

# Undertreated Pain is a Public Health Challenge

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## Relieving Pain in America: A Moral Imperative



INSTITUTE OF MEDICINE  
OF THE NATIONAL ACADEMIES

- More than 100 million adults in the United States suffer from common chronic pain conditions.<sup>1</sup>
- Chronic pain costs the American economy between \$560-\$635 billion in added healthcare expenditures and lost productivity.<sup>1</sup>

<sup>1</sup> Institute of Medicine 2011. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education and Research*, Washington, DC; The National Academies Press.



## Goals for Reformulation

1. Make OxyContin less abusable, less desirable for abusers, and decrease diversion events
2. Help prevent medical errors among patients and adverse effects from inadvertent exposures, eg family members

# FDA Approval Letter Requiring Post-Marketing Studies

## POSTMARKETING REQUIREMENTS UNDER 505(o)

As you were informed in our December 30, 2009, Complete Response Letter, FDA has determined that you are required to conduct post-marketing studies of OxyContin to assess the known serious risks of OxyContin, in particular, whether the changes made to the formulation that are the subject of this application and which are intended to deter misuse and abuse actually result in a decrease in the risks of misuse and abuse, and their consequences.

Specifically, we have determined that you are required, pursuant to section 505(o)(3) of the FDCA, **to conduct epidemiological studies to address whether the changes made to the OxyContin formulation that are the subject of this application result in a decrease in misuse and abuse, and their consequences: addiction, overdose, and death.**

We acknowledge receipt of your proposal that contains brief descriptions of possible post-marketing studies to fulfill this requirement. Because of design and methodology challenges, we continue to be concerned that the proposed studies will not successfully capture the necessary information that will allow us to assess the impact, if any, attributable to the change in the OxyContin formulation. Therefore, we will continue discussion of your post-marketing study proposals at an advisory committee meeting in the fall of 2010 on the design and methodology of the proposed studies.

# Purdue's Goals for Post-Marketing Epidemiology Studies

1. Meet the FDA post-marketing study requirement
2. Demonstrate reformulated OxyContin:
  - Is less abused and diverted than original OxyContin historically
  - Has fewer adverse consequences of abuse
  - Is associated with fewer medication errors among patients
  - Has fewer serious consequences from child or inadvertent exposures
3. Provide FDA convincing data and evidence on the positive public health impact of reformulation
4. Facilitate FDA's decision that products without abuse-deterrent/tamper-deterrent formulations are not appropriate substitutes
5. Demonstrate value to payers

# Epidemiologic studies – Post-Marketing Requirement

Studies	Routes	Usage/ demand	Addiction	Overdose	Death
NAVIPPRO - Substance Abuse Treatment Centers	✓	✓			
Kaiser Permanente – Overdoses among insured members				✓	✓
RADARS–Poison Centers	✓			✓	✓
National Surveys – RADARS College Survey, NSDUH	✓	✓	✓		
RADARS– Drug Diversion Program		✓			
Prescription Monitoring Programs - Doctor-shopping patients		✓			

## Epidemiologic studies - Supplemental

Studies	Routes	Usage/ demand	Addiction	Overdose	Death
Internet monitoring for tamper recipes and abuse	✓	✓			
Abuser cohort in Kentucky	✓	✓	✓		
IMS prescription data – national and “region” 0 TRx		✓			
National poison data system – Poison Centers	✓			✓	✓
Purdue Adverse Event data base				✓	✓
State Medical Examiners Database					✓

# Four Surveillance Systems of Abuse and Diversion

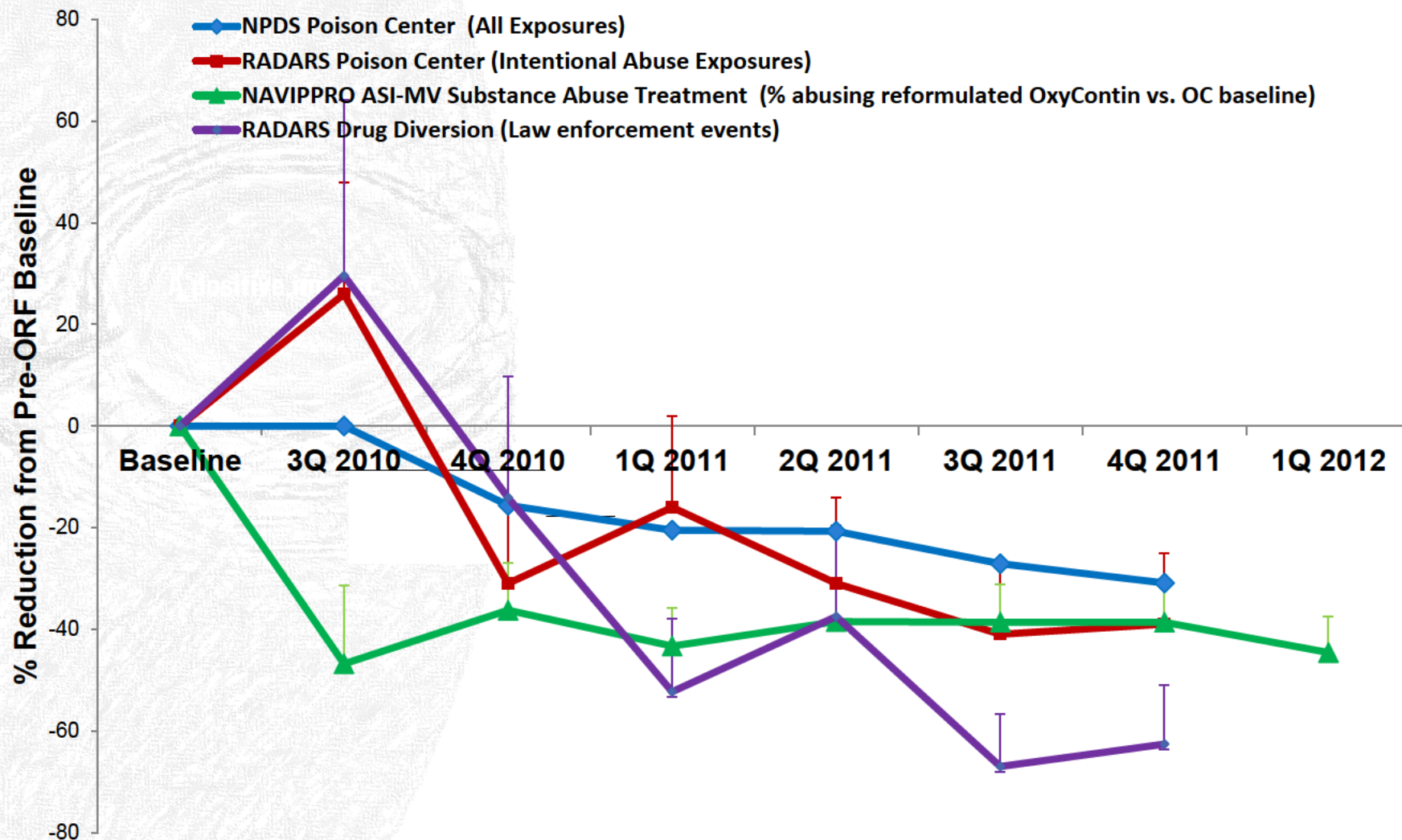
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1. Poison Center calls/reports: RADARS® System
  - 49 of 57 Poison Centers covering 86% of US population
2. Drug diversion/ law enforcement events: RADARS® System
  - Law enforcement staff (n=280) in all 50 states
3. Substance abuse treatment centers: NAVIPPRO ASI-MV
  - Individuals assessed in substance abuse treatment
  - Computerized version of Addiction Severity Index
4. Poison Center calls/reports: National Poison Data System
  - Covers all poison centers in US

