REVIEW ARTICLE

Mitigation of IV Abuse Through the Use of Abuse-Deterrent Opioid Formulations: An Overview of Current Technologies

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■ **Abstract:** Providers who treat patients with chronic pain face a dual challenge: providing adequate access to opioid therapies for appropriate pain management while adopting strategies to minimize the risk for abuse. Commonly prescribed opioids have substantial abuse potential when administered intravenously, and extended-release (ER)/long-acting (LA) opioids may be targeted for intravenous (IV) abuse because of the higher per-dose medication level. The consequences of IV opioid abuse are severe and increase the risks for adverse outcomes, including mortality due to acute health events, serious infections, and deep vein thrombosis, to name a few. To reduce the potential for abuse of prescription opioids by both recreational and experienced drug abusers, abuse-deterrent formulations (ADFs) of opioid medications employ either physical/chemical barriers or agonist-antagonist combinations. Here we review the development and use of opioid ADFs as a harm-reduction strategy, and their potential for mitigating IV opioid abuse. The approved ER/LA opioids with ADF labeling in the United States include formulations of oxycodone, hydrocodone, and morphine. Findings from in vitro laboratory tests of abuse deterrence for opioid ADFs are described herein, as are data from human abuse potential studies for IV abuse of those ADF products, for which such studies are feasible (ie, abuse-deterrent agonist-antagonist formulations). The available ADF opioids may decrease both the attractiveness and the feasibility of IV abuse. The adoption of ADF opioids represents one tactic for providing access to needed medication for patients with chronic pain, while potentially reducing the risk for opioid abuse, in a comprehensive effort to combat the opioid epidemic. ■

Key Words: opioids, analgesics, chronic pain, extended-release, intravenous, abuse potential, abuse-deterrent formulation

INTRODUCTION

The United States is in the midst of 2 contemporaneous epidemics, as both chronic pain and opioid abuse are highly prevalent.[1] A nationally representative survey study conducted in 2012 found that an estimated 25.3 million adults in the United States suffer from chronic pain.[2] Patients with chronic pain need effective analgesics, yet the long-term use of opioid therapy is a matter of substantial debate.[3–8] In the 1990s, opioid prescribing increased dramatically, without adequate consideration of the potential risks.[4,9] In the current context, an overly narrow focus on activities intended to mitigate the devastating effects of the opioid epidemic

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may cause the legitimate need for opioid analgesics for some patients with chronic pain to be overlooked.[10,11] At the same time, it is crucial to mitigate the risks associated with opioid use. Thus, providers face the dual challenges of ensuring patients with chronic pain have adequate access to opioid therapies while adopting strategies to minimize the risk for abuse.[12]

Risk reduction strategies employed by clinicians include screening and risk stratification of patients presenting with pain, prescription drug monitoring programs, the Centers for Disease Control and Prevention (CDC) guideline for prescribing opioids for chronic pain, compliance monitoring (eg, urine screening), patient education regarding drug storage and sharing, and prescription of abuse-deterrent formulations (ADFs) of opioid medications.[13,14] ADFs have properties (eg, physical/chemical barriers, agonist-antagonist combinations) shown to meaningfully deter intentional, nontherapeutic use of a drug product.[15] When prescribers have concerns about potential abuse, they may be unwilling to prescribe opioids, even to appropriate patients; thus, ADFs serve as one way to protect access to opioid medications for patients who need them. Patients with chronic pain include known and potential substance abusers, as well as patients who use medications only as prescribed, and ADFs add to the treatment armamentarium, enabling clinicians to provide responsible health care.[1,10,16]

Abuse-deterrent formulations reduce the potential for manipulation of opioid medications (eg, chewing, crushing, solvent extraction) for abuse via oral, intranasal, and intravenous (IV) routes.[15] Among common routes of drug abuse, IV abuse is associated with especially severe consequences.[17] The objective of this article is to review the development and use of abuse-deterrent opioids as a harm-reduction strategy and, in particular, to explore the potential for mitigating IV opioid abuse. This article focuses on the deterrence of IV opioid abuse, for which laboratory manipulation and extraction studies (category 1) are required as a first step for demonstrating ADF characteristics.

