OPANA® ER (oxymorphone HCl) Benefit-Risk

March 13, 2017
Anesthetic & Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee
**Introduction**

Harris Rotman, PhD  
Vice President, US Regulatory Affairs  
Endo Pharmaceuticals Inc.
Reformulated OPCA ER

- 2006 Original OPCA ER approved
- 2011 Reformulated OPCA ER approved
  - Only Reformulated OPCA ER available
  - Endo not currently seeking abuse-deterrent labeling
OPANA ER: Important Treatment Option for Chronic Pain Patients (Intended Use)

- Indication: Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
- Opioids are an important option
  - Patients have unique situations
  - Physicians need multiple opioid options
Opioid Abuse Evaluated Using Epidemiology Data

- Referred to as “Category 4” in FDA guidance finalized in 2015
- There are challenges inherent with evaluating abuse epidemiology data
  - Often conflicting analyses
Observational Epidemiology Studies Use a Pre-Post Design

<table>
<thead>
<tr>
<th>Pre-Reformulation (3-year)</th>
<th>Market Transition</th>
<th>Post-Reformulation (3-year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 2009</td>
<td>Q2 2009</td>
<td>Q1 2012</td>
</tr>
<tr>
<td>Q3 2009</td>
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<td>Q2 2013</td>
</tr>
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</tr>
<tr>
<td>Q3 2010</td>
<td>Q4 2010</td>
<td>Q4 2015</td>
</tr>
<tr>
<td>Q1 2011</td>
<td>Q2 2011</td>
<td>Q1 2016</td>
</tr>
<tr>
<td>Q3 2011</td>
<td>Q4 2011</td>
<td>Q2 2016</td>
</tr>
</tbody>
</table>

Reformulated OPA NA ER

Year/Quarter
OPANA ER Abuse Epidemiology Data Interpretation

- After reformulation of OPANA ER
  - Benefit-risk profile remains positive
  - Intranasal abuse lower
  - IV abuse increased, then stabilized in TN; IV abuse stable or decreasing in other states
- Data limited by collection methodology
- Survey population may not represent those that choose to abuse opioids
- Provide insight for potential areas of investigation
OPANA ER Reformulated to Maintain ER Properties and Resist Crushing

- Polyethylene Oxide (PEO) formulation
- Extremely hard tablet resistant to crushing
  - Barrier to efforts to reduce particle size
- Gelling in aqueous solution
- PEO used for several ADF products
  - Approved: OxyContin®, Arymo™ ER, Hysingla® ER
OPANA ER: ADF Labeling Timeline

2010: Endo previously sought ADF labeling in the new formulation NDA

2013: Endo submitted sNDA to obtain ADF labeling; FDA requested an intranasal abuse study

2016: Endo submitted the intranasal abuse study and interim Category 4 studies requesting ADF labeling, but there was missing information in our Category 4 data

2016: Endo withdrew the submission, as final Category 4 study results imminent
Endo Completed Category 1-3 Studies, and Post-Marketing Category 4 Studies

**Category 1**
Lab-based *in vitro*
Manipulation & Extraction Studies

**Category 2**
Pharmacokinetic Clinical Trial

**Category 3**
Human Abuse Potential Clinical Trial

**Category 4**
Postmarketing Confirmation of Reduction in Abuse

- Physical & Chemical Manipulation Studies
- Route Specific Studies
- Study 114 *(Manipulated Intranasal)*
- NAVIPPRO®
- RADARS® Poison Center Program
- RADARS® Drug Diversion Program

Hypothesis Generating

Real World Evidence

Two Events Confound Epidemiology Interpretations for OPANA ER

1. Introduction of an abuse deterrent formulation of OxyContin® while original OPANA ER was on the market

2. Launch of generic oxymorphone products immediately before and after the introduction of Reformulated OPANA ER
Changing Environment Affected OPANA ER Abuse Patterns

<table>
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<th>Pre-Reformulation (3-year)</th>
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<th>Post-Reformulation (3-year)</th>
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</thead>
<tbody>
<tr>
<td>Generic Oxymorphone ER (crushable) (7.5 &amp; 15 mg)</td>
<td>Reformulated OPANA ER</td>
<td>Generic Oxymorphone ER (crushable) (5, 10, 20, 30 &amp; 40 mg)</td>
</tr>
<tr>
<td>Original OPANA ER Discontinued (7.5 &amp; 15 mg)</td>
<td>Original OPANA ER Discontinued (5, 10, 20, 30 &amp; 40 mg)</td>
<td></td>
</tr>
<tr>
<td>Reformulated OxyContin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Year/Quarter:
- Q1 2009
- Q2 2010
- Q3 2010
- Q4 2010
- Q1 2011
- Q2 2011
- Q3 2011
- Q4 2011
- Q1 2012
- Q2 2012
- Q3 2012
- Q4 2012
- Q1 2013
- Q2 2013
- Q3 2013
- Q4 2013
- Q1 2014
- Q2 2014
- Q3 2014
- Q4 2014
- Q1 2015
- Q2 2015
- Q3 2015
- Q4 2015
- Q1 2016
- Q2 2016
OPANA ER Benefit-Risk Remains Favorable Following Reformulation

- Discuss benefits and safety of OPANA ER when used as intended in chronic pain patients
  - Oxymorphone has characteristics making it a meaningful choice for chronic pain
- Abuse patterns changed prior to and following the introduction of Reformulated OPANA ER, but cause-effect cannot be determined
- Overall positive benefit-risk profile unchanged
<table>
<thead>
<tr>
<th>Agenda</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain, Opioids and Personalized Medicine</td>
<td>Perry Fine, MD</td>
</tr>
<tr>
<td></td>
<td>Professor of Anesthesiology</td>
</tr>
<tr>
<td></td>
<td>Pain Research Center, School of Medicine</td>
</tr>
<tr>
<td></td>
<td>University of Utah</td>
</tr>
<tr>
<td>Category 1-3 Studies</td>
<td>Harris Rotman, PhD</td>
</tr>
<tr>
<td></td>
<td>Vice President, US Regulatory Affairs</td>
</tr>
<tr>
<td></td>
<td>Endo</td>
</tr>
<tr>
<td>Category 4: Post-marketing Epidemiology Studies</td>
<td>Neil Shusterman, MD</td>
</tr>
<tr>
<td></td>
<td>Chief Medical Officer</td>
</tr>
<tr>
<td></td>
<td>Endo</td>
</tr>
<tr>
<td>Understanding Complicated Observational Data</td>
<td>Alexander Walker, MD, DrPH</td>
</tr>
<tr>
<td></td>
<td>Former Chair of Department of Epidemiology</td>
</tr>
<tr>
<td></td>
<td>Harvard T.C. Chan School of Public Health</td>
</tr>
<tr>
<td>Benefit-Risk Assessment</td>
<td>Richard Dart, MD, PhD</td>
</tr>
<tr>
<td></td>
<td>Director, Rocky Mountain Poison &amp; Drug Center</td>
</tr>
<tr>
<td></td>
<td>Executive Director, RADARS® System</td>
</tr>
</tbody>
</table>
Additional Experts