# Four Drug Abuse/Diversion National Surveillance Systems

## % Reduction from Pre-Reformulation Baseline

(Baseline is 12 or 14 months prior to ORF introduction; Population rates shown)

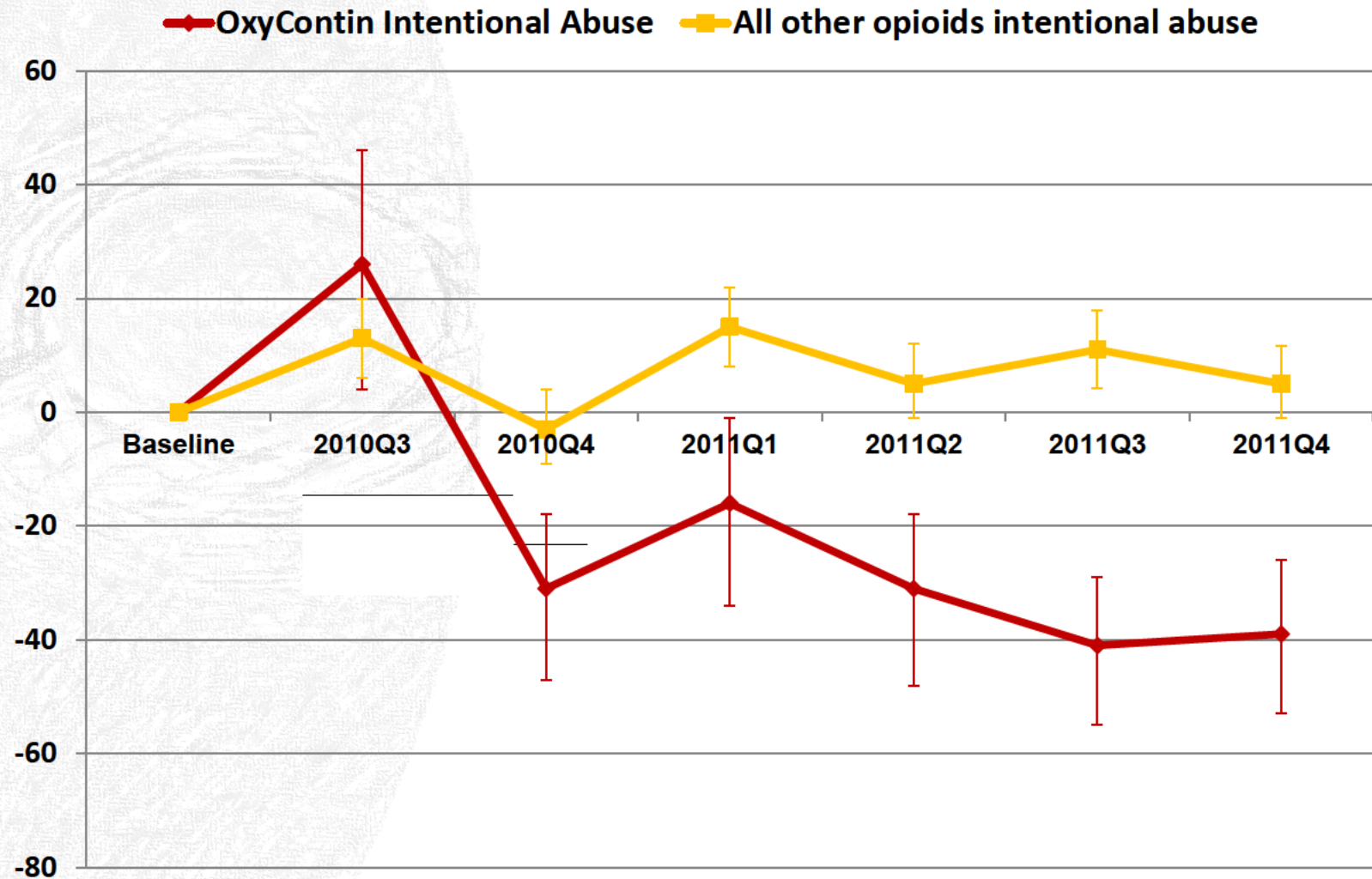


Note: Upper 95% confidence interval shown (lower bound not shown for simplicity of display)

# Poison Center Exposures in RADARS® Poison Center Program

## % Reduction from Pre-Reformulation Baseline in Intentional Abuse

(Baseline is 12 months prior to ORF introduction; Population-adjusted rates)

