*Deborah J. Culley, M.D., Editor*

# Abuse-deterrent Opioid Formulations

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## ABSTRACT

Abuse-deterrent opioid formulations have been suggested as one way to decrease the abuse, addiction, and overdose of orally prescribed opioids. Ten oral opioid formulations have received abuse-deterrent labeling by the U.S. Food and Drug Administration (FDA). Their properties consist of physical and/or chemical means by which the pills resist manipulation and create a barrier to unintended administration, such as chewing, nasal snorting, smoking, and intravenous injection. In this review, we describe the mechanisms of abuse-deterrent technology, the types of premarketing studies required for FDA approval, the pharmacology of the currently approved abuse-deterrent opioid formulations, and the evidence for and against their influence on opioid abuse. We conclude that there is currently insufficient evidence to indicate that the availability of abuse-deterrent opioid formulations has altered the trajectory of opioid overdose and addiction; however, postmarketing studies are in their infancy, and novel deterrent formulations are continually being developed and submitted for marketing approval. **(Anesthesiology 2018; 128:1015-26)**

## Framing the Problem

As the opioid addiction and overdose crisis destroys the fabric of cities and towns across the United States, lawmakers, physicians, and patient advocacy organizations search for effective solutions to this multifaceted and challenging dilemma. A major component of this crisis consists of the continued illegal abuse of orally prescribed opioid formulations.[1,2] For example, by 2014 it was estimated that 1.9 million people met the diagnostic criteria for prescription opioid use disorder,[3] and as of 2015, more than 12 million individuals illicitly used prescription pain relievers.[2] The rate of fatal overdoses due to oral formulations of natural and semisynthetic opioids (*e.g.*, oxycodone, hydrocodone, hydromorphone, and oxymorphone) has risen steadily since 2000, and in 2015 was approximately the same rate as fatal overdoses from heroin.[4] These overdoses are the direct consequence of the use of the oral formulations in unintended ways, such as smoking, snorting, and IV administration. The use of these more satiating modes of delivery, often called *dose dumping*, comes at the expense of an enhanced risk for development of tolerance, addiction, and overdose.[5]

## Prevention of Oral Opioid Abuse

There are many directions from which to approach the prevention of oral opioid abuse. They are summarized in the FDA's Opioids Action Plan and include expanding the use of advisory committees, developing warnings and safety information for immediate-release (IR) opioids, strengthening postmarket research requirements, updating the Risk Evaluation and Mitigation Strategy (REMS) program (see ADF Approval Process below), and expanding access to abuse-deterrent opioid formulations (ADFs).[6]

The primary focus of this review is to describe the pharmacology, approval process, and effectiveness of ADFs, which possess unique physical and/or chemical properties that are designed to impede the ability of opioid abusers to use the drug in an unintended and illegal manner, while also retaining the drug's clinical effects and potency to provide legitimate users with necessary pain relief.[7] The White House Executive Office of the President and numerous federal agencies, including the FDA, have encouraged the pharmaceutical industry to research and develop ADFs for oral administration.[8] In fact, the FDA has stated that it "considers the development of these products [to be] a high health priority," and in 2015 released a document entitled "Guidance for Industry: Abuse-deterrent Opioids—Evaluation and Labeling."[9]

## Abuse-deterrent Technologies

Although only the first three of the following deterrent methods currently exist in the marketplace, the FDA has described[9] seven possible general categories of abuse-deterrent technology:

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1. physical or chemical barriers that provide resistance to mechanical alteration of the opioid that releases active drug for nasal inhalation or IV injection. Physical barriers are designed to resist damage from common household tools (*e.g.*, coffee bean grinder), and chemical barriers resist penetration and dissolution by water, alcohol, and other organic solvents, and may change the form of the active drug to render it difficult to snort or inject IV;
2. agonist/antagonist combination pills that retain analgesic properties when swallowed (because the antagonist is not effectively absorbed into the bloodstream), but when used by nasal snorting or IV injection, the antagonist portion of the pill will reduce or counteract the opioid-induced euphoria[10];
3. inclusion of aversive substances to the active opioid to decrease its "likeability" when used in unintended ways. For example, an ADF may include a substance that causes a burning sensation in the nasal mucosa when snorted, or unpleasant symptoms, such as nausea, sweating, and headache, when opioid pills are swallowed in great quantities[11];
4. unconventional opioid delivery systems such as sustained-release depot injectable formulations or subcutaneous implants that are difficult to manipulate once they have been deposited internally by medical personnel;
5. prodrugs or new molecular entities that undergo enzymatic activation or other chemical transformations in the gastrointestinal tract to release the active ingredients of the opioid[12];
6. combinations of two or more of the previous five technologies; and
7. novel approaches or new technologies that were not described in the previous six categories.

## ADF Approval Process

The FDA guidance document describes the kinds of studies that should be performed by a manufacturer to substantiate a formulation's abuse-deterrent qualities, proposes ways in which these investigations should be conducted and evaluated, and reviews how to describe the results of these studies and the implications for product labeling.[9] There are three types of premarket studies, plus a required postmarket evaluation. The outcome variables are surrogate outcomes for more serious real-world outcomes such as abuse likelihood. Postmarket studies are targeted to outcome measures that describe real-world use of ADFs and the ways in which they influence abuse and addiction.