**Stephen Butler, PhD**
Chief Scientific Officer
Inflexxion

**Gavril Pasternak, MD, PhD**
Anne Burnet Tandy Chair of Neurology
Memorial Sloan Kettering Cancer Center
Professor of Neurology, Weill Medical School of Cornell University

**Kerri Schoedel, PhD**
Principal in Altreos Research Partners
Former Senior Director of Clinical Pharmacology,
INC Research, Toronto
Pain, Personalized Medicine and Opioid Therapy

Perry Fine, MD
Professor of Anesthesiology
Pain Research Center, School of Medicine
University of Utah
Key Points

- Severe intractable pain is a major public health problem
- Opioid therapy may be needed in selected patients to affect positive therapeutic outcomes
- Responses to opioids are highly variable, due to:
  - Variability in drug metabolism among diverse clinical populations
  - Potential drug-drug interactions
  - Receptor polymorphism
- A wide variety of opioids are needed - including oxymorphone - to optimize outcomes
Impact of Unrelieved Pain

- Anxiety/irritability/frustration
- Low self-esteem
- Decreased productivity
- Loss of income
- Inability to concentrate
- Decreased driving ability
- Fatigue
- Increased healthcare need/costs
- Reduced functional capacity
- Impaired relationships
- Suicide risk
- Sexual dysfunction
- Depression

UNRESOLVED PAIN
Safe, Effective Pain Management Requires Comprehensive Assessment + Integrated Care

- Physical Medicine and Rehabilitation
- Lifestyle Changes
- Interventional Approaches
- Complementary and Alternative Medicine
- Psychological Support
- Pharmacotherapy

Therapeutic Approaches to Pain as a Complex Condition

3. CDC Guidelines, 2016
Personalized Medicine is Critical to Effective Pain Management

- “One size fits all” approach is a failing formula
- Unique social, cognitive, psychological, genetic circumstances\(^1\)
- PK PD variability of opioids relevant to pharmacogenetic differences in patients
- Currently requires “trial and error” or “N of 1” treatment design\(^2\)
  - Matching drug characteristics and effects to patient characteristics and responses

Reasons for Variable Responses

- People are not the same
  - Drug metabolism differs among diverse populations
  - Clinical factors influence drug effects
    - Polypharmacy
    - Variability in diseases and clinical condition over time
  - Genetic backgrounds differentially impact drug sensitivity
Drugs Are Not the Same: Unique Metabolic Profile of Oxymorphone

- Not a substrate for CYP450-based metabolism
- Pharmacogenetics and metabolism play an important role in analgesic efficacy and adverse effects
- Receptor polymorphism is well-established in opioid pharmacology gene splice variants coding for mu receptors determine dose-response$^{1,2}$
  - Opioids have both class and individual effects

Variability in Opioid Responsiveness & Risk

- Therapeutic and adverse effects are a function of patient-specific factors\(^1\)
- Alternatives are necessary to account for these differences
  - Opioid rotation during initial titration and during ongoing treatment is a well established and necessary practice\(^2\)

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Case Study

- Middle age professional woman with severe neuropathic facial pain
- Modest benefits from non-opioid and opioid therapies
- Hospitalized 4 times for out-of-control pain and AEs
- Switched to IR, then ER oxymorphone with paroxetine (CYP2D6) and carbamazepine (CYP3A4)
- No ER or hospitalization in 12 months
Lesson from “the Trenches”

- No risk-free solutions
- Until such time that there is a class of drugs as efficacious and versatile as the opioids, clinicians need to learn how to select patients for opioid therapy, when indicated, and manage them as safely and effectively as possible.
Category 1
Lab-based *in vitro* Manipulation and Extraction Studies

Harris Rotman, PhD.
Vice President, US Regulatory Affairs
Endo Pharmaceuticals Inc.
Category 1: Lab-based *in vitro* Manipulation and Extraction Studies

- Physical & Chemical Manipulation Studies
- Route Specific Studies

- Category 2: Pharmacokinetic Clinical Trial

- Category 3: Human Abuse Potential Clinical Trial

- Category 4: Postmarketing Confirmation of Reduction in Abuse

- Study 114 (Manipulated Intranasal)

- NAVIPPRO®
- RADARS® Poison Center Program
- RADARS® Drug Diversion Program
Reformulated OPANA ER vs Generic Non-ADF Oxymorphone

Category 1
Reformulated OPANA ER Resists Reduction in Particle Size

- **Reformulated OPANA ER**
- **Generic non-ADF Oxymorphone ER**

**Tool A**

<table>
<thead>
<tr>
<th>Particle Size (mm)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
<td>60</td>
</tr>
<tr>
<td>0.5-1.0</td>
<td>20</td>
</tr>
<tr>
<td>&gt;1.0</td>
<td>20</td>
</tr>
</tbody>
</table>

**Tool M**

<table>
<thead>
<tr>
<th>Particle Size (mm)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
<td>90</td>
</tr>
<tr>
<td>0.5-1.0</td>
<td>10</td>
</tr>
<tr>
<td>&gt;1.0</td>
<td>10</td>
</tr>
</tbody>
</table>

**Tool N**

<table>
<thead>
<tr>
<th>Particle Size (mm)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
<td>40</td>
</tr>
<tr>
<td>0.5-1.0</td>
<td>30</td>
</tr>
<tr>
<td>&gt;1.0</td>
<td>30</td>
</tr>
</tbody>
</table>

* No particles generated for Reformulated OPANA ER
Generic Products (Non-ADF Oxymorphone ER) Readily Convert to IR when Manipulated

- Reformulated OPANA ER
- Generic A
- Generic B

≥ 80% at 30 Minutes

Percent Dissolved at 30 Minutes

0 10 20 30 40 50 60 70 80 90 100

Tool A Tool B
Reformulated OPANA ER Had Lower Extraction Rate than Generic Non-ADF Oxymorphone ER

- Reformulated OPANA ER
- Generic A
- Generic B

% Percent Extracted

Extraction Time

- 15 minutes
- 1 hour

≥ 80%

Manipulated with Tool B, 30mL of Solvent ‘a’
Reformulated OPANA ER had Lower Percent Extraction than Generic Oxymorphone

<table>
<thead>
<tr>
<th>Tool</th>
<th>Solvent a (mL)</th>
<th>% API Extracted</th>
<th>Reformulated OPANA ER</th>
<th>Generics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tool B</td>
<td>5 mL</td>
<td>26% - 40%</td>
<td>61% - 80%</td>
<td></td>
</tr>
<tr>
<td>Tool A</td>
<td>5 mL</td>
<td>N/A</td>
<td>79%</td>
<td></td>
</tr>
<tr>
<td>Tool V</td>
<td>3 mL</td>
<td>Not syringeable</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>
Reformulated OPANA ER vs OxyContin (ADF)

Category 1
Reformulated OPANA ER & OxyContin (ADF) Resist Particle Size Reduction

![Bar Chart]

- Reformulated OPANA ER
- OxyContin (ADF)

**Particle Weight (%)**
- <0.5
- 0.5-1.0
- >1.0

**Particle Size (mm)**
Reformulated OPANA ER & OxyContin (ADF) Have Similar *in vitro* Dissolution

![Bar graph showing percent dissolved in 30 minutes for different manipulation tools.]

