Pain Ther (2016) 5:171–186
DOI 10.1007/s40122-016-0062-1

REVIEW

Oxycodone DETERx®: A Novel Abuse-Deterrent, Extended-Release Analgesic Option for the Treatment of Patients with Chronic Pain

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Received: September 28, 2016 / Published online: November 21, 2016

ABSTRACT

Background: Extended-release (ER) opioid analgesics are commonly used to provide safe and effective pain relief to treat pain severe enough to require around-the-clock, long-term dosing. These ER opioid formulations usually contain more drug per dosage unit than immediate-release (IR) agents, and therefore bring with them challenges related to both opioid abuse and misuse, often through manipulation of the dosage form. Oxycodone DETERx® (Xtampza® ER, Collegium Pharmaceutical, Inc.) is a novel abuse-deterrent, ER formulation developed to deter common methods of manipulation. In addition to having abuse-deterrent properties, oxycodone DETERx was developed to provide alternative modes of administration for patients with chronic pain and difficulty swallowing.

Scope: Using published articles, abstracts, and prescribing information, data supporting the use of oxycodone DETERx are reviewed.

Findings: Oxycodone DETERx was effective at reducing chronic pain in patients enrolled in a pivotal clinical trial, and had a tolerability profile expected of opioids. In addition to administration of the intact capsule, oxycodone DETERx can also be administered by sprinkling directly into the mouth from a dosing cup, onto soft foods, or through nasogastric or gastrostomy tubes, thus providing flexible dosing options for patients who have difficulty swallowing. In vitro studies demonstrated the reduced ability of oxycodone DETERx to be manipulated by common techniques used by abusers to defeat the ER characteristics or prepare the formulation for injection. Pharmacokinetic studies demonstrated that the ER characteristics of oxycodone DETERx are maintained if chewed or crushed. As a result, oxycodone DETERx is currently the only ER-formulated opioid without a boxed warning against crushing or chewing. Human abuse-potential studies conducted in a population of recreational opioid users demonstrated lower drug-liking

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scores for oxycodone DETERx administered intranasally and orally when compared with IR oxycodone.
Funding: Collegium Pharmaceutical, Inc.

Keywords: Abuse deterrence; Chronic pain; Drug abuse; Extended-release opioids; Opioid analgesics; Oxycodone

INTRODUCTION

Chronic pain affects an estimated 100 million people in the United States [1]. Opioid analgesics, particularly extended-release (ER) formulations, are commonly used to treat pain severe enough to require long-term daily, around-the-clock dosing, and for which alternative treatment options are inadequate [2]. Extended-release opioids may provide more consistent control of pain by minimizing fluctuations in plasma concentrations of the drug, thus reducing breakthrough pain [3]. Extended-release analgesics may also reduce the number of sleep disturbances that result from nighttime breakthrough pain [3].

Although usually a safe and effective treatment option for patients with chronic pain who are appropriately managed and monitored, ER opioid formulations are associated with high rates of misuse (the use of prescription medications for medical purposes, but not as indicated or prescribed), abuse (the use of drugs for nonmedical purposes, e.g., to get high), and diversion (the channeling of regulated pharmaceuticals to the illicit marketplace, including selling or giving a drug product to any individual for any purpose, even therapeutic) [4]. This is in large part because oral ER opioids may carry a large opioid load [5]. Abusers often manipulate (e.g., cut, crush, or dissolve) ER formulations to more rapidly release most, if not all, of the active drug, with the goal of achieving a more rapid drug high [5]. Further, unintentional misuse can occur when patients or their caregivers manipulate ER formulations for any number of reasons, including to reduce the dose or make the medication easier to swallow. Manipulation of most ER opioid formulations, regardless of intent, can result in greater exposure to the drug than intended, which can lead to adverse consequences or even death [6–10].

An additional challenge to healthcare providers is managing chronic pain in patients who have difficulty swallowing. There are an estimated 11 million people in the United States who experience chronic pain with dysphagia [11]. Although ER formulations offer many benefits in treating chronic pain, there are limited alternative dosing options for patients who have difficulty swallowing. Currently available alternative modes of administration (e.g., rectal or transmucosal/buccal) for treating chronic pain are limited by such factors as variable absorption rates [11, 12], ceiling doses, and boxed warnings provided in package inserts advising against crushing or chewing pellet formulations when sprinkled onto food [6, 7, 13].

Treatment of pain in this patient population is further complicated because newer analgesics that are abuse deterrent may be formulated as hard, monolithic tablets and with agents that gel when exposed to water (e.g., polyethylene oxide), making the exterior of the tablet "sticky" when moistened and more difficult to swallow. There have been several reports of currently marketed abuse-deterrent tablet formulations that have become stuck in patients' throats, causing choking, gagging, or regurgitation [8, 10]. Therefore, patients with chronic pain who have difficulty swallowing may manipulate their opioid analgesic to make it easier to

swallow. In a survey of more than 1000 patients, 29% reported having difficulty swallowing pills and 10% reported that they sometimes or always manipulate their opioids (e.g., cut, break, crush) to facilitate swallowing [11]. For incapacitated patients, caregivers may manipulate the medication on behalf of the patient. Unfortunately, patients and caregivers are often unaware that this misuse of an ER opioid by manipulation can lead to an increased risk for adverse reactions, overdose, and death [11].