Category 1 (premarket) studies evaluate the ability of an abuser to defeat or compromise the integrity of the formulation by physical manipulation or chemical extraction, and evaluate the *syringeability* (ease with which it can be drawn into and injected from a syringe for IV use) of the formulation once it has been compromised. Methods may include crushing, grating, cutting, or grinding, among others, using readily available devices (*e.g.*, coffee grinders) under different temperatures, and using readily available solvents under different conditions of time, temperature, pH, and agitation. For this phase of evaluation, the FDA asks the manufacturer to manipulate the drug to the point of defeating its abuse-deterrent properties and compare it to non-ADFs of the same drug. These studies are primarily laboratory-based *in vitro* analyses and compare the study drug with a reference drug, such as OxyContin (Purdue Pharma; Stamford, Connecticut), since it was the first ADF to be approved and the most prescribed ADF currently on the market.

Category 2 (premarket) studies evaluate the *in vivo* pharmacokinetic properties of the new ADF when compared to the same non-ADF product under intact and manipulated conditions and routes of administration. Studies on the oral formulation are performed in healthy volunteers who are administered naltrexone to block the pharmacodynamic effects of the opioids, and under conditions of concomitant food and alcohol intake. *In vivo* studies on nasal administration may be performed on volunteers with a history of previous nasal abuse.

Category 3 (premarket) studies evaluate the potential for clinical abuse by enrolling experienced recreational opioid abusers to determine the likeability of a manipulated ADF using randomized, double-blind, placebo-controlled, and positive-controlled crossover studies. The ADF is compared with the non-ADF of the same opioid at the same dose (or an opioid with similar pharmacologic properties if the non-ADF does not exist), which is compared with placebo. These studies are performed on subjects that have been prequalified to determine that they can reliably distinguish between active drug and placebo. Experienced drug users are best qualified to determine these differences. The routes of abuse to study are based on historically relevant ways in which the non-ADF has been used, and in nearly all cases will consist of nasal snorting and IV injection. The outcome measures include drug-liking visual analog scales and assessments of desire to repeat it *via* that route. The FDA has stated that there is no accepted standard for a clinically significant difference in "drug liking," and each formulation will be evaluated on a case-by-case basis.[9]

FDA approval of an ADF has been contingent upon satisfactory demonstration of these three premarketing studies, and subsequent continuous evaluation of the drug's use *via* postmarketing studies. Approval is also accompanied by the obligation to institute a REMS program. The REMS program, which was authorized by the FDA Amendments Act of 2007, consists of management and education plans to ensure that a drug's benefits outweigh its risks.[13] The REMS program is created by the drug's manufacturer and implemented by prescribing practitioners. It is unclear if REMS programs are associated with increased patient safety.[14]

Category 4 (postmarketing) studies will attempt to evaluate the real-world impact of use of the drug. The goal of postmarketing studies is to "determine whether the marketing of a product

with abuse-deterrent properties results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death in the post-approval setting."[9,15] Examples provided by the FDA include monitoring of the drug's utilization relative to comparators, route-specific abuse outcomes, chatter on Internet forums, spontaneous adverse events, or the conduction of formal observational studies.

Postmarketing studies may consist of analyses of existing databases that, although imperfect, indirectly reflect the current climate of abuser use of ADFs in different geographical regions throughout the United States. Two of several will be briefly discussed here. The Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) program obtains data on opioids from most regional poison control centers, covering more than 90% of the U.S. population. RADARS personnel conduct additional quality checks on the call data, based on review of case narratives.[16,17] Since these data arise from calls to poison control centers, it is unknown how it reflects the population as a whole because relatively few overdose cases will generate a call (especially those that result in immediate death), and the factors that are likely to generate a call are unknown. Thus, this database may disproportionately fail to capture cases involving drugs with the highest risk of fatal overdoses.

Another database that has been used is the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO), which measures abuse patterns for selected prescription and illicit drugs. A component of NAVIPPRO called the Addiction Severity Index—Multimedia Version (ASI-MV) is a continuous, computerized, real-time, national data stream that assesses pharmaceutical abuse by patients entering substance abuse treatment centers. These particular data are also limited in that they are only representative of those abusers seeking treatment, and are dependent upon their voluntary admissions of use.[18]

The FDA has emphasized that since the science and evaluation of abuse-deterrent technology are in their formative stages, they will take a "flexible and adaptive approach" to the evaluation and labeling of potentially abuse-deterrent opioid products.[9] In July 2017, the FDA convened a public meeting to discuss ways in which to determine the effectiveness of ADFs.[19] The methods could include existing known databases on drug abuse, as well as those that are developed for future use. One of the conclusions of the meeting was the recommendation that opioid manufacturers institute greater prescriber education about IR opioids through the REMS program. The program has already been in place for extended-release (ER) opioid formulations and, to date, the program has been voluntary, but the FDA is considering mandatory education for all opioids, including IR formulations.

## Characteristics of ADFs

At the time of writing, the FDA has approved 10 opioids with ADF labeling (table 1), five of which are currently available in the United States. All of these formulations have been associated with bioequivalent pharmacologic profiles as their non-ADF counterparts and have demonstrated premarket evidence of feasible deterrent properties. All except IR oxycodone (RoxyBond; Inspirion Delivery Sciences, LLC; Morristown, New Jersey) are ER preparations. This is because illegal abusers need to crush the ER formulation to achieve a sufficient and satisfying "high."[20] Abuse deterrency is relatively unimportant for the IR formulations because multiple pills can be swallowed to achieve an enhanced euphoric effect. Nevertheless, manufacturers will now begin to formulate IR products as ADFs to comply with FDA mandates and to capture market share over generic formulations in states with mandatory ADF laws (see State Legislature Proposals or Laws below).