- Reformulated OPANA ER
- OxyContin (ADF)

**Manipulation Tool**
- Intact
- Tool B
- Tool I
- Tool N

**Percent Dissolved in 30 Minutes**
- 0
- 20
- 40
- 60
- 80
- 100
Similar Extraction Rate in a Variety of Aqueous and Non-Aqueous Solvents

- Reformulated OPANA ER
- OxyContin (ADF)

Two sets of bar charts show the percent extracted for solvents labeled 'a' to 'l' over 1 hour and 6 hours.
Reformulated Opana ER has similar extraction to OxyContin (ADF)

<table>
<thead>
<tr>
<th>Tool</th>
<th>Solvent a (mL)</th>
<th>% API Extracted</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Reformulated Opana ER</td>
<td>OxyContin (ADF)</td>
<td></td>
</tr>
<tr>
<td>Tool V</td>
<td>3 mL</td>
<td>Not syringeable</td>
<td>Not syringeable</td>
<td></td>
</tr>
<tr>
<td>Tool B</td>
<td>5 mL</td>
<td>26% - 40%</td>
<td>42% - 46%</td>
<td></td>
</tr>
<tr>
<td>Tool I</td>
<td>2 mL, 5 times</td>
<td>39%</td>
<td>36%</td>
<td></td>
</tr>
</tbody>
</table>
Reformulated OPANA ER is more resistant to physical and chemical manipulations than generic oxymorphone ER.

Reformulated OPANA ER and OxyContin (ADF) demonstrate similar physical & chemical properties:
- Resist physical and chemical manipulations.
Category 2 and 3 Intranasal PK and Abuse Potential Study
Category 2/3: PK and Human Abuse Potential Study for Intranasal Route of Abuse

- **Category 1**
  - Lab-based *in vitro* Manipulation & Extraction Studies

- **Category 2**
  - Pharmacokinetinc Clinical Trial

- **Category 3**
  - Human Abuse Potential Clinical Trial

- **Category 4**
  - Postmarketing Confirmation of Reduction in Abuse

- \[\text{Study 114 (Manipulated Intranasal)}\]

- NAVIPPRO®
- RADARS® Poison Center Program
- RADARS® Drug Diversion Program
Study Design Consistent with Regulatory Guidelines for Abuse Deterrent Opioids

- Randomized, double-blind, placebo-controlled crossover design

**Qualification Phase**
- Oxymorphone powder and placebo
- Dose = 7.5mg
- Administered intranasally (fasted)

**Treatment Phase**
- 4-period, single dose
- Medication given Day 1 of each period
- 4-day washout period between doses

**Manipulated Reformulated Opana ER¹**
- Manipulated Placebo to Match Reformulated Opana ER¹
- Oxymorphone Powder
- Placebo to Match Oxymorphone Powder

1. Reformulated Opana ER and matching placebo manipulated using tool V
Manipulated Reformulated OPANA ER Retains ER Properties Following Intranasal RoA

![Graph showing plasma concentration over time for Oxymorphone Powder and Reformulated OPANA ER.](image)

- **Oxymorphone Powder (intranasal)**
- **Reformulated OPANA ER (intranasal manipulated)**

- Plasma Concentration (ng/mL)
- Time (hours)

n=38
Category 3: Drug Liking Endpoints to Measure Pharmacodynamics Effects

- Primary endpoint
  - $E_{\text{max}}$ of Drug Liking Visual Analog Scale (VAS)
- Primary comparison
  - Manipulated Reformulated OPANA ER vs. oxymorphone powder
Lower Drug Liking for Manipulated Reformulated OPANA ER than Oxymorphone Powder

![Graph showing drug liking over time for Oxymorphone Powder, Reformulated OPANA ER, and Placebo.](Image)

- **Strong Liking**
  - Oxymorphone Powder
  - Reformulated OPANA ER (Manipulated)
  - Placebo to Match OPANA ER (Manipulated)
  - Placebo to Match Oxymorphone Powder

- **Mean Drug Liking VAS (mm)**

- **Neutral**

- **Time (h)**: 0, 2, 4, 6, 8

- **n=38**
Lower “Take Drug Again” for Manipulated Reformulated OPANA ER Compared to Oxymorphone Powder

Mean Take Drug Again VAS (mm)

- Placebo to Match Oxymorphone Powder
- Placebo to Match OPANA ER (Manipulated)
- OPANA ER (Manipulated)
- Oxymorphone Powder

n=38

p<0.001
Reformulated OPANA ER Retains Extended Release Properties Following Manipulation

- PK shows lower $C_{\text{max}}$ and delayed $T_{\text{max}}$ compared to oxymorphone powder
- Significantly lower drug liking effects compared to oxymorphone powder
- Intranasal PK/PD study met prespecified endpoints
Post-Marketing Observational Data: Category 4 Abuse Epidemiology

Neil Shusterman, MD
Chief Medical Officer
Endo Pharmaceuticals Inc.
Evaluation of Opioid Abuse Comes From 3 Epidemiology Sources

<table>
<thead>
<tr>
<th>Data Source</th>
<th>Primary Epidemiology</th>
<th>Secondary Epidemiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®)</td>
<td>Substance Abuse Treatment</td>
<td></td>
</tr>
<tr>
<td>Researched Abuse Diversion and Addiction-Related Surveillance System (RADARS®)</td>
<td>Poison Center</td>
<td>Drug Diversion</td>
</tr>
</tbody>
</table>
NAVIPPRO® Study Design

- Cross-sectional, observational, post-market data
- Data from Addiction Severity Index Multimedia Version (ASI-MV) from 2009-2016
  - 459,240 interviews / 1,084 sites / 40 states
  - 4,984 mentions of OPANA ER
- Two denominators –
  - per 100 ASI-MV assessments
  - per 10,000 tablets dispensed
NAVIPRO® Pre-Specified Primary Objectives

- Compare abuse of Reformulated Opana ER by alternate routes of administration to
  - Historic control - original Opana ER
  - Concurrent control - generic oxymorphone ER

- Alternate routes of administration – combined endpoint of intranasal or intravenous

- Compare abuse of Reformulated Opana ER to historic control and concurrent control by individual routes of
  - Intranasal
  - Intravenous
NAVIPPRO® Limitations

- Convenience sample
- No direct abuse-related outcomes
- Sampling is non-random
  - Not nationally representative
- Sampling changes over time
- Self-reported responses subject to recall bias
- Accuracy and honesty cannot be verified
All Sites Included in NAVIPPRO® Prespecified Primary Analysis