Although rates of misuse and abuse have stabilized over the past few years, they are still high; in 2014, approximately 4.3 million people aged 12 years and older reported past-month nonmedical use of prescription opioids in the United States [14], and a comprehensive literature review found that 22–29% of patients misuse opioids [15]. Because of concerns about public health, the US Food and Drug Administration (FDA) considers the development of abuse-deterrent opioids to be a priority [16]. To help guide development of new abuse-deterrent opioid analgesics, the FDA released a final guidance document in 2015 on the evaluation of abuse-deterrent opioids, which outlined four categories needed to comprehensively evaluate prospective abuse-deterrent opioids in the premarket and postmarket contexts [16]. The FDA guidelines included laboratory-based in vitro manipulation and extraction studies (category 1), in vivo pharmacokinetic studies assessing manipulated drugs (category 2), human abuse-potential studies (category 3), and postmarketing studies (category 4) [16].

Different approaches have been used in the development of abuse-deterrent technologies to make opioids tamper resistant, including incorporating components that create a physical or chemical barrier, thus making misuse and abuse associated with tampering with these medications more difficult [5]. However, many of these formulations may still be vulnerable to misuse and abuse. For example, reformulated ER oxycodone was designed to be more difficult to crush than the original version, and incorporates a gelling agent (polyethylene oxide) which activates on exposure to water. As a result, the selection of reformulated oxycodone as a primary drug of abuse via snorting and injecting reduced significantly ($p < 0.001$) [17, 18]. However, 76% of abusers of reformulated ER oxycodone report abusing the formulation via the oral route (which could include manipulation prior to oral abuse) [18]. In a separate but similar analysis of oral abusers of various crush-resistant tablets with gelling properties, 42% of patients undergoing substance-abuse treatment reported that they manipulate these drugs before using them orally (e.g., chewing, dissolving in mouth, or drinking after dissolving in liquid) [19].

In addition, there are limited abuse-deterrent options for patients who experience difficulty swallowing. Thus, there is a need for abuse-deterrent opioid treatment options that are not easily manipulated but can be administered by multiple modes (e.g., intact, sprinkled, and via enteral tubes). These formulations may also help to mitigate the misuse of these opioid analgesics associated with product manipulation by patients as well as their caregivers (e.g., crushing ER opioids to facilitate swallowing in patients with dysphagia).

The objective of this article is to review the literature describing a novel treatment option for chronic pain, oxycodone DETERx® (Xtampza® ER, Collegium Pharmaceutical, Inc., Canton, MA, USA), which was formulated to have abuse-deterrent properties and offer

multiple administration options. Included in this review are data supporting the use of oxycodone DETERx for the treatment of moderate-to-severe chronic pain.

METHODS

All articles and abstracts published on oxycodone DETERx (5 published manuscripts and 2 manuscripts submitted as of May 25, 2016), as well as the prescribing information, were used to review the data on the use of oxycodone DETERx for the treatment of chronic pain. This article is based on previously conducted studies and does not involve any new studies on human or animal subjects. However, some studies referenced in this article were performed by the authors. In those instances, the authors declare that all procedures followed were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients included in the referenced studies.

EXTENDED-RELEASE OXYCODONE WITH DETERX TECHNOLOGY: A MICROSPHERE-IN-CAPSULE FORMULATION

Oxycodone DETERx is an opioid analgesic indicated for the management of moderate-to-severe chronic pain requiring long-term around-the-clock opioid treatment when other treatment options do not provide adequate pain relief [20]. Oxycodone DETERx is a microsphere-in-capsule formulation (Fig. 1), with each individual microsphere acting as its own drug delivery system and maintaining its ER pharmacokinetic profile even after chewing and crushing. The microspheres consist of oxycodone homogeneously dispersed in a hydrophobic matrix of fatty acid and waxes; the oxycodone is present as a salt with myristic acid (an ingredient that is generally recognized as safe and is commonly found in foods). The small particle size (median size of $\sim$300 μm) and waxy, hydrophobic nature contribute to the abuse-deterrent and ER properties of oxycodone DETERx. Several studies (described in detail in this review) have demonstrated that this microsphere technology ensures the maintenance of the ER characteristics if the capsule contents are crushed or chewed and ingested orally or crushed and insufflated (snorted) intranasally; as a result, oxycodone DETERx is the first oral ER-formulated opioid without language in its boxed warning pertaining to crushing or chewing leading to potential exposure to a fatal dose of opioid. The oxycodone DETERx formulation allows for alternative modes of administration, including

Fig. 1 Photograph showing the spherical, microparticulate nature of oxycodone DETERx capsule contents. Republished with the permission of Weston Medical Publishing, LLC, from the article "Impact of physical manipulation on in vitro and in vivo release profiles of oxycodone DETERx: an extended-release, abuse-deterrent formulation" (Kopecky EA et al. *Journal of Opioid Management* 2014;10(4):233–246); permission conveyed through Copyright Clearance Center, Inc. [23]

sprinkling directly into the mouth from a dosing cup or onto soft foods, as well as administering via nasogastric or gastrostomy tubes [21, 22], making oxycodone DETERx an option for patients with chronic pain who also have difficulty swallowing.