In 2016, there were an estimated 4.3 million prescriptions dispensed for ADF products from U.S. outpatient retail pharmacies. This represents approximately 20% of all dispensed opioids in that time period. There has been a slow and steady decline in the overall number of prescribed opioids since 2012, and the ratio of ADF to non-ADF prescriptions has been steady throughout.[21] The salient features of the currently approved ADFs are listed in table 1 and discussed herein.

### *OxyContin*

OxyContin, an ER formulation of oxycodone, was released into the market in 1996. Despite studies showing that OxyContin is not significantly more effective when compared to other opioids,[22,23] by 2001 the product became one of the leading opioids for treatment of moderate-to-severe chronic pain in the United States.[24] Concomitant to this growth, OxyContin became one of the most widely abused drugs in the United States less than a decade after it was first introduced.[7] In 2010, Purdue Pharma (Stamford, Connecticut) was granted approval from the FDA to begin replacing the original formulation of OxyContin with a new formulation containing ADF technology. Abuse-deterrent OxyContin has been reformulated using proprietary thermal processing and curing of high-molecular-weight polyethylene oxide (PEO) to form a coating around each tablet that impedes an abuser's ability to crush the pill and access the inner active drug.[12] When the outer PEO capsule encounters a liquid solvent, it becomes a viscous gel that hinders nasal snorting and IV injection. In 2013, reformulated OxyContin was granted ADF labeling for the IV and nasal routes, and the original non-ADF of OxyContin was withdrawn from the market over concerns of safety and effectiveness. The FDA asserted that it would no longer approve applications of generic OxyContin if the proposed drug does not contain abuse-deterrent properties.[25,26]

### *Xtampza ER*

Xtampza ER was the second oxycodone ER formulation to be approved with ADF labeling. Xtampza ER capsules are manufactured by *in situ* salt formation and spray congealing

**Table 1.** FDA-approved Opioids with ADF Labeling

| Generic Compound | Year of Approval | Availability on the Market | ADF Mechanism | Dosages Available |
|---|---|---|---|---|
| Oxycodone | | | | |
| OxyContin (oxycodone extended-release) | 2010 | Available | Hinders crushing of the tablet into a fine powder. If powder of the tablet is formed and dissolved in solvent, the drug product becomes a viscous gel that is difficult to inject IV. | 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, 80 mg |
| Xtampza ER (oxycodone extended-release) | 2016 | Available | Capsules contain microspheres of oxycodone and inactive ingredients that hinder dosage dumping *via* intranasal and oral abuse. Microspheres cannot be readily dissolved and will solidify within a needle to resist injection. | 9 mg, 13.5 mg, 18 mg, 27 mg, 36 mg |
| Troxyca ER (oxycodone + naltrexone extended-release) | 2016 | Unavailable (as of July 27, 2017) | Capsules consist of pellets containing oxycodone hydrochloride surrounding sequestered naltrexone hydrochloride. When crushed, sequestered naltrexone is released and able to impede the effects of extended-release oxycodone and block opiate-induced euphoria. | 10 mg/1.2 mg, 20 mg/2.4 mg, 30 mg/3.6 mg, 40 mg/4.8 mg, 60 mg/7.2 mg, 80 mg/9.6 mg |
| Targiniq ER (oxycodone and naloxone extended-release) | 2014 | Unavailable (as of July 27, 2017) | Pill containing extended-release oxycodone and opioid antagonist naloxone in a 2:1 ratio. If the tablet is crushed for administration *via* nasal or IV routes, the naloxone will counteract the effects of oxycodone and impede opiate-induced euphoria. Tablet also has a polyethylene oxide matrix to resist mechanical stress, such as crushing. | 10 mg/5 mg, 20 mg/10 mg, 40 mg/20 mg |
| RoxyBond (oxycodone IR) | 2017 | Unavailable (as of July 27, 2017) | Contains layered inactive ingredients that make the tablet resistant to physical manipulation (*e.g.*, crushing). Chemical extraction and dosage dumping are hindered by superabsorbent excipients and insoluble coatings within the layers. When taken as directed, extended-release of oxycodone is facilitated by the layers *via* diffusion. | 5 mg, 15 mg, 30 mg |
| Hydrocodone | | | | |
| Hysingla ER (hydrocodone extended-release) | 2014 | Available | Difficult to crush because of a polyethylene oxide matrix and, when dissolved, the tablet forms a viscous hydrogel that hinders an abuser's ability to inject the extracted product through a syringe in intravenous abuse. | 20 mg, 30 mg, 40 mg, 60 mg, 80 mg, 100 mg, 120 mg |
| Vantrela ER (hydrocodone extended-release) | 2017 | Unavailable (as of July 27, 2017) | Designed with lipids and other excipients that resist crushing and maintain thermoplasticity. Fat and wax polymers present in the tablet's granules establish low solubility of the crushed drug product, hindering IV injection. | 15 mg, 30 mg, 45 mg, 60 mg, 90 mg |
| Morphine | | | | |
| Embeda (morphine + naltrexone extended-release) | 2014 | Available | Capsules contain pellets of morphine around a core of sequestered naltrexone. When taken as directed, morphine is released and absorbed and the naltrexone core passes through the gastrointestinal tract. If the pellets undergo physical manipulation, naltrexone is released from the core to block euphoria caused by rapid morphine release. | 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, 100 mg/4 mg |
| MorphaBond ER (morphine extended-release) | 2015 | Unavailable (as of July 27, 2017) | The tablet contains multiple layers that are resistant to physical manipulation (*e.g.*, crushing). The layers also prevent chemical extraction and dosage dumping by utilizing superabsorbent excipients and insoluble coatings. When taken as directed, extended-release of morphine is facilitated by the layers *via* diffusion. | 15 mg, 30 mg, 60 mg, 100 mg |
| Arymo ER (morphine extended-release) | 2017 | Available | Polyethylene oxide matrix and morphine polymers surrounded by a hard shell make the tablet dense, less porous, and resistant to physical manipulation (*e.g.*, crushing). When the manipulated product encounters a solvent, a viscous hydrogel is formed, preventing the abuser from drawing the product into a syringe for injection. | 15 mg, 30 mg, 60 mg |