- Fixed site was prespecified sensitivity analysis
- Fixed site pattern of results comparable to all sites
NAVIPPRO®: Abuse Prevalence by Route of Administration (100 ASI-MV)

- Original OPANA ER (3-yr Pre-period)
- Reformulated OPANA ER (3-yr Post-period)

Abuse Rate per 100 ASI-MV Assessments

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Pre-period</th>
<th>Post-period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternate Routes</td>
<td>0.73</td>
<td>0.89</td>
</tr>
<tr>
<td>Intranasal</td>
<td>0.61</td>
<td>0.23</td>
</tr>
<tr>
<td>Intravenous</td>
<td>0.13</td>
<td>0.68</td>
</tr>
</tbody>
</table>
NAVIPPRO®: Abuse Prevalence by Route of Administration (10,000 Tablets Dispensed)

- Original OPANA ER (3-yr Pre-period)
- Reformulated OPANA ER (3-yr Post-period)

<table>
<thead>
<tr>
<th>Route</th>
<th>Abuse Rate per 10,000 Tablets Dispensed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternate Routes</td>
<td>0.18</td>
</tr>
<tr>
<td>Intranasal</td>
<td>0.15</td>
</tr>
<tr>
<td>Intravenous</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>0.19</td>
</tr>
</tbody>
</table>
NAVIPPRO®: Abuse Prevalence by Route of Administration (100 ASI-MV)

- Reformulated Opana ER (3-yr Post-period)

<table>
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<th>Abuse Rate per 100 ASI-MV Assessments</th>
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<tr>
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<td>0.89</td>
</tr>
<tr>
<td>Intranasal</td>
<td>0.23</td>
</tr>
<tr>
<td>Intravenous</td>
<td>0.68 and 0.66</td>
</tr>
</tbody>
</table>
NAVIPPRO®: Abuse Prevalence by Route of Administration (10,000 Tablets Dispensed)

- Reformulated OPANA ER (3-yr Post-period)
- Generic Oxymorphone ER (3-yr Post-period)

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Reformulated OPANA ER</th>
<th>Generic Oxymorphone ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternate Routes</td>
<td>0.25</td>
<td>0.67</td>
</tr>
<tr>
<td>Intranasal</td>
<td>0.06</td>
<td>0.44</td>
</tr>
<tr>
<td>Intravenous</td>
<td>0.19</td>
<td>0.28</td>
</tr>
</tbody>
</table>
Tennessee Accounted for 75% of Reports for Reformulated OPANA ER

Percent of All Abuse Cases

States Providing ≥1 Case (N=20)
NAVIPPRO®: OPANA ER Rate of Abuse by Route of Administration (Non-Tennessee)
NAVIPPRO®: OPIANA ER Rate of Abuse by Route of Administration (Non-Tennessee)
NAVIPPRO®: OPIANA ER Rate of Abuse by Route of Administration (Non-Tennessee)
NAVIPPRO®: OXANNA ER Rate of Abuse by Route of Administration (TN & Non-TN)
NAVIPPRO®: OPANA ER Rate of Abuse by Route of Administration (TN & Non-TN)

- **Pre-Reformulation (3-year)**: Reformulated OxyContin
  - Line colors: Blue
  - Legend: Alternate Routes
  - Year/Quarter: Q1-Q4 2009, Q1-Q4 2010

- **Market Transition**
  - Line colors: Green
  - Legend: Intranasal
  - Year/Quarter: Q1-Q4 2012, Q1-Q4 2013

- **Post-Reformulation (3-year)**: Non-TN
  - Line colors: Orange
  - Legend: Intravenous
  - Year/Quarter: Q1-Q4 2014, Q1-Q4 2015, Q1-Q4 2016

**Per 100 ASI-MV Assessments**

- Y-axis: Past 30-day abuse
Tennessee Abuse Pattern is Distinctly Different From Non-Tennessee

- Noted in initial NAVIPPRO® ASI-MV publication from 2008\(^1\)
- Tennessee intravenous abuse rate is not specific for OPANA ER

Rate of Intravenous Abuse High in TN Prior to Reformulation of Opana ER

Pre-Reformulation (3-Year)

Per 100 ASI-MV Assessments

- Tennessee
- Non-Tennessee

Original Opana ER
Oxymorphone IR
Oxycodone IR (single entity)
Morphine ER
OxyContin
Rate of Intravenous Abuse in TN Remained High Following Opana ER Reformulation

![Graph showing the rate of intravenous abuse in Tennessee and non-Tennessee regions post-reformulation of Opana ER.](image)
# TN Addiction Population Different from Other States

<table>
<thead>
<tr>
<th>Grouping</th>
<th>Tennessee Only</th>
<th>Non-Tennessee</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre Reformulated OPANA ER (n = 400)</td>
<td>Post Reformulated OPANA ER (n = 1250)</td>
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<tr>
<td>Drug Treatment Setting</td>
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<tr>
<td>Residential / Inpatient</td>
<td>67%</td>
<td>89%</td>
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<tr>
<td>Outpatient / Non-Methadone</td>
<td>18%</td>
<td>8%</td>
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<tr>
<td>Methadone / LAAM</td>
<td>1%</td>
<td>0%</td>
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<tr>
<td>Corrections</td>
<td>2%</td>
<td>&lt; 1%</td>
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<tr>
<td>Other</td>
<td>13%</td>
<td>4%</td>
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<tr>
<td>Missing</td>
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<tr>
<td>History of Prescription Opioids Injection</td>
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<tr>
<td>Number Injected (≥1 Rx Opioid)</td>
<td>48%</td>
<td>81%</td>
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</table>
Summary of NAVIIPRO® Data

- Abuse of OPANA ER increased during the pre-period
- In the post-period compared to the pre-period:
  - Tennessee: Intravenous abuse was higher although levels of alternate routes and intranasal abuse were lower
  - Intravenous abuse was high for a number of opioids
  - Outside of TN: alternate route and intranasal abuse was lower and intravenous abuse was similar
RADARS® Post-marketing Studies

RADARS® Poison Center

RADARS® Drug Diversion
RADARS® Poison Center

- Data from US poison centers covering 48 states
  - > 90% of US population
  - Nationally representative of PC calls
- Callers seeking advice / help about potentially toxic exposures, including opioids
- Detect product-specific prescription drug abuse and misuse including outcomes
- > 2.3 million exposure calls per year
- Incidence-based analyses
  - Per 100,000 population
  - Per 100,000 tablets
RADARS® Poison Center: Primary Objectives

Determine if rates of OPANA ER mentions:

- by intentional abuse
- resulting in major outcome or death
- through non-oral routes of administration
- resulting in overdose

were lower following the introduction of Reformulated OPANA ER compared to the pre-period
RADARS® Poison Center: Limitations

