An Overview of Abuse-Deterrent Formulations

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Disclosures

- Ernest J. Dole is a speaker for Millennium Health
- Jeffrey Fudin is on the speakers’ bureaus for Millennium Healthcare and AstraZeneca and he is a consultant to Millennium Healthcare and Zogenix. He also serves as a section editor for Pain Medicine and on the editorial board of Practical Pain Medicine.
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Development and Support

This activity was developed by the American Pharmacists Association and supported in part by an independent educational grant from Purdue Pharma L.P.
This webinar is intended to be primer for APhA Annual Meeting – held March 27-30, 2015 in San Diego. To register go to: aphameeting.org.

2-hour live session held at APhA2015, “A Review of Abuse Deterrent Formulations”

Other Abuse Deterrent webinars located at pharmacist.com: (available after 12/15/14)

“The Burgeoning Role of Pharmacy in Opioid Therapeutics and Mitigating Abuse”

**Attendance Code**

14DM

To obtain CPE credit for this activity, you are required to actively participate in this session. The attendance code is needed to access the evaluation and CPE form for this activity. Your CPE must be filed by December 16, 2014 in order to receive credit.

**Accreditation Information**

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity, An Overview of Abuse Deterrent Formulations is approved for 1 hour of continuing pharmacy education credit (0.1 CEUs). The ACPE Universal Activity Number assigned by the accredited provider is: 0202-0000-14-178-L04-P.

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Initial Release Date: December 2, 2014

Target Audience: Pharmacists

ACPE Activity Type: Knowledge-based

Learning Level: 2

Fee: There is no fee for this activity
Learning Objectives

- Identify the characteristics that make various opioids desirable among abusers.
- Explain how oral formulations of opioids are abused.
- Describe the technology of abuse deterrent formulations (ADFs) and how they can deter opioid abuse.
- Discuss the paradigm shift of abused opioids with the advent of prescription drug monitoring programs (PDMPs).

The opioid of choice among individuals who abuse prescription opioids is:
A. Hydrocodone
B. Hydromorphone
C. Morphine
D. Oxycodone

Which abuse-deterrent formulation has the highest probability of adverse events?
A. Physical barriers
B. Osmotic agents
C. Sequestered aversive agents
D. Sequestered antagonistic agents
Regarding PDMPs, which of the statements below is true?

A. The use of PDMPs has been associated with an increase in prescribing of opioid medication by providers  
B. The use of PDMPs has been associated with a decrease in prescribing opioid medication  
C. The use of PDMPs has been associated with a “chilling effect” in prescription opioid medication  
D. The primary purpose of PDMPs is law enforcement

Anatomy of Reward

Mesolimbic Dopaminergic Pathway  
VTA: ventral tegmental area  
Sometimes called the “pleasure pathway” or the “reward pathway”. It actually mediates motivated behavior, rather than the specific experience of a given drug.

Opioid Attractiveness Scale

Intrinsic Properties
- Ease of extractability
- Rapidity of onset
- Duration of effect
- Presence of impurities
- Ease of hiding

Extrinsic Properties
- Price
- Availability
- Availability of alternatives
- Stigma

Characteristics of Opioids That Predispose to Abuse

- **Rapid Bioavailability**
  - Crushing
  - Grinding/Chewing
  - Dissolving
  - Needle aspiration
  - Filtration and Solvent Extraction
  - Cmax and t1/2

- **Oral**
  - Time to Cmax

- **Intravenous**

Choice of Oral Opioids Without ADFs

- **1st**: Oxycodone

- **2nd**: Morphine and hydromorphone


How to Abuse Opioids: A Short Tour of the Internet and What Your Patients May Be Reading

- **How to Abuse OP OxyContin, How to Get High OP OxyContin**: "Compress the pill with the pliers in the circled area many times in a sense that the pill is standing up, then the opposite direction, and then keep repeating it until you see the coating start to break. This will totally ruin the coating and will not take more than 5-10 min" — [http://www.bluelight.org/vb/threads/526671](http://www.bluelight.org/vb/threads/526671)