Abuse of Prescription and Illicit Opioids

Drug overdose is the leading cause of accidental death in the United States.[18] In 2016, opioids were associated with more than 42,000 overdose deaths, of which 40% involved a prescription opioid.[19] Prescription drug abuse is the intentional nontherapeutic use of a prescription drug, even once, to achieve a desirable psychological or physiological effect.[20] Both immediate-release (IR) and extended-release (ER)/long-acting (LA) opioids are subject to abuse and diversion.[21] ER/LA formulations may be especially attractive for abuse because of their higher per-dose level of medication.[22] The first ER oxycodone formulation (OxyContin®) was widely prescribed after its introduction in the 1990s.[23] When the ease of extracting the oxycodone load was recognized, ER OxyContin became widely abused, particularly by injection and intranasal inhalation.[24] However, the problem of prescription opioid abuse is not limited to ER/LA formulations.[25] Prescriptions for IR opioids outnumber those for ER opioids, and epidemiologic studies have reported that IR opioids have been abused and diverted more frequently than ER products.[21,26]

The most common route of abuse for prescription opioids is via the intended route of administration (ie, swallowing the intact product); however, manipulation before oral abuse (eg, via chewing or dissolving) has been reported (by 35.6% to 37.8% of respondents indicating prescription opioid abuse in one nationwide survey,[27] and by 41.5% of people who abused crush-resistant tablet formulations in another nationwide study[28]). Inhalation and injection are also common among people reporting prescription opioid abuse.[29] The incidence of intranasal and IV abuse was 38.2% and 32.4% of respondents, respectively, in one nationwide study.[27] Findings were similar for patients who abused the original formulation of OxyContin and entered a drug rehabilitation program; for this population, 60% reported intranasal abuse and 15% reported IV abuse.[30] Physical (eg, crushing) and chemical (eg, solvent extraction) manipulation may be used to defeat the ER mechanism and release the entire opioid load (dose-dumping) and prepare the drug for nonoral administration (eg, intranasal inhalation, injection).[15,31]

Commonly prescribed opioid medications have substantial abuse potential when administered intravenously.[32] In the United States, the rates of prescription opioid abuse via injection have been increasing. Based on data from the 2003 to 2014 National Surveys on Drug Use and Health (NSDUH), the rate of prescription opioid injection among individuals 12 years of age and older increased significantly, from 1.6 people in 1,000 between 2003 and 2005 to 2.7 people in 1,000 between 2012 and 2014.[33] Among people who inject drugs, the rates of prescription opioid injection also increased significantly, from 109.2 people in 1,000 to 161.8 people in 1,000, during the same

respective time frames.[33] Between 2004 and 2013, the percentage of substance use treatment admissions reporting prescription opioid injection abuse increased by 54.7%, from 11.7% to 18.1%.[34]

Consequences of IV Opioid Abuse

Although not the most commonly abused route, IV opioid abuse has severe consequences.[17] The relative risk for exposure that results in death, a life-threatening outcome, or significant disability is 2.6-fold greater for injection compared with oral administration.[17] Further, persons who inject drugs are at increased risk for acquiring a variety of serious infections via needle sharing,[35–38] including hepatitis C,[37,39] human immunodeficiency virus,[38,40,41] and endocarditis.[42] For example, an outbreak of endogenous fungal endophthalmitis, a severe intraocular infection caused by blood-borne dissemination of mycotic pathogens to the eye, was reported among IV drug abusers in New England between May 2014 and May 2016.[43] Notably, an analysis of data from the 2012 to 2014 NSDUH found that almost 20% of individuals who injected prescription opioids reported reusing another person's needle, thus exposing IV users to risk for infection.[33]