- Spontaneous reports subject to bias
- Rates underestimated due to limited reporting
- Difficult to accurately identify toxic exposure
  - If can’t accurately ID product, listed as “not otherwise specified” (NOS)
RADARS® Poison Center: Increase of Intentional Abuse During Pre-Period

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<thead>
<tr>
<th>Year/Quarter</th>
<th>Pre-Reformulation (3-year)</th>
<th>Market Transition</th>
<th>Post-Reformulation (3-year)</th>
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Rate per 100,000 Population

- Original OPANA ER
RADARS® Poison Center: Rate of Intentional Abuse Mentions During Pre- and Post-Period

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<th>Year/Quarter</th>
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<th>Post-Reformulation (3-year)</th>
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<td>Q1 2009</td>
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</table>

- **Reformulated OPANA ER**
- **Original OPANA ER**
RADARS® Poison Center: Rate of Intentional Abuse Mentions During Pre- and Post-Period (100,000 Dosage Units)

![Graph showing the rate of intentional abuse mentions during pre- and post-periods. The graph plots rate per 100,000 dosing units over years and quarters. The pre-reformulation period shows a steady increase, while the post-reformulation period shows variability with peaks and troughs.]
RADARS® Poison Center: Rate of Death & Major Outcomes During Pre- and Post-Periods

Pre-Reformulation (3-year) | Market Transition | Post-Reformulation (3-year)

Rate per 100,000 Population

- Reformulated OPANA ER
- Original OPANA ER
RADARS® Poison Center: Rate of Death & Major Outcomes during Pre- and Post-Periods (100,000 Dosage Units)
RADARS® Poison Center: Rate of Intentional Non-Oral Abuse During Pre- and Post-Periods

Pre-Reformulation (2-year)  Market Transition  Post-Reformulation (3-year)

Rate per 100,000 Population

Q1  Q2  Q3  Q4  Q1  Q2  Q3  Q4  Q1  Q2  Q3  Q4  Q1  Q2  Q3  Q4  Q1  Q2  Q3  Q4  Q1  Q2

Reformulated OPANA ER
Original OPANA ER

* Data not available in 2009
RADARS® Poison Center: Rate of Intentional Non-Oral Abuse During Pre- and Post-Periods (100,000 Dosage Unit)

- Pre-Reformulation (2-year)
- Market Transition
- Post-Reformulation (3-year)

Rate per 100,000 Dosing Units

Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2 Q3 Q4 Q1 Q2

Reformulated OPANA ER
Original OPANA ER

* Data not available in 2009
RADARS® Poison Center: Rate of Intentional Intranasal Abuse, Pre- and Post-Periods

<table>
<thead>
<tr>
<th>Year/Quarter</th>
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<tr>
<td>Pre-Reformulation (2-year)</td>
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<td>Market Transition</td>
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- **Reformulated OPANA ER**
- **Original OPANA ER**
RADARS® Poison Center: IV Abuse Rates for OPCA NA ER are Not Increasing

<table>
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<th>Year/Quarter</th>
<th>Pre-Reformulation (2-year)</th>
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* Data not available in 2009
RADARS® Poison Center: IV Abuse Rates for OPIANA ER are Not Increasing (100,000 Dosage Unit)

* Data not available in 2009

* Reformulated OPIANA ER
* Original OPIANA ER

* Year/Quarter
  - Q1 2009
  - Q2 2009
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  - Q4 2009
  - Q1 2010
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  - Q2 2016
Number of Dispensed OPANA ER Tablets – Rise and Fall

Pre-Reformulation (2-year) | Market Transition | Post-Reformulation (3-year)

OPANA ER Tablets Dispensed (Millions)

Year/Quarter

RADARS® Poison Center Program
RADARS® Poison Center: Number of IV Injection Cases Not Increasing

- Pre-Reformulation (2-year)
  - Reformulated OxyContin

- Market Transition

- Post-Reformulation (3-year)
  - Reformulated OPANA ER
  - Original OPANA ER

* Data not available in 2009
RADARS® Poison Center: Summary of Data

- OPANA ER abuse increased throughout the pre-period, particularly after the introduction of reformulated OxyContin

- Rates of intentional abuse, death and major medical outcomes, non-oral abuse, and overdose were lower for OPANA ER during the post-period compared to the pre-period
RADARS® Post-marketing Studies

RADARS® Poison Center

RADARS® Drug Diversion
RADARS® Drug Diversion

- Supportive epidemiological study
- Examines differences in diversion rates before and after Reformulated OPANA ER introduction
- Prevalence-based analysis:
  - Per 100,000 population
RADARS® Drug Diversion

- Collects reports of prescription drugs found outside of controlled distribution channels
  - Reported by law enforcement
  - Samples from 110 participating agencies in 45 states within US
- Number of cases may reflect drug desirability
- Diversion decline support abuse deterrence
- Inclusion of oxymorphone data started in 2011
RADARS® Drug Diversion: Limitations

- Drug diversion investigators not randomly drawn from pool of all possible officers
- Investigations may vary between calendar quarters
- Data do not distinguish route of abuse
RADARS® Drug Diversion: Increased with OPANA ER During Baseline Period

**Chart Description:**
- The chart compares drug diversion rates before and after the reformulation of OPANA ER.
- **Pre-Reformulation (1-year):** Rates are shown for the years 2009 to 2011.
- **Market Transition:** A notable increase in rates is observed from 2011 onwards.
- **Post-Reformulation (3-year):** Rates remain high from 2012 to 2016, with no significant decrease.

**Key Points:**
- The rate per 100,000 population is depicted along the y-axis.
- The x-axis represents quarters from Q1 to Q4 of each year (2009-2016).

*Data not available in 2009-2010.
RADARS® Drug Diversion: Decline Following Introduction of Reformulated OPANA ER

The graph shows the rate of drug diversion per 100,000 population over time, categorized into three periods:

- **Pre-Reformulation (1-year)**: Years 2009* and 2010*
- **Market Transition**
- **Post-Reformulation (3-year)**: Years 2011 to 2016

The data indicates a decline in drug diversion post-reformulation. The graph also notes that data is not available for 2009-2010.

