Prescription Opioid Abuse: Abuse-Deterrent Opioids as Part of a Multipronged Approach
Table of Contents

• Chronic Pain and Prescription Opioids
• Source of Prescription Opioids and Patient Risk Assessment
• Routes of Prescription Opioid Abuse & Adverse Health Outcomes
• FDA Evaluation and Labeling of Abuse-Deterrent Opioids (ADOs)
• The Potential Role of Abuse-Deterrent Opioids (ADOs) in Helping to Deter Opioid Abuse
Chronic Pain: A Serious Public Health Issue

• Chronic pain is a major concern for individuals, families, and society, with an increasing prevalence, cost, and impact on quality of life
  • Millions of Americans are affected by chronic pain
  • Estimated annual cost of $560-635 billion

• While the use of prescription opioids has been linked to abuse, misuse, diversion, these medications still serve as an efficacious treatment option for patients in the management of chronic pain

• However, clinical guidelines for chronic pain recommend that opioids be considered only after an adequate trial of non-opioid options


Opioids Are Frequently Used to Treat Pain, Even Though Guidelines Recommend Use Only After Other Therapies

Opioid Prescriptions Dispensed by Retail Pharmacies (US, 1991-2015)

The Increase in Opioid Prescriptions Is Associated With Serious Health Consequences

Prescription opioid overdose deaths quadrupled from 1999-2010; emergency department (ED) visits increased by 183% from 2004-2011

53% to 80% of people who die from prescription opioid overdoses have a history of chronic pain.

3. Lanier WA et al. Presented at: Annual Epidemic Intelligence Service Conference; April 19-23, 2010; Atlanta, GA.
The CDC estimates that for every opioid overdose death in 2010, there were:

- **10** Abuse treatment admissions*
- **26** ED visits for misuse/abuse†
- **108** who abused/were dependent ‡
- **733** past-year nonmedical users‡

* Treatment admissions are for primary use of opioids: Treatment Exposure Data Set.
‡ Abuse/dependence and nonmedical use: National Survey on Drug Use and Health.

Note: Compiled by CDC from separate 2010 databases
Prescription Opioid Abuse: CDC Statistics

Today, at least half of all U.S. opioid overdose deaths involve a prescription opioid.¹

- Overdose deaths involving prescription opioids have quadrupled since 1999¹
- From 1999 to 2014, more than 165,000 people have died in the U.S. from overdoses related to prescription opioids.¹
- In 2014, more than 14,000 people died from overdoses involving prescription opioids.¹
- In 2014, almost 2 million Americans abused or were dependent on prescription opioids.²

²Substance Abuse and Mental Health Services Administration. National Survey on Drug Use and Health. 2014.
The Increase in Opioid Prescriptions Has Been Associated With a Dramatic Rise in Overdose Deaths

Age-Adjusted Opioid Overdose Death Rates\(^1\)*

*Age-adjusted death rates calculated by applying age-specific death rates to the 2000 US standard population age distribution. Overdose deaths involving opioids identified using ICD-10 codes. Deaths might involve >1 drug.

2. Lanier WA et al. Presented at: Annual Epidemic Intelligence Service Conference; April 19-23, 2010; Atlanta, GA.
Source of Prescription Opioids and Patient Risk Assessment
Understanding the Terminology

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
</table>
| Misuse¹  | • Intentional *therapeutic use* of a drug product in an inappropriate way  
           • Specifically excludes the definition of abuse                                    |
| Abuse¹   | • Intentional, *nontherapeutic use* of a drug product or substance, even once, to achieve a desirable psychological or physiological effect |
| Diversion² | • Intentional removal of a medication from legitimate distribution and dispensing channels  
                • Also involves the sharing or purchasing of drugs between family and friends, or individual theft from family and friends |

According to a 2013 Survey, About 70% of Nonmedical Users of Prescription Pain Relievers Get Them From Friends or Relatives

Note: Due to rounding, percentages do not add up to 100%.

*Other includes: “Wrote Fake Prescription,” “Stole from Doctor’s Office/Clinic/Hospital/Pharmacy,” and “Some Other Way.”

Identifying Patients at High Risk for Opioid Misuse and Abuse Is Extremely Challenging

Based on a Study of Primary Care Physicians

100%
N=367 patients confirmed as at high risk for opioid misuse and abuse*

74%
Incorrectly identified as at moderate risk (n=275)

5%
Correctly identified as at high risk (n=18)

5%
Incorrectly identified as at low risk (n=73)

Open-label, nonrandomized, noncomparative study in which PCPs were asked to identify patients at high risk for opioid misuse and abuse.

*Confirmed using SOAPP®-R (Screener and Opioid Assessment for Patients With Pain-Revised, a patient-completed 24-item questionnaire to identify risk for future misuse and/or abuse of opioids). For this study, SOAPP®-R score 0-9 = low risk; 10-21 = moderate risk; and ≥22 = high risk.

†Patients at high risk for opioid abuse (SOAPP®-R score ≥22 at baseline). Due to rounding, percentages do not add up to 100%, and n's do not = 367.


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Routes of Prescription Opioid Abuse & Adverse Health Outcomes
Prescription Opioids Can Be Misused and Abused by Different Routes

Examples of Abuse Methods

- The most common form of abuse is swallowing a number of intact capsules or tablets to achieve a feeling of euphoria
- Product manipulated in pursuit of more intense high resulting from rapid increase in opioid in the blood
- Methods vary among products, based on pharmacokinetic properties, bioavailability via different routes, ease of tampering, nature of euphoria, and presence of dangerous excipients

In a 2012 Survey, Half of People Abusing Prescription Opioids Reported Product Manipulation\(^1\)

Abuse Methods Involving Manipulation of the Product\(^2\)

- The most common form of abuse is swallowing a number of intact capsules or tablets to achieve a feeling of euphoria\(^1\)
- Product manipulation is more common with extended-release opioids, due to a higher drug content, than with immediate-release opioids\(^3\)

ER Opioids Are Tampered With for Purposes of Misuse and Abuse

Abuse of ER Formulations of Prescription Opioid Medications by Route of Administration (June 1, 2009 to August 8, 2010*)

*Prior to introduction of reformulated ER oxycodone and ER oxymorphone.
Note: Percentages for each drug do not add up to 100% because respondents could report multiple routes of administration.

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In One Study, Patients Admitted to an Abuse Treatment Center Reported Progression From Oral Ingestion to Snorting/Injection

Study looked at route of administration of controlled-release oxycodone at initiation of use/misuse and admission to an addiction-treatment center (October 2000 to March 2002; N = 187).

Initial Route of Administration (n = 112/187)
- Oral, 83%
- Snorting, 16%
- Injecting, <1%

Route of Administration at Treatment Admission (n = 133/187)
- Oral, 14%
- Snorting, 62%
- Injecting, 26%

Mean duration of prescription opioid use: 19.2 months*

*Average time between first use/misuse and addiction-treatment admission.

Non-oral (vs Oral) Misuse and Abuse Is Associated With Up to a Twofold Higher Risk for Severe Health Consequences

Proportion of Cases of Misuse/Abuse

- Oral: 92%
- Inhaling: 5%
- Injecting: 3%

Percentage of Cases Leading to Major Effect* or Death

- Oral: 8.6%
- Inhaling: 10.2%
- Injecting: 16.5%

*Symptoms that were life-threatening or resulted in significant residual disability or disfigurement.

FDA Evaluation and Labeling of Abuse-Deterrent Opioids (ADOs)
FDA Considers Development of Abuse-Deterrent Opioids To Be a “High Public Health Priority”

• Abuse-deterrent properties are defined as those shown to **meaningfully deter abuse**, even if they do not fully prevent it

• Abuse-deterrent technologies to date are intended to make:
  - manipulation (crushing, chewing, dissolving, extracting) of the opioid more difficult, or
  - the effect of the manipulated opioid less attractive or rewarding

• FDA guidance describes the studies to be conducted to demonstrate a given formulation has abuse-deterrent properties, how studies will be evaluated, and what labeling claims may be approved based on results. FDA remains supportive of ADO development.  

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### Potential Abuse-Deterrent Opioid Product Categories (FDA Defined)

<table>
<thead>
<tr>
<th>Technology</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical/chemical barrier</strong></td>
<td>• Physical barriers can prevent/deter manipulation&lt;br&gt;• Chemical barriers can resist extraction of the opioid&lt;br&gt;• Physical and chemical barriers can change the physical form of an oral drug, rendering it less amenable to abuse</td>
</tr>
<tr>
<td><strong>Agonist/antagonist combination</strong></td>
<td>• Antagonist added to interfere with, reduce, or defeat euphoria associated with abuse</td>
</tr>
<tr>
<td><strong>Aversion</strong></td>
<td>• Substances can be added to the product to produce an unpleasant effect if the dosage form is manipulated or is used at a higher dosage than directed</td>
</tr>
<tr>
<td><strong>Delivery system</strong></td>
<td>• Drug-release design or method of drug delivery (eg, depot injectable) offers resistance to abuse</td>
</tr>
<tr>
<td><strong>New molecular entities and prodrugs</strong></td>
<td>• Properties could include the need for enzymatic activation, different receptor-binding profiles, slower penetration into the CNS, or other novel effects&lt;br&gt;• Prodrugs with abuse-deterrent properties could provide a chemical barrier to the in vitro conversion to the parent opioid, which may deter abuse of the parent opioid</td>
</tr>
<tr>
<td><strong>Combination</strong></td>
<td>• Two or more of the above methods</td>
</tr>
<tr>
<td><strong>Novel approaches</strong></td>
<td>• Novel approaches or technologies not captured in the previous categories</td>
</tr>
</tbody>
</table>
2015 FDA Guidance: Premarketing and Postmarketing Studies of Abuse Deterrence

Category 1: Laboratory-based in vitro manipulation and extraction
Purpose: evaluate in vitro the ease with which the abuse-deterrent properties can be defeated or compromised

Category 2: Pharmacokinetic
Purpose: understand the in vivo properties of the formulation by comparing PK profiles

Category 3: Clinical abuse potential*
Purpose: measure and collect subjective response data predictive of the likelihood of product abuse

Category 4: Postmarketing studies
Purpose: determine whether the marketing of a product with abuse-deterrent properties results in meaningful reductions in abuse

*Also known as human abuse liability (HAL) studies.

Category 1: Laboratory-Based in vitro Manipulation and Extraction Studies

Purpose: evaluate in vitro the ease with which the abuse-deterrent properties can be defeated or compromised

- Designed with knowledge of properties of formulation and abuse methods
- Should fully characterize abuse-deterrent properties and effort to defeat them
- Assess simple and sophisticated mechanical and chemical ways to manipulate:
  - Defeating or compromising the controlled release of an opioid from an ER formulation
  - Preparing an IR formulation for alternative routes of administration
  - Separating opioid antagonist, if present, from opioid agonist
- Compare to appropriate non-ADO formulations

### Hypothetical Example of a Category 1 Extractability and Syringeability Study

#### Extractability
Amount of drug from new formulation and comparator that can be extracted after soaking for increasing lengths of time in various liquids

<table>
<thead>
<tr>
<th>Substance</th>
<th>ADO</th>
<th>Non-ADO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cola</td>
<td>1%</td>
<td>91%</td>
</tr>
<tr>
<td>Hot tea</td>
<td>6%</td>
<td>60%</td>
</tr>
<tr>
<td>Vinegar</td>
<td>0%</td>
<td>90%</td>
</tr>
<tr>
<td>Baking soda solution</td>
<td>1%</td>
<td>74%</td>
</tr>
</tbody>
</table>

#### Syringeability
Whether the dissolved product can be drawn up into a syringe, based on the temperature, plunger speed, and needle size

<table>
<thead>
<tr>
<th>Gauge</th>
<th>ADO</th>
<th>Non-ADO</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>21</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>25</td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
</table>

Drug composition may vary based on technology.

Data for illustrative purposes only.
Category 2: Pharmacokinetic Studies

The rate of rise of drug concentration should be assessed when possible, because it is thought to contribute to differential abuse potential among drugs, formulations, and routes of administration.

Category 3: Clinical Abuse Potential* Studies

**Purpose:** measure and collect subjective response data predictive of the likelihood of product abuse

- Pharmacology assessments that provide unique information relevant to CNS-active drugs
- Compare subjective responses to “drug liking,” “drug high,” and “willingness to take drug again” for each active agent and placebo

**Study design principles:**
- Randomized, double-blind, placebo-controlled, positive comparator-controlled, crossover
- Enrollment of an appropriate abusing population
- Prequalification phase
- Relevant routes of administration
- Preparation of samples with consideration of blinding
  - Potential use of a proxy solution for IV injection

*Also known as human abuse liability (HAL) studies.

Understanding Clinical Abuse Potential Study Data

Graph for illustrative purposes only.

Category 4: Postmarketing Studies

Purpose: determine whether the marketing of a product with abuse-deterrent properties results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes

Examples of abuse-related clinical outcomes

- Addiction data
- Overdoses/poisonings
- Deaths

“Given the changing landscape, a numerical threshold cannot define what would be considered a meaningful reduction.”

Where to Find Abuse-Deterrent Data and Labeling

• Refer to prescribing information section 9: DRUG ABUSE AND DEPENDENCE
  - Includes descriptions and data regarding the specific product’s abuse-deterrent studies (will vary by product)

• If such information does not appear in a product’s labeling under section 9, that product is not an ADO, by FDA standards

The pharmacokinetic data demonstrate that crushing [Tradename] results in the simultaneous release and rapid absorption of opioid and antagonist. These data along with the results from oral and intranasal clinical abuse potential studies and a clinical abuse potential study of intravenous opioid and antagonist to simulate crushed [Tradename] indicate that [Tradename] has properties that are expected to deter abuse via the oral, intranasal, and intravenous routes. However, abuse of [Tradename] by these routes is still possible.