In addition, people who use IV opioid drugs are at a substantially increased risk for deep vein thrombosis (DVT). The estimated annual DVT incidence of 3%, noted in a study of patients receiving treatment for opioid addiction, is 100 times greater than the incidence in the general population, and the risk for current IV opioid users was 5.6 times greater than that for opioid abusers who had never injected drugs.[44] It is believed that the causes of opioid injection–related DVT may differ from the etiology of DVT in the general population and may include endothelial damage from injections, reduced blood flow from inactive muscle pumps during episodes of intoxication, and elevated coagulation factors resulting from infections contracted via injections.[44] Chronic IV opioid abuse has also been associated with cardiac dysfunction in a retrospective study comparing myocardial specimens from IV opioid users and nondrug users.[45] Also, women with histories of IV drug abuse have an increased risk (relative risk of 2.00) of alloimmunization in pregnancy[46]—possibly related to needle sharing—that may result in significant hemolytic disease of the fetus and newborn.[47]

It is difficult to determine the psychiatric and economic consequences of IV opioid abuse because these factors (eg, depression, anxiety, unemployment) may also serve as precipitating factors. Data from a large surveillance program have shown that injection of prescription opioids, heroin, or other substances is significantly associated with unemployment and homelessness.[48] Among a population of young injection drug users (99% with IV heroin use in the previous 6 months), major depression was found to be highly prevalent (lifetime prevalence rates: 25% for men, 31% for women), as were antisocial (23% for men, 17% for women) and borderline (20% for men, 25% for women) personality disorders.[49,50] Further analysis of this population found that prescription opioid misuse over the past year was significantly associated with substance-induced major depression in the past year, antisocial personality disorder, and prior post-traumatic stress disorder, which was identified as a significant risk factor for prescription opioid misuse.[49] Additional research is needed to further characterize the psychiatric and socioeconomic causes and consequences of IV opioid abuse.

ABUSE-DETERRENT ER/LA OPIOID FORMULATIONS

The development of abuse-deterrent opioids is considered a public health priority by the U.S. Food and Drug Administration (FDA)[15] as one strategy for reducing opioid abuse and diversion.[51] Abuse-deterrent formulations of opioid medications were designed primarily to mitigate the abuse of prescription opioids by both recreational and experienced drug abusers.[22] In addition, ADFs are intended to provide protection for patients with chronic pain who unwittingly (eg, crushing large tablets to make them easier to swallow) or intentionally (eg, to enhance pain relief or other desirable effects) attempt to manipulate opioid medications.[52] Table 1 summarizes the approaches for achieving abuse deterrence.[15,53] Although ADFs may reduce the potential for product manipulation (eg, crushing, chewing, solvent extraction) for known or expected routes of abuse (eg, oral, inhalation, smoking, injection),[15] these formulations cannot prevent the overconsumption of an intact product.

All currently available ADF opioids employ either physical/chemical barriers or an agonist-antagonist combination (Table 2).[53–65] Because some ADF opioids contain the same active ingredient (eg, morphine, oxycodone), each product has been assigned a unique generic name for use in this article: oxycodone OP (OxyContin), oxycodone DETERx® (Xtampza® ER),

oxycodone-naloxone ER (Targiniq™ ER), hydrocodone ER (Hysingla® ER), morphine/naltrexone (Embeda®), morphine-ARER (abuse-resistant, ER; MorphaBond™ ER), and morphine-ADER-IMT (abuse-deterrent, ER, injection-molded tablets; Arymo® ER).

Each ER/LA opioid in Table 2 is approved by the FDA for a similar indication: "management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate."[59–65] A systematic review and meta-analysis of the research literature found significantly greater pain relief from treatment with opioid analgesics compared with placebo, with comparable efficacy for ADF and non-ADF opioids.[66] The ADFs in Table 2 are commercially available in the United States, with the exception of oxycodone-naloxone ER.[54]

Table 1. Overview of Abuse-Deterrent Approaches[15,53]

Abuse-Deterrent Approach	Properties
Physical and chemical barriers	Resists chewing, crushing, cutting, grating, grinding, pulverizing; dissolving produces a viscous substance that cannot be drawn into a syringe
Agonist-antagonist combination	Opioid with a corresponding antagonist (to reduce or defeat euphoria associated with abuse; antagonist released only through tampering)
Aversive agent	Opioid is combined with an aversive agent released during tampering (eg, nasal irritant)
Delivery system	Method of drug delivery offers resistance to abuse (eg, sustained-release depot injectable, subcutaneous implant)
Prodrug	Opioid is released after the parent drug is ingested and metabolized (usually requires stomach enzyme); opioid is not activated through alternative route of administration

