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REVIEW

Review of Opioid Abuse-Deterrent Formulations: Impact and Barriers to Access

Lynn Webster[1], Jeffrey Gudin[2]

[1]Dr. Vince Clinical Research, Overland Park, KS, USA; [2]Department of Anesthesiology and Pain Management, University of Miami, Miller School of Medicine, Miami, FL, USA

Correspondence: Lynn Webster, Dr. Vince Clinical Research, 1285 3rd Avenue, Salt Lake City, UT, 84103, USA, Tel +1 801-560-1707, Email LRWebsterMD@gmail.com

Abstract: The misuse and abuse of opioid analgesics continue to pose a serious public health concern, but for some patients, opioids remain an important analgesic option. Extended-release (ER) opioid formulations are effective for treating chronic pain and are supported by multiple 12-week efficacy studies. ER opioids often contain a high opioid content, and similar to immediate-release (IR) formulations, are subject to abuse, misuse, and diversion. Unintentional misuse may also occur when ER formulations are manipulated for medicinal administration, such as crushing a dose for easier oral intake. As part of a multipronged strategy designed to fight the opioid epidemic, abuse-deterrent formulations (ADFs) were developed to deter misuse, abuse, and diversion of opioids by making manipulation more difficult and nonoral routes of administration less rewarding. Although ADF opioids have been shown to decrease rates of abuse and diversion, they are not equally effective in terms of deterring manipulation for abuse or misuse. Xtampza ER utilizes DETERx technology, which allows it to retain ER characteristics when chewed or crushed, making it the only ER opioid without a boxed warning against these types of manipulation. OxyContin was also developed as an ADF but uses RESISTEC technology, making the tablet hard to crush and viscous in aqueous solutions. ADF utilization has been hampered by patient access issues, including high prices due to lack of insurance coverage. Postmarket real-world studies demonstrate lower rates of abuse, misuse, and diversion for ADF ER opioids compared with non-ADF formulations. However, similar studies comparing abuse-related effectiveness and health care costs for ADF opioids are warranted if clinicians are expected to utilize these potentially safer opioid formulations. These studies would support further education surrounding the benefits and utilization of ADFs and manipulation potential of different ADFs.

Keywords: opioid analgesics, opioid crisis, chronic pain, tamper, abuse-deterrent, extended release

Introduction

Pain and chronic pain (lasting >3 months) are unpleasant sensory and emotional experiences associated with or resembling those associated with potential or actual tissue damage, which are highly debilitating and affect the quality of life of many adults in the US.[1–3] In 2021, an estimated 51.6 million adults in the US were affected by chronic pain and 17.1 million adults experienced high-impact chronic pain, defined as having pain every day or on most days during a 3-month period that substantially restricted participation in life or work activities.[2] Despite opioid misuse and abuse posing a serious and challenging public health problem, for a subset of patients with refractory pain, opioid analgesics remain an important component of pain management.[4] Common prescription opioids (limited to natural, semisynthetic, and methadone) were involved in 17,000 deaths (45 deaths per day) in the US in 2021.[5] Opioid use disorder (OUD) diagnoses and fatal overdoses increased dramatically during the COVID-19 pandemic.[6] A recent analysis by the Joint Economic Committee estimated that in 2020, the economic burden of illicit and licit opioid abuse and misuse reached almost $1.5 trillion.[7] A separate analysis considering the societal costs of OUD and opioid overdose deaths found that the greatest loss was the reduced quality of life from OUD and the value of life lost due to fatal opioid overdose.[8] These findings illustrate the magnitude of OUD as a persistent public health crisis and the devastating impact it has on individuals, families, and society.

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Support for opioid treatment has come under scrutiny despite therapeutic benefit. Regulatory agencies including the US Food and Drug Administration (FDA) encourage the development of abuse-deterrent formulations (ADF) as part of a multipronged approach for combating opioid misuse and abuse while ensuring that appropriate patients are treated effectively. The aim of this review is to discuss the properties of the available ADF products with evidence for abuse deterrence (eg, physical and chemical barriers) and how these properties may reduce abuse potential. The barriers that limit access to effective opioid treatment are also discussed.