* RADARS® Drug Diversion

* Data not available in 2009-2010
RADARS® Drug Diversion: Supports Less Desirability With Reformulated OPANA ER

- Increased investigations with original OPANA ER in 2011
- Decreased investigations following introduction of Reformulated OPANA ER
- Decrease suggests less desirability of Reformulated OPANA ER
Conclusions From Post-Marketing Epidemiology Studies & Safety

NAVIPPRO®
RADARS® Poison Center
RADARS® Drug Diversion
Concordant Epidemiologic Findings

- Increased abuse of original OPANA ER from 2009 to 2011, primarily as intranasal abuse
- Coincident with the introduction of Reformulated OPANA ER
  - Intranasal abuse was lower
  - IV abuse increased in TN, but not in other states
  - Law enforcement reports of diversion were lower
- Consistency across multiple epidemiology methods
  - NAVIPPRO®
  - RADARS® Poison Center
  - RADARS® Drug Diversion
- Reformulated OPANA ER has not increased IV abuse rates observed with original formulation in 2011
Post-Marketing Pharmacovigilance

- Thrombotic Thrombocytopenic Purpura (TTP) in Tennessee
- HIV in Indiana
Reports of Thrombotic Thrombocytopenic Purpura (TTP) and Response

- Aug 2012: 5 cases of TTP reported from Tennessee
  - Associated with IV injection of OPANA ER tablets
- Endo response
  - Promptly informed FDA and met with federal and state officials
  - Discussions with sales representatives
  - Contacted local anti-drug organization
  - Worked with law enforcement
  - Maintained contact with local HCPs treating patients
Cases of TTP

Endo Drug Safety Database
TTP Associated with IV Administration of Polyethylene Oxide (PEO)

- PEO - listed in FDA’s database of inactive ingredients for oral administration
- Potential link to inactive ingredient
  - Animal investigations – IV administration of PEO can recapitulate some TTP features
- Reported with IV administration of OxyContin (ADF) tablets
- Should be considered IV administration risk of any oral pharmaceutical containing PEO
Needle Sharing Leads to HIV Outbreak in March 2015

- Health emergency declared - Scott County, IN
  - Outbreak of HIV due to needle sharing among a group of abusers of IV drugs
- Various health agencies (e.g., CDC, Indiana State DOH) intervened to stop spread of HIV
- Oxymorphone ER most prevalent abused drug
  - Both brand and generic were identified
- Heroin, methamphetamine, cocaine, and oxycodone were also being abused IV

1. CDC., MMWR 2015; Peters P., NEJM 2016
Endo Committed to Understanding IV Abuse & Assisting Communities

- Conduct ethnographic study
- New 3-year program with targeted interventions:
  - Conduct parent coaching trainings
  - Pilot mobile texting parent support program
  - Toll Free Hotline for families / patients
  - Media awareness campaign
  - Increase in law enforcement outreach
  - Increase in local treatment center outreach
  - Increase outreach with local communities leaders
- Continued monitoring of NAVIPPRO® and RADARS®
Decision-Making with Incomplete Observational Data

Alexander Walker, MD, DrPH
Former Chair of Department of Epidemiology
Harvard T.C. Chan School of Public Health
Epidemiologist’s Approach to NAVIPPRO and RADARS

- Public health decisions time sensitive, often made before all data are in
- Information – less complete, less accurate, less representative than study designed from scratch
  - Still tells a coherent story
We Can’t Always Measure What We Want to Measure

- Quantification of drug abuse – based on ratios
- Available sources provide crude measures, i.e., National Survey on Drug Abuse and Health
  - Limited information on specific drugs available prior to 2015
- No real numerator at product-specific level
  - No estimates of diversion for specific entities
  - No census estimates of deaths associated with individual products
Substitutes are Used if Populations are Not Directly Observable

- Registry
- Monitoring programs
- Spontaneous reports
- Counts in a relevant subset, e.g. poison center calls or deaths
Proxy Denominators for Abuse Prevalence or Overdose Incidence

- Population (RADARS)
  - Poison center overdose events
- Persons entering rehab (NAVIPPRO)
  - Represent abuser community
- Number of tablets dispensed (RADARS and NAVIPPRO)
  - Product-specific denominator adjustments
- None leads to direct estimate of incidence or prevalence
  - Look for consistent pattern of results with multiple approximate measures
Regional Tablets Sold are not a Measure of Regional Tablets Diverted

“Prescription-adjusted abuse was estimated … using quarterly total dosage units associated with the individual home 3-digit ZIP code areas … in order to approximate ‘local availability.’”

Tablets sold fails as denominator on regional level

- Two-thirds of diverted drugs come from drug dealers

- Illegal movement will tend to
  - Inflate event-to-tablet ratios in areas of high demand
  - Diminish the same ratios in levels of low demand

1. NAVIPPRO© 2016
Confounding = “Ecological Fallacy”

Reformulation of OPANA \rightarrow \text{Increased # of inpatient sites} \rightarrow \text{IV Abuse}
Fixed Sites Analysis May Not Generalize to Broader Population

- Holding population constant across pre- and post-periods partially addresses shift
  - Pre-specified fixed sites sensitivity analysis performed
  - Sites must have $\geq 1$ ASI-MV each quarter
- Only 26% of the full data set
- Only 2 Tennessee sites
  - 85% of Reformulated OPANA ER reports
- Restricted data set may not generalize
Confronting the Challenges of Proxy Measures and the Ecological Fallacy

- Decisions must be made on incomplete data
- Interpretation requires that we consider processes that generated the data
- My own view on reformulation of OPANA ER
  - Has deterred intranasal abuse
  - Has had limited effect on IV abuse
- Tennessee is an important anomaly
  - Not likely to be resolved today
  - Not a basis for national decisions
Benefit-Risk Assessment of Opana ER

Richard Dart, MD, PhD
RADARS® System
Rocky Mountain Poison & Drug Center
Professor, University of Colorado
How Can We Measure Abuse Behavior?

- Abusers seek to hide their behavior
- Measured when abusers choose or forced to reveal themselves
  - Acute events and poison center cases
  - Law enforcement of drug transaction
  - Substance treatment
  - Voluntary disclosure
Challenges of Post-Marketing Surveillance

- Individual programs do not include every geographic region
- Spontaneous reporting susceptible to bias
- Self-reporting involves recall bias
- Cannot make direct causal links between outcomes and drugs
- Respondents accuracy cannot be verified
- Dramatic increase in abuse prevalence for all comparators
Benefits and Risks of Regulatory Action of Reformulated OPANA ER

- **Benefits**
  - Opioid analgesics needed for chronic pain that does not respond to alternative treatments
  - Multiple opioids with different characteristics are needed to address multiple patient needs

- **Risks**
  - All opioid drugs abused
  - Overdose, addiction, death

- Is Reformulated OPANA ER different?
RADARS Poison Center: Outcomes of OPIANA ER Abuse are Not Worsening

![Graph showing outcomes of OPIANA ER abuse over time.](image)

**CII Opioids:** ER oxycodone, ER hydrocodone, ER morphine, ER hydromorphone, and tapentadol ER

**Year/Quarter:** Q1, Q2, Q3, Q4

**Rate per 100,000 Population**

- **Pre-Reformulation (3-year):** 2009, 2010, 2011
- **Market Transition:** 2012, 2013
- **Post-Reformulation (3-year):** 2014, 2015, 2016

**Graph Lines:**
- Reformulated OPIANA ER
- Original OPIANA ER
- CII Opioids

RADARS® Poison Center Program
RADARS Poison Center: Outcomes of OPANA ER Abuse are Not Worsening (100,000 Dosage Unit)