Adapted with permission from Institute for Clinical and Economic Review[53]; with additional data from U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research.[15]

The abuse-deterrent mechanisms of oxycodone OP, hydrocodone ER, and morphine-ADER-IMT involve a polyethylene oxide (PEO) polymer matrix (see Table 2).[53] Prescribers should be aware that IV abuse of certain PEO-containing formulations has been associated with the development of thrombotic microangiopathies (TMAs), including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome.[67,68] Three cases of unexplained TTP that occurred in IV drug users were initially reported in 2012 to the Tennessee Department of Health.[67] A statewide investigation revealed an association between TTP-like illness and the injection of a reformulated ER formulation of oxymorphone (Opana ER) that, unlike the original formulation, contained inactive ingredients including PEO. Additional cases of TMA were subsequently reported in patients using IV Opana ER.[68–71]

A study that examined the possible relationship between PEO and the development of TMA in a guinea pig model reported that IV infusion of solubilized PEO (with or without other inert components of Opana ER) produced hallmark features of TMA.[71] The

Table 2. FDA-Approved Long-Acting Opioid Medications With FDA-Approved Abuse-Deterrent Labeling[53–65]

Brand Name	Active Ingredient	Generic Name*	Technology	Abuse Deterrence Mechanism	Year Approved
OxyContin® (reformulated)	Oxycodone hydrochloride	Oxycodone OP	INTAC	Crush-/extraction-resistant tablets Oxycodone hydrochloride is dispersed within a PEO polymer matrix	2010
Embeda®	Morphine sulfate and naltrexone hydrochloride	Morphine-naltrexone	Sequestered naltrexone	Capsules contain ER morphine pellets, each with a sequestered naltrexone core	2010
Targiniq™ ER	Oxycodone hydrochloride and naloxone hydrochloride	Oxycodone-naloxone ER	Naloxone	Tablets contain oxycodone combined with naloxone	2014
Hysingla® ER	Hydrocodone bitartrate	Hydrocodone ER	RESISTEC	Crush-/extraction-resistant tablets Hydrocodone bitartrate is dispersed within a PEO polymer matrix	2015
MorphaBond™ ER	Morphine sulfate	Morphine-ARER	SentryBond	Crush-/extraction-resistant tablets	2015
Xtampza® ER	Oxycodone	Oxycodone DETERx®	DETERx	Capsules contain waxy microspheres of oxycodone base combined with inactive ingredients to form a lipophilic salt	2016
Arymo® ER	Morphine sulfate	Morphine-ADER-IMT	Guardian	Crush-/extraction-resistant tablets PEO matrix and injection molding process	2017

*Because some ADF opioids contain the same active ingredient (eg, morphine and oxycodone), each product has been assigned a unique generic name for use in this article. ADER-IMT, abuse-deterrent, extended-release, injection-molded tablets; ADF, abuse-deterrent formulation; ARER, abuse-resistant, extended-release; ER, extended release; FDA, U.S. Food and Drug Administration; PEO, polyethylene oxide.

development of TMA has also been noted in case reports of people injecting oxycodone OP[72–74]; a review of the literature did not identify any reports of TMA associated with IV injection of hydrocodone ER or morphine-ADER-IMT.