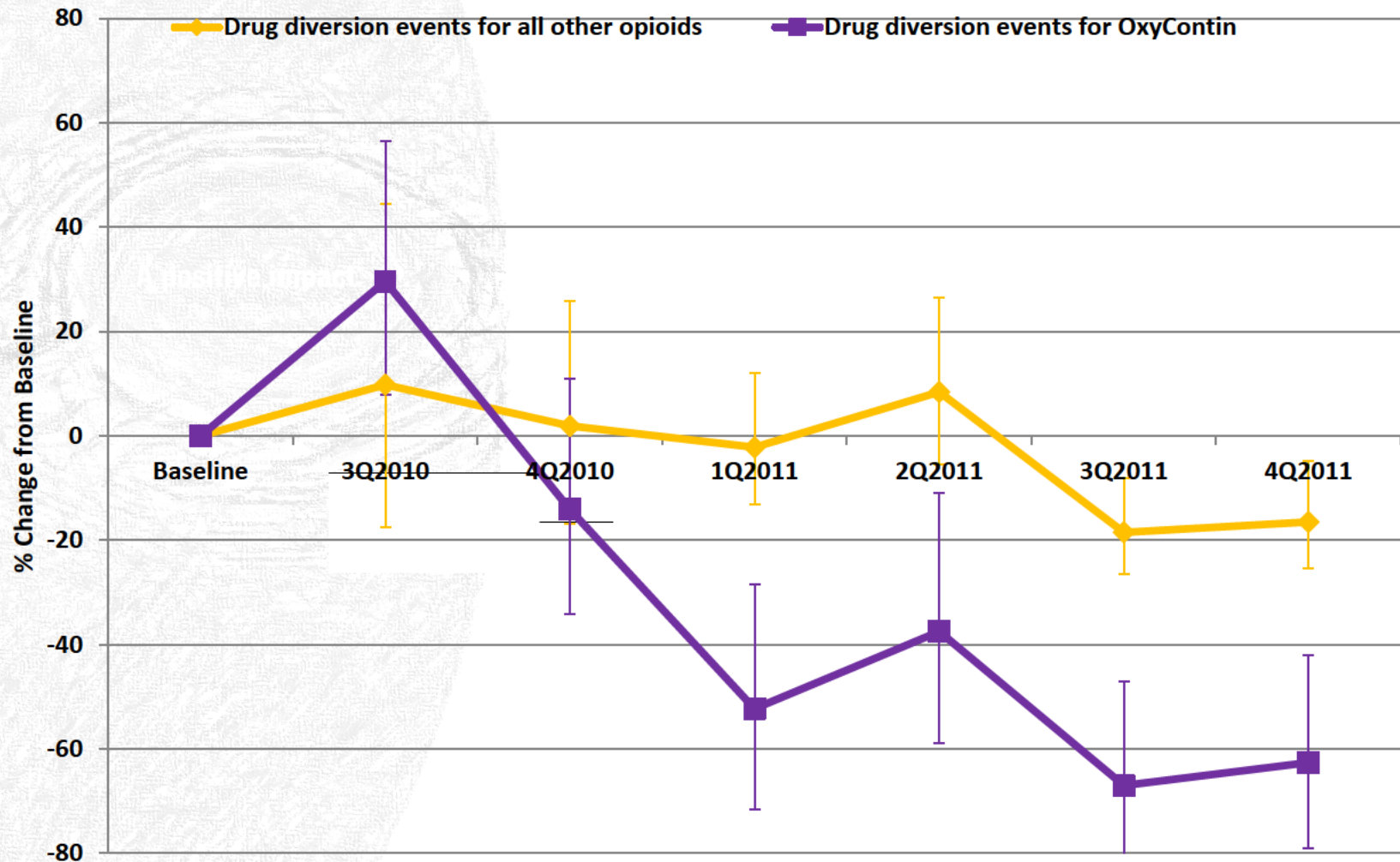


95% confidence intervals shown

# Drug Diversion/Law Enforcement Events in RADARS® Drug Diversion Program

## % Reduction from Pre-Reformulation Baseline

(Baseline is 12 months prior to ORF introduction; Population-adjusted rates)

