Abuse-Deterrent Opioid Formulations — Putting the Potential Benefits into Perspective

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Death rates among middle-aged adults, the largest demographic group in the United States, are on the rise for the first time in several decades. This trend can largely be explained by an increase in drug-overdose deaths, the majority of which involve opioids. The opioid crisis has attracted attention from all corners of the health care field and from policymakers at all levels, including the nation's highest office. In 2016, the Centers for Disease Control and Prevention (CDC) took the important step of releasing guidelines on prescribing opioids for chronic pain in an attempt to shift U.S. physicians away from an opioid-centric strategy. Concomitant with the release of those guidelines and other public health initiatives, some health systems are finally seeing decreases in the number of long-term opioid prescriptions, which will be an important component of efforts to reverse the trend in opioid-related deaths.

At the same time, opioid manufacturers, in keeping with their fiduciary responsibility, are working to ensure access to their products. The Associated Press and the Center for Public Integrity recently reported that pharmaceutical companies and their associated advocacy groups spent $880 million between 2006 and 2015 on activities that included efforts to influence federal and state opioid policies — outpacing spending by the gun lobby. The organizations employed an average of 1350 lobbyists per year.[1] Among their goals was to promote expensive opioid formulations described as "abuse-deterrent" (see table).

Proponents of such products cite recent data — some from industry-backed studies — suggesting that reformulated opioids designed to deter abuse are less likely to be diverted or abused than traditional opioids. According to their argument, a primary problem is that when prescription opioids fall into the wrong hands, standard formulations allow people to tamper with them to achieve heightened euphoric effects through nasal inhalation or injection. An abuse-deterrent opioid formulation might help to prevent intentional misuse, while leaving opioids safe and effective for their approved uses. A May 2017 draft review by the Institute for Clinical and Economic Review rated such evidence as a "C+," indicating that the reviewers were not able to determine with high certainty that a small, moderate, or large net health benefit to abuse-deterrent opioid formulations existed. These findings mirrored a California Health Benefits Review Program's systematic review finding that the impact of abuse deterrent formulations on abuse was ambiguous.

Although we wholeheartedly support efforts to make long-term opioid therapy safer, we believe a strategy that focuses on only one of the risks of opioid prescribing (intentional abuse) requires closer scrutiny. Such an approach may distract prescribers, patients, and policymakers from considering the limited evidence supporting the benefits of long-term opioid use for most patients with chronic pain, the myriad other risks associated with all opioid formulations, and the need to follow the CDC's lead in emphasizing nonopioid therapies and treatment for opioid-use disorder (addiction) when indicated.

One problem with simply shifting opioid prescribing to abuse-deterrent formulations is that we lack evidence that opioids — regardless of their formulation — are typically effective for treating chronic pain. A Cochrane review examined results from 26 treatment groups including 4768 participants and determined that there wasn't enough evidence to draw firm conclusions on the effectiveness of long-term opioid therapy for chronic pain.[2] Although the review found a medium-sized effect favoring opioid use in people who completed a study, such participants accounted for only 30% of the overall sample. What's more, no studies involving more than 16 weeks of treatment examined functional outcomes, the optimal measure for assessing benefit. A more recent review came to similar conclusions regarding efficacy and found no studies that assessed outcomes in patients who used opioids for a year or longer.[3] Reformulating opioids to deter abuse doesn't improve their efficacy, and opioids haven't been shown to relieve pain or improve func-

Opioid Products with Food and Drug Administration (FDA)–Approved Abuse-Deterrent Labeling.*

Brand Name	Type of Opioid	Year of Approval	Reported Abuse-Deterrence Mechanism	Commercially Available
OxyContin (reformulated)	Oxycodone	2010	When dissolved, forms a viscous gel that is difficult to inject through a hypodermic needle.	Yes
Targiniq ER	Oxycodone	2014	Combination pill containing extended-release (ER) oxycodone and naloxone; if the formulation is crushed and administered intravenously or intranasally, high naloxone concentrations block opiate-induced euphoria and can induce withdrawal symptoms.	No
Embeda	Morphine	2010	Capsules of ER morphine pellets that contain a sequestered core of naltrexone; if the pellets are 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, the naltrexone is released, blocking morphine-induced euphoria.	Yes
Hysingla ER	Hydrocodone	2015	When dissolved, forms a viscous gel that is difficult to inject through a hypodermic needle.	Yes
MorphaBond	Morphine	2015	Formulated with inactive ingredients that make the tablet harder to adulterate while maintaining ER characteristics if the tablet is subjected to physical manipulation or chemical extraction.	No
Xtampza ER	Oxycodone	2016	Capsules containing microspheres formulated with oxycodone base and inactive ingredients that make the formulation harder to manipulate.	Yes
Troxyca ER	Oxycodone	2016	Contains pellets that consist of oxycodone that surround sequestered naltrexone. When taken orally, the naltrexone is intended to remain sequestered and patients receive ER oxycodone. When the pellets are crushed, the naltrexone is released and counteracts the effects of oxycodone.	No
Arymo ER	Morphine	2017	A polymer matrix tablet technology with controlled-release properties as well as physical and chemical barriers that resist manipulation. The technology results in a viscous hydrogel on contact with liquid, making the product very difficult to draw into a syringe.	Yes
Vantrela ER	Hydrocodone	2017	Incorporates abuse-deterrent technology designed to resist drug extraction through the most common routes: oral, intranasal, and intravenous.	No
RoxyBond	Oxycodone	2017	Includes inactive ingredients that make the tablets harder to misuse by physical manipulation, chemical extraction, or both; in vitro data suggest physicochemical properties that are expected to make abuse through injection difficult.	No