Laboratory Evidence of IV Abuse Deterrence

Abuse deterrence is evaluated by the FDA based on evidence from multiple types of studies (Table 3).[15,75] For each ER/LA opioid with FDA-approved ADF labeling, in vitro laboratory tests (category 1) were performed using the methods of manipulation that are commonly employed by drug abusers to prepare opioids for administration by various routes (eg, swallowing, inhaling, injecting, smoking) to evaluate the success of physical and chemical conditions and extraction methods in defeating the formulation.[59–65] Category 1 testing requires the investigation of all potential routes of abuse and relevant manipulation methods, including physical manipulation, large-volume extraction, small-volume extraction, and syringeability/injectability, under a wide array of experimental conditions.[15,76] For some ADFs, more detailed results of in vitro laboratory studies relevant to IV abuse potential are available from publications and congress presentations. Table 4 summarizes the findings of category 1 testing for ER/LA opioids with FDA-approved ADF labeling.[52,59–65]

The potential for the IV abuse of oxycodone DETERx was evaluated in a series of laboratory studies that included small-volume extraction (into 5 or 10 mL of water), syringeability of intact or crushed microspheres suspended in water, and syringeability of melted microspheres, using a variety of testing conditions.[77] The extraction recoveries from oxycodone DETERx were minimal (mean <12% for both intact and crushed product under all testing conditions), compared with extraction of up to 83% for oxycodone OP and 98% for IR oxycodone. Syringeability and injectability studies showed that injection of oxycodone DETERx microspheres was not feasible via suspension in water (<1.4% of starting oxycodone content was passed through the syringe) or after melting the active ingredient (some material could be drawn into a large-bore [18-gauge] needle, but it was not possible to expel any drawn material).[77]

One study determined particle size and analyzed dissolution profiles after the physical manipulation of oxycodone DETERx and oxycodone OP using a range of 10 common household utensils,[78] and found that the physical manipulation of oxycodone DETERx resulted in either no or only minor changes in particle size. In contrast, oxycodone OP was deformed or reduced in size by 7 of the 10 utensils, 6 of which reduced the tablet into smaller pieces that consisted of chunks or small particles. The dissolution profiles and ER properties remained relatively intact after the physical manipulation of oxycodone DETERx, whereas greater changes to the dissolution profile were observed after the physical manipulation of oxycodone OP.[78] Similarly, crushing oxycodone DETERx with common household tools resulted in the release of just 10% more opioid relative to intact drug after 15 minutes of dissolution; in comparison, oxycodone OP released slightly less than 60% more opioid, and other non-ADF ER formulations released ≥60% more opioid relative to intact drug after 15 minutes of dissolution.[52] Oxycodone DETERx was the only ER opioid to maintain a slow release of study drug early in the dissolution time course after physical manipulation.[52]

Table 3. FDA Guidelines for the Approval of ADF Labeling[15,75]

Category	Type of Studies	Description	Goals
1	Laboratory manipulation and extraction	Studies designed to evaluate physiochemical properties and characterize a product's abuse-deterrent properties, as well as the degree of effort required to defeat those properties	The product is formulated with physiochemical barriers of abuse
2	Pharmacokinetic	Studies designed to compare pharmacokinetic profiles of an intact and manipulated ADF product to a comparator drug through 1 or more routes of administration	Manipulation of the product does not increase the rate/extent of opioid release or receptor binding
3	Clinical abuse potential	Studies conducted in drug-experienced, recreational user populations designed to assess the impact of potentially abuse-deterrent properties	The product is expected to result in a meaningful reduction in abuse
4	Postmarket	Studies designed to determine whether an ADF product results in meaningful reductions in abuse, misuse, and related adverse clinical outcomes	The product has demonstrated reduced abuse in the community

ADF, abuse-deterrent formulation; FDA, U.S. Food and Drug Administration.
Adapted with permission from Nguyen et al., *J Clin Pharm Ther*. 2015;40:629–634; © 2015 John Wiley & Sons Ltd[75]; with additional data from the U.S. Department of Health and Human Services, U.S. Food and Drug Administration, Center for Drug Evaluation and Research.[15]

Table 4. Summary of Findings From In Vitro Laboratory Tests of Abuse Deterrence[52,59–65]

