Setting the Stage: Are Abuse-Deterrent Opioids Formulations Ready for Prime Time?

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New York City Poison Control Center
Research and Development:

- Expedite research, through grants, partnerships with academic institutions, and priority New Drug Application review by FDA, on the development of treatments for pain with no abuse potential as well as on the development of abuse-deterrent formulations (ADF) of opioid medications and other drugs with abuse potential. (NIDA/FDA)
Opioid Abuse Liability

- the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect.

FDA Guidance 2015

- Reinforcing
- Rapid onset
- High intensity
- Rapid offset
- Low cost
- Low effort
**WARNING:**

OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

OxyContin Tablets are NOT intended for use as a prn analgesic.

OxyContin 60 mg, 80 mg, and 160 mg Tablets, or a single dose greater than 40 mg, ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. A single dose greater than 40 mg, or total daily doses greater than 80 mg, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids.

OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.
What does Abuse Deterrent Mean?

- Reinforcing
- Rapid onset
- High intensity

Improve the Risk:Benefit Relationship

- Low cost
- Low effort

Individual Patients & Public Health
What does Abuse Deterrent Mean to FDA?

- 2008: has to be shown to deter abuse in appropriately designed (epidemiologic) studies
- 2012: likely to reduce abuse based on preclinical testing

Excludes the definition of abuse. This guidance uses the term *abuse-deterrent* rather than *tamper-resistant* because the latter term refers to, or is used in connection with, packaging requirements applicable to certain classes of drugs, devices, and cosmetics.

Guidance for Industry, April 2015

- Does not mean that the formulation deters abuse per se
  - Deter misuse by specific routes
  - Included in labeling information
Concepts in ADF

- Physico-chemical barriers to tampering
- Combination with antagonist that is released during inappropriate use
- Inclusion of noxious ingredients

The medication still needs to work as intended
Examples of ADFs

- OxyContin (oxycodone, crush/extraction resistant): April, 2013
- Targeniq (oxycodone hydrochloride and naloxone, aversive): July, 2014
- Embeda (morphine/naltrexone, aversive): October, 2014
- Hysingla (hydrocodone, crush/extraction resistant): November, 2014
- MorphaBond (morphine, crush/extraction resistant): October, 2015
Potential Abuse Deterrent Formulations

Probuphine Implant

benzoate-hydrocodone
FDA Guidance

- The FDA outlines the abuse deterrence of solid oral opioid drug products
- Requires post-marketing study to assess the impact of the new formulation
Tiered Approach For Assessment of Formulations with Potential Abuse Deterrent Features

**Premarketing**
1. Laboratory based in vitro manipulation and extraction studies
   - Ability to compromise preparation of drug product for administration by other routes
2. Pharmacokinetic/Pharmacodynamic (PK/PD) studies
   - Compared to original formulation
   - Assessments may depend on route of administration
3. Human abuse liability studies
   - Real world potential

**Postmarketing**
4. Assess the impact of an abuse-deterrent formulation on actual abuse

FDA: “Adaptive, flexible approach”
Acquiring Category 4 Data

- The sources of post-marketing data have critical limitations
  - Unable to identify individual products
  - Cannot reliably differentiate routes of abuse or methods of tampering
  - Under-reporting and miscoding
  - Denominator issues

Denominator issues

The Perfect ADF

- Let's just say it existed... would it help.

The Holy Grail
Survey pre-reformulation

- 27,816 patients
  - 157 treatment programs
- 1425 had used OC

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Population</th>
<th>Ingestion (%)</th>
<th>Inhalation (%)</th>
<th>Injection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCabe et al. (7)</td>
<td>College students who admit being lifetime nonmedical users of POs</td>
<td>97</td>
<td>13</td>
<td>.5</td>
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<tr>
<td>Davis and Johnson (8)</td>
<td>Drug users in New York City</td>
<td>66</td>
<td>15</td>
<td>4</td>
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<tr>
<td>TEDS (37)</td>
<td>Persons admitted to substance abuse treatment in 2006</td>
<td>71</td>
<td>15</td>
<td>12</td>
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<td>TEDS (DASIS report 2004) (9)</td>
<td>Persons admitted to substance abuse treatment in 2002</td>
<td>77</td>
<td>8</td>
<td>11</td>
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<tr>
<td>NIDA-CEWG 2007 (38)</td>
<td>Persons admitted to substance abuse treatment in San Diego</td>
<td>79</td>
<td>8</td>
<td>10</td>
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<tr>
<td>NIDA-CEWG 2007 (volume 2) (38)</td>
<td>Persons admitted to substance abuse treatment and primarily addicted to “other opiates”1 in various US states in 2006</td>
<td>ND</td>
<td>ND</td>
<td>3–142</td>
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<tr>
<td>RADARS College Survey 20093</td>
<td>College students</td>
<td>79% swallow whole, 64% chew and swallow</td>
<td>52</td>
<td>28</td>
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</tbody>
</table>