ADF = abuse-deterrent opioid formulation; FDA = Food and Drug Administration; IR = immediate release.

to combine the active oxycodone base with hydrophobic fatty acids and waxes into small microspheres that homogeneously fill each capsule.[12,27] The microspheres contain physical and chemical barriers to resist crushing, chewing, heating, and dissolving, and will solidify when they come in contact with solution, making it difficult to uptake and dispel the drug through a needle for IV abuse.[27–29] Xtampza ER capsules are a good option for patients whose pain or illness prevents them from swallowing tablets. The capsules can be opened so that the microspheres may be safely poured into a feeding tube, sprinkled onto food, or put directly into the mouth to relieve pain.[28] Xtampza ER has received ADF labeling for the IV, nasal, and oral routes.

### Troxyca ER

Troxyca ER, which received ADF labeling in 2016, is a capsule consisting of pellets containing oxycodone ER surrounding a sequestered naltrexone core.[30] When taken orally, the naltrexone remains sequestered and the patient will experience pain relief from the oxycodone that is released over an extended period of time. If the pellets within the capsule are crushed or chewed, the naltrexone will be released from its sequestered state and will counteract the effects of the oxycodone. Troxyca ER is also a viable option for patients with difficulty swallowing, as the pellets can be sprinkled on food.[30] Troxyca ER, which has received ADF labeling for the IV, nasal, and oral routes, is not currently available in the United States.

### Targiniq ER

In 2014, Targiniq ER became the second ER opioid to be approved with ADF labeling.[31] Targiniq ER is a combination ADF. The tablets contain an ER formulation of oxycodone surrounding naloxone in a 2:1 ratio.[32] Naloxone has low oral bioavailability due to high first-pass metabolism, and thus will not interfere with analgesia when the pill is administered orally as intended, but will exhibit opioid antagonism with nasal or IV administration.[33] In addition to this antagonistic ADF mechanism, a proprietary PEO matrix around the capsule serves as a physical barrier to deter crushing and maintains insolubility in an aqueous medium.[12] This PEO barrier is made using the same manufacturer-specific thermal processing employed in the making of OxyContin.[12,34] Targiniq ER, which has received ADF labeling for the IV and nasal routes, is not currently available in the United States.

### RoxyBond

Approved in 2017, RoxyBond, which consists of IR oxycodone, is the first and only IR opioid formulation available with ADF labeling. The tablets are made up of multiple layers and coatings with different functions.[12] When used orally as intended, the oxycodone will diffuse through a time-release barrier layer and is ultimately taken up into the bloodstream for clinical effect. However, if the tablet is crushed in an unintended manner, an underlying layer containing xanthan gum and hypromellose will absorb the oxycodone, rendering it unavailable for systemic absorption. RoxyBond, which has received ADF labeling for the IV and nasal routes, is not currently available in the United States.

### Hysingla ER

In 2014, Hysingla ER became the first opioid consisting of hydrocodone to be approved with ADF labeling.[35] The abuse-deterrent product uses the manufacturer's proprietary ADF technology to resist crushing, grinding, and chewing, and when dissolved, the manipulated product will become a viscous hydrogel that is difficult to IV inject.[36] These properties of Hysingla ER are mediated by a PEO coating that is created by the same proprietary thermal processing technique used to produce the ADF versions of OxyContin and Targiniq ER. Hysingla ER has received ADF labeling for the IV, nasal, and oral routes.

### Vantrela ER

Vantrela ER was the second approved hydrocodone ER product, receiving abuse-deterrent labeling in 2017. The core of the pill contains granules of polymers formed by hydrocodone and fat or wax excipients.[37] These granules are coated with excipients to reinforce crush resistance and thermoplasticity, then they are compressed into tablet form.[12] These excipients also have low solubility, making IV preparation difficult. Vanrela ER, which has received ADF labeling for the IV, nasal, and oral routes, is not currently available in the United States.

### Embeda

Embeda is a morphine ER product with FDA-approved ADF labeling. Embeda capsules contain pellets with a sequestered naltrexone core. This core is made by applying the opioid antagonist and cellulose solution to sugar spheres and subsequently coating the core with an impermeable membrane to facilitate sequestration.[12] Morphine sulfate is layered onto the naltrexone core and the entire pellet is coated with an ER polymer coating.[38] This process of coating and drug layering ensures that, if the pellets are crushed, the sequestered naltrexone and active drug product will come together and counteract opiate-induced euphoria if administered by a nonoral route.[39] Embeda has received ADF labeling for the nasal and oral routes.

