

The Evolution of Abuse-Deterrent Extended-Release Opioid Formulations: Is there a Place in the Armamentarium for More Products?

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Abstract

Abuse deterrent formulations (ADFs) are one means of combatting the epidemic of prescription opioid abuse. ADF products make it more difficult to tamper with the drug to prepare it for smoