Understanding Abuse Deterrent Opioids

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Learning Objectives

• Identify and differentiate abuse-deterrent properties
• Describe the role of abuse-deterrent opioids in the opioid epidemic
• List the types of studies involved in abuse-deterrent opioids
• Summarize the impact of abuse-deterrent opioids may have on healthcare providers
Opioid Epidemic

• On an average day in the US...
  – More than 650,000 opioids are dispensed
  – 3,900 people initiate nonmedical use of a prescription opioid
  – 78 people die from an opioid related overdose
FDA Opioids Action Plan

To reverse the epidemic while still providing patients with access to effective relief

- Advisory Committees
- IR Labeling
- Post-market
- REMS
- Abuse Deterrent
- Supporting Treatment
- Risk-Benefit
FDA Opioids Action Plan

To reverse the epidemic while still providing patients with access to effective relief

**Advisory Committees**
- Expand the use and advice from external experts

**IR Labeling**
- Develop warnings and safety information

**Post-market**
- Better evidence on the serious risks of misuse and abuse with long-term use

**REMS**
- Update and increase number of prescribers who receive training on pain management and safe prescribing

**Abuse Deterrent**
- Spur innovation and generic abuse-deterrent formulations and product development

**Supporting Treatment**
- Access to overdose treatment, safer prescribing, new classes of pain medicine

**Risk-Benefit**
- Reassess risk-benefit framework and incorporate broader public health impact
Identifying Opioid Abuse and Misuse

• Abuse – intentional, *non-therapeutic use* of a drug product or substance, even once, to achieve a desirable psychological or physiological effect

• Misuse – intentional *therapeutic use* of a drug product in an inappropriate way and specifically excludes the definition of abuse
What is an Abuse Deterrent Opioid

• Abuse-deterrent formulation properties that are expected to meaningfully deter certain types of abuse and/or make abuse more difficult or less rewarding
Challenge Question

- Select the ways abuse-deterrent opioids can be abused?
  - Swallowed
  - Crushed and swallowed
  - Crushed and snorted
  - Crushed and smoked
  - Dissolved and injected
  - Abuse-deterrent opioids CANNOT be manipulated and abused.
Challenge Question

• Select the ways abuse-deterrent opioids can be abused?
  ✓ Swallowed
  ✓ Crushed and swallowed
  ✓ Crushed and snorted
  ✓ Crushed and smoked
  ✓ Dissolved and injected
  ❏ Abuse-deterrent opioids CANNOT be manipulated and abused.
What is an Abuse Deterrent Opioid

• AD formulations target the known or expected routes of abuse, such as:
  – crushing in order to snort
  – dissolving in order to inject
• The science of abuse deterrence is relatively new, and both the formulation technologies and the analytical, clinical, and statistical methods for evaluating those technologies are rapidly evolving.
Challenge Question

• Which of the following is the most common form of abuse?
  - Smoking
  - Injecting
  - Swallowing
  - Snorting
Challenge Question

• Which of the following is the most common form of abuse?
  - Smoking
  - Injecting
  - **Swallowing**
  - Snorting
What is an Abuse Deterrent Opioid

• Abuse-deterrent, not abuse-proof or tamper-resistant
• Most common form of opioid abuse: swallowing
• Purpose of opioid medications is to deliver opioids to a patient
Role of Abuse-Deterrent Opioids

• “Abuse-deterrent properties are still evolving and is only one piece in a much broader strategy to combat the problem of opioid abuse. Encouraging innovation to increase access to generic forms of AD opioid medications is an important element in that strategy.”

-FDA Commissioner Robert Califf, MD
Challenge Question

• Select all of the recognized abuse-deterrent formulations
  ☐ Physical/chemical barriers
  ☐ Agonist/antagonist combinations
  ☐ Aversion effects
  ☐ Delivery system
  ☐ New Molecular Entities and prodrugs
Challenge Question

• Select all of the recognized abuse-deterrent formulations

✓ Physical/chemical barriers
✓ Agonist/antagonist combinations
✓ Aversion effects
✓ Delivery system
✓ New Molecular Entities and prodrugs
Abuse-Deterrent Categories

- Physical/chemical barriers
- Agonist/antagonist combinations
- Aversion
- Delivery system
- New molecular entities and prodrugs
- Combination
- Novel approaches
## Abuse-Deterrent Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical/chemical barriers</strong></td>
<td>Prevent chewing, crushing, cutting, grating, or grinding and can include chemical barriers like gelling agents or solvents to limit mechanical manipulation.</td>
</tr>
<tr>
<td><strong>Agonist/antagonist combinations</strong></td>
<td>Antagonist added to release upon manipulation and interfere, reduce, or defeat euphoria associated with abuse.</td>
</tr>
<tr>
<td><strong>Aversion</strong></td>
<td>Added substances to produce unpleasant effect upon manipulation e.g. nasal irritant.</td>
</tr>
<tr>
<td><strong>Delivery system</strong></td>
<td>Release designs or drug delivery that offers resistance to abuse e.g. sustained-release depots.</td>
</tr>
<tr>
<td><strong>New molecular entities and prodrugs</strong></td>
<td>New molecular entity or prodrug with different receptor binding profiles, need for enzymatic activation, CNS penetration, or other novel effects.</td>
</tr>
<tr>
<td><strong>Combination</strong></td>
<td>Two or more of the above methods combined to deter abuse.</td>
</tr>
<tr>
<td><strong>Novel approaches</strong></td>
<td>A new approach or technology not captured in aforementioned categories.</td>
</tr>
</tbody>
</table>
Determining AD Properties

