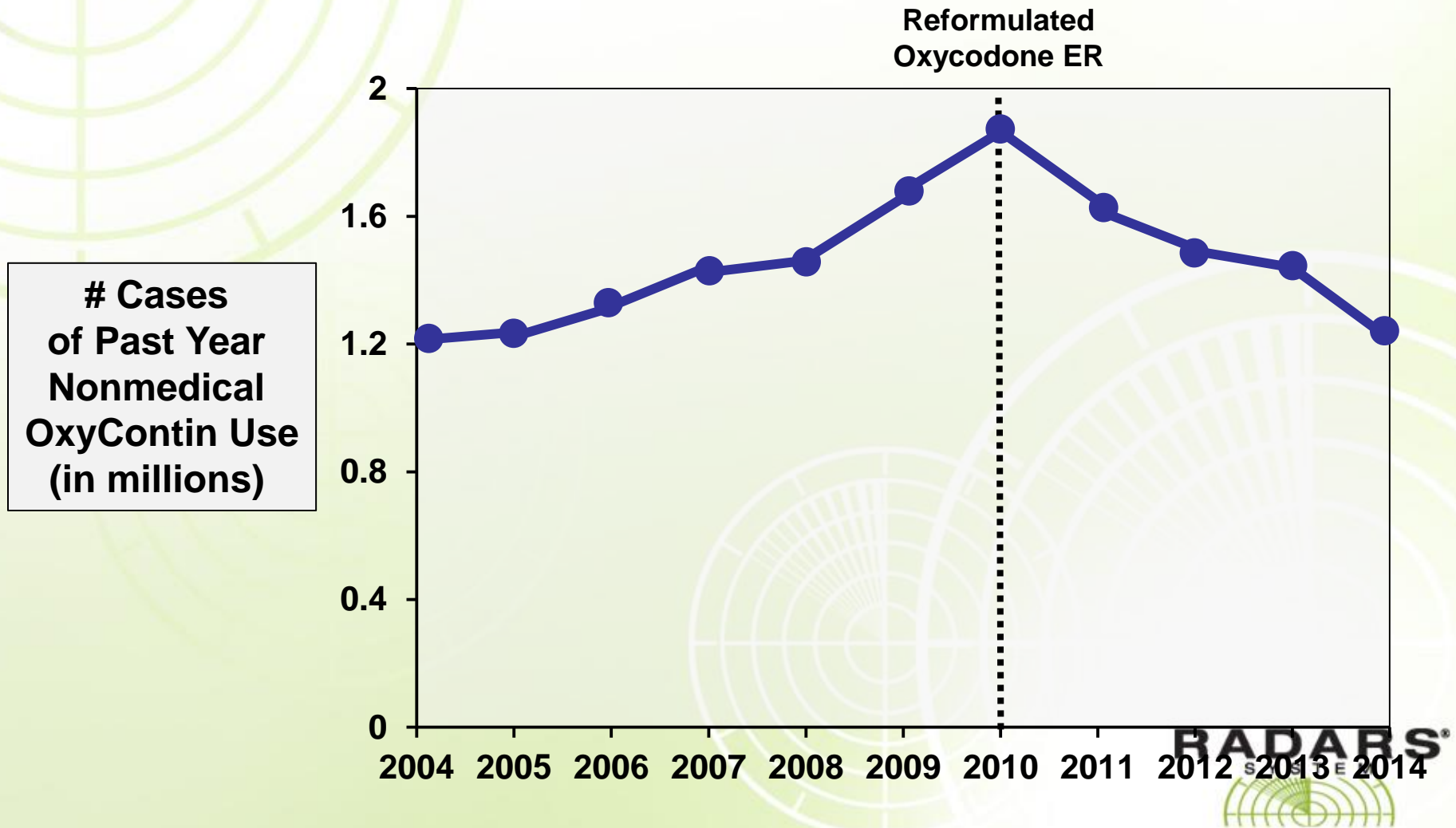
- Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect



# Consistency: Oxycodone ER Associated with Lower Rates Across Many Data Sources



# National Survey of Drug Use and Health, OxyContin Nonmedical Use





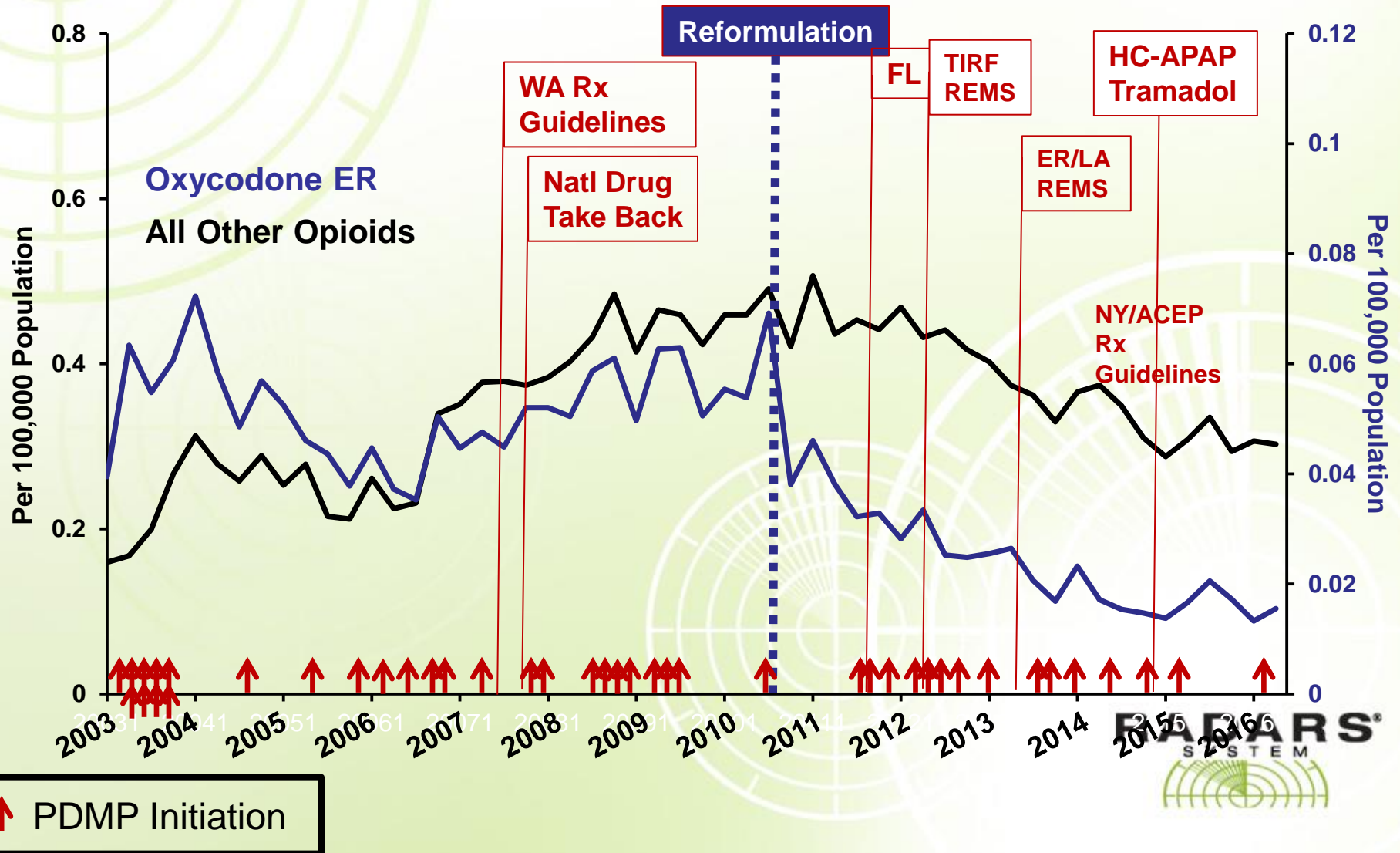
# Hill Criteria: *Specificity*

- The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship<sup>1</sup>
- Results specific to oxycodone ER compared to other analgesic opioids



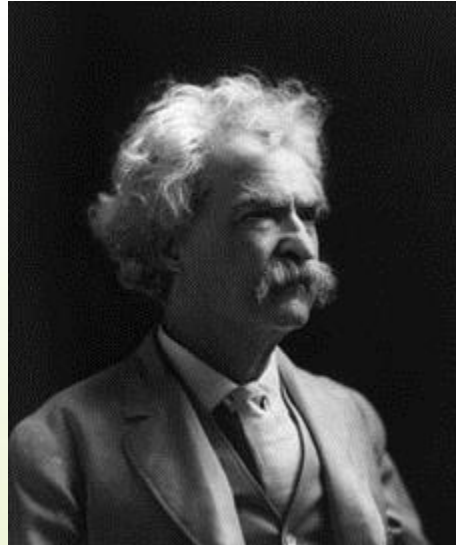


# Alternate Explanations Fail the Hill Temporality and Specificity Criteria



# What Will Capture Category 4?

March is one of the peculiarly dangerous months to speculate...



“The others are July, January, April, October, May, November, June, September, December, August and February.”

# FDA Guidance on ADFs

- Demonstrate abuse-deterrent properties “meaningfully ***deter abuse***, even if they do not fully prevent abuse”
  - Abuse: intentional, non-therapeutic use of a drug or substance, even once, to achieve a desirable psychological or physiological effect
- “Results in meaningful reductions in ***abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death*** in the post-approval setting”
- Add to the ***totality of evidence*** to support ADF claim



# Conclusions and Implications

- Specificity, consistency and effect size indicate that abuse deterrent opioids are likely to be effective in reducing abuse and its outcomes
- Similar effects for crush-resistant oxymorphone ER
- Widespread use would reduce prices and reduce the crucial transition from intact swallowing to crushing
- Education, training, and other interventions needed as well