### MorphaBond ER

MorphaBond ER, an ER morphine product that was approved in 2015, uses the same manufacturer-specific ADF technology utilized by RoxyBond. A series of layers reinforces the physical integrity of the tablet and hinders chemical manipulation of the product for use *via* snorting and IV administration. MorphaBond ER, which has received ADF labeling for the IV and nasal routes, is not currently available in the United States.

### *Arymo ER*

Arymo ER, which received ADF labeling in 2017, is a morphine ER product designed with proprietary ADF technology. Arymo ER tablets are made by injection molding, a process by which PEO and morphine are blended together and injected into a mold containing a hard shell.[12,40] The shell has two openings at its ends to allow ER of the drug when taken orally.[12] Physical manipulation of the tablet is hindered by the strength of its shell and the PEO matrix, and chemical manipulation is prevented due to the properties of PEO matrices, discussed previously under "OxyContin." Arymo ER has received ADF labeling for the IV route only.

## The Opana Story

In 2011, Endo Pharmaceuticals (Malvern, Pennsylvania) received approval from the FDA to begin replacing the original formulation of Opana ER (oxymorphone hydrochloride) with a newly formulated version containing abuse-deterrent properties. The reformulated Opana was designed with a proprietary high-molecular-weight polyethylene oxide matrix around the pill that contains crush-resistant properties to deter intranasal and IV preparations of the opioid for unintended use.[11] Data presented to the FDA indicated that the reformulated product has equivalent analgesic properties without known side effects, but the agency did not approve ADF labeling because of a lack of data demonstrating Opana's potential to effectively deter abuse.[41] In 2012, after the reformulated product began circulation on the market, Endo submitted a citizen's petition to the FDA in an effort to bring about the withdrawal of generic oxymorphone products that referenced the original (non-ADF) Opana formulation. The company requested that the agency publicly state that the original product was replaced with an abuse-deterrent formulation for safety reasons.[41] The petition was denied, and the FDA noted that the rate of IV abuse of the newly designed opioid had been increasing in the months after its introduction to the market. Since then, several more safety concerns developed. In March 2017, Endo presented postmarketing data to the FDA that contained evidence of serious health concerns with IV abuse of the reformulated product,[41] such as thrombotic thrombocytopenic purpura,[42,43] and an outbreak of human immunodeficiency virus infections in Indiana.[44] As a result of these findings, based on a request from the FDA that stated that "the benefits of the drug may no longer outweigh its risks," Endo agreed to remove reformulated Opana from the market in July 2017.[45]

It has been speculated that the cases of thrombotic thrombocytopenic purpura that resulted from IV administration of crushed Opana were due to the uniquely high molecular weight of the polyethylene oxide coating that became lodged in the arterioles of the kidneys of IV abusers.[42] The safety of excipients has not been a condition of FDA approval when the excipient is not administered as intended. But the FDA must now consider how to approach the issue of excipients in ADF opioid formulations amid mounting concerns that these inactive ingredients may lead to detrimental and unintended consequences.[21]

## Effectiveness of ADFs

There are two overarching goals of ADF technology. The first is to deter or dissuade nasal or IV abuse of the altered pill. Besides life-threatening respiratory depression resulting from a relative overdose, IV administration is associated with health hazards such as human immunodeficiency virus, hepatitis C, and endocarditis infections, among others. The second goal is to deter and prevent new or more intense addictions in persons who have the potential to transition from oral to nasal or IV abuse. Will these individuals be effectively deterred if it becomes more difficult to snort or inject the pill? Or will they transition to ingesting large amounts of IR oxycodone, or injecting IV heroin? The answers are as yet unknown, but all evidence to date is not encouraging. To begin with, ADFs are not universally available. The recently released Tufts Center for the Study of Drug Development Impact Report[46] noted that 96% of all opioid products prescribed in the United States in 2015 (predominantly IR formulations) lacked abuse-deterrent properties, and the low reimbursement by payers remains a major challenge limiting ADF prescriptions. Recent analyses (fig. 1) show that even while prescriptions for OxyContin steadily decrease, IR oxycodone prescriptions continue to climb. Although OxyContin is the most prescribed ADF (fig. 1), it is the third most prescribed ER prescription behind (non-ADF) ER morphine and transdermal fentanyl.[21] Even when available, there is conflicting evidence as to their effectiveness to decrease opioid abuse, or whether small gains will be cost-effective and will not financially penalize legitimate users.[7,16,47–52] For example, postmarketing studies that compared original and reformulated OxyContin demonstrated that the reformulated crush-resistant ADF reduced, but did not eliminate, unintended and illegal abuse.[7,47,52] Using data from 2009 through 2012 from the NAVIPPRO Addiction Severity Index—Multimedia Version network, Butler *et al.* reported a nearly 25% reduction in past 30-day abuse of OxyContin *via* snorting and an approximately 20% reduction in IV abuse, suggesting that reformulation of the opioid successfully reduced its rate of abuse.[47] However, approximately one in four individuals entering treatment still reported snorting reformulated OxyContin in the past 30 days, and approximately 16% reported injecting OxyContin in the past 30 days, suggesting that abuse is still possible, even with ADF technology in place.

Evidence from the RADARS system indicates that abusers will gravitate toward non-ADFs when available but will also find ways to abuse ADFs when they are the only option.[53] Websites and online forums (http://www.bluelight.com; accessed December 1, 2017) have enabled opioid abusers to share information about how to overcome the deterrent properties of ADFs.[53–55] Alternatively, abusers can use greater amounts of IR non-ADF oral formulations. A worrisome recent analysis demonstrated that from 2012 to 2016, while OxyContin outpatient pharmacy prescriptions steadily declined, IR oxycodone prescriptions continued to climb (fig. 2).