- **Meds Chat.com, The People's Medicine Community: Can you snort OxyContin?**: "Oxy 80 DP can be broken down into a powder form that in fact can be snorted. You will need to obtain a Nutmeg Grinder with a sealed container to catch the shavings (powder). From there you can figure it out. I only say this because of being a chronic pain patient myself, and I know what its like to wait for the time release to actually release and it doesn’t." — [http://www.medschat.com/topics/how-to-snort-the-new-oxycontin/](http://www.medschat.com/topics/how-to-snort-the-new-oxycontin/)
**How to Abuse Opioids: A Short Tour of the Internet and What Your Patients May Be Reading**

- Question is regarding both pain relief and getting high (MS Contin vs fent): “My doctor has been pretty straight forward as far as the oxycontin 40s go, he told me “look, these are supposed to last 12 hours but all my patients say after 8-9 hours the pain relief is gone” which is why he bumped me an extra 40 roxy 30s for that part. There are some months i will binge and do my script over 15 days and deal with the withdrawals either by suboxone or what not still i refill. other times i know i’m going to be in a busy month I take my meds properly.”

- Top Three Weirdest Ways to Abuse New OxyContin “Tamper-Proof” Pills:
  - “…need to take the coating off (tablet) after that chop up into as much pieces as you can take a shot glass fill it 3 quarters of the way with coca cola or pepsi and put the pill in and let it sit for an hour and take the glass scoop up the gel off the top of the soda and then take the shot”

**FDA Goals for ADFs**

- Incentivize the development of opioid medications with progressively better abuse-deterrent properties and support their use when indicated
- Assure appropriate development and availability of generics, reflecting their importance in U.S. health care
- Provide appropriate access to pain treatments for patients, including opioid medications
- Reduce the misuse and abuse of prescription opioids


**The Search for the Magic Bullet**

- Analogy is antibiotics
- Reformulating long-acting opioid analgesics to make them more difficult to abuse by those with substance use disorders (SUD) but innocuous to the compliant patient
- ADFs depend on differences in the way drug abusers and adherent patients use opioids

2013 FDA Draft Guidance for Industry: Criteria for Studies to Identify Characteristics for ADFs

- Scientifically rigorous
- Consider the most common routes of abuse

FDA Criteria for Label Claims for ADFs

- Grouped according to source and type of data
  - Tier 1: Physical/Chemical Barriers to Abuse
    - Examples: data on crushing and extraction
  - Tier 2: PK Data
    - Clinical serum concentrations (e.g., Tmax, Cmax)
  - Tier 3: Demonstration of Reduced Abuse Potential
    - Clinical Abuse Potential Studies

FDA Evaluation of ADFs: Pre-Market

<table>
<thead>
<tr>
<th>Study type</th>
<th>Advantages</th>
<th>Drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1, in vitro studies</td>
<td>Tailored and product-specific testing</td>
<td>To identify abuse deterrent characteristics not well established</td>
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<td></td>
<td>Differences observed in vitro might not correlate with clinically important abuse deterrent characteristics.</td>
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<td></td>
<td></td>
<td>False-negative findings</td>
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<td></td>
<td>Effects unrelated to opioid exposure may impact subject's experience</td>
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<tr>
<td>Category 2, PK studies</td>
<td>Characterisation/local availability of manipulated formulations administered via specific route</td>
<td>Relationship between PK and abuse potential study results is not well established.</td>
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<tr>
<td></td>
<td></td>
<td>Effects unrelated to opioid exposure may impact subject's experience</td>
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<td></td>
<td></td>
<td>Drug manipulation method can impact study outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conducting such studies might not always be feasible</td>
</tr>
<tr>
<td>Category 3, clinical abuse potential studies</td>
<td>Examines the interaction between manipulated drug product and subjective response of drug abusers</td>
<td>Drug manipulation method can impact the study outcomes. Conducting such studies might not always be feasible</td>
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</table>
FDA Criteria for Label Claims for ADFs

– Tier 4: Demonstration of Reduced Abuse
  – Post-marketing data on use and misuse of marketed product


FDA Evaluation of ADFs: Post-Marketing

<table>
<thead>
<tr>
<th>Study type</th>
<th>Advantages</th>
<th>Limitations</th>
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</thead>
<tbody>
<tr>
<td>Post-marketing</td>
<td>Ultimate demonstration of the ADF effectiveness</td>
<td>Data sources directly measuring abuse are limited</td>
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<tr>
<td></td>
<td></td>
<td>• Formulation-specific exposure can be difficult to determine</td>
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<tr>
<td></td>
<td></td>
<td>• For new market entrants, it could take years or if not decades to</td>
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<td>collect sufficient data demonstrating epidemiological impact</td>
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Abuse Studies Checklist

• Construct: What are you trying to measure?
• Measure: Is your measure of that construct valid?
• Population: Implications for generalizability? For sample size?
• Exchangeability: Are your groups comparable?