DOSING CONSIDERATIONS AND OPTIONS

Oxycodone DETERx is formulated with oxycodone base, which has a molecular weight 90% that of oxycodone hydrochloride (HCl). Therefore, a 9-mg dose of oxycodone DETERx contains an amount of active drug equivalent to a 10-mg dose of oxycodone HCl. Table 1 shows the available strengths of oxycodone DETERx along with the equivalent amount of oxycodone HCl present in other oxycodone products.

Oxycodone DETERx provides delivery of oxycodone over 12 h, and should be administered twice daily, every 12 h, with food. Because of its lipophilic microsphere design, the peak plasma concentration (C_{max}) and extent of absorption (area under the curve, AUC) are both lower when oxycodone DETERx is dosed under fasted conditions compared with fed conditions. Therefore, each dose of oxycodone DETERx should be taken with approximately the same amount of food to ensure adequate absorption and consistent plasma concentrations.

Table 1 Equivalent dosage strengths of oxycodone hydrochloride salt and oxycodone base (oxycodone DETERx)

Oxycodone hydrochloride (mg)	Oxycodone base (oxycodone DETERx) (mg)
10	9
15	13.5
20	18
30	27
40	36

The peak plasma concentration of oxycodone from oxycodone DETERx occurs approximately 4.5 h after fed dose administration. The apparent elimination half-life ($t_{1/2}$) of oxycodone following the administration of oxycodone DETERx when dosed in the fed state was 5.6 h. On repeated dosing with oxycodone DETERx in healthy subjects in pharmacokinetic studies, steady-state levels were achieved within 24–36 h.

The recommended initial dose for opioid-naïve patients is one 9-mg capsule orally every 12 h with food. Patients who have developed tolerance to opioids of comparable potency may be prescribed doses of oxycodone DETERx greater than 36 mg or a total daily dose greater than 72 mg (refer to the full prescribing information for complete dosing instructions [20]). The maximum daily dose of oxycodone DETERx is 288 mg per day (eight 36-mg capsules, equivalent to 320 mg oxycodone HCl per day), as the safety of certain inactive ingredients in oxycodone DETERx in doses exceeding that has not been studied. These inactive ingredients (myristic acid, beeswax, and carnauba wax) are generally recognized as safe and have a long history of use in foods and pharmaceutical products, but have not been systematically studied at consumption levels above a 288-mg-per-day dose.

Flexible Dosing/Alternative Administration

In a survey of more than 1000 patients, 10% reported that they sometimes or always cut, crush, or grind their pain medication; however,

65% of patients did not know that manipulating their medication could alter the pharmacokinetic profile [11]. The flexible-dosing options of oxycodone DETERx allow patients who have difficulty swallowing to sprinkle the capsule contents (microspheres) onto soft foods (e.g., applesauce, pudding, yogurt, ice cream, or jam) without needing to cut, crush, or grind the analgesic [21]. The pharmacokinetics of oxycodone DETERx microspheres sprinkled onto applesauce were compared with those of intact oxycodone DETERx capsules. The mean plasma oxycodone concentrations over time were superimposable for sprinkled and intact oxycodone DETERx (Fig. 2a), and the peak serum concentration and extent of oxycodone absorption were bioequivalent (Table 2) [20, 22].

Alternatively, patients may sprinkle the capsule contents into a cup, then pour the microspheres directly into the mouth and swallow [21, 23]. Patients should be instructed to rinse their mouths to ensure all microspheres have been swallowed.

The contents of oxycodone DETERx capsules (microspheres) may also be administered through nasogastric or gastrostomy tubes [21]. After flushing the tube, the microspheres should be poured directly into the tube, which should then be flushed several times with water to ensure that no microspheres remain. Milk or liquid nutritional supplements may be used in place of water for administration of the microspheres.