~ Example of potential labeling for an ADO with category 2 and 3 data
The Potential Role of Abuse-Deterrent Opioids in Helping to Deter Opioid Abuse
Progression of Opioid Abuse: A Multipronged Approach in Addressing Abuse

Initial Opioid Treatment

Suspected Abuse or Misuse

Addiction

Overdose

Potential Strategies:

- Patient Agreements
- Patient Education
- Safe storage & Disposal
- PDMP
- ADOs

- Urine Tests
- Pill limits

- Medication-Assisted Treatment Programs

- Naloxone
- Addiction Counseling


Epidemiological Data From Actual Use Indicate That Abuse-Deterrent ER Oxycodone Reduced Its Abuse

Among Patients Reporting Abuse of Prescription Opioids, Abuse* of ER Oxycodone Decreased ~50% After Introduction of its Reformulation

Before Reformulation
(n=2894/12,211)

23.7%
June 1, 2009–August 8, 2010

After Reformulation
(n=1705/14,091)

49% reduction in abuse of opioid
(P<.0001)

12.1%
August 9, 2010–March 31, 2012

* In past 30 days.
Using the Addiction Severity Index-Multimedia Version (ASI-MV), 140,496 subjects were assessed for substance use problems at 357 US centers, which were part of the NAVIPPRO surveillance system. Data collected during a 34-month period (~11 quarters) from June 1, 2009 to March 31, 2012. Among total sample, 18.8% reported abuse of any prescription opioid.
Impact of a Tamper Resistant Opioid Formulation: NAVIPPRO Data Shows a Change in Frequency of Abuse

The average number of days in the past 30 days abusing ER oxycodone and comparators before and after the introduction of ADO oxycodone ER

<table>
<thead>
<tr>
<th></th>
<th>Original Oxycodone ER (Days) Before period (6/09-8/8/10)</th>
<th>After Reformulated ADO Oxycodone ER (Days) (8/9/12-3/31/12)</th>
<th>Pre-Post Percentage Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER oxycodone</td>
<td>10.8</td>
<td>7.5</td>
<td>-30.4%*</td>
</tr>
<tr>
<td>ER oxymorphone</td>
<td>5.1</td>
<td>7.8</td>
<td>+52.2%*</td>
</tr>
<tr>
<td>ER morphine</td>
<td>9.1</td>
<td>10.0</td>
<td>+10.6%†</td>
</tr>
</tbody>
</table>

N=140,496 individuals assessed for substance abuse treatment at 357 U.S. centers

* p<.0001, † p=0.0909

## Summary of Observed Changes in ER Oxycodone Upon Introduction of ADO ER Oxycodone

<table>
<thead>
<tr>
<th>Observation</th>
<th>Data Source</th>
<th>Timeframe</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self reported abuse</td>
<td>NAVIPPRO Drug Treatment(^1)</td>
<td>1 year prior, 18 months post</td>
<td>-41% (P&lt;0.0001)</td>
</tr>
<tr>
<td>Self reported abuse</td>
<td>RADARS Opioid Treatment Program(^2)</td>
<td>5.5 years prior, 3 years post</td>
<td>Decreased (% not reported)</td>
</tr>
<tr>
<td>Self reported abuse</td>
<td>RADARS Survey of Key Informants(^2)</td>
<td>2.5 years prior, 3 years post</td>
<td>Decreased (% not reported)</td>
</tr>
<tr>
<td>Drug abuse related poison center exposures</td>
<td>RADARS Poison Center Exposures(^3)</td>
<td>1 year prior, 2 years post</td>
<td>-36% (P&lt;0.001)</td>
</tr>
<tr>
<td>Drug diversion rates</td>
<td>RADARS Drug Diversion(^4)</td>
<td>2 years prior, 18 months post</td>
<td>-53% (P&lt;0.001)</td>
</tr>
<tr>
<td>Drug price – law enforcement</td>
<td>RADARS Drug Diversion(^4)</td>
<td>Time of switch to 1 year post</td>
<td>-22% (P=0.002)</td>
</tr>
<tr>
<td>Self reported street price</td>
<td>RADARS StreetRX(^5)</td>
<td>Single time period comparison post switch</td>
<td>-37%</td>
</tr>
</tbody>
</table>

Prescription Opioid Abuse: Consider ADOs as part of a Multipronged Approach

Opioid abuse is a growing epidemic, as shown in overdose deaths, and all patients are at risk\(^1,2\)

Those who abuse often obtain opioids from legitimate prescriptions\(^4\)

Oral overconsumption is most common; non-oral misuse and abuse has a higher rate of severe consequences\(^5\)

ADO technologies are intended to make product manipulation more difficult or the effect of the manipulated product less rewarding\(^3\)

Consider ADOs as part of a multipronged approach to responsible opioid prescribing\(^6\)

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