Pain Management and Risk of OUD

A trial of opioid therapy may be warranted if conservative and interventional analgesic treatments fail, and an individual's risk for OUD should be taken into consideration before opioids are prescribed.[9] OUDs range from mild to severe and have been defined as possibly present "when a person craves or continues use and is unable to stop, even when physical, psychological, social, occupational, and other difficulties arise".[9] OUD is not only a disease of exposure; rather, its etiology is multifaceted, involving psychosocial, genetic, and environmental factors.[10] Individuals at the highest risk for experiencing OUD may be genetically predisposed[11,12] and/or exposed to opioids at a vulnerable time (eg, while experiencing mental or physical distress or having a psychological disorder).[13–16] Other risk factors for OUD include a personal or family history of a substance use disorder, poor social support, preadolescent sexual abuse, stress due to uncontrolled pain, mental and emotional pain from histories of childhood or adult trauma, and/or nonfunctional status due to pain.[9] Geriatric patients have frequent comorbid medical conditions and age-related pain syndromes (eg, osteoarthritis) conferring specific risk factors for opioid-related harm because of polypharmacy; in addition, adverse effects related to opioid use, including sedation, risk of falls, and impaired cognitive functioning, need to be considered when initiating opioid treatment.[17–19] Certain other populations may be more vulnerable to OUD and adverse outcomes, including children and adolescents.[20] Key risk factors for opioid misuse in adolescents and young adults are prescription opioid use and age at exposure.[20,21] However, acute exposure alone is usually insufficient for severe OUD to occur. For example, a long duration of first opioid treatment and administration of long-acting opioids have the potential to increase the risk of opioid misuse in young individuals.[22,23] Therefore, the benefits of initiating opioid therapy must outweigh the risks of opioid addiction, abuse, and misuse in all patients, but particularly in more vulnerable and special-risk populations.

The abuse potential of an opioid is influenced by pharmacologic factors including route of administration, rate of administration, and absorption rate.[24] Drug manipulation (eg, crushing, injecting, or snorting) achieves a fast rate of drug onset,[25] and rapid administration of opioids results in higher plasma levels, increased drug effect, and greater drug liking.[24] Immediate-release (IR) opioids generally provide a faster absorption rate, resulting in greater drug exposure when doses are equivalent, and may lead to greater drug liking when compared to intact extended-release (ER) formulations.[24] ER opioids are designed to provide an extended period of analgesia with less frequent dosing compared to IR formulations.[26] This is achieved by a controlled release of the active agent to provide consistent and prolonged plasma drug levels.[25] Furthermore, the time to peak blood concentration level (T_{max}) is generally longer with ER formulations, reducing abuse liabilities when taking whole tablets as intended.

ER opioid analgesics are indicated for the treatment of severe and persistent pain that requires an extended treatment period for which alternative pain management options are inadequate.[26–29] ER opioids have shown safety and efficacy in clinical trials for the control of various chronic pain conditions.[30–33] However, ER formulations typically have higher levels of active drugs that are appealing for nonmedical use and abuse and are therefore susceptible to abuse through tampering or swallowing multiple tablets.[25,26] The Research Abuse, Diversion and Addiction-Related Surveillance (RADARS) system found that prescription-adjusted rates of abuse and diversion (defined as an instance of unlawful channeling of a product of interest from legal sources that results in a written report or complaint) for ER opioids were 2.8-fold and 2.1-fold higher, respectively, than IR opioids.[34] This may be due to high-risk patients preferring to abuse ER medication.[34] On the other hand, prescription opioid abuse and diversion are declining more rapidly for ER than for IR opioid medications.[34] The American Academy of Pain Medicine Board of Directors has endorsed 8 key principles for safer opioid prescribing, including risk assessment of patients for opioid misuse prior to initiating opioid therapy and monitoring of patients during therapy as well as avoidance of long-acting opioid formulations for acute, postoperative, or trauma-related pain.[35,36] Moreover, the Department of Veterans Affairs and Department of Defense practice guidelines

also recommend against the use of long-acting opioids on initiation of opioid therapy, and IR opioids should be prescribed at the lowest effective dose for acute pain.[37]

Role of Abuse Deterrent Formulations in Reducing Abuse and Misuse

Three key characteristics of opioid medications that have been found to influence the risk of harms are the chemical compound, the formulation, and the intended route of administration.[38] ADFs were developed as a component of a multifactorial strategy to combat the opioid epidemic by addressing these characteristics via modification of the opioid formulation to prevent unintended routes of administration. ADFs may hinder manipulation or make the tampered formulation less rewarding, reducing drug liking and, potentially, diversion. In support of their intended abuse-deterrent functions, the introduction of ADF analgesics has been associated with decreased rates of diversion and abuse.[39] This finding indicates that ADFs have the potential to substantially reduce the incidence of opioid abuse relative to non-ADFs, although ADFs can still be abused and misused, mostly through oral overconsumption.[40,41]