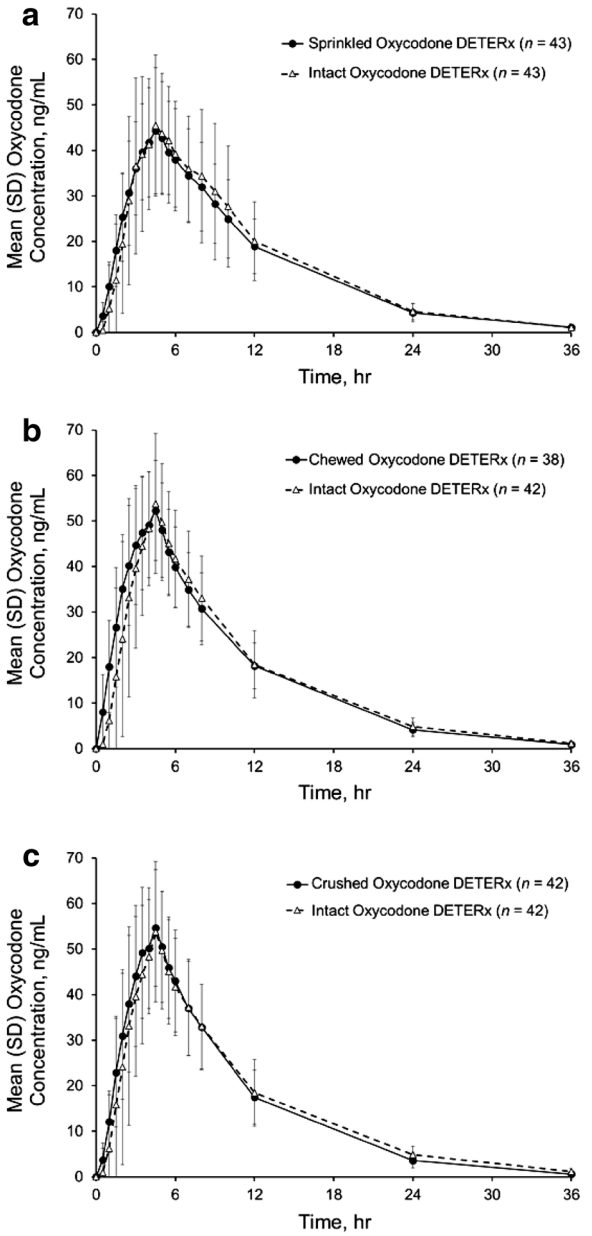

Fig. 2 Oxycodone DETERx plasma concentration over time: comparison of intact capsule administration with **a** sprinkled capsule contents, **b** chewed capsule contents, and **c** crushed capsule contents. **b** and **c** were adapted with permission from [23]. *SD* standard deviation

EFFICACY

The efficacy of oxycodone DETERx was assessed in a phase 3, double-blind, enriched-enrollment, randomized-withdrawal study [24] in 740 opioid-naïve and opioid-experienced patients with persistent moderate-to-severe chronic low-back pain. After a screening period, patients were titrated to a stable and tolerated dose of oxycodone DETERx between 18 and 72 mg twice daily in an

Table 2 Pharmacokinetics of oxycodone DETERx and IR oxycodone

Treatment[a]	C_{max}, ng/mL	T_{max}, h	$AUC_{0-\infty}$, h·ng/mL
Intact and sprinkled PK study			
Intact oxycodone DETERx capsule (fed)	55.3 (13.6)	4.5 (1.5–9.0)	540 (143)
Sprinkled oxycodone DETERx capsule contents (fed)	48.1 (12.0)	4.5 (2.5–9.0)	528 (130)
Crushed and chewed oral PK study			
Intact oxycodone DETERx capsule (fed)	62.3 (13.0)	4.0 (1.5–6.0)	561 (124)
Crushed oxycodone DETERx capsule contents (fed)	57.6 (12.6)	4.5 (2.5–6.0)	553 (134)
Chewed oxycodone DETERx capsule contents (fed)	55.6 (10.9)	4.5 (2.5–8.0)	559 (113)
IR oxycodone solution (fasted)	115 (27.3)	0.75 (0.5–2.0)	489 (80.2)
Crushed oral PK study			
Intact oxycodone DETERx capsule (fed)	67.5 (17.6)	3.5 (1.3–6.0)	581 (138)
Crushed oxycodone DETERx capsule contents (fed)	62.9 (12.6)	4.0 (2.0–7.0)	597 (149)
Crushed IR oxycodone tablets (fed)	79.4 (17.1)	1.8 (0.5–4.0)	561 (146)
Intranasal PK study[b]			
Intact oxycodone DETERx capsule (oral)	41.0 (10.0)	5.1 (1.6–8.1)	477 (89.6)
Crushed oxycodone DETERx capsule contents (nasal)	29.8 (6.6)	5.1 (1.6–12.1)	459 (106)
Crushed IR oxycodone tablets (nasal)	60.9 (11.9)	2.6 (0.3–6.1)	577 (124)

$AUC_{0-\infty}$ area under the plasma concentration versus time curve from time zero to infinity, C_{max} maximum observed plasma concentration, *IR* immediate release, *PK* pharmacokinetic, T_{max} time to reach maximum plasma concentration

[a] Arithmetic mean (standard deviation), except for T_{max}, for which the median (range) is reported

[b] Subjects in the nasal administration study received oxycodone DETERx dosed in the absence of naltrexone (all others included naltrexone). Naltrexone has been shown to enhance oxycodone absorption [8]

open-label fashion during the first 6 weeks of the study. After the titration phase, 389 patients met the study randomization criteria of adequate analgesia and acceptable tolerability of oxycodone DETERx. These 389 patients then entered the randomized, double-blind maintenance phase in which they received oxycodone DETERx ($n = 193$) or placebo ($n = 196$). Patients randomized to placebo were slowly tapered off oxycodone DETERx. During the double-blind maintenance phase, 122 (63%) patients completed the 12-week treatment with oxycodone DETERx and 100 (51%) patients completed with placebo [24]. During both the titration and double-blind maintenance phases, acetaminophen (up to 2 g per day) was the only rescue medication allowed.