  – Katz N. Clinical studies of abuse deterrent opioid analgesics: definitions, current approaches, and critical issues. Tufts University.
  – Adams et al. J Pain Symptom Manage. 2006
Human Abuse Liability Studies

- Main focus tends to be euphoria under different treatment conditions
- Unclear predictive validity for “real-world” drug abuse
- Validity of commonly used measures unclear
- Target population rarely if ever studied
  - Katz N. Clinical studies of abuse deterrent opioid analgesics: definitions, current approaches, and critical issues. Tufts University.

Clinical Trials for Analgesia

- Prospective measures related to abuse rarely implemented
- Appropriate method for deriving predictive measures of abuse from AEs unclear
- High-risk patients typically excluded
  - Katz N. Clinical studies of abuse deterrent opioid analgesics: definitions, current approaches, and critical issues. Tufts University.

Clinical Trials for Abuse

- Few precedents exist
- Need to choose which construct to measure
- Unclear which measures to choose; none validated in active vs. active studies
- Sample size requirements unclear
- Impact of study population on (1) generalizability of results and (2) sample sizes are unclear
  - Katz N. Clinical studies of abuse deterrent opioid analgesics: definitions, current approaches, and critical issues. Tufts University.
Pharmaceutical Strategies for ADFs

- Physical barriers to prevent crushing, chewing, or dissolution in liquids
- Sequestered aversive components that create adverse effects if the product is crushed or chewed
- Sequestered antagonists to neutralize opioid effects in the event of crushing or chewing


Current Opioid ADFs: Advantages and Disadvantages

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
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<tbody>
<tr>
<td>Physical barriers</td>
<td>Prevents abuse from chewing or crushing tablets</td>
<td>Does not prevent abuse of intact tablets. Only 1 FDA approved formulation available.</td>
</tr>
<tr>
<td>Aversive components</td>
<td>May prevent abuse by crushing or chewing tablets.</td>
<td>FDA approved formulation available.</td>
</tr>
<tr>
<td>Sequestered antagonists</td>
<td>Prevents abuse by crushing or chewing tablets.</td>
<td>FDA approved formulation available.</td>
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FDA Approved ADFs

- Embeda: Morphine/naltrexone
- Targiniq: Oxycodone/Naloxone
- Oxycontin: Oxycodon reformulated

### Recommendations for Selecting an Opioid ADF

<table>
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<th>Population</th>
<th>Recommendation</th>
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<tr>
<td>Patients at risk of abuse</td>
<td>- Use of a crush-resistant opioid or one with a sequestered antagonist or aversive component</td>
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</table>
| Elderly patients | - Consider a crush-resistant opioid for older patients to help swallowing  
- Avoid opioids with sequestered antagonists or aversive components in elderly as these may precipitate withdrawal symptoms or AEs  
- It is better to prevent chewing/crushing by an older patient than to deny analgesia or cause AEs for a nonabusing patient who makes a mistake |
| Patients who may be targeted for theft | Prescribe any available tamper-resistant opioid to patients who may be targeted for theft; this will protect the compliant patient and create a barrier to the abuser, who will have to go elsewhere for an opioid supply |


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### The Impact of ADFs on Prescription Opioid Abuse

- None of the current approaches to deterrence has been validated by long-term post-marketing data as actually succeeding in deterring abuse
- Currently the impact of ADFs has been shown to have a mixed effect
- The introduction of an ADF opioid may cause a shift away from that opioid and an increase in comparable opioids


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### Future Directions

- The FDA may not approve new opioids or opioid formulations that lack meaningful abuse-deterrent properties, unless the new entrant fulfills an unmet clinical need or provides a unique therapeutic benefit
- Meaningful abuse-deterrent properties should be defined as those supporting a claim that “a product is expected to result in a meaningful reduction in abuse” for a given route of abuse (Tier 3 labeling)
- ADFs of all major opioids marketed; no opioids w/o ADF
- With the marketing of new products with meaningful abuse-deterrent properties, the FDA will assess the risk/benefit ratio of those opioid products without abuse-deterrent properties
Prescription Drug Monitoring Programs and Diversion

- Statewide electronic databases that collect prescribing and dispensing data on controlled substances dispensed in the state
- Congress appropriates funds to support state PDMPs through DOJ-administered grants as well as HHS-administered grant.