The FDA outlines 4 categories (Table 1) of research to evaluate abuse deterrence, including 3 types of premarket studies (Categories 1–3) and 1 postmarket study (Category 4):[42,43] Category 1 consists of in vitro manipulation and extraction studies to evaluate the ease with which the potential abuse-deterrent properties can be defeated or compromised; Category 2 includes pharmacokinetic (PK) studies to understand in vivo properties of the formulation by comparing the PK profile of the manipulated formulation with the intact formulation and with manipulated and intact formulations of comparator drugs; Category 3 involves human abuse-potential studies to evaluate the impact of potentially abuse-deterrent properties by assessing drug liking, willingness to take drug again, and other abuse-related measures in recreational users; and Category 4 incorporates data from postmarket epidemiologic studies to determine the real-world impact on abuse, misuse, and other adverse clinical outcomes.[42,43] Currently, no ADF has been labeled as Category 4 by the FDA, underscoring the need for more postmarketing assessments of the real-world abuse-deterrent effects of currently available ADFs.

To date, there are 4 opioids (1 IR and 3 ER) with FDA-approved abuse-deterrence label claims—Roxybond IR (oxycodone hydrochloride), reformulated OxyContin (oxycodone hydrochloride), Hysingla ER (hydrocodone bitartrate), and Xtampza ER (oxycodone)—each designed with mechanisms to deter abuse and potentially avoid intentional misuse (Table 2).[43]

Roxybond is the only abuse-deterrent IR opioid formulation currently available. Roxybond includes inactive ingredients that make the tablets harder to tamper with by physical manipulation and chemical extraction for intranasal or intravenous (IV) abuse.[49] OxyContin (oxycodone controlled-release) was first approved by the FDA in 1995. It was subsequently reformulated to include abuse-deterrent properties, and the ADF version was approved in 2010 under the same name.[50,51] The current formulation of OxyContin uses physical and chemical properties that make it more difficult to crush the tablet and make it resistant to ethanol and other chemical-extraction techniques that enhance dose dumping.[49,52] The reformulated OxyContin is designed to prevent manipulation for intranasal and IV administration but can be manipulated for oral use.[49] Similar to OxyContin, Hysingla ER is formulated with physical and chemical

Table 1 US Food and Drug Administration–Recommended Studies of Abuse Deterrent Technologies

	Category 1	Category 2	Category 3	Category 4
Type of study	Laboratory-based in vitro manipulation and extraction studies	PK studies	Clinical abuse potential studies	Postmarket studies
Objective	To evaluate the ease of defeating or compromising abuse-deterrent properties of the formulation	To determine in vivo properties of the formulation by comparing the PK profiles of the manipulated vs intact formulations and with comparator drugs through 1 or more routes of administration	To assess the abuse potential of the formulation, preferably in a randomized, double-blind, placebo-controlled trial with a drug-experienced, recreational user population	To demonstrate meaningful reductions in abuse, misuse, and related adverse clinical outcomes including addiction, overdose, and death in postapproval settings

Abbreviation: PK, pharmacokinetic.

Table 2 Evidence of Abuse Deterrence for Currently Available ADFs

ADF	Manufacturer	Active Compound	Year of Approval	Mechanism of Deterrence	Deterred Routes of Abuse
OxyContin	Purdue Pharma LP	Oxycodone	2010	Intac technology employs a matrix drug delivery system that controls the rate of release of the active ingredient[44] RESISTEC employs a combination of polymer and processing that confers tablet hardness, imparts viscosity when dissolved in aqueous solutions, and resists drug release rate when mixed with alcohol[45]	Injection: becomes viscous in liquid Intranasal: tablets are difficult to crush
Hysingla ER	Purdue Pharma LP	Hydrocodone bitartrate	2015	RESISTEC employs a combination of polymer and processing that confers tablet hardness and imparts viscosity when dissolved in aqueous solutions[46]	Injection: becomes viscous in liquid Intranasal: tablets are difficult to crush
Roxybond IR	Protega Pharmaceuticals LLC	Oxycodone	2017	SentryBond combines inactive ingredients with the active opioid to slow the IR properties when manipulated[47]	Injection: becomes viscous in liquid Intranasal: slow and low absorption
Xtampza ER	Collegium Pharmaceutical, Inc	Oxycodone	2016	DETERx employs hydrophobic, waxy microspheres, which have ER properties that are resistant to manipulation, including cutting, crushing, grinding, chewing, dissolving in solutions (becomes viscous in liquid), injecting after crushing, melting, or extracting[48]	Injection: becomes viscous in liquid Oral: retains ER properties when crushed or chewed Intranasal: retains ER properties when crushed and snorted