Oxycodone DETERx was significantly better at maintaining pain control than placebo, based on the primary endpoint of change in average pain intensity from randomization baseline to week 12 ($p < 0.0001$; Fig. 3) [24]. Responder rate analysis revealed significantly more patients receiving oxycodone DETERx had 30% ($p = 0.0013$) and 50% ($p = 0.0032$) improvements in pain intensity when compared with patients taking placebo [24]. Survival analysis showed that patients treated with oxycodone DETERx remained in the study significantly longer than patients who were

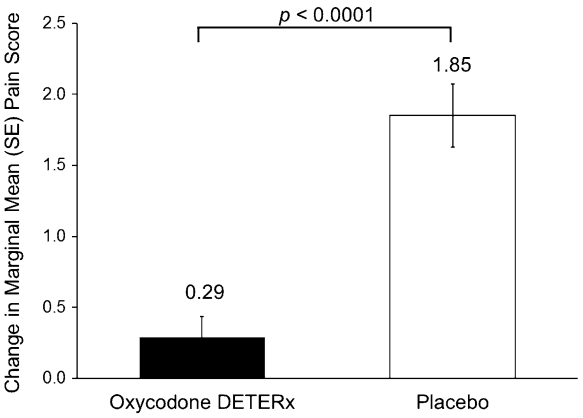

Fig. 3 Change in the marginal mean (pain score) from randomization baseline to week 12. Pain intensity was rated on a numerical rating scale of 0–10 (0 = "no pain", 10 = "pain as bad as you can imagine"). Data are presented as the marginal mean ± standard error. *$p < 0.0001$

randomized to placebo ($p = 0.0102$) [24]. In addition, Patient Global Impression of Change scores indicated that significantly more patients in the oxycodone DETERx group reported their pain to be "very much improved" and "improved" when compared with patients taking placebo ($p < 0.0001$) [24]. Overall use of acetaminophen as a rescue medication in the oxycodone DETERx treatment group was low (mean dose per day of 145 mg [24], up to 2 g allowed per day).

SAFETY AND TOLERABILITY

The safety of oxycodone DETERx was evaluated in multiple phase 1 single-dose studies [22, 23, 25–27] and one randomized, double-blind, phase 3 study [24]; the treatment-emergent adverse events (AEs) reported during the titration and maintenance portions of the phase 3 study are shown in Table 3. Treatment-related AEs were reported in 366 (50%) patients in the open-label titration phase. As is common with opioid treatment and an enriched-enrollment, randomized-withdrawal study design, the rate of AEs decreased in the double-blind maintenance phase, in which treatment-related AEs were reported in 65 (34%) patients receiving oxycodone DETERx and 39 (20%) patients receiving placebo [24]. During the titration phase, the most common AEs were gastrointestinal-related disorders (248 [34%] patients) and nervous system disorders (216 [29%] patients) [24]. The most common AEs (>5%) reported during the double-blind maintenance phase were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness (Table 3). During the titration

Table 3 Common adverse reactions (>5%) reported during the phase 3 study

Adverse reaction, *n* (%)	Titration	Maintenance	
	Oxycodone DETERx *n* = 740	Oxycodone DETERx *n* = 193	Placebo *n* = 196
Nausea	123 (16.6)	21 (10.9)	9 (4.6)
Headache	103 (13.9)	12 (6.2)	23 (11.7)
Constipation	96 (13.0)	10 (5.2)	1 (0.5)
Somnolence	65 (8.8)	1 (0.5)	0
Pruritus	55 (7.4)	5 (2.6)	3 (1.5)
Vomiting	47 (6.4)	8 (4.1)	3 (1.5)
Dizziness	42 (5.7)	3 (1.6)	0

phase, 13% of patients discontinued due to AEs; during the double-blind maintenance phase, 7% of patients receiving oxycodone DETERx and 7% of patients receiving placebo discontinued due to AEs. Of the total number of subjects entered into the titration phase, 88 (12%) patients were aged 65 years and older; no untoward or unexpected adverse reactions were seen in these patients. No unexpected safety findings were noted; AEs were consistent with those associated with the opioid pharmacological class. Oxycodone DETERx was safe and well tolerated by patients.

ABUSE DETERRENCE

To help guide the development of new abuse-deterrent opioid analgesics, the US FDA published a guidance document in 2015 outlining study categories recommended for the premarket evaluation of formulations with potentially abuse-deterrent properties [16]. These categories include laboratory-based in vitro manipulation and extraction studies, pharmacokinetic studies on manipulated formulations, and human abuse-potential studies. Oxycodone DETERx was assessed in studies consistent with all three categories.

Category 1 Abuse-Deterrence Studies: In Vitro Assessments

In accordance with the FDA guidance category 1 recommendations [16], in vitro physical and chemical manipulation studies were performed to evaluate the abilities of different methods commonly used by abusers to defeat the ER properties of oxycodone DETERx (Table 4) [23, 28]. When compared with immediate-release (IR) oxycodone tablets, oxycodone DETERx was less susceptible to the effects of grinding, crushing, and extraction using a variety of tools and solvents [23, 28]. Oxycodone DETERx did not effectively pass through hypodermic needles whether the microspheres were dissolved in water or melted [28]. These in vitro data demonstrate that oxycodone DETERx has physicochemical properties that are expected to make manipulation and abuse by injection difficult.