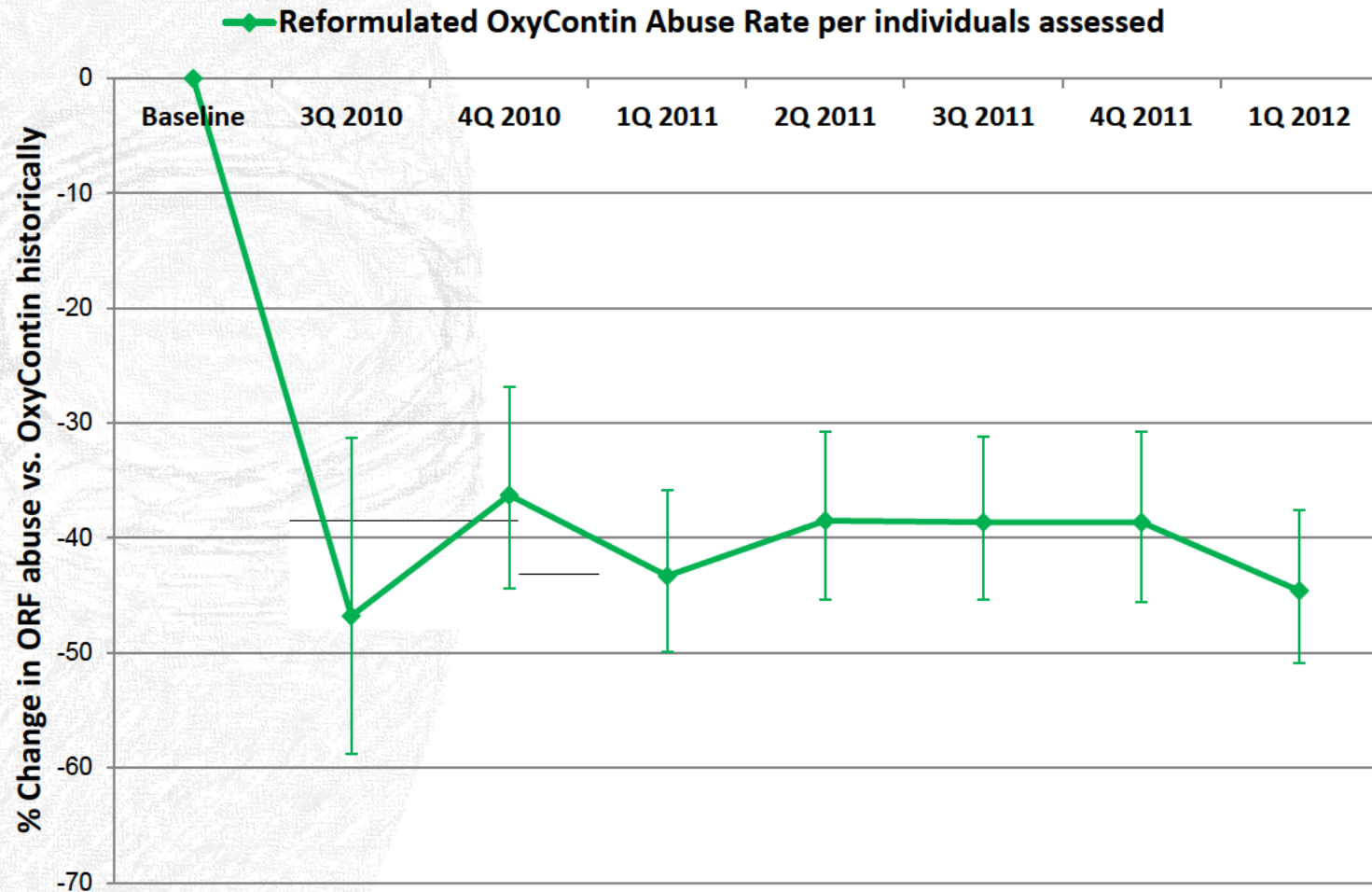


95% confidence intervals shown

# Abuse by Individuals Assessed for Substance Abuse Treatment

## % Reduction from Baseline in NAVIPPRO® System

(Baseline is 14 months prior to ORF introduction)



95% confidence intervals shown

## Abuse by Individuals Assessed for Substance Abuse Treatment OxyContin and Comparator Opioids (June 2009 to March 2012)

<b>Drug</b>	<b>Abusing* Before (%)</b> (July '09 to Aug '10)	<b>Abusing After (%)</b> (Aug '10 to Mar '12)	<b>Change in Abuse (%)</b>	<b>p-value for change</b>
<b>OxyContin</b>	<b>23.7</b>	<b>12.1</b>	<b>-49</b>	<b>&lt;.0001</b>
<b>- OxyContin orally</b>	<b>12.4</b>	<b>9.0</b>	<b>-27</b>	<b>&lt;.0001</b>
<b>- OxyContin by injecting, snorting or smoking</b>	<b>17.8</b>	<b>5.2</b>	<b>-71</b>	<b>&lt;.0001</b>
<b>ER oxymorphone</b>	<b>1.9</b>	<b>5.5</b>	<b>+196</b>	<b>&lt;.0001</b>
<b>ER morphine</b>	<b>5.4</b>	<b>4.7</b>	<b>-12</b>	<b>0.0209</b>

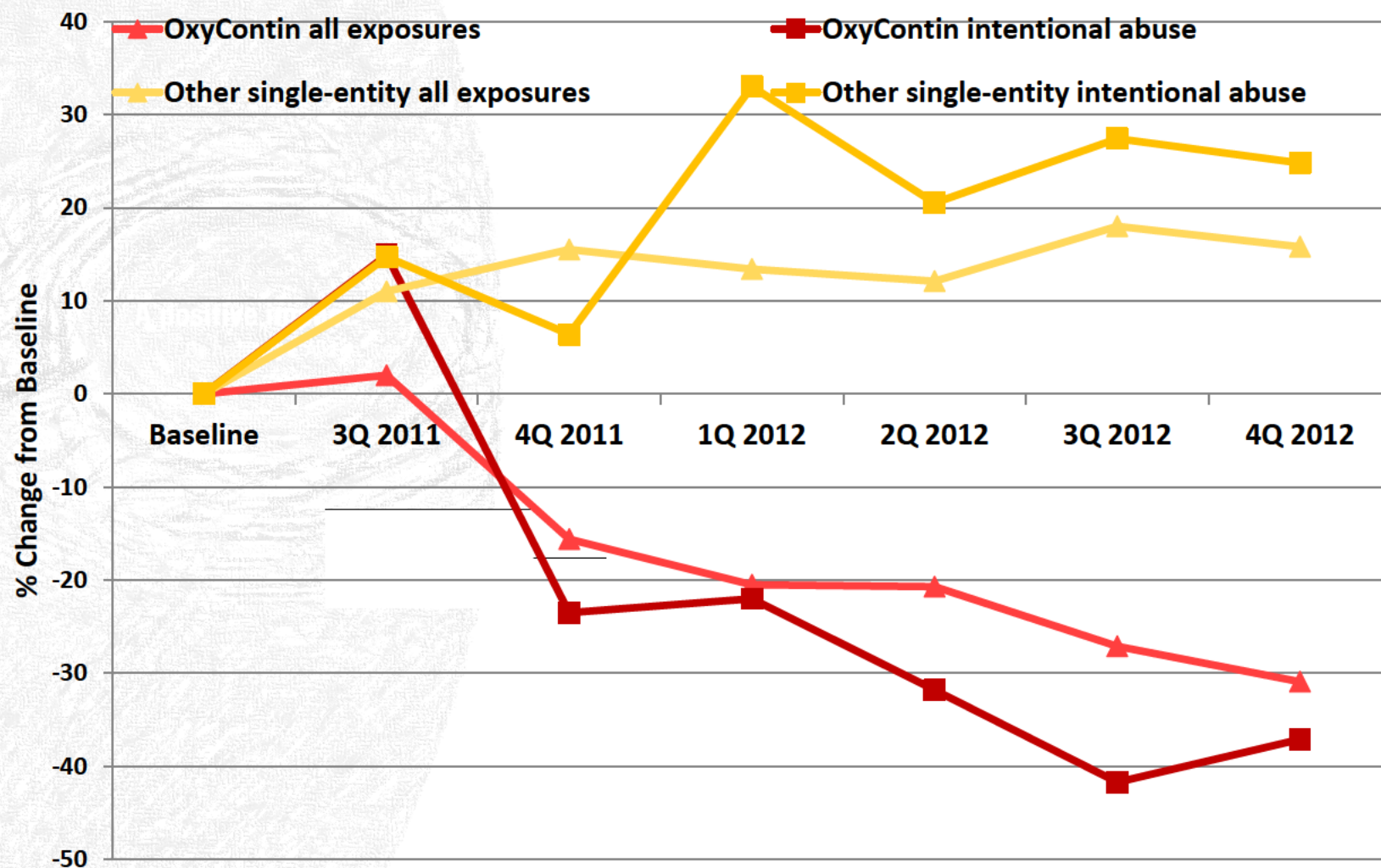
Source: Inflexxion NAVIPPRO® ASI-MV System