Abbreviations: ADF, abuse-deterrent formulation; ER, extended-release; IR, immediate-release.

properties that render it difficult to crush, break, or dissolve and are expected to deter intranasal and IV abuse and oral abuse when chewed.[49]

Xtampza ER differs from the other 3 ADF opioids; it is an ER opioid formulation that utilizes DETERx technology, a microsphere-in-capsule formulation with each individual microsphere acting as its own drug delivery system to maintain its ER PK profile even after chewing and crushing.[49,53] Xtampza ER is relatively resistant to crushing because of 3 unique physicochemical characteristics. First, the waxy nature of the formulation can cause microspheres to smear instead of breaking into small particles, which could reduce drug release.[54] Second, the hydrophobic nature of Xtampza ER formulation and the uniform composition of microspheres that distribute the active pharmaceutical ingredients (API) evenly limit the rate of extraction of the API.[54] Finally, the median particle size of the microspheres is approximately 300 µm, and the changes to the surface area caused by crushing are inconsequential.[54] When crushed and heated for intended IV use, Xtampza ER will become viscous and difficult and perhaps dangerous to inject.[48] Therefore, it is neither cost- nor time-effective and is potentially dangerous to attempt oxycodone extraction from Xtampza ER.[48] Xtampza ER was designed to have significantly lower abuse potential compared to IR oxycodone via the oral route.[55] Xtampza ER's purported lower abuse potential is partially due to its slower T_{max} than, for example, oral administration of crushed oxycodone IR or crushed OxyContin (Figure 1).[53,56]

All 3 ER ADFs include abuse-deterrence claims in section 9.2 in the product labeling with supporting results from Category 1 and 3 studies; Xtampza ER also has data supporting Category 2 evaluation.[42] In vitro (Category 1) studies demonstrated that Hysingla has physical and chemical properties expected to deter intranasal and IV abuse, while OxyContin and Xtampza ER have physiochemical properties expected to make abuse via injection difficult.[42] Human