Poison Center Data

<table>
<thead>
<tr>
<th>Route of misuse, abuse, or withdrawal</th>
<th>No effect</th>
<th>Minor effect</th>
<th>Moderate effect</th>
<th>Major effect</th>
<th>Death</th>
<th>Total</th>
<th>%</th>
<th>% of route leading to major/death</th>
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<tbody>
<tr>
<td>Ingestion</td>
<td>1030</td>
<td>2320</td>
<td>1982</td>
<td>432</td>
<td>67</td>
<td>5831</td>
<td>91.8</td>
<td>8.6</td>
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<tr>
<td>Inhalation</td>
<td>55</td>
<td>121</td>
<td>112</td>
<td>31</td>
<td>2</td>
<td>321</td>
<td>5.1</td>
<td>10.2</td>
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<tr>
<td>Parenteral</td>
<td>23</td>
<td>62</td>
<td>82</td>
<td>32</td>
<td>1</td>
<td>200</td>
<td>3.1</td>
<td>16.5</td>
</tr>
<tr>
<td>Total</td>
<td>1108</td>
<td>2503</td>
<td>2176</td>
<td>495</td>
<td>70</td>
<td>6352</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Mixed methods analysis using SKIP program, entering treatment programs
- 11,782 surveyed
- 244 interviewed

Evaluating OxyContin to get high in previous 30 days
- Pre-reformulation (pre-2010)
  - 45%
- Following reformulation (2012)
  - 26%

**A** Did the formulation change of OxyContin have any impact on the drugs you chose to get high with?

- Yes, I stopped using all drugs to get high
- No, I did not use OxyContin enough for my choice of drugs to change
- No, I continued to use OxyContin after the formulation change
- Yes, I replaced OxyContin with other drugs

**B** Which of the following ways apply to your use of both new and old formulations of OxyContin to get high/alter your mood?

- I primarily swallowed the old version of OxyContin and continued to swallow the new one
- I continued to inject/snort the new OxyContin like I did with the previous version
- I switched from primarily injecting/snorting the old version of OxyContin to primarily swallowing the new OxyContin
Addiction vs Abuse

- Clearly related phenomena
  - National Institutes of Health: about 5% of patients taking opioids as directed for a year develop addiction
  - Meta-analysis (Vowles) found addiction rate (high quality studies) was between 0.7% and 23%

- The majority of addicted patients did NOT abuse

Addiction vs Abuse

- DSM-5 excludes tolerance and withdrawal from the diagnosis of opioid use disorder
- Arises during medical drug therapy
- Only aberrant behaviors count
- May not reflect prescription drug users’ behaviors

Unintended consequences

103 Surveyed

Entering treatment program for PO addiction

24% overcame tamper resistance

66% said they switched to another opioid, primarily heroin

Cicero et al., 2012, NEJM Vol. 367
Abuse-Deterrent Formulations and the Prescription Opioid Abuse Epidemic in the United States: Lessons Learned From OxyContin

Theodore J. Cicero, PhD; Matthew S. Ellis, MPE

Figure 1. Respondents Who Endorsed Past-Month Use of OxyContin or Heroin Before and After the Introduction of an Abuse-Deterrent Formulation (ADF)


SKIP data
Figure 3. Drugs Used to Replace OxyContin After the Introduction of the Abuse-Deterrent Formulation (ADF)

Data show the drugs used by the 51 participants in the Researchers and Participants Interacting Directly (RAPID) study sample in response to the question, “What drugs did you replace OxyContin with?” Because multiple drugs were used, percentages total more than 100. OxyContin is a proprietary formulation of oxycodone hydrochloride.
Large claims database

Timed around introduction of OxyContin OP and withdrawal of propoxyphene

Unintended consequences

ORF = OxyContin ADF (Q3, 2010)
CRF = Opana ER ADF (Q1, 2012)

RADARs Newsletter; 2013. Vol 8(3)
Opana (oxymorphone)

- Rural county in Southeastern Indiana
- Epidemic (>160 cases/normal 5) of:
  - TTP
  - Hepatitis C
  - HIV

http://emergency.cdc.gov/han/han00377.asp
FDA Statement: Original Opana ER Relisting Determination

FDA conclusions include:

- While there is an increased ability of the reformulated version of Opana ER to resist crushing relative to the original formulation, study data show that the reformulated version’s extended-release features can be compromised when subjected to other forms of manipulation, such as cutting, grinding, or chewing, followed by swallowing.