\* % individuals who abuse opioid among those who abused any prescription opioid in past 30 days

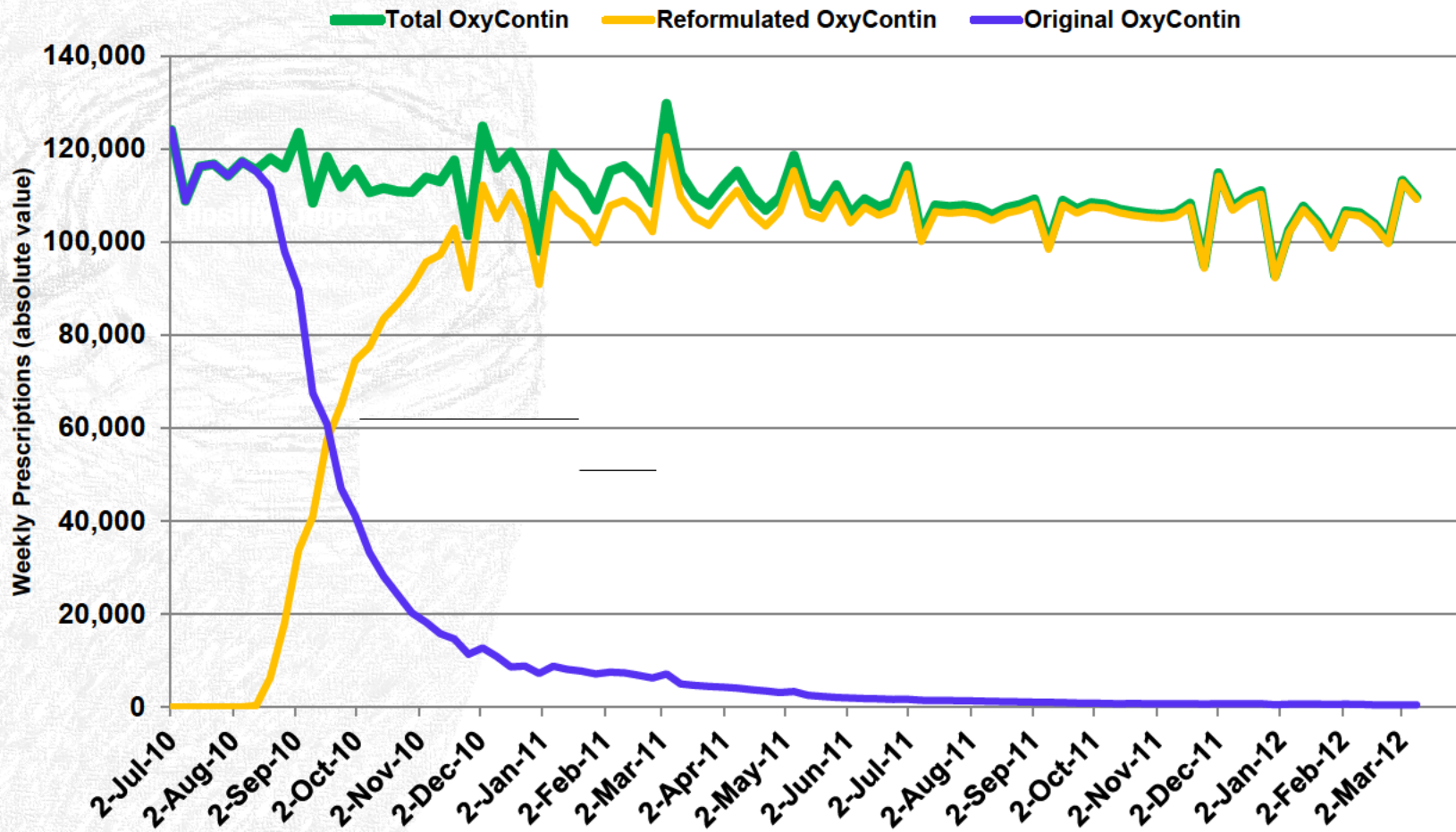
# Poison Center Exposures in National Poison Data System

## % Reduction from Baseline in All and Intentional Abuse

(Baseline is 12 months prior to ORF introduction; Population-adjusted rates)



# Prescription Numbers for OxyContin Over Time



## Internet chat room posts reporting abuse of reformulated OxyContin by injecting or snorting (August 9, 2010 and April 30, 2012)

- Reformulated OxyContin mentioned in 4,563 posts by 2,065 unique authors between August 9, 2010 and April 30 2011
- Of 4,563 posts, 558 discussed “recipes” to overcome reformulated OxyContin

Recipes to tamper with reformulation for abuse	Abuse by injecting	Abuse by snorting
- Crisp	11	9
- Crush/Shave, Heat, then Freeze	4	33
- Crush/Shave, Heat, and Dissolve/Soak	4	1
- Crush/shave	0	33
- Crush/Shave and Heat	1	9
- Crush/Shave, Add Chemicals, and Evaporate	0	10
- Crush/Shave, Heat, Dissolve/Soak, and Filter	3	0
- Take with acidic foods or beverages	0	1
- Other	7	13
<b>Total Abuse Reports</b>	<b>30</b>	<b>109</b>
<b>Total Posts</b>	<b>4563</b>	<b>4563</b>
<b>Percent of Posts Reporting Abuse</b>	<b>0.66%</b>	<b>2.39%</b>