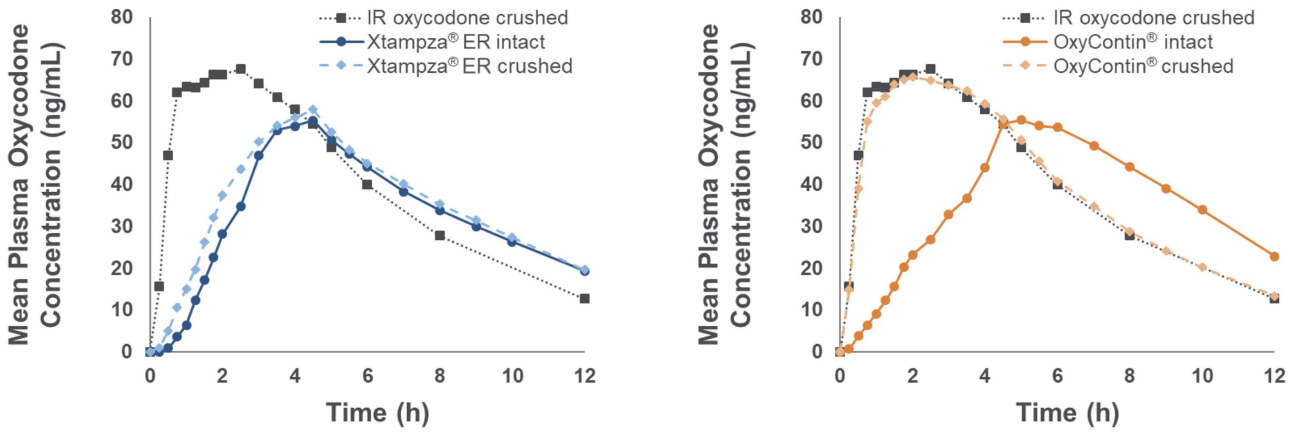

Figure 1 The mean plasma oxycodone concentration over time following oral administration of Xtampza ER (intact and crushed; left panel), OxyContin (intact and crushed; right panel), and crushed oxycodone IR. In an open-label, randomized, active-controlled, 5-treatment, 5-period, naltrexone-blocked crossover comparison study, blood samples were collected from healthy participants to compare the pharmacokinetics profile of Xtampza ER with OxyContin. IR oxycodone crushed, n=38; Xtampza ER intact, n=38; Xtampza crushed ER, n=40; Oxycontin intact, n=39; OxyContin crushed, n=39. Used with permission of Future Medicine Ltd, from Brennan MJ, Kopecky EA, Marseilles A, O'Connor M, Fleming AB. The comparative pharmacokinetics of physical manipulation by crushing of Xtampza® ER compared with OxyContin®. *Pain Manag*. 2017;7(6):461–472; permission conveyed through Copyright Clearance Center, Inc.[56]

abuse potential (Category 3) studies showed that Hysingla is expected to reduce intranasal abuse and oral abuse when chewed, while OxyContin is expected to reduce abuse by the intranasal route and Xtampza ER is expected to reduce abuse via the oral and intranasal routes.[42] Data from in vivo PK (Category 2) studies in Xtampza ER indicate a lack of dose dumping, with no increase in oxycodone levels when crushed or chewed compared with intact Xtampza ER.[42]

Manipulation Methods

Abuse, misuse, and diversion of opioids, including ADF opioids, remain a public health problem. ADFs do not alter the addictive properties of the opioid molecule itself, and while ADFs may deter abuse, they are not resistant to all abuse. For example, current ADF technologies do not deter swallowing several intact capsules or tablets to achieve a feeling of a desired drug effect like euphoria. For this reason, ADFs still carry a risk of overdose (Table 3).

The current prevailing ADF technology and most frequently prescribed is the reformulated hard-to-crush tablet OxyContin. A recent analysis of data from the RADARS system found that severe life-threatening events and death are twice as likely to occur with intentional abuse of prescription opioids when taken via nonoral routes of administration

Table 3 Impact of ADF on Abuse and Misuse Behaviors in Individuals Seeking or Entering Opioid Treatment Programs

Publications	Key Findings
Cicero TJ et al. *JAMA Psychiatry*. 2015[57]	Abusers who used both pre-ADF and reformulated OxyContin were able to successfully overcome the ADF mechanism and effectively manipulate the reformulated OxyContin for use via IV and inhalation routes.
Butler SF et al. *Pain Med*. 2018[58]	Although the reformulated OxyContin was designed as a crush-resistant tablet (ADF mechanism), individuals who orally abused opioids reported being able to manipulate the crush-resistant tablets (eg, chewing or dissolving) before oral ingestion.
Green JL et al. *J Pain Res*. 2021[59]	Rates of nonmedical use (deviation from legitimate medical use) of Xtampza ER were lower than other oxycodone ER (eg, OxyContin) and IR products.
Severtson SG et al. *Pain Med*. 2020[60]	Rates of abuse, misuse, and diversion were lower for Xtampza ER compared with other ADF ER opioids (eg, Oxycontin), non-ADF ER opioids (eg, nonbranded ER morphine), and IR oxycodone.
Jewell J et al. *Clin Drug Investigation*. 2023[61]	The odds of tampering (oral and nonoral) with an ADF opioid (eg, Xtampza ER and OxyContin) were reduced at least 70% compared with other non-ADF opioids.

Abbreviations: ADF, abuse-deterrent formulation; ER, extended-release; IR, immediate-release; IV, intravenous.

compared to oral routes.[62] One study showed that 34% of abusers (N=88) successfully overcame the ADF mechanism and effectively manipulated OxyContin for use via IV and inhalation routes.[57] Moreover, abuse of OxyContin occurs orally. For example, a real-world analysis of individuals seeking substance abuse treatment (N=18,135) found that up to 42% of oral abusers of crush-resistant tablets reported manipulating the pill (eg, chewing or dissolving).[58] In a separate study of OxyContin abusers (N=1705), up to 76% reported oral abuse of OxyContin (Figure 2).[63]