Table 4 Category 1 in vitro studies

Route	Assessment
General manipulations	
Physical	Impact of household tools on time-release mechanism [23]
Chemical	Extraction in common household solvents and more advanced solvents (data on file)
Route-specific manipulations	
Injection	Extraction in small volumes of water [28]
Direct injection	Injectability after suspension in water or melting [28]

Category 2 Abuse-Deterrence Studies: Pharmacokinetic Assessments

Chewing or crushing medications before oral administration are methods of manipulation often used by abusers to increase drug exposure, which can lead to "dose dumping." Per the FDA guidance document, the most effective physical manipulation technique established in category 1 laboratory studies was applied in category 2 pharmacokinetic studies to establish whether such manipulation leads to altered drug exposure when ingested or insufflated. The pharmacokinetic profiles of chewed and crushed oxycodone DETERx were compared with those of oral oxycodone DETERx (intact) and IR oxycodone. In 2 separate studies, crushing or chewing

oxycodone DETERx before oral administration did not increase the maximum or overall exposure relative to intact microspheres (Table 2) [23, 25]. The mean plasma oxycodone concentrations over time were similar for chewed or crushed oxycodone DETERx when compared with intact oxycodone DETERx (Fig. 2b, c). The pharmacokinetic profile of physically manipulated microspheres was bioequivalent to that of intact oxycodone DETERx capsules. When compared with crushed IR oxycodone, the C_{max} for all oxycodone DETERx treatments was lower and the time to maximum plasma concentration (T_{max}) was longer, which is consistent with an ER profile [23, 25].

Insufflation is the second most common form of oxycodone abuse [18], and is a practice associated with adverse consequences including nasal/palatal necrosis and perforation, overdose, and death [29]. The pharmacokinetic profile of intranasally administered crushed oxycodone DETERx was assessed in nondependent subjects. Intranasal administration of crushed oxycodone DETERx did not result in higher peak plasma concentrations than did orally administered oxycodone DETERx, unlike that of intranasal administration of crushed IR oxycodone, which produced as much as twice the oxycodone C_{max} (Table 2) [26]. The time to peak concentration was the same for both intranasal and oral administration of oxycodone DETERx [26], indicating that intranasal administration of oxycodone DETERx does not provide rapid increases in plasma concentrations (i.e., central exposure to oxycodone).

Category 3 Abuse-Deterrence Studies: Human Abuse Potential

As described in the FDA guidance document [16], category 3 abuse-deterrence studies are intended to assess the abuse potential of a drug in a controlled clinical setting. In these studies, manipulated product is administered to recreational opioid abusers (not patients with pain) and multiple subjective pharmacodynamic measures related to drug effect are assessed, including drug liking, which is the primary outcome measure per FDA guidance [16]. A randomized, double-blind, active- and placebo-controlled crossover study was conducted to assess the human abuse potential of oral oxycodone DETERx. [27]. Of the 61 nondependent, nontolerant recreational opioid abusers (with a history of oral drug abuse) enrolled in the study, 38 subjects completed the following treatments: intact oxycodone DETERx, chewed oxycodone DETERx, crushed IR oxycodone HCl in water, and placebo. The mean maximum (peak) effect (E_{max}) for drug liking was significantly lower for chewed and intact oxycodone DETERx than for crushed IR oxycodone ($p < 0.0001$ for both; Fig. 4). The differences in "take drug again" scores for chewed and intact oxycodone DETERx compared with crushed IR oxycodone were small and not statistically significant.

Intranasal administration is the second most common mode of abuse for oxycodone [18]. The intranasal abuse potential of oxycodone DETERx was assessed in a (category 3) randomized, double-blind, positive- and placebo-controlled crossover study [26]. The four treatments included oxycodone DETERx administered as either an intact oral capsule or a crushed intranasal preparation, IR oxycodone administered intranasally, and placebo. Of the 39 nondependent, nontolerant, recreational opioid abusers (with a history of intranasal abuse) enrolled in the study, 36 subjects completed all four treatment periods. Intranasal administration of crushed oxycodone DETERx was associated with significantly lower mean