Brand Name	Generic Name*	Results of Laboratory Manipulation and Extraction Studies
OxyContin® (reformulated)	Oxycodone OP	• Results support that, relative to original OxyContin, there is an increase in the ability of reformulated OxyContin to resist crushing, breaking, and dissolution using a variety of tools and solvents • The results of these studies also support this finding for reformulated OxyContin relative to IR oxycodone • When subjected to an aqueous environment, reformulated OxyContin gradually forms a viscous hydrogel (ie, a gelatinous mass) that resists passage through a needle
Embeda®	Morphine-naltrexone	• When Embeda is crushed and mixed in a variety of solvents, both morphine sulfate and naltrexone hydrochloride are simultaneously extracted
Targiniq™ ER	Oxycodone-naloxone ER	• Laboratory test data demonstrate that Targiniq ER can be crushed and dissolved in solution • However, complete separation or complete inactivation of naloxone from oxycodone was not achieved despite using various techniques and conditions
Hysingla® ER	Hydrocodone ER	• Results support that Hysingla ER resists crushing, breaking, and dissolution using a variety of tools and solvents and retains some ER properties despite manipulation • When subjected to an aqueous environment, Hysingla ER gradually forms a viscous hydrogel (ie, a gelatinous mass) that resists passage through a hypodermic needle
MorphaBond™ ER	Morphine-ARER	• The laboratory test data demonstrated that, relative to morphine sulfate extended-release tablet, MorphaBond ER has increased resistance to cutting, crushing, or breaking using a variety of tools • When subjected to a liquid environment, the manipulated MorphaBond ER formulation forms a viscous material that resists passage through a needle
Xtampza® ER	Oxycodone DETERx®	• Results support that, relative to IR oxycodone tablets, Xtampza ER is less susceptible to the effects of grinding, crushing, and extraction using a variety of tools and solvents • Xtampza ER resisted attempts to pass the melted capsule contents or the microspheres suspended in water through a hypodermic needle
Arymo® ER	Morphine-ADER-IMT	• Arymo ER tablets, in comparison to morphine sulfate ER tablets, have increased resistance to cutting, crushing, grinding, or breaking using a variety of tools • When subjected to a liquid environment, the manipulated Arymo ER tablets form a viscous hydrogel (ie, a gelatinous mass) that resists passage through a hypodermic needle

*Because some ADF opioids contain the same active ingredient (eg, morphine, oxycodone), each product has been assigned a unique generic name for use in this article. ADER-IMT, abuse-deterrent, extended-release, injection-molded tablets; ADF, abuse-deterrent formulation; ARER, abuse-resistant, extended-release; ER, extended release; IR, immediate release.

The potential for IV abuse of morphine-ADER-IMT was evaluated in a series of laboratory studies that included small-volume extraction using a variety of solvents and testing conditions, and the syringeability of intact tablets and powder under various conditions.[79–81] Extraction recoveries from morphine-ADER-IMT were frequently low (<20% during the first 2 hours, with minimal increases through 8 to 24 hours) under all testing conditions.[80] Syringeability and injectability studies that involved exposing untreated and heat-pretreated morphine-ADER-IMT tablets to a variety of solvents produced a viscous mass with low syringeability (syringe content <10% of starting content), compared with 30% to 60% of non-ADF ER morphine that was syringeable in volumes suitable for injection.[81,82] In addition, an evaluation of the degree of effort required to manipulate morphine formulations with different household tools reported that morphine-ADER-IMT was extremely difficult to manipulate and required considerably more effort and time to manipulate than non-ADFs of IR and ER morphine, which may reduce the attractiveness of morphine-ADER-IMT for misuse and abuse since it cannot be readily prepared for injection.[83] None of the extraction tools enabled complete or substantial powdering of morphine-ADER-IMT, whereas using the same tools for manipulation resulted in complete or substantial powdering for 97.2% of IR morphine sulfate tablets and 77.1% of ER morphine sulfate tablets.[83]