OxyContin is problematic for patients with chronic pain who also have dysphagia or odynophagia and who must crush or break tablets to ingest their medication or have it administered via an enteral tube.[64] Xtampza ER is the only form of oxycodone that can be taken by sprinkling the capsule contents on soft foods or into a cup and then administering directly into the mouth or through a gastrostomy or nasogastric feeding tube. In addition to being less attractive to illicit drug users, this formulation provides a viable option for patients who require such crushing or dissolving of their medication (due to difficulty swallowing).[64] A randomized, double-blind, placebo-controlled study showed that both chewed and intact Xtampza ER were bioequivalent, whereas crushed oxycodone IR yielded higher peak plasma concentrations (C_{max}) compared with similar Xtampza ER doses using any method of administration.[65] Crushed oxycodone IR had an approximately 10-fold higher abuse quotient score (estimation of the relative abuse potential of different formulations based on a ratio of C_{max} to T_{max}) compared with both chewed and intact Xtampza ER.[65] The T_{max} was significantly longer for intact or chewed Xtampza ER (~3–5 hours) than for crushed IR oxycodone (1 hour).[65] If the time to onset is attractive to misusers, these findings would suggest that Xtampza ER should have less appeal to individuals seeking a more rapid drug effect.

Real-world evidence (RWE) provides supporting information on the relative risk of abuse of currently available opioid medications. An analysis of the Addiction Severity Index-Multimedia Version found that Xtampza ER had significantly lower rates of nonmedical use and nonoral nonmedical use than OxyContin and non-ADF oxycodone IR products in individuals seeking substance abuse treatment.[59] A study evaluating the RADARS system found low rates of abuse/misuse (composite endpoint of cases by combining 3 exposure categories: intentional abuse, intentional misuse, and intentional unknown exposures as defined in the annual report of the National Poison Data System) and diversion of Xtampza ER compared with other prescription opioid analgesics.[60] Moreover, abuse and misuse did not increase for 3 years (July 1, 2016, through June 30, 2019) after initial marketing of Xtampza ER into the US market.[60] A recent postmarketing study found that Xtampza ER demonstrated reduced odds of tampering compared to non-ADF oxycodone IR and ER oxymorphone in a treatment-center population; no differences in tampering were observed between Xtampza ER and other ER oxycodone ADF opioids.[61] After the introduction of reformulated OxyContin in 2010, the rate of

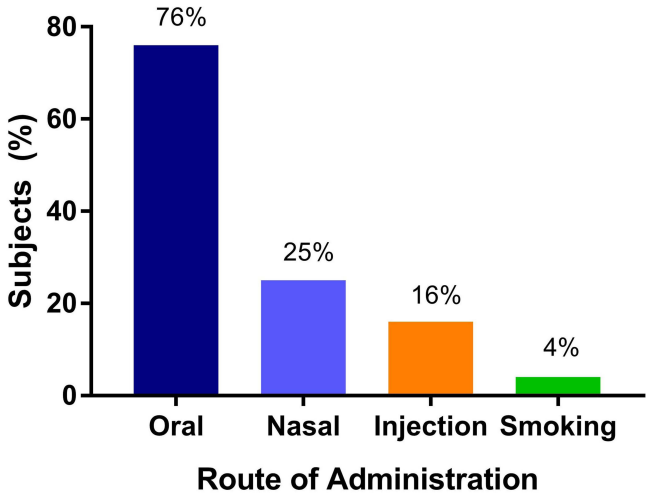

Figure 2 OxyContin abusers and their route of administration. A sentinel surveillance sample of 140,496 individuals assessed for substance abuse treatment at 357 US centers between June 1, 2009, and March 31, 2012, was examined. Data on the route of administration used (percent) by OxyContin abusers (N=1705) after the introduction of reformulated OxyContin are shown. Adapted from *J Pain*, volume 14(4), Butler SF, Cassidy TA, Chilcoat H, et al. Abuse rates and routes of administration of reformulated extended-release oxycodone: initial findings from a sentinel surveillance sample of individuals assessed for substance abuse treatment. 351–358, Copyright 2013, with permission from Elsevier.[63]

doctor-shopping for OxyContin declined by 50% over 3 years, which is the practice of obtaining multiple prescriptions from visiting multiple physicians. The decline was less for other prescription opioid comparators (eg, IR hydromorphone), ranging only from 9% to 25%, while an increase was observed for ER oxymorphone (66%). These findings suggest that ADF opioids reduce doctor-shopping, which is associated with high risks for abuse and diversion due to the amount of excess drugs procured.[66,67] In the same 3-year period, diversion events for OxyContin decreased by 66%, as reported by law enforcement officials in the RADARS drug diversion study.[67] In a postmarketing analysis, rates of diversion were found to be 4.1-fold higher for other ADF ER opioids (eg, Oxycontin), 3.7-fold higher for IR oxycodone, and 3.4-fold higher for non-ADF ER opioids compared with Xtampza ER over 3 years.[60] Taken together, these RWE studies suggest that drugs employing ADF technology, specifically Xtampza ER, reduce the likelihood of abuse, misuse, and diversion when compared with non-ADF prescription analgesics.