• To meet the FDA’s standards
  – Supported by evidence from in vitro (laboratory) and, where appropriate, in vivo (human) studies
  – Sponsor communications must be truthful and not misleading, supported by sound science, and the totality of the data
Guidance on Evaluation and Labeling

• Based on totality of evidence

• Premarket studies
  1) Laboratory manipulation and extraction
  2) Pharmacokinetic studies
  3) Clinical abuse potential studies

• Postmarket Studies
Laboratory Studies

• Understand product characteristics and performance with spoons, cutters, coffee grinders, heat, cold, etc.

• Attempt to extract with solvents including water, vinegar, ethanol, etc.

• Collect data on particle size distribution (nasal), amount from vaporization (smoking), and melting/liquid extraction (injection), etc.
Pharmacokinetic Studies

• Understand *in vivo* properties comparing pK of manipulated and intact formulations

• Healthy volunteers with naltrexone to understand ADME ($C_{\text{max}}$, $T_{\text{max}}$, AUC, $t_{1/2}$) with routes relevant to proposed product

• Collect data on how food and alcohol can alter pharmacokinetic parameters

• Collect adverse events and insights related to abuse potential
Clinical Studies

• Double-blind, placebo-controlled, and positive controlled crossover preferred
• Study population includes opioid-experienced, recreational drug users
• Attention should be paid to interpreting subjective results of preference to manipulated and intact formulation
• Overall goal to assess abuse potential outcome measures and decrease in responses for potentially abuse-deterrent formulation compared to a positive control
Postmarket Studies

• Determine whether the marketing of abuse-deterrent opioids results in meaningful reductions in abuse, misuse, and adverse clinical outcomes, including addiction, overdose, and death in the “real world”

• Categorized as either:
  – Formal studies
  – Supporting information
Generics

• Ensure widespread access to safe and effective generic versions of abuse-deterrent opioids to patients needing safe and effective analgesia

• Generics should not exacerbate the public health problems associated with prescription opioid abuse

• Comparative evaluation of reference and test product should be conducted
Labeling

• FDA encourages labeling that includes in vitro, pharmacokinetics, and clinical abuse potential for providers
• Should reflect predictive quality of premarket studies and include results of relevant completed postmarket studies
• Should describe specific routes the product has been developed to deter
Challenge Question

• True or False: The label will disclose how the drug can be abused
  - True
  - False
Challenge Question

• True or False: The label will disclose how the drug can be abused
  - True
  - False
Approved ER/LA Opioids with AD Properties

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>OxyContin®</td>
<td>Oxycodone—crush/extraction resistant</td>
<td>April 2013</td>
</tr>
<tr>
<td>Targiniq™ ER</td>
<td>Oxycodone hydrochloride and naloxone</td>
<td>July 2014</td>
</tr>
<tr>
<td>Embeda®</td>
<td>Morphine sulfate and naltrexone</td>
<td>October 2014</td>
</tr>
<tr>
<td>Hysingla™ ER</td>
<td>Hydrocodone—crush/extraction resistant</td>
<td>November 2014</td>
</tr>
<tr>
<td>Morphabond™</td>
<td>Morphine sulfate—crush/extraction resistant</td>
<td>October 2015</td>
</tr>
<tr>
<td>Xtampza™ ER</td>
<td>Oxycodone—crush/extraction resistant</td>
<td>April 2016</td>
</tr>
<tr>
<td>Troxyca® ER</td>
<td>Oxycodone hydrochloride and naltrexone hydrochloride</td>
<td>August 2016</td>
</tr>
</tbody>
</table>

- There are currently no immediate-release opioids with abuse-deterrent labeling
- None of these products contain data deterring abuse in the real world
Challenge Question

• True or False: All companies with approved brand name opioids with abuse-deterrent properties must conduct post-marketing studies.
  ☐ True
  ☐ False
Challenge Question

• True or False: All companies with approved brand name opioids with abuse-deterrent properties must conduct post-marketing studies.
  ✓ True
  ❏ False
Abuse-Deterrent Opioids in Postmarket

• All approved brand name opioids with AD properties are required to conduct postmarket studies
  – Determine the impact that AD technologies are having in the real world

• Having that information is critical, and will allow the Agency to take the next important policy steps in this area.
Key Points for Clinicians

- Addiction with or without abuse-deterrent properties
- Abuse can still occur even in abuse-deterrent opioids
- Generics should demonstrate abuse-deterrent properties equivalent to or better than brand-name counterpart
- ER/LA REMS is a program required by FDA for companies to educate prescribers
Patient Pearls

• Keep medications in a secure location out of reach and sight of children and pets
• Properly dispose of medications that are no longer needed
Questions?

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