# University of Kentucky Study of OxyContin Abusers

## 189 Abusers in Rural Eastern Kentucky

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Route of Abuse	Original OxyContin Before August 2010 (days/month)	Reformulated OxyContin After August 2010 (days/month)	IR Oxycodone Before August 2010 (days/month)	IR Oxycodone After August 2010 (days/month)
Injecting	8.5	0.01	5.7	10.5
Snorting	6.0	0.22	7.4	10.3
Swallow	0.06	1.5	1.4	3.7
Chew	0.17	0.19	0.48	1.2
All Routes	13.5	1.7	12.6	18.5

# Studies of Patient Therapeutic Error and Overdose, and Unintentional General Exposures

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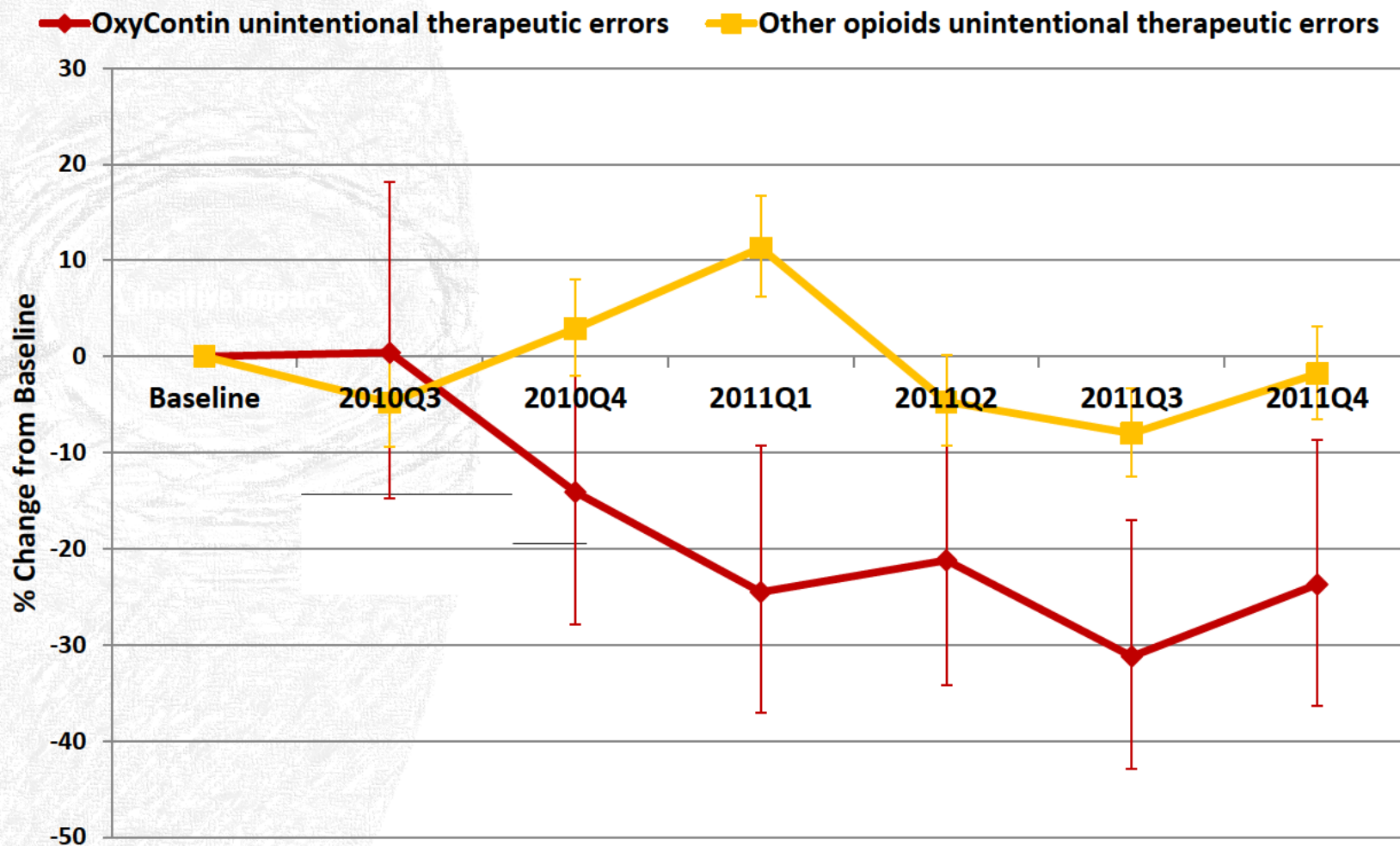
1. Poison Center calls/reports: RADARS® System
  - Unintentional therapeutic error exposures
    - deviation from proper therapeutic regimen resulting in wrong dose; incorrect route of administration, administration to wrong person, or administration of wrong substance<sup>†</sup>
  - Unintentional general exposures
    - All unintended exposures that are not specifically defined
    - Exposures causing death in children ≤5 years mostly coded as “Unintentional-General”
2. Poison Center calls/reports: National Poison Data System
  - Therapeutic errors, Unintentional general exposures
3. Kaiser Permanente Study of opioid poisoning overdoses
  - Rates among people prescribed an opioid
  - Kaiser Northern California and Kaiser Northwest(Oregon)

<sup>†</sup> Bronstein AL, et al. Clinical Toxicology (2011), **49**, 910–941.