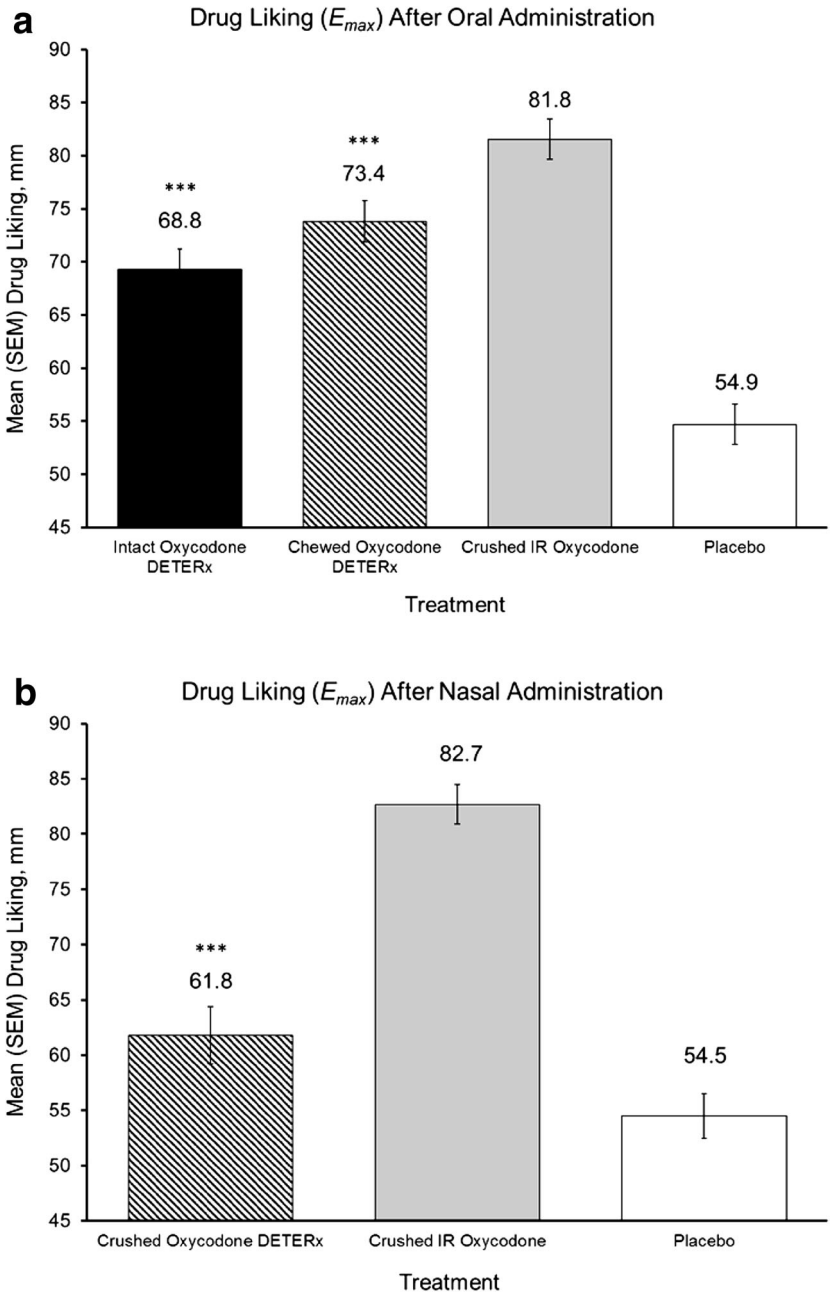

Fig. 4 Maximum drug liking (E_{max}) after **a** oral and **b** intranasal administration. Drug liking was assessed using a 100-mm bipolar visual analog scale (0 = strong disliking, 50 = neutral, 100 = strong liking). Data are presented as the mean ± standard error of the mean. ***$p < 0.0001$ compared with crushed IR oxycodone. E_{max} maximum (peak) effect, *IR* immediate release, *SEM* standard error of the mean

drug liking (Fig. 4) and "take drug again" scores compared with crushed intranasal IR oxycodone ($p < 0.0001$ for both). More than half of the subjects (58%) had a 50% or greater reduction in drug liking with intranasal oxycodone DETERx relative to intranasal IR oxycodone; 92% of subjects had some reduction in drug liking relative to intranasal IR oxycodone (Fig. 5). Therefore, data from the pharmacokinetic studies (indicating lower drug exposure of

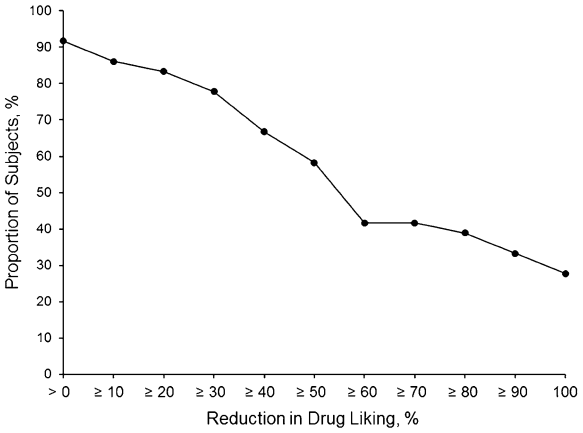

Fig. 5 Percent reduction of drug liking visual analog scale (E_{max}) for crushed oxycodone DETERx vs. crushed immediate-release oxycodone after intranasal administration. Adapted with permission from [26]

oxycodone DETERx compared with IR oxycodone) and human-abuse potential studies (both drug liking and "take drug again" scores) indicate that oxycodone DETERx has physicochemical properties that may reduce abuse via the intranasal route.

CONCLUSIONS

Oxycodone DETERx is a novel abuse-deterrent, ER formulation of oxycodone indicated for the management of pain that is severe enough to require long-term daily, around-the-clock opioid treatment, and for which alternative treatment options are inadequate. Oxycodone DETERx exhibits the expected tolerability profile of an opioid. In a clinical trial involving both opioid-naïve and opioid-experienced patients with lower back pain, patients receiving oxycodone DETERx experienced a significant reduction in pain intensity with minimal use of rescue pain medication [24]. Oxycodone DETERx has physicochemical properties that make the formulation less susceptible to the effects of grinding, crushing, and extraction, using a variety of tools and solvents, relative to immediate-release oxycodone tablets. Furthermore, oxycodone DETERx can be administered via multiple modes, providing options for patients who have difficulty swallowing, and can offer continuity in treatment using the same product if a patient's ability to swallow worsens over time.