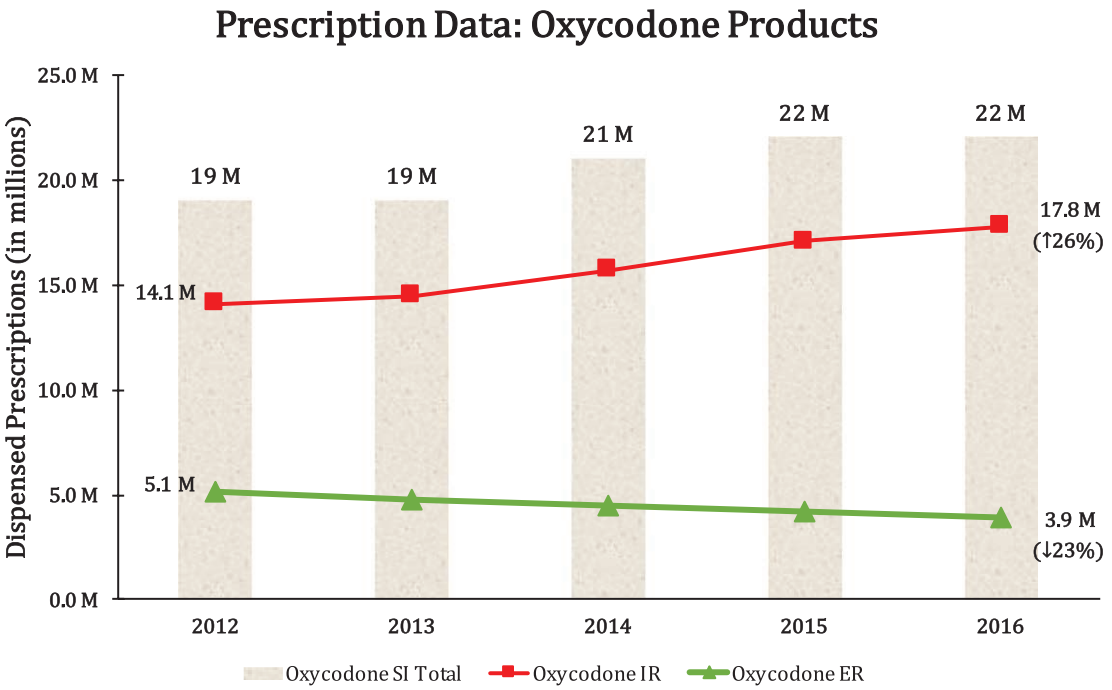



Fig. 1. Nationally estimated number of prescriptions dispensed for available ADF opioids from U.S. outpatient retail pharmacies, 2012–2016. Source: Quintiles IMS, National Prescription Audit. Data abstracted by the FDA. Reprinted with permission from FDA Briefing Document, Joint Meeting of Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee, July 26, 2017. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM568075.pdf. Accessed December 1, 2017. ADF = abuse-deterrent opioid formulation; ER = extended release; FDA = Food and Drug Administration; IR = immediate release; SI = single ingredient.

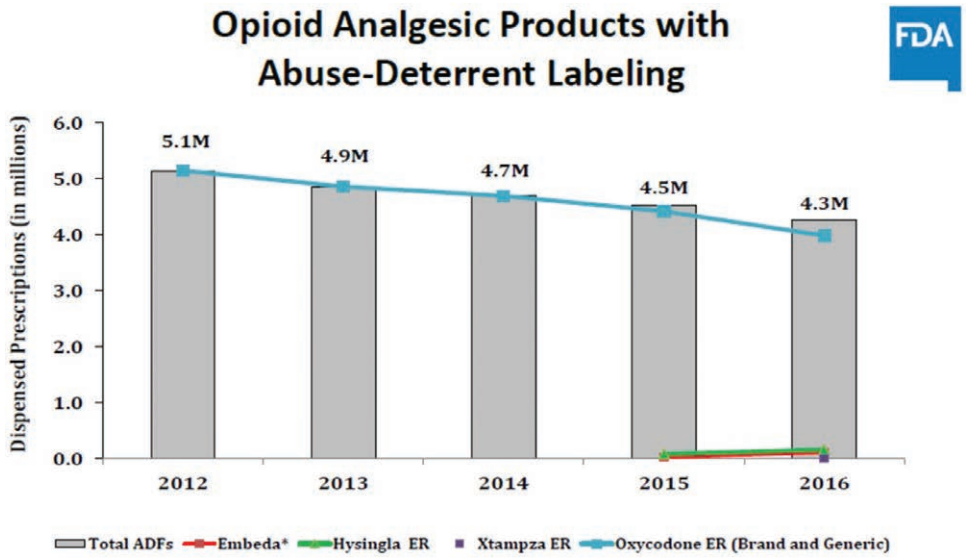



Fig. 2. Nationally estimated number of dispensed prescriptions for oral single-ingredient oxycodone from U.S. outpatient retail pharmacies. Source: Quintiles IMS, National Prescription Audit. Data abstracted by the FDA. Reprinted with permission from FDA Briefing Document, Joint Meeting of Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee, July 26, 2017. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM568075.pdf. Accessed December 1, 2017. ADF = abuse-deterrent opioid formulation; ER = extended release; FDA = Food and Drug Administration.