- Reformulated Opana ER can be readily prepared for injection, despite Endo’s claim that these tablets have “resistance to aqueous extraction (i.e., poor syringeability).” It also appears that reformulated Opana ER can be prepared for snorting using commonly available tools and methods.

- The postmarketing investigations are inconclusive, and even if one were to treat available data as a reliable indicator of abuse rates, one of these investigations also suggests the troubling possibility that a higher percentage of reformulated Opana ER abuse is via injection than was the case with the original formulation.
Where there's a will, there's a way

25-09-2010 20:13
Method for IV'ing OP OxyContin Tablets:

TOOLS REQUIRED for Injecting/Banging/IV:

Tool 1.) Standard Kit for Injecting OxyContin pills -- including filters
- I recommend Qtip, it seems to work better on OP's than cigarette filters do
- Tool 2.) Use a 1 CC syringe. A 20 CC WILL WORK. SO IF YOU CAN'T DO VERY MUCH.
- So a 1 CC syringe is very recommended, as it can hold more water and more pill.

Tool 3.) Acetol and sterile water.

Step 1.) FOR Injecting/Banging/IV: Follow the instructions above ALL THE WAY TO below:

Step 2.) Prepare a spoon with water & TWO (2) filters - preferably QTip filters.

Step 3.) Now, like before, scrape the Oxy, and try to chop it up into small pieces. I don't want too.
- Chopping the Oxy a little makes it a bit easier to mix up.

Step 4.) After you have water in the spoon, add an extra 20 more units of water

Step 6.) Now very carefully mix it up, and very EXTRA CAREFULLY cook the mixture times to boil over

Step 7.) Now add only 10 (TEN) units of water from the syringe into the mix, and cook VERY CAREFULLY again

I DO NOT ADVISE OR RECOMMEND INJECTING, SNIORTING OR ABUSING DRUGS SUCH AS OXYCONTIN.
I AM MAKING THIS GUIDE FOR PEOPLE WHO HAVE TROUBLE DIGESTING THE NEW OP PILLS**
OR PEOPLE WHO WANT BREAKTHROUGHS OR IMMEDIATE PAIN RELIEF EVEN WITH THE NEW OP PILLS.
- I AM NOT RESPONSIBLE FOR ANY DAMAGES CAUSED BY THIS METHOD OR ABUSING OXYCONTIN!!-

Step 13.) After it's cooked again, drop in the 2nd filter right next to the first filter and QUICKLY draw the mix.
- IT should be a LOT easier and a syringe quicker to draw into the syringe after the second cooking.

Step 14.) Now, 17, and ONLY IF, there is any room

Step 15.) Before you get me all bubbles out, the

** The new OP pills give some people moderate stomach pain and very moderate to severe head-aches.

GOOD LUCK EVERYONE!!!
I really hope it works well for you.

www.bluelight.org/vb/threads/526460-
Method-for-snorting-IV-OP-OxyContin
Primary Care Physicians’ Knowledge And Attitudes Regarding Prescription Opioid Abuse and Diversion

National survey of 1000 primary care physicians
May 2104
58% response rate

<table>
<thead>
<tr>
<th>Abuse-deterrent formulations (ADFs)</th>
<th>Strongly or Somewhat Agree (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>An ADF of a drug will have a lower addictive potential than a non-ADF of the same drug</td>
<td>46</td>
</tr>
<tr>
<td>ADFs of prescription opioids will result in large or moderate reductions of morbidity and mortality</td>
<td>27</td>
</tr>
<tr>
<td>I have a lot or some experience prescribing ADFs</td>
<td>12</td>
</tr>
</tbody>
</table>

False sense of security

We need better education, training, and marketing

WASHINGTON — Doctors who prescribe painkillers should be required to undergo training aimed at reducing misuse and abuse of the medications, according to federal health experts, though they acknowledge the challenge of putting such a mandate in place.

The group of advisers to the Food and Drug Administration voted unanimously Wednesday that the agency should change its risk-management programs for opioid painkillers, highly addictive medications at the center of a national epidemic of addiction and abuse.
“We recognize that abuse-deterrent technology is still evolving and is only one piece of a much broader strategy to combat the problem of opioid abuse. But strongly encouraging innovation to increase access to generic forms of abuse-deterrent opioid medications is an important element in that strategy.”

FDA Commissioner Robert Califf
Final thoughts

- The many moving parts make it difficult to discern causality of interventional effectiveness.

- Epidemiologic proof of abuse or addiction reduction should be obtained to allow advanced labeling claims.
  - Needed to justify the increased expense of ADF, especially branded.

- We must continue to educate patients and prescribers about ADFs and opioids in general.
  - Rationalize expectations.
  - Harm reduction efforts.

- Need to focus on primary prevention.
  - ADF have a role, but we cannot rely on engineering controls to fix the epidemic of opioid abuse and addiction.
Thank you!