# Therapeutic Errors among Patients in RADARS® Poison Center Program

## % Reduction from Baseline

(Baseline is 12 months prior to ORF introduction; Population-adjusted rates)



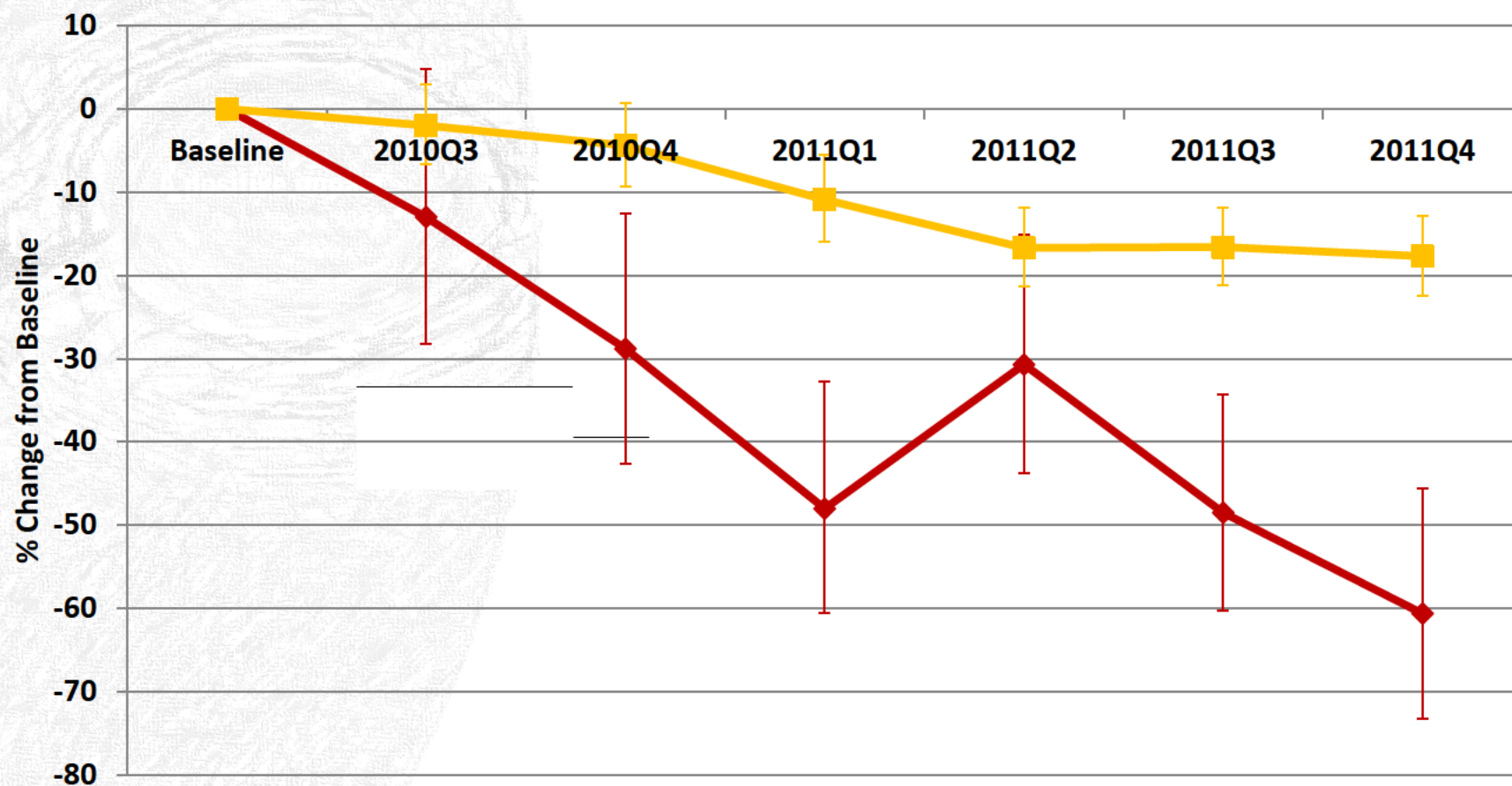
95% confidence intervals shown

# Unintentional General Exposures in RADARS® Poison Center Program

## % Reduction from Baseline

(Baseline is 12 months prior to ORF introduction; Population-adjusted rates)

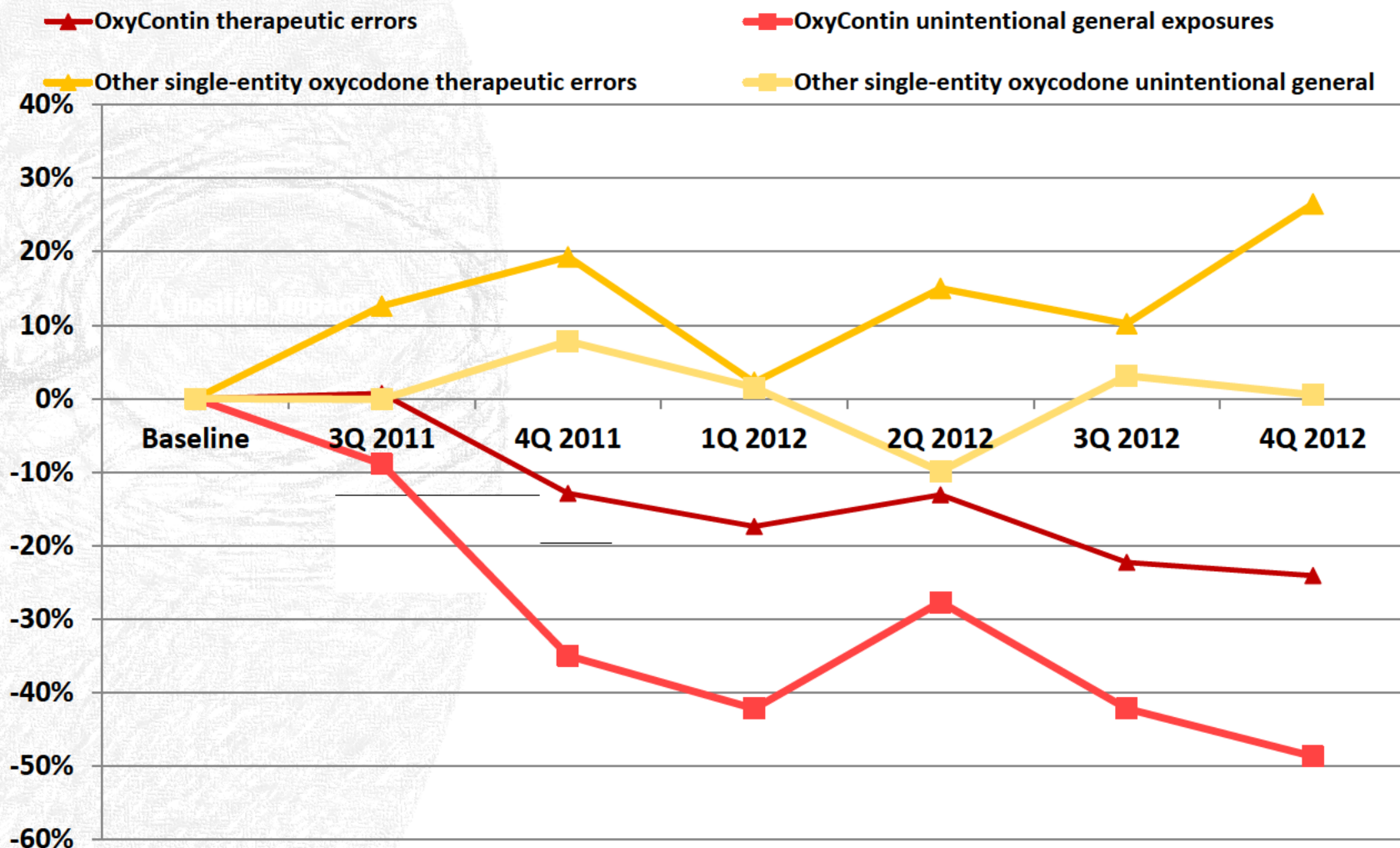
—●— OxyContin unintentional general exposures —■— Other prescription opioids unintentional general exposures