Since the early 2010s, the amount of opioids prescribed and dispensed has decreased, which corresponds to the introduction of ADF opioids, including the reformulated OxyContin and Xtampza ER.[68–71] A recent analysis using a large nationally representative prescription database found a 32% decrease in the total number of opioid analgesic prescriptions between 2016 and 2021.[70] This decrease in the amount of opioids prescribed and dispensed may be attributed to several reasons, including strict regulations for opioid distribution[72] and cautious opioid prescribing practices.[70,73]

Prescriber and Insurance Perspective

Health care providers are generally aware of oxycodone's efficacy, but there appears to be little insight into the potential for manipulation with different oxycodone formulations (Table 4). A survey of licensed physicians found that >50% believe that all ADFs are equally effective in preventing abuse and misuse by various routes of internalization (eg, intact oral vs crushing/grinding) despite explicit labeling, while about a third of physicians were unsure.[74] These findings indicate a need for improved prescriber education, beyond product labels, regarding the abuse-deterrent mechanisms for different ADFs.[74] Patient education by practitioners needs to include information on the risks of opioid abuse and diversion, appropriate use of opioid formulations, and proper medication storage and disposal.[49] Effective patient education can only be possible when prescribers are well educated in pain management and safe opioid usage. To ensure that the benefits of opioid formulations outweigh the risk of addiction, abuse, and misuse, the FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for opioid products.[75] For this reason, the FDA recommends that all health care practitioners involved in the management of pain in patients should be educated about the fundamentals of acute and chronic pain management, including the risks and safe use of opioids and the prevention, diagnosis, and management of OUD.[75]

Table 4 Barriers to Opioid Treatment Access

Publications	Key Findings
Dasgupta N et al. *Pain Ther.* 2022[74]	Provider barriers: Many clinicians have insufficient training and education regarding the potential efficacy of ADFs in preventing abuse and misuse despite explicit labeling.
Brooks A and Kominek C. *Pain Med.* 2018;[76] Petrilla A et al. *Am Health Drug Benefits.* 2020;[77] Kumar VM et al. *Value Health.* 2019[78]	Financial barriers: High costs and lack of insurance coverage for ADF opioids exclude access for many patients. Financial burden to the health care system was found to be greater in a cost-effectiveness model, mostly due to higher ADF opioid drug costs.
Gill S et al. *BJGP Open.* 2022[79]	Institutional barriers: Fragmented care for pain management, including lack of continuity of care and resources for pain management support for difficult-to-treat patients, impede effective prescribing practices by physicians.
Litman RS et al. *Anesthesiology.* 2018[80]	Regulatory barriers: Although some states have approved legislation mandating insurance coverage and availability of ADFs on formularies, the legislation is not introduced or approved in a majority of states.

Abbreviation: ADF, abuse-deterrent formulation.

In order to continue to improve outcomes and define the standard of care associated with the use of opioid analgesics, regulatory policy and medical guidelines need to be evidence-based. Understanding the factors that influence prescribing IR vs ER or ADFs over non-ADF opioid formulations is critical. In a survey evaluating physician beliefs, behaviors, and psychology, one-third (n=130) of 374 physicians considered whether an opioid had tamper-deterring properties when prescribing.[74] Their motivation for prescribing ADFs was largely influenced by potential patient/family diversion and reducing the societal supply and less related to patient-level abuse concerns.[74] A lack of ADF opioid utilization by prescribers may be influenced by selective prescribing and the bias that opioid abuse is a family and societal issue rather than a patient abuse and misuse issue. In support of this theory, this survey also found that only 57% of prescribers agreed that opioid abuse was a problem in their practice, while emergency department physicians were more likely to acknowledge opioid abuse as a problem among their patients.[74] Lack of continuity of care and pain management support resources, especially for chronic pain patients, contribute to fragmented care for pain management and hinder optimal prescribing practices.[79]