Human Abuse Potential Studies

Human abuse potential studies (category 3) for IV abuse are informative, with regard to opioid medications that contain naltrexone or naloxone, for evaluation of the deterrent effect of releasing the opioid antagonist when

the product is manipulated.[15] Excipients used in oral formulations may render them unsafe for IV administration; therefore, clinical studies utilize parenteral formulations appropriate for IV administration.[15] The IV abuse liability of crushed morphine-naltrexone was evaluated in a clinical simulation in which IV morphine and naltrexone were administered to nondependent recreational prescription opioid users at the same ratio as contained in the capsules (100:4).[84] Participant ratings of subjective drug effects (eg, drug liking, high, euphoria) were significantly lower for IV morphine plus naltrexone compared with IV morphine alone, indicating that the sequestered naltrexone in morphine-naltrexone capsules was sufficient to reduce subjective effects obtained from product manipulation, thereby potentially reducing the attractiveness to opioid abusers. Case reports[85,86] and a clinical trial[87] have found that chewed or crushed oral administration of morphine-naltrexone may precipitate withdrawal in opioid-dependent individuals, indicating that opioid withdrawal is also possible with IV injection of the dissolved product.[62]

The potential for oxycodone-naloxone to deter IV abuse was evaluated in a randomized, double-blind, placebo-controlled, 3-way crossover study.[88] Nondependent recreational opioid users each received the following IV treatments over 3 visits: oxycodone 0.07 mg/kg along with naloxone 0.035 mg/kg (selected to simulate the 2:1 ratio of the oxycodone-naloxone formulation), oxycodone 0.07 mg/kg, or matching placebos. Subjective measures, including drug liking, propensity to take the drug again, feeling high, and good effects, were significantly greater with oxycodone than with oxycodone-naloxone and were not significantly different between oxycodone-naloxone and placebo. These results indicate that the naloxone concentrations in oxycodone-naloxone were sufficient to reduce the reinforcing effects of oxycodone when taken intravenously.[88]

POTENTIAL FOR ABUSE-DETERRENT FORMULATIONS TO REDUCE THE RISK FOR IV OPIOID ABUSE

As described above, the results of in vitro testing (category 1 studies) support the reduced feasibility and attractiveness of IV abuse of ADF opioids compared with non-ADF products. However, results of these laboratory studies may not reflect real-world abuse of opioid medications.

Postmarketing Surveillance

Postmarketing data (category 4 studies), which demonstrate the effects of ADFs on opioid abuse and diversion in community settings, are currently available for oxycodone OP (the first abuse-deterrent opioid, developed in response to the widespread abuse of the original formulation).[89] Converging evidence from multiple sources (eg, poison centers, substance abuse treatment centers, law enforcement drug diversion investigators, commercial prescription drug databases, third-party claims databases) indicates a marked reduction in the abuse and diversion of oxycodone OP relative to the previous, non-ADF ER formulation,[55,90] including low rates of successful injection of oxycodone OP among prescription opioid abusers.[91,92] A survey of individuals entering treatment for opioid use disorder, followed by a focused online survey of a subset of participants, found that the proportion of responders who abused oxycodone ER decreased from 44% in the 2 years before the introduction of oxycodone OP to 25% after its introduction.[55] The ADF formulation was associated with a significant ($P = 0.001$) reduction in the prevalence of oxycodone ER injection among users, from 42.7% (original formulation) to 21.4% (oxycodone OP).[55] However, data from the U.S. Researched Abuse Diversion and Addiction-Related Surveillance (RADARS) system found that 34% of abusers of the reformulation successfully defeated the abuse-deterrent mechanism to inject or inhale the drug.[89] Similarly, more than 20% of users reported in a separate RADARS analysis that they continued to abuse oxycodone OP intravenously,[55] which indicates that they were able to defeat the ADF and demonstrates a need for more effective abuse-deterrent technologies.

Postmarketing studies for other ADFs, as required by the FDA, are currently ongoing.[53,93] Interpreting the results of such studies will be complicated, however, because of the concurrent interventions intended to reduce opioid abuse and other changes in the therapeutic landscape that preclude the identification of a numerical threshold for defining a meaningful reduction in abuse.[15] Unlike oxycodone OP, newer drugs (eg, hydrocodone ER, morphine-ADER, morphine ADER-IMT, oxycodone DETERx) do not have non-ADF formulations that can be used in pre–post-testing. In addition, for medications with low population exposure, the feasibility of conducting such studies is limited, because detection of misuse/abuse-related outcomes, particularly those that occur infrequently, requires large

study populations.[94] Paradoxically, the introduction of a hard-to-crush formulation of oxymorphone (Opana ER) was associated with an increase in IV abuse.[76] Although the crush-resistant formulation successfully reduced the potential for intranasal inhalation (as was intended), drug users identified methods for defeating the product's gelling properties and extracted oxymorphone for IV injection. In June 2017, the FDA requested the removal of Opana ER from the market due to public health concerns about potential abuse.[95]