The unique, microsphere-in-capsule formulation of oxycodone DETERx incorporates oxycodone homogeneously dispersed within fatty acids and waxes; each microsphere acts as an ER drug-delivery system. Pharmacokinetic studies of the manipulated microspheres indicate that crushing, chewing, and snorting had little to no effect on the pharmacokinetic profile of oxycodone DETERx. This is important for two reasons: first, because abusers may chew or crush ER opioids in an attempt to increase drug release, and second, patients or their caregivers may manipulate the tablets to facilitate administration. Insufflation (snorting) of oxycodone DETERx led to significantly less drug liking and significantly lower desire to take the drug again when compared with IR oxycodone. As many as 92% of subjects reported a reduction in drug liking of insufflated oxycodone DETERx when compared with IR oxycodone. Additionally, data from in vitro studies have demonstrated that oxycodone DETERx has physicochemical properties that are expected to make abuse by injection difficult. Opioid abuse often begins with the oral route; however, as abusers attempt to obtain a more rapid drug release, they frequently progress to the manipulation of opioids for oral and other routes of abuse [5]. Reducing the propensity of a formulation to "dose dump" on manipulation may interrupt the progression of abuse from oral abuse as a gateway to intranasal or other more dangerous routes, which could in turn reduce morbidity and mortality related to opioids [5].

Other abuse-deterrent formulations incorporate components that make them resistant to manipulation and reduce human abuse potential in category 3 studies; however, many of these formulations are still vulnerable to relatively simple physical manipulations, as indicated by the inclusion of language in each drug's label warning against chewing and crushing the product [6–10, 13]. Because of the product's properties, the oxycodone DETERx label does not include language warning against rapid release and absorption of a potentially fatal dose of oxycodone after crushing, chewing, or dissolving the capsule or its contents. This not only has implications for abuse, but also for misuse, as patients or their caregivers may manipulate ER formulations for a number of reasons: to reduce the dosage, to decrease the time to onset of action, or to facilitate swallowing [11].

An additional concern in many patients with chronic pain is difficulty swallowing. There are limited abuse-deterrent opioid options appropriate for patients who experience difficulty swallowing; currently available abuse-deterrent formulations designed to be sprinkled onto soft foods still carry a warning against chewing the product [6, 7], and reformulated ER formulations of hydrocodone, oxycodone, and oxymorphone have all been reported to be difficult to swallow and have caused choking or have resulted in esophageal obstruction [8–10]. Oxycodone DETERx provides flexible dosing options (e.g., given intact, sprinkling onto food, or administered through nasogastric/gastrostomy tubes), so healthcare practitioners can choose the mode of administration that best fits their patients' needs.

As new abuse-deterrent agents come to market, it is important that clinicians review results from both pharmacokinetic and abuse-potential studies to help them evaluate products individually. For example, oxycodone DETERx resists changes to its ER profile when manipulated and administered orally, exhibits a lower nasal abuse potential compared with IR oxycodone, and has physicochemical properties expected to make abuse by injection difficult. Clinicians should consider using abuse-deterrent formulations in their practice, but should still recognize that, although they possess properties conferring some level of abuse deterrence, the abuse of these agents is still possible.

In conclusion, oxycodone DETERx provides clinicians with an alternative for the treatment of chronic pain that has a safety, efficacy, and tolerability profile consistent with the opioid class. The formulation can be given to patients intact, by sprinkling on food, or through enteral tubes. This dosing flexibility allows physicians and patients to use a single product as their needs change. The ability to change the mode of administration without changing the product provides a continuum of care that reduces the chance of painful flares and AEs that may occur when switching opioids. Abuse-deterrent opioid formulations are an important part of a more comprehensive effort to reduce opioid abuse, misuse (both intentional and unintentional), and diversion. Oxycodone DETERx offers a novel formulation approach to abuse deterrence that provides a differentiated product profile.

ACKNOWLEDGEMENTS

Medical writing assistance was provided by Kelly M. Cameron, Ph.D., of J. B. Ashtin, who, on behalf of Dr. Gudin, provided assistance in writing the first draft and implementing revisions throughout the editorial process.

This assistance and publication charges were funded by Collegium Pharmaceutical, Inc. Dr. Gudin would like to thank Ernest A. Kopecky, Alison B. Fleming, Christy A. Thompson, and Michael K. DeGeorge, of Collegium Pharmaceutical, Inc., who critically reviewed this manuscript. Dr. Gudin meets the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, takes responsibility for the integrity of the work as a whole, and has given final approval to the version to be published.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Disclosures. Dr. Gudin declares he has received fees for speakers' bureau participation or consulting services from Collegium, Endo, Quest Diagnostics, Scilex, Kaleo, Cara, Purdue, AstraZeneca, Iroko, Teva, Pernix, Insys, and Depomed. Dr. Gudin critically reviewed the manuscript, approved the final version for submission, and accepts overall responsibility for the accuracy of the data, its analysis, and this final version of the report.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects. However, some studies referenced in this article were performed by Collegium Pharmaceutical, Inc. In those instances, the authors declare that all procedures followed were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Institutional review board approval was obtained prior to the start of the clinical studies with human subjects. Informed consent was obtained from all subjects included in the referenced studies.

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