There are several types of individuals that use opioids, legally and illegally, and it is no easy task to try to predict which of these particular subsets will benefit from ADF products.[56] Patients with chronic pain who use ER opioids for maintenance or breakthrough and who have not developed tolerance will generally not develop withdrawal symptoms if doses are not escalated. This group of patients will not usually transition from oral administration to the nasal or IV route, and thus will not benefit from the advantages of ADFs.

Oral opioids such as IR oxycodone or hydrocodone are commonly prescribed for patients with self-limited acute pain, such as in the postoperative period or for several days after an injury. Most of these patients will wean off or discontinue the opioid as the acute pain subsides, but a small percentage will continue the opioid after the pain has subsided.[1] ADFs will discourage but not entirely eliminate the transition from oral to nasal or IV abuse, and it is currently impossible to determine which patients at this stage will be so discouraged that they decide to never try or to abandon nasal or IV abuse. Other users, in an attempt to achieve a more satisfactory high, will transition to nasal or IV administration of the oral formulation, and despite the barriers presented by the ADF, will devise ways to overcome these barriers.

Observational studies have indicated that the early abuse of OxyContin is overwhelmingly by oral administration, with only 1% of abusers using it IV and about 16% nasally snorting.[57,58] However, at the time of admission to a rehabilitation center, presumably after sufficient progress in severity of opioid abuse and dependence, nasal snorting increased to 62% and IV administration increased to 26%, with only 14% maintaining oral abuse. Very little is known about individuals who transition to these more advanced stages of opioid abuse after being prescribed opioids for a self-limited bout of acute pain. Undoubtedly, this behavior related to many different factors, such as age, geographic location, socioeconomic status, and concomitant comorbidities[1] or medication administration,[59] among many others.

Still, other addicted users at this juncture will choose to inject heroin instead, which is increasingly available and less expensive than ADF pills. Approximately 35% of OxyContin abusers reported that the opioid's reformulation influenced their decision to switch to other drugs for abuse, most of whom switched to heroin.[7] A survey from Purdue Pharma, maker of OxyContin, demonstrated a 42% increase in heroin abuse after OxyContin was redesigned as an ADF.[48] Another recent analysis of IV opioid abuse among treatment admissions between 2004 and 2013 indicated that as oral opioid abuse trended downward, smoking and IV abuse continued to rise.[60] Most recently, a 2017 study estimated that up to 80% of the threefold increase in heroin mortality since 2010 could be attributed to the formulation change of OxyContin.[61]

Thus, the subset of individuals that might benefit from ADF deterrence (*i.e.*, those who transition from oral to nasal or IV administration) may be too small to influence the overall opioid abuse dilemma. And, as pointed out by Becker and Fiellin in their *New England Journal of Medicine* editorial,[62] a shift in opioid prescribing to ADFs is not only problematic because of the lack of evidence that opioids are effective in the treatment of chronic pain,[63–65] but they also emphasize that opioids are not only harmful when people tamper with them.

Most importantly, ADFs may not be as necessary as first thought because the root of the opioid crisis may lie elsewhere.[66] For example, there is evidence that the recognition of the overprescribing of opioids has resulted in an overall decrease in prescriptions nationally. A Centers for Disease Control and Prevention report from July 2017 revealed that although the prescription rate for opioids is still triple the level it was in 1999 and four times that of some European countries, prescriptions for opioids such as oxycodone dropped 13.1% from 2012 to 2015, from 81.2 per 100 people to 70.6.[67] This decline was confirmed by the Centers for Disease Control and Prevention when it published data from the Blue Cross Blue Shield of Massachusetts program indicating a 15% drop in opioid prescriptions that they attributed to the introduction of physician education programs designed to reduce opioid prescribing.[68] Some of this decrease in overall opioid prescribing may have resulted from the availability of the Prescription Drug Monitoring Program, an interstate database of prescription opioids that is now in place in all U.S. states that has been designed to detect when individuals have received opioids from multiple healthcare providers.[69] But despite all efforts to curb the number of written prescriptions and availability of oral opioids, a significant number of overdose deaths are now caused by contamination of bootleg opioids that contain more powerful substances, such as fentanyl or carfentanil.[70] Representatives of the National Institute on Drug Abuse and the National Institutes of Health have opined that ADFs cannot be considered a long-term solution.[71]

In a recently released analysis, the Institute for Clinical and Economic Review, a nonprofit organization that analyzes the financial impact of health advances,[72] analyzed 15 premarket randomized controlled trials that evaluated abuse potential endpoints, and 26 postmarket observational studies that evaluated the real-world impact of ADFs on levels of abuse and misuse. The researchers assessed the comparative clinical effectiveness and value of 10 ADFs, and were unable to establish a link between ADF use and decreased opioid abuse. Their conclusions were based on the "…uncertainties regarding the balance between reductions in abuse and transition to abuse of heroin and other opioids," as well as the significantly increased cost to society (an additional $533 million) to transition to ADF opioids. The Institute for Clinical and Economic Review gave all existing ADFs except OxyContin a "promising but inconclusive" overall

rating, based on a balance between experimental evidence that ADFs are a less attractive option to abuse but lack of real-world outcome evidence of their effects on abuse and overdose. They gave OxyContin a grade of C+, owing to the minimal number of studies that definitively show benefit from the abuse-deterrent version.