The lower rates of abuse and diversion of oxycodone OP observed relative to rates with the previous, non-ADF oxycodone ER formulation in postmarketing studies[55,90] may have been accompanied by increases in the abuse prevalence of other prescription and nonprescription opioids such as buprenorphine, oxymorphone ER, and heroin.[96–98] For example, a large U.S. surveillance study found that, after the introduction of oxycodone OP, abuse rates for buprenorphine and oxymorphone ER increased significantly; among those who only inject prescription opioids, the rates of buprenorphine and morphine ER abuse also increased significantly during the same period.[97] Thus, the benefits of ADFs may be limited, while nondeterrent alternatives are easy to obtain.[99]

ADF Opioids and Heroin Use

People already abusing a specific opioid intravenously are likely to replace an ADF opioid with another more easily injected opioid.[53] It has been suggested that the introduction of ADF opioids precipitated an increase in heroin use.[100] However, temporal patterns are not indicative of a causal link between ADF opioids and heroin use. For example, increased heroin use preceded changes in opioid policies and formulations in many instances.[12] In addition, market forces (eg, increased accessibility, reduced price, high purity) are likely contributors to the recent increase in heroin use.[12] Notably, heroin has become more common than prescription opioids as the first opioid of abuse in a recent study of individuals entering substance abuse treatment.[101] Heroin was also more commonly the first opioid of abuse before the widespread escalation in opioid prescribing beginning in the 1990s.[102] Although the recent increases of heroin as the initiating opioid of abuse are alarming, these findings may also signal a shift away from IV prescription opioid abuse as a gateway to heroin use. ADFs might reduce the potential for transitions to IV abuse in persons who are not yet injecting opioids; however, the impact of ADFs on the progression from medical to nonmedical use in patients with chronic pain is unclear at this time.[53]

PRESCRIBING PRACTICES FOR ABUSE-DETERRENT OPIOIDS

Although ADF medications are effective for reducing opioid abuse and diversion,[90] they are not widely prescribed.[103] One critical barrier to the use of ADFs is lack of payer coverage, which is tied to the higher cost of ADF opioids relative to non-ADF products.[103] Several analyses have demonstrated benefits of ADFs in terms of health care and societal costs.[104–106] However, because these cost reductions do not provide direct benefits to the payer, the savings may not be perceived as an adequate rationale for insurers to provide coverage. Price is also a critical barrier to ADF access for patients who are not covered by insurance.

The development of novel non-opioid analgesics (that are highly effective for pain relief but have reduced potential for abuse and addiction) is a priority at the National Institute on Drug Abuse.[107] Currently, however, opioid analgesics are the best pharmacologic option for many patients with moderate to severe chronic pain.[3] Responsible prescribing practices can provide access to opioid medications for patients who need them, while reducing associated risks.[10] Physicians should consider the potential benefits of ADFs when prescribing opioids to patients with chronic pain and challenge payers whose policies drive providers and patients to medications that are potentially less safe.

CONCLUSIONS

ADFs have reduced the ease of manipulation, opioid yield, and syringeability of ER/LA opioids, thereby decreasing the attractiveness and feasibility of IV abuse. However, non-ADF alternatives (particularly IR opioids) are widely available. ADFs may reduce the potential for progression to nonmedical opioid use in patients with chronic pain but are unlikely to stop established IV opioid users from switching to another drug, such as a non-ADF prescription opioid or heroin. That said, the introduction of abuse-deterrent opioids is one tactic in a comprehensive effort for combating the opioid epidemic.[54,108] It is incumbent upon physicians to consider the potential benefits of ADFs when prescribing opioids to patients with moderate to severe chronic pain.

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CONFLICTS OF INTEREST

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