Opioid Abuse-Deterrent Formulations: A High Public Health Priority

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Prescription opioid products are commonly prescribed and essential for pain management. An estimated 20 percent of patients with non-cancer pain symptoms or pain-related diagnoses are prescribed opioids. However, abuse and misuse of these products have created a serious and growing public health problem.¹

According to the Centers for Disease Control and Prevention, deaths from prescription opioid pain medication overdose in the United States more than quadrupled from 1999 to 2011.² Of the 43,982 drug overdose deaths in 2013, 37 percent were associated with prescription opioid analgesics such as oxycodone, hydrocodone and methadone.³,⁴ From 1999 to 2014, more than 165,000 people died from an opioid-related overdose in the United States.⁵

Diversion, the intentional removal of a medication from legitimate distribution systems, is a major contributor to opioid abuse and misuse. The 2013 National Survey on Drug Use and Health reported that 67.6 percent of people who used prescription analgesics for non-medical use got them from a friend or relative by stealing them, buying them or getting them for free.⁶

The severity of the opioid problem has made the development of opioid abuse-deterrent formulations (ADFs) a high public health priority for the FDA. Abuse-deterrent technologies make manipulation of opioids for administration by different routes more difficult.¹ Abuse is defined as the compulsive, excessive and harmful use of addictive substances; misuse is the intentional therapeutic use of a drug in an inappropriate way. Drug seekers are particularly interested in extended-release (ER) formulations because they provide a higher maximum concentration of the drug than immediate-release (IR) formulations. The FDA is moving toward a requirement for all future formulations of ER opioids to contain abuse-deterrent properties.⁷

Abuse-deterrent properties of opioids do not prevent abuse, but are designed to deter it. Because opioid products must be able to deliver pain relief to the patient, there may always be some potential for abuse. For example, these technologies cannot deter someone from swallowing a large number of intact pills (the most common form of abuse). However, they can lower the risk of other forms of abuse compared to products without such properties. 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.⁷

The FDA believes it is critical to address the problem of opioid abuse while ensuring that patients in pain have appropriate access to opioid products. Moreover, it is important that opioids without abuse-deterrent properties remain available for use in some clinical settings. For example, patients in hospice care who have difficulty swallowing may need opioid products that are in solution or that can be crushed.¹
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Abuse-Deterrent Technologies

There are numerous ways that opioid products can be abused. For example, they can be swallowed whole, crushed and swallowed, crushed and snorted, crushed and smoked or crushed, dissolved and injected. Abuse-deterrent technologies are designed to target known or expected routes of abuse and can fall into one or more of these categories:

- **Physical/chemical barriers**: Physical barriers prevent chewing, crushing, cutting, grating or grinding of the dosage form. Chemical barriers resist extraction of the opioid using common solvents like water, simulated biological media, alcohol or other organic solvents. Physical and chemical barriers work by limiting drug release following mechanical manipulation of the product or change the physical form of a drug, making it more impervious to abuse.1

- **Agonist/antagonist combinations**: An opioid antagonist, such as naltrexone or naloxone, can be added to the formulation to reverse the pharmacologic effects of the drug, including euphoria. The antagonist is not clinically active when swallowed but becomes active when crushed, injected or snorted.1

- **Aversion**: Substances can be added to the product to produce an unpleasant effect if the dosage form is manipulated or exceeds the directed dosage. For example, the formulation can include a substance irritating to the nasal mucosa if ground and snorted.1

- **Delivery System**: Certain drug release designs, such as depot injections and implants, are formulations that are resistant to abuse. For example, a sustained-release depot injectable formulation or a subcutaneous implant may be difficult to manipulate.1

- **New molecular entities and prodrugs**: The properties of a new molecular entity or prodrug could include the need for enzymatic activation, different receptor binding profiles, slower penetration into the central nervous system or other novel effects. Prodrugs with abuse-deterrent properties could provide a chemical barrier to the in vitro conversion to the parent opioid, which may deter the abuse of the parent opioid.1

Pre-marketing and Post-marketing Assessments

The FDA requires that pharmaceutical manufacturers conduct pre-marketing and post-marketing assessments for claims of abuse deterrence to be included in the labeling of an opioid formulation. Pre-marketing studies are primarily expected to characterize the abuse-resistance properties of a product under controlled conditions. Required laboratory tests include:

1. Assessment of how easily the abuse-deterrent properties of the formulation can be manipulated

2. In vivo studies to compare the pharmacokinetic profiles of the formulation before and after manipulation

3. A randomized, double-blind, placebo- and active-controlled study to evaluate subjective effects of the formulation, such as differences in “drug liking” in recreational drug users
Post-marketing epidemiological studies determine whether the marketed ADF results in meaningful decreases in adverse clinical outcomes related to abuse in real-world settings. One study evaluating changes in drug abuse patterns found that reformulation of OxyContin was associated with a 32 percent reduction in the rate of ER oxycodone-related poison control abuse cases. The study also found a 15 percent reduction in the rate of poisonings related to therapeutic ER oxycodone use. The rate of ER oxycodone diversion declined by 50 percent and the street price of ER oxycodone declined by 22 percent.

As part of a Risk Evaluation and Mitigation Strategy (REMS) program, the FDA has required the manufacturers of long-acting opioids to make training in their use available to prescribers.

**FDA-Approved Abuse-Deterrent Formulations**

- **Embeda ER** (morphine and naltrexone) is formulated as capsules of ER morphine pellets that contain a sequestered core of the opioid antagonist naltrexone. When swallowed, the morphine is gradually released and absorbed, while the naltrexone core passes through the gut intact. If the pellets are crushed, chewed or dissolved, naltrexone is released, blocking morphine-induced euphoria.
- **Hysingla ER** (hydrocodone) forms a viscous gel when dissolved, making it difficult to inject through a hypodermic needle.
- **MorphaBond ER** (morphine) and **OxyContin ER** (oxycodone) are formulated to make it difficult to cut, crush or break and when dissolved forms a viscous material that resists passage through a needle.
- **Targiniq ER** (oxycodone and naloxone) is an opioid agonist/antagonist combination. If the formulation is crushed and administered intravenously or intranasally, high naloxone concentrations block opiate-induced euphoria and can induce withdrawal symptoms.
- **Xtampza ER** (oxycodone) is mixed with wax and fatty acids to form microspheres that each contain active drug. The wax keeps the opioid from being dissolved and injected; it also prevents rapid release of the oxycodone if the capsules are mashed. Additionally, capsules can be opened to sprinkle on soft foods and then given to patients who cannot swallow whole capsules.
- **Zohydro ER** (hydrocodone) incorporates excipients that form a viscous gel when the capsules are crushed and dissolved.

Several other opioids have abuse-deterrent properties but have not been approved by the FDA as an ADF. These include Exalgo ER (hydromorphone), Nucynta ER (tapentadol), Oxaydo IR (oxycodone), Opana ER (oxymorphone), Xartemis (oxycodone and acetaminophen).
Table 1: FDA-Approved Abuse-Deterrent Products

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Abuse-Deterrent Technology</th>
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<tbody>
<tr>
<td>Embeda ER (morphine and naltrexone)</td>
<td>Uses an opioid antagonist</td>
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<tr>
<td>Hysingla ER (hydrocodone)</td>
<td>Uses chemical barriers</td>
</tr>
<tr>
<td>MorphaBond ER (morphine)</td>
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**Generic ADFs**

Although no generic ADFs are commercially available, it is important that generic versions of opioids are developed to ensure widespread access to safe and effective analgesics for patients who need them. The FDA recommends comparative in vitro studies to demonstrate that a generic solid oral opioid is no less abuse-deterrent than the original formulation with respect to all potential routes of abuse.

Moreover, it is important that the availability of such generics do not exacerbate the public health problems associated with prescription opioid abuse. If the generic formulation is less abuse-deterrent it could lead opioid abusers to preferentially seek out and abuse this easier-to-abuse version.\(^\text{11}\)

**Conclusion**

Post-marketing epidemiologic studies of opioid ADFs show declines in ADF abuse patterns, therapeutic errors, accidental exposures and diversion of prescription opioids. The evidence indicates that reformulating abused prescription opioids to include abuse-resistant properties may be an effective approach to reduce abuse of these medications. However, a major observation from these studies shows that ADFs were associated with increased abuse of other opioids and illicit drugs. Therefore, a reasonable inference may be that the drug is being replaced with other opioids and agents that are more amenable to manipulation.

It may be concluded that the current ADF methodologies alone will not likely be adequate to curb nonmedical opioid use. However, they may be effective as part of a comprehensive effort that includes other interventional strategies such as REMS programs, state prescription monitoring and overdose prevention programs.\(^\text{12}\)
References