* There are no currently approved generic versions of opioids with approved abuse-deterrent labeling. Information is from the FDA.

tioning any better than nonopioid medications or nonpharmacologic treatments — which is the primary reason the CDC recommended those alternatives for managing chronic noncancer pain.

There's also a problem with the implicit idea that opioids cause harm only when people tamper with them. Federal guidance regarding abuse-deterrent formulations acknowledges that even when taken orally, full-agonist opioids, which include oxycodone, hydrocodone, and morphine, act on mu receptors in the midbrain to stimulate reward pathways — a process that can precipitate addiction in susceptible people. Abuse-deterrent formulations don't prevent patients from taking higher doses than prescribed, which is the most common way opioids are misused. Yet one survey showed that nearly half of primary care physicians think abuse-deterrent formulations are less addictive than standard formulations.

A related and problematic misunderstanding involves the notion that using abuse-deterrent formulations protects people from other important harms associated with opioids. In fact, the myriad dose-dependent adverse effects of opioids extend beyond their potential for abuse and include immune, endocrine, cardiovascular, gastrointestinal, neuropsychiatric, and respiratory effects. Most important, all-cause mortality is higher among patients receiving

long-term opioid treatment than among similar people who aren't treated with opioids.[4]

Moreover, opioids with abuse-deterrent properties are not abuse-proof. Federal regulators acknowledge the emerging science in this area and the challenges yet to be addressed. Comments on YouTube videos instructing viewers on how to tamper with various products imply that abuse-deterrent formulations have spawned a cottage industry of sophisticated ways of defeating them. An HIV outbreak in southern Indiana in 2015 was linked to a reformulated version of Opana ER (oxymorphone) that apparently deterred nasal inhalation — but could be injected. A study involving people who had misused OxyContin (oxycodone) and were entering treatment programs revealed that although use of the pills decreased after the release of an abuse-deterrent formulation, 25 to 30% of participants had continued to use the new formulation — either because they found a way to defeat the abuse-deterrent features or because they were taking the pills orally, perhaps to prevent opioid withdrawal. More strikingly, the majority of people who were discouraged by the new formulation reported switching to heroin.[5] Finally, abuse-deterrent formulations don't protect against theft or accidental ingestion by infants or children (whereas simple lock boxes, available for less than $20, do).

Efforts by the pharmaceutical industry and others to influence legislative and purchasing decisions can ultimately determine what products are available at the bedside. We believe it is important for policymakers and the clinical and research communities to examine the totality of the evidence regarding the benefits and risks of opioids. In particular, evidence from recent systematic reviews that long-term opioid therapy is often not effective and that prolonged use, especially of high-dose therapy, is associated with harm — as reflected in the CDC guidelines — should guide decisions. We believe clinicians, researchers, and policymakers should invest in alternative chronic-pain treatments and models of care, as well as strategies for avoiding opioid dose escalation and achieving de-escalation or treatment of opioid-use disorder when indicated.

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Delegalizing Advance Directives — Facilitating Advance Care Planning

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When Luis Kutner, a human rights lawyer, first proposed the idea of the "living will" in 1969, he conceptualized it as a document establishing a trust, with the patient as the beneficiary and physicians as trustees. Kutner expected that such a document would be signed by two witnesses, notarized, and carried in the patient's pocket at all times.[1] In 1976, California became the first state to create a living-will statute; today, 47 states have similar laws. States have also codified the ability to choose a surrogate decision maker — a right modeled after a legal construct, the power of attorney. The advance directive has now come to denote a legal document designating a health care decision maker, a living will, or both.

Although many legal documents don't require formal witnessing, notarization, or specific templates, most states' advance-directive statutes require witnesses or a notary, and some stipulate use of a statutory form.[2] Perhaps