**CO-114**

**Rate per 100,000 Dosing Units**

**Pre-Reformulation (3-year)**

<table>
<thead>
<tr>
<th>Year/Quarter</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td></td>
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<tr>
<td>Q3</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Q4</td>
<td></td>
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</tr>
</tbody>
</table>

**Market Transition**

<table>
<thead>
<tr>
<th>Year/Quarter</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
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<td>Q1</td>
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<td>Q2</td>
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<td>Q3</td>
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</tr>
<tr>
<td>Q4</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Post-Reformulation (3-year)**

- Reformulated OPANA ER
- Original OPANA ER
- CII Opioids

**CII Opioids:** ER oxycodone, ER hydrocodone, ER morphine, ER hydromorphone, and tapentadol ER
OPANA ER Deaths are Low and Not Increasing in Poison Centers

Pre-Reformulation (3-year)  |  Market Transition  |  Post-Reformulation (3-year)

- Reformulated OPANA ER
- Original OPANA ER

Year/Quarter

RADARS® Poison Center Program
Risks of OPANA ER Similar to Other ER/LA Opioids

- All opioids carry risks
  - OPANA ER: small portion of total abuse cases
  - OPANA ER: risks similar to other ER/LAs
- Rates of abuse are similar to other opioid analgesics since reformulation
- Consistent trends observed in 3 different programs (PC, DD, ASI-MV)
- Reformulated OPANA ER: physical / chemical barriers likely decrease attractiveness for abuse
OPANA ER Should Remain Available for Patients with Chronic Pain

- OPANA ER data show no new net harm
  - Not worse than other opioid analgesics
- OPANA ER provides consistent and predictable 12-hour pain relief
- Diversion and abuse similar to other opioids
- Interventions may be needed in specific locations, but not appropriate for entire US
- Removal of OPANA ER would be major burden to patients with no evidence of net gain
OPANA® ER (oxymorphone HCl)
Benefit-Risk

March 13, 2017
Anesthetic & Analgesic Drug Products
Advisory Committee and
Drug Safety and Risk Management Advisory Committee
Back-Up Slides
## NAVIPPRO: Selected Demographic Characteristics

<table>
<thead>
<tr>
<th>Selected Demographic Characteristics</th>
<th>Total Analytic Sample (N=459,240)</th>
<th>Original OPANA ER Abusers Pre-Period (n=1,570)</th>
<th>Reformulated OPANA ER Abusers Post-Period (n=1,675)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21 to 34</td>
<td>50.4</td>
<td>71.4</td>
<td>69.4</td>
</tr>
<tr>
<td>35 to 54</td>
<td>36.3</td>
<td>12.4</td>
<td>23.1</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>63.8</td>
<td>50.7</td>
<td>45.6</td>
</tr>
<tr>
<td>Female</td>
<td>36.2</td>
<td>49.3</td>
<td>54.3</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>59.4</td>
<td>91.7</td>
<td>93.5</td>
</tr>
<tr>
<td>Black</td>
<td>18.9</td>
<td>1.5</td>
<td>1.8</td>
</tr>
<tr>
<td>Hispanic</td>
<td>15.2</td>
<td>5</td>
<td>2</td>
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<tr>
<td>Other</td>
<td>6.5</td>
<td>1.8</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>28.4</td>
<td>26.1</td>
<td>27.9</td>
</tr>
<tr>
<td>High school degree</td>
<td>41.8</td>
<td>44.3</td>
<td>45.6</td>
</tr>
<tr>
<td>Some college</td>
<td>23.8</td>
<td>26.8</td>
<td>21.7</td>
</tr>
<tr>
<td>College degree</td>
<td>3.9</td>
<td>2</td>
<td>2.6</td>
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<tr>
<td><strong>Self-Reported Pain Problem</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>32.6</td>
<td>50.9</td>
<td>58</td>
</tr>
<tr>
<td>No</td>
<td>67.3</td>
<td>49</td>
<td>41.9</td>
</tr>
<tr>
<td>Unknown/ Missing</td>
<td>&lt; 1.0</td>
<td>&lt; 1.0</td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td><strong>Chronic Medical Problem</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30</td>
<td>30</td>
<td>38</td>
</tr>
<tr>
<td>No</td>
<td>69.7</td>
<td>69.7</td>
<td>61.9</td>
</tr>
<tr>
<td>Unknown/ Missing</td>
<td>&lt; 1.0</td>
<td>&lt; 1.0</td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td><strong>Criminal Justice-Required Substance Abuse Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>58.7</td>
<td>25</td>
<td>26.7</td>
</tr>
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</table>
# Metabolic Pathways of Common Opioids

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Phase I Metabolism</th>
<th>Phase II Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>CYP2D6 &amp; CYP3A</td>
<td>UGT2B7</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>CYP2D6 &amp; CYP3A</td>
<td>UGT1A3, UGT2B2, dihydromorphine ketone reductase</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>CYP3A &amp; CYP2D6</td>
<td>UGT2B7</td>
</tr>
<tr>
<td>Methadone</td>
<td>CYP3A, CYP2B6, CYP2D6, CYP2C9&lt;sup&gt;a&lt;/sup&gt;, CYP2C19&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>CYP3A &amp; CYP2D6</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>CYP3A</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>(CYP3A)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>UGT2B7</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td></td>
<td>UGT1A3 &amp; UGT2B7</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td></td>
<td>UGT2B7</td>
</tr>
</tbody>
</table>

<sup>a</sup> Minor pathways/clinical significance unknown

Thrombotic Thrombocytopenic Purpura (TTP) in OPANA ER and OxyContin

- TTP has been reported with reformulated OxyContin containing PEO
- FAERS Database contains 6 cases of TTP with OxyContin
- Literature reports 2 cases of TTP with OxyContin
## Thrombotic Thrombocytopenic Purpura (TTP) and OxyContin – FAERS 6 Cases

<table>
<thead>
<tr>
<th>Event Date</th>
<th>Location</th>
<th>Gender</th>
<th>Age</th>
<th>Primary Suspect Drug</th>
<th>Route</th>
<th>Secondary Suspect Drugs</th>
<th>Concomitant Drugs</th>
<th>Outcome</th>
<th>Published</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Apr-14</td>
<td>Australia</td>
<td>F</td>
<td>29</td>
<td>OxyContin</td>
<td>Intravenous</td>
<td>None</td>
<td>Acetaminophen Desenlafaxine Vitamin B9</td>
<td>Hospitalized</td>
<td>Yes (Clin Kid J 2016)</td>
</tr>
<tr>
<td>21-Oct-15</td>
<td>Australia</td>
<td>M</td>
<td>28</td>
<td>OxyContin</td>
<td>Intravenous</td>
<td>None</td>
<td>None</td>
<td>Hospitalized Life Threatening</td>
<td>No</td>
</tr>
<tr>
<td>27-Feb-15</td>
<td>Canada</td>
<td>F</td>
<td>19</td>
<td>Oxycodone</td>
<td>Unknown</td>
<td>Diclofenac</td>
<td>Amitriptyline Celecoxib Fentanyl Pregabalin</td>
<td>Other</td>
<td>No</td>
</tr>
<tr>
<td>6-Apr-12</td>
<td>US</td>
<td>F</td>
<td>-</td>
<td>OxyContin</td>
<td>Oral</td>
<td>None</td>
<td>None</td>
<td>Hospitalized</td>
<td>No</td>
</tr>
<tr>
<td>26-Sep-12</td>
<td>US</td>
<td>F</td>
<td>27</td>
<td>Oxycodone</td>
<td>Unknown</td>
<td>None</td>
<td>None</td>
<td>Hospitalized Life Threatening</td>
<td>No</td>
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</tbody>
</table>
NAVIPPRO: Distribution of OPIANA ER Abuse Cases, ASI-MV Assessments and Number of Opioid Prescriptions by State