ADF opioid analgesics are currently only available as branded drugs and are therefore significantly more expensive than non-ADF opioid analgesics. Moreover, ADFs generally have higher costs than IR formulations and non-ADFs due to the added cost of manufacturing the advanced technology.[76] The Institute of Clinical and Economic Review performed a cost-effectiveness model and estimated that 2300 new cases of abuse may be prevented with ADF opioids compared with 6600 abuse-years that may be associated with non-ADF opioids over a 5-year time period; however, the financial burden to the health care system (approximately $525 million) was greater, mostly due to higher ADF opioid drug costs.[78] To achieve cost-neutrality (ie, $0 cost to the health care system) between ADFs and non-ADFs, the relative risk of diversion in the ADF cohort would need to decrease by approximately 43%.[78] A recent US retrospective claims analysis comparing health care costs of patients transitioning from an IR opioid to either Xtampza ER or OxyContin found that outpatient ER opioid costs were lower for Xtampza ER compared to OxyContin during a 9-month follow-up ($2645 vs $3141, $p<0.001$),[81] although this could be influenced by the payer. Nevertheless, further studies on postmarket real-world data comparing abuse-related effectiveness and health care costs associated with ADF opioids and non-ADF counterparts are warranted.[78]

Cost is a significant barrier for patients not receiving an opioid ADF. In fact, cost was found to be one of the most common motivating factors for not prescribing ADFs. Among physicians who prescribed ADFs, 25.4% recalled a patient asking for a non-ADF, putatively because of cost. In the same survey, 64% of prescribers were concerned about third-party payer costs. When contacted by a pharmacist to switch an ADF-containing opioid to a non–ADF-containing opioid due to cost, prescribers reported capitulating in nearly every instance, but these instances were reported by a low percentage (3.8%) of surveyed prescribers.[74] Adding to cost-hindrance, access to ADFs may be limited by inadequate insurance coverage and prior authorization requirements.[76] To reduce or eliminate barriers to ADF access, several companies that produce ADF opioids include on their websites information about cost-saving programs and tools for determining payer coverage.[76] As of January 2022, 38 states had implemented policies and/or guidelines setting opioid supply limits or requiring that doctors prescribe the lowest effective dose.[82]

Broad formulary coverage for ADF opioids has been associated with decreased rates of opioid abuse and overdose in real-world managed care populations.[77] Some states have introduced legislation mandating insurance coverage and availability of ADF opioids on formularies.[49] Several states have also introduced legislation mandating automatic replacement of non-ADF opioids with an ADF counterpart at no additional cost to the patient.[76,80] As of April 2017, this type of legislation had passed in 5 states (West Virginia, Florida, Maryland, Maine, and Massachusetts) and had been introduced in 10 more states.[80]

Conclusions

Prescription opioid abuse may be stabilizing or decreasing due to a variety of factors, including reductions in opioid prescribing and dispensing rates; introduction of ADFs; and local, state, and federal programs to improve opioid prescribing practices.[57,83,84] ADFs, such as Xtampza ER and OxyContin, were designed as part of a multifactorial strategy to address the opioid epidemic; however, not all ADFs are equivalent in their ability to deter opioid diversion and manipulation. Xtampza ER is formulated to provide prolonged pain relief with a controlled release of the active

agent to provide consistent and prolonged plasma drug levels. Xtampza ER requires less frequent dosing, leading to fewer pills compared with IR opioids, and offers multiple dosing options. The DETERx technology maintains Xtampza's ER PK profile even after chewing or crushing, making it difficult to manipulate Xtampza ER for IV or oral abuse. Cost is an important barrier to patients accessing ADF opioids, although the economic (eg, increased health care, criminal justice, and lost productivity) and societal (eg, lost health-related quality of life, death, substantially reduced quality of life for friends and family for a loved one with OUD) costs of OUD are high. Health care providers need increased awareness and education on opioids in general, the benefits of ADFs, manipulation potential of different ADFs, and guidance on how to educate their patients to safely store and dispose of prescription opioids.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. All authors were involved in writing and reviewing the manuscript.

Disclosure

LW is a consultant for CognifiSense, Collegium, Elysium Pharmaceuticals, Ensysce Biosciences, Quivive Pharma, Salix Pharmaceuticals, Trevi Therapeutics; advisory board of AdhereRx, Ensysce Biosciences, KemPharm, MedLogix; travel expenses from AdhereRx, Elysium Pharmaceuticals, Ensysce Biosciences, PainScript. JG is a consultant for Collegium, Hisamitsu, Kailo, Protega, Quest Diagnostics, Sanofi; shareholder for Virpax. The authors report no other conflicts of interest in this work.

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