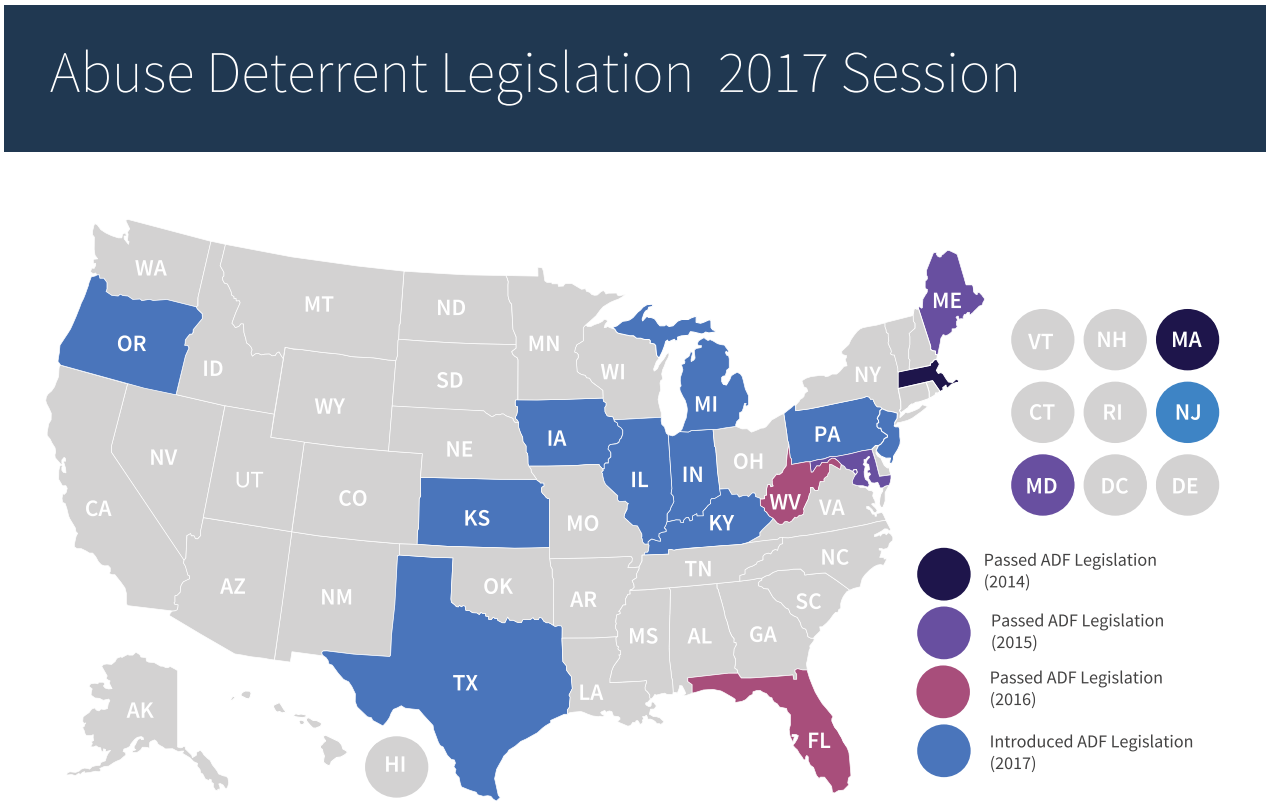
Finally, provider education in pain management and opioid utilization for chronic pain is also expected to contribute to the overall decrease in opioid prescriptions in the future. In 2016 the Centers for Disease Control and Prevention published new guidelines on prescribing opioids for chronic pain.[73] These guidelines stressed the importance of nonpharmacologic analgesia interventions, and when using opioids, setting realistic goals, expectations, and stopping points. In 2017, the FDA updated its blueprint for pain management guidelines to emphasize nonopioid and nonpharmaceutical pain treatment options, and enhanced its guidance and recommendations for physicians who prescribe opioids.[6]

## State Legislature Proposals or Laws

A number of state legislatures have enacted or are considering legislation that requires physicians to prescribe only ADF opioids where they are available (fig. 3).[74] In 2014, Massachusetts became the first state to pass legislation requiring pharmacies to automatically substitute ADFs for chemically equivalent non-ADF opioid prescriptions, and to require insurance carriers to cover these ADFs with no additional cost burden to patients. At this point, however, data on the impact of these state policy interventions are limited and inconsistent.[75] There is currently inadequate evidence showing that the benefits of ADFs (*i.e.*, decreased addiction or overdose) are worth the increased cost to taxpayers compared to non-ADF opioids, and a legitimate opioid user with severe pain may be priced out of an ADF if a non-ADF opioid is inaccessible.

### *Conclusions*

The pharmaceutical industry is increasingly developing abuse-deterrent formulations of opioids that are intended to decrease, but not eliminate, illegal and unintended abuse of oral opioid formulations. ADFs will likely benefit a relatively small subset of patients who are tempted to transition from oral to more intense opioid use (*i.e.*, nasal or IV). Early postmarketing studies have demonstrated conflicting results between a decrease of abuse of oral opioids and an increase in transition to IV-administered heroin. ADFs will continue to be manufactured, approved, and marketed, but it will




Source: MultiState Issue Management service.
Note: As of April 19, 2017

MULTISTATE

**Fig. 3.** Abuse-deterrent legislation by state, as of April 2017. Printed with permission of Multistate Issue Management, Alexandria, Virginia. ADF = abuse-deterrent opioid formulation.

require more study to determine their overall impact on the opioid crisis in the United States and worldwide. Even then, with additional changes in opioid prescription policies and provider engagement over time, it will be difficult to discern the benefits of any one change.

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