Goals of PDMPs

- To reduce prescription drug abuse and diversion
- To educate and inform practitioners and the public
- To develop and advance public health initiatives
- To facilitate early identification and intervention in cases of drug misuse or abuse
- To aid investigation and law enforcement, and to safeguard the integrity and access to the programs’ database

Advantages of Using PDMP Data in Evaluation

<table>
<thead>
<tr>
<th>Examples of Intervention</th>
<th>PDMP Data Can Evaluate</th>
</tr>
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<tbody>
<tr>
<td>PDMP improvements</td>
<td>Changes in drug use, prescriber use of the system</td>
</tr>
<tr>
<td>Doctor shopping and pain clinic laws</td>
<td>Rates of behaviors and prevalence of clinics with extraordinary volumes</td>
</tr>
<tr>
<td>High level of drug detail available to medical and pharmacy personnel, involving monitoring of C II through C IV medications, including formulation, prescriber, and dispenser identifications</td>
<td></td>
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<tr>
<td>Timelessness better than most other data sources</td>
<td></td>
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<tr>
<td>Longitudinal linkage of patient and provider data</td>
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Effectiveness of PDMP

- States without PDMPs are more likely to experience higher rates of controlled substance diversion
  - An independent evaluation of Kentucky’s PDMP noted that in 2006, distribution of oxycodone was highest in Florida compared with other states on interstate Route I-75, while distribution of hydrocodone was highest in Tennessee.
  - Since 2004, oxycodone distribution in Kentucky, a state with a well-established PDMP, rose at a much lower rate than in either Florida or Tennessee, neither of which had active PDMPs during this period.

- States with PDMPs use PDMP data to improve clinically appropriate prescribing and reduce doctor shopping
  - A study of medical providers in Ohio emergency departments found that 41% of those given PDMP data altered their prescribing for patients receiving multiple simultaneous narcotics prescriptions.
  - Data so far suggest that such programs reduce abuse practices

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Effectiveness of PDMP

- PDMPs offer states a more efficient means of detecting and deterring illegal diversion
  - These programs provide state health care licensing and regulatory agencies and law enforcement with quick access to comprehensive information on the prescribing, dispensing, and purchasing of controlled substances that are most likely to be targets for diversion

Impact of PDMP on Prescribing of Controlled Substances

- PDMPs Do Not Inhibit Physician Prescribing of Controlled Substances for Legitimate Medical Conditions
  - Data provided by California, Idaho, Kentucky, New York and Ohio reflect that the number of controlled substance prescriptions and/or doses has generally increased after implementation of a PDMP.
  - Anecdotal evidence suggests that physicians in PDMP states are more comfortable writing controlled substance prescriptions for their patients because the PDMP provides a tool for them to monitor their patients’ controlled substance usage, and to verify the patients are adhering to their treatment regimen.
  - Twilman report suggests that prescription programs caused a shift in prescription practice, while the actual rate of abuse may not have been reduced; however, more recent data suggest that proactive use of the PDMPs results in the decreased growth of prescription medication sales, possibly reflecting less abuse/diversion.

Conclusions

- Those abusing opioid medication favor opioids with short time to Cmax and t1/2
- Oxycodone appears to be the opioid of choice to abuse
- The FDA wishes to incentivize the development of opioid medications w/ ADFs, while at the same time assuring reliable access to patients needing these medications.
Conclusions

• The FDA has provided industry guidance for the development of ADFs
• Currently, there are only 3 products on the market that have been granted abuse-deterrent labeling
• No ADF currently on the market has been shown by post-marketing research to decrease abuse
• The FDA would like to see a future where ADFs are the only products on the market
• The use of PDMPs is an effective tool to help combat diversion and does not appear to have a chilling effect on the prescribing of opioids

The opioid of choice among individuals who abuse prescription opioids is:
A. Hydrocodone
B. Hydromorphone
C. Morphine
D. Oxycodone

Which abuse-deterrent formulation has the highest probability of adverse events?
A. Physical barriers
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Regarding PDMPs, which of the statements below is true?

A. The use of PDMPs has been associated with an increase in prescribing of opioid medication by providers
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