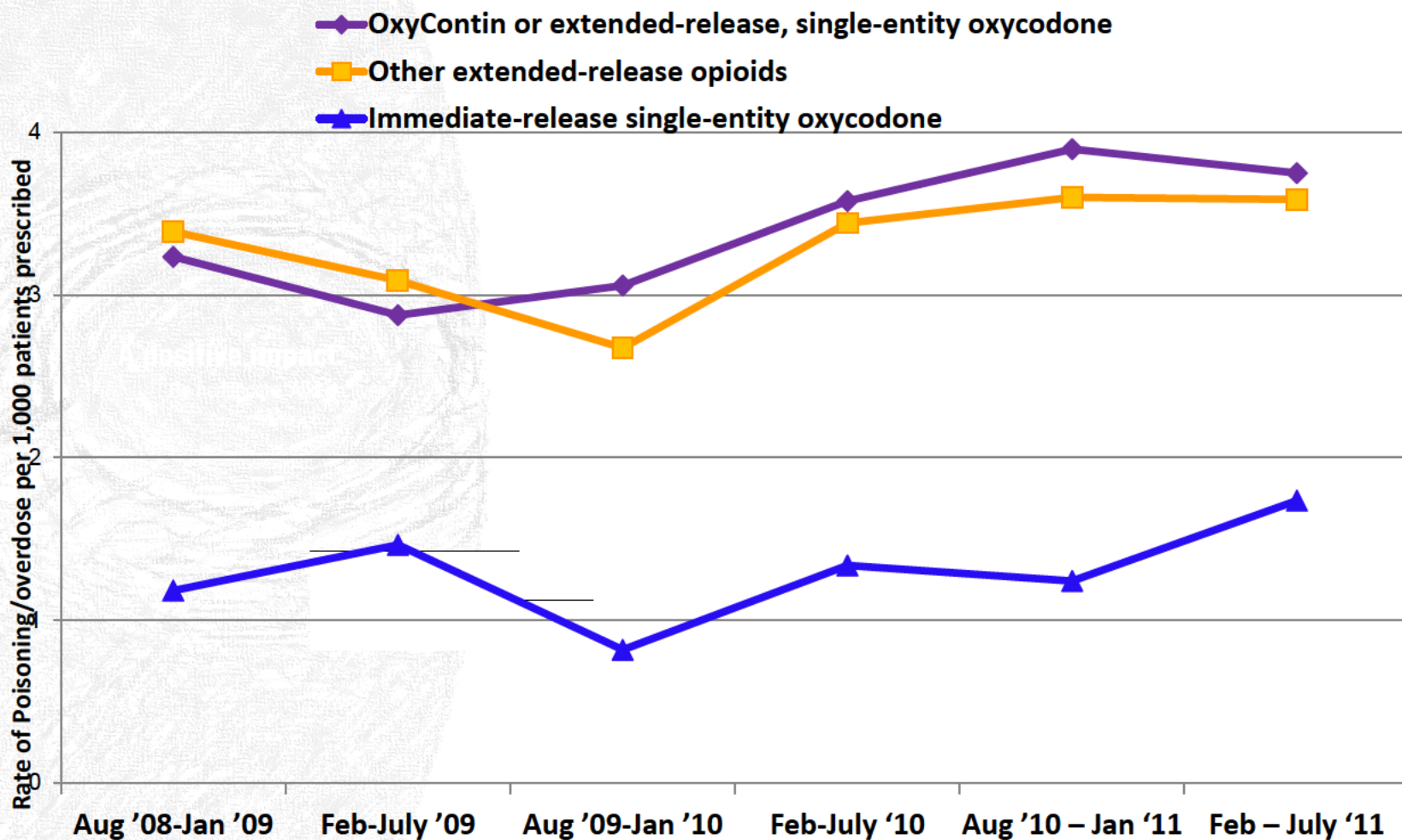
95% confidence intervals shown

# Therapeutic Errors and Unintentional General Exposures in National Poison Data System: % Reduction from Baseline

(Baseline is 12 months prior to ORF introduction; Population-adjusted rates)



## Opioid Poisoning/Overdose in Kaiser Permanente Patients Rate per 1,000 Patients Prescribed Opioids Per Six Month Period



Source: Kaiser Permanente Northern California and Northwest (Oregon) regions  
Opioid poisoning events identified by ICD-9 code 965.0\*