**Background** In response to the mounting public health crisis regarding opioid-related deaths from misuse, the Food and Drug Administration (FDA) has issued guidance to pharmaceutical manufacturers on the development of abuse-deterrent formulations of opioids (1). This *Fast Fact* will focus on the different types of abuse-deterrent opioid formulations and their role in palliative care.

**Opioid Abuse in the Palliative Care Population** Opioid abuse is the intentional, nontherapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect (2). Opioids may be ingested, either whole or crushed, inhaled, via snorting, smoking, or vaping, or injected in an attempt to more quickly achieve a euphoric “high” (1,3). Previous literature suggests that 29-46% of palliative care patients possess risk factors for opioid misuse defined as a positive score (≥4 points) on the Screener and Opioid Assessment for Patients with Pain version 1.0—Short Form (SOAPP-SF) (4,5).

**Opioid Abuse-Deterrent Categories**

1. **Physical/Chemical Barriers**: Physical barriers, such as polymers and high resistance coatings, can prevent mechanical manipulation, such as chewing, crushing, cutting, or grinding, of the medication. Chemical barriers, such as gelling agents, can resist dissolution of the opioid using common solvents (water, alcohol, or other organic solvents).
2. **Agonist/Antagonist Combinations**: The addition of an opioid antagonist, most commonly naloxone or naltrexone, can interfere with the euphoria and analgesia associated with opioid abuse. Pharmaceutical designers often aim to sequester the antagonist so that it only becomes clinically active if the product is crushed for injection or snorting.
3. **Aversion**: Substances can be added to the product to produce an unpleasant effect, such as irritation to the nasal mucosa, if the dosage form is manipulated or is used at a higher dosage than directed.
4. **Delivery System**: Certain drug release and delivery methods, such as sustained-release depot injections and subcutaneous implants, can offer resistance to abuse as they cannot be tapered to quickly release the opioid and produce a drug high.
5. **New Molecular Entities and Prodrugs**: These opioids require enzymatic activation, different receptor binding, slower penetration into the central nervous system, or other novel effects to thereby provide a chemical barrier to the in vitro conversion to the parent opioid, which may deter the abuse of the parent opioid by continuing to have controlled release of the drug even if it is crushed.

**Opioid Abuse-Deterrent Formulations** There are several brand-name extended release (ER) opioid formulations available with FDA-approved labeling describing abuse-deterrent properties (6,7). There is one immediate release oxycodone agent with abuse deterrent properties, but it does not possess FDA-approved labeling (8). Moving forward, greater availability of abuse deterrent opioid formulations is expected as the FDA has issued guidance on the development of generic versions (9).

<table>
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<th>Opioid (brand)</th>
<th>US Market</th>
<th>Abuse-Deterrent Properties</th>
<th>Comparative Cost to Long Acting Morphine</th>
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| Oxycodone ER (OxyContin®) (9) | Reformulated: 4/5/2010 | **Physical/Chemical Barrier**  
• Difficult to crush or break  
• Resistant to chemical extraction  
• Forms a viscous gel when dissolved | 2 times the cost |
| Oxycodone/naloxone ER (Targiniq®) (10) | Approved: 6/23/2014 | **Agonist/Antagonist Combination**  
• Naloxone released if crushed | Not yet available in the US |
| Morphine/naltrexone ER (Embeda®) (11) | Approved: 8/13/2009 | **Agonist/Antagonist Combination**  
• Naltrexone released if crushed | 7 times the cost |
Evidence  To be considered abuse-deterrent by the FDA, formulations must undergo long term epidemiological study to assess their clinical abuse potential (17). Most often this is done utilizing a drug-liking and a subjective feeling of getting “high” scale of 0-100, where 0 represents maximum disliking, 50 represents a neutral response, and 100 represents maximum liking. FDA approved abuse deterrent agents showed statistically significant decreases in drug-liking and drug high when compared to other opioid formulations (10-16). Retrospective reviews found that 3.5 years after the reformulation of OxyContin®, opioid abuse, doctor-shopping, the amount of OxyContin® dispensed, and OxyContin-related fatalities were reduced (18,19). However, heroin overdoses increased by 23% during that same time (18). There is concern that even if these formulations reduce opioid-specific abuse, they may contribute to a shifting pattern of heroin abuse. No palliative care specific studies have yet been conducted.

Cost Effectiveness  There is a lack of robust, controlled trials to determine if the expense of these formulations is justified. Most of these formulations are not covered by insurance policies. One cross-sectional study of Oklahoma Medicaid claims suggested that abuse-deterrent opioids may be related to slightly lower overall health care costs for members with ICM-9 codes associated with opioid abuse; this finding was not replicated among members without comorbidities of addiction (19).

Summary  Abuse-deterrent opioids may have a role in the palliative care population, however cost may limit their use. These opioid formulations should be limited to opioid-appropriate patients who are at risk for opioid-specific problems.

References:

| Hydrocodone ER (Hysingla ER®) | Approved: 11/20/2014 | Physical/Chemical Barrier | 8 times the cost |
| Mornhine ER (Morpha-Bond ER®) | Approved: 10/2/2015 | Physical/Chemical Barrier | Not yet available in the US |
| Oxycodone ER (Xtampza ER®) | Approved: 4/26/2016 | Physical/Chemical Barrier | 4 times the cost |
| Oxycodone/ naltrexone ER (Troxyca ER®) | Approved: 8/19/2016 | Agonist/Antagonist Combination | Not yet available in the US |
OXYCONTIN® oral extended-release tablets, oxycodone HCl oral extended-release tablets. Purdue Pharma L.P (per FDA), Stamford, CT, 2015.


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