<table>
<thead>
<tr>
<th></th>
<th>Tennessee</th>
<th>North Carolina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid Prescriptions</td>
<td>19,281,864</td>
<td>16,495,810</td>
</tr>
<tr>
<td>Prescription Opioid Abusers</td>
<td>10,432</td>
<td>2,542</td>
</tr>
<tr>
<td>ASI-MV Sites</td>
<td>38</td>
<td>125</td>
</tr>
<tr>
<td>ASI-MV Assessments</td>
<td>20,964</td>
<td>20,284</td>
</tr>
<tr>
<td>OPIANA ER Abuse Cases</td>
<td>1250</td>
<td>80</td>
</tr>
<tr>
<td>OPIANA ER Abuse Cases (% Total)</td>
<td>74.6%</td>
<td>4.8%</td>
</tr>
</tbody>
</table>
Why TN Experience is an Anomaly and Not a Sentinel Occurrence

- IV abuse of nearly all opioids very high for some time without appreciable spread
- Very particular abuse ecology
  - Complicated set of factors
- Pockets of increased IV drug use occurring in other locations around the country have not led to OPANA ER signals
NAVIPPRO: OPANA ER Tablets Dispensed (TN)
Table 2-3: Extraction Results for Reformulated OPANA ER, 40-mg Tablets – 5 mL

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Sample Type</th>
<th>Solvent ‘a’</th>
<th>Solvent ‘e’</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Filterable/Needle Size</td>
<td>Extraction Solution (mL)</td>
</tr>
<tr>
<td>P3</td>
<td>Intact/Heated/Grated</td>
<td>No / N3</td>
<td>2.2, 3.3, 2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No / N3</td>
<td>3.1, 2.8</td>
</tr>
<tr>
<td>P4</td>
<td>Intact/Heated/Grated</td>
<td>No / N3</td>
<td>2.3, 2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No / N3</td>
<td>4.1, 3.0, 4.3</td>
</tr>
<tr>
<td>P6</td>
<td>Intact/Heated/Grated</td>
<td>No / N4</td>
<td>3.5, 3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No / N4</td>
<td>3.1, 3.3</td>
</tr>
<tr>
<td>P7</td>
<td>Intact/Heated/Grated</td>
<td>No / N3</td>
<td>1.8, 2.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No / N3</td>
<td>3.0, 3.1</td>
</tr>
<tr>
<td>P8</td>
<td>Intact/Heated/Grated</td>
<td>No / N4</td>
<td>3.4, 3.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No / N3</td>
<td>2.1, 2.8, 2.1</td>
</tr>
</tbody>
</table>

*a* Needle size results represent the smallest bore needle used to collect >1 mL extraction solution.

*b* Individual results reported, average result in bold.

*c* Additional sample preparation and extraction performed due to variability of the duplicate results.
Factors Affecting Syringeability/Extractability

- Particle Size of Sample
- Volume of Liquid
- Duration
- Temperature
- Agitation
- Needle Size
- Filter Type
RADARS® Poison Center: Rate of Intentional Abuse Mentions During Pre- and Post-Period

![Graph showing rate of intentional abuse mentions with pre-reformulation, market transition, and post-reformulation periods.](https://radarspoisoncenter.org/data/images/AA-12.png)

- **Pre-Reformulation (3-year)**
- **Market Transition**
- **Post-Reformulation (3-year)**

Rate per 100,000 Population


- Reformulated OPANA ER
- Original OPANA ER

**Predicted**

**95% CI**
### NAVIPPRO®: Abuse Prevalence by Alternate Routes of Administration (100 ASI-MV) - Tennessee vs Non-Tennessee

<table>
<thead>
<tr>
<th></th>
<th>Pre-Period</th>
<th>Post-Period</th>
<th>Percent Change from Pre- to Post-Period (%)</th>
<th>Percent Change 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tennessee Only</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Original OPANA ER</td>
<td>8.26</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Reformulated OPANA ER</td>
<td>N/A</td>
<td>5.69</td>
<td>-31.1</td>
<td>(-38.4, -22.9)</td>
</tr>
<tr>
<td><strong>Non-Tennessee</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Original OPANA ER</td>
<td>0.54</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Reformulated OPANA ER</td>
<td>N/A</td>
<td>0.24</td>
<td>-55.9</td>
<td>(-61.0, -50.1)</td>
</tr>
<tr>
<td></td>
<td>Pre-Period</td>
<td>Post-Period</td>
<td>Percent Change from Pre- to Post-Period (%)</td>
<td>Percent Change 95% CI</td>
</tr>
<tr>
<td>------------------------</td>
<td>------------</td>
<td>-------------</td>
<td>--------------------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td><strong>Tennessee Only</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Original OPANA ER</td>
<td>7.12</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Reformulated OPANA ER</td>
<td>N/A</td>
<td>1.47</td>
<td>-79.4</td>
<td>(-82.4, -75.9)</td>
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<tr>
<td><strong>Non-Tennessee</strong></td>
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<tr>
<td>Original OPANA ER</td>
<td>0.45</td>
<td>N/A</td>
<td>N/A</td>
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<td>Reformulated OPANA ER</td>
<td>N/A</td>
<td>0.06</td>
<td>-87.0</td>
<td>(-89.6, -83.8)</td>
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</table>
### NAVIPPRO®: Abuse Prevalence by Intravenous Route of Administration (100 ASI-MV) 
Tennessee vs Non-Tennessee

<table>
<thead>
<tr>
<th></th>
<th>Pre-Period</th>
<th>Post-Period</th>
<th>Percent Change from Pre- to Post-Period (%)</th>
<th>Percent Change 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tennessee Only</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Original OPANA ER</td>
<td>1.24</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Reformulated OPANA ER</td>
<td>N/A</td>
<td>4.53</td>
<td>264.6</td>
<td>(177.4, 379.1)</td>
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<tr>
<td><strong>Non-Tennessee</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Original OPANA ER</td>
<td>0.10</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Reformulated OPANA ER</td>
<td>N/A</td>
<td>0.16</td>
<td>56.1</td>
<td>(28.7, 89.4)</td>
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