Understanding Abuse Deterrent Opioids

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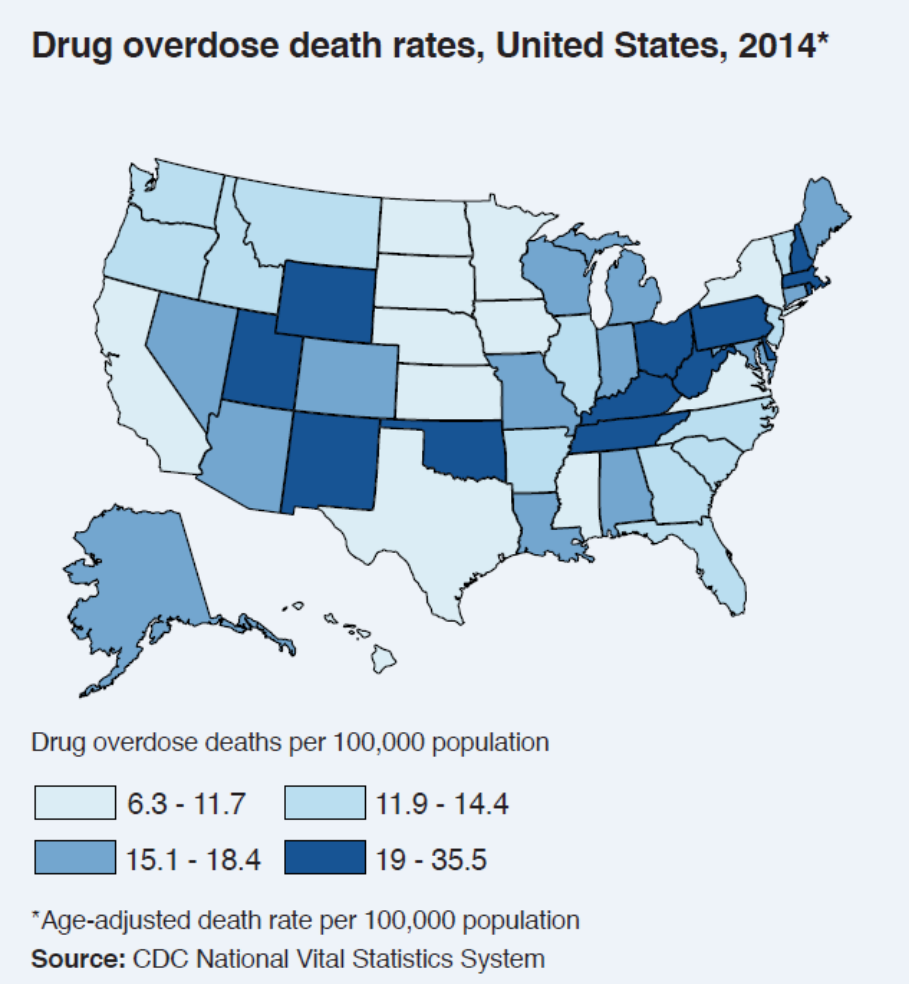
Learning Objectives

- 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

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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

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  - ✓**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

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  - ❑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

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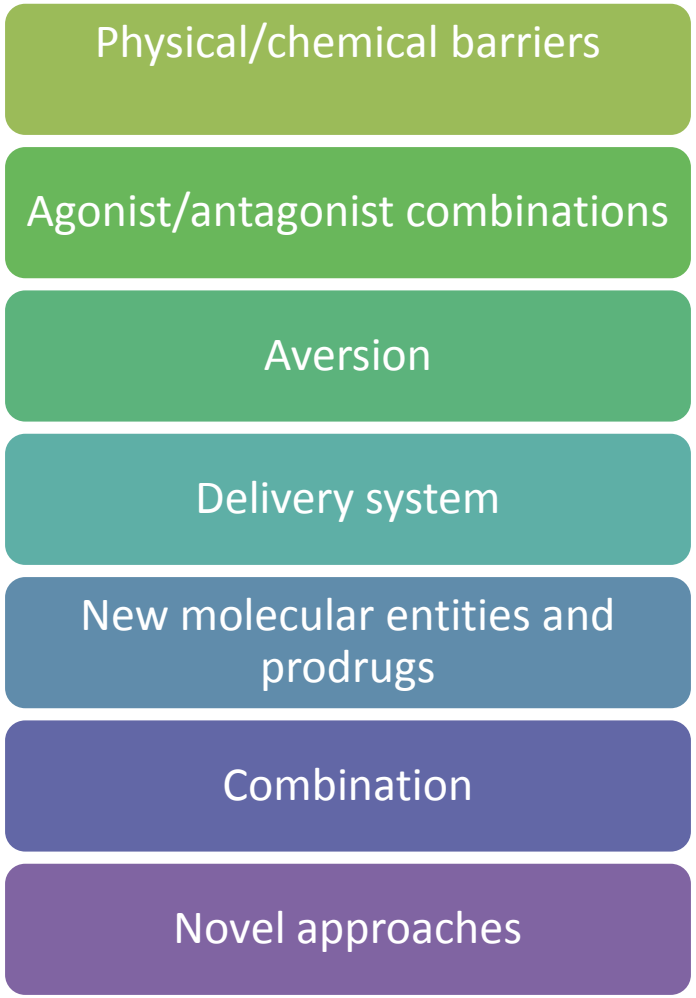
Abuse-Deterrent Categories



Abuse-Deterrent Categories

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

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_{max}, T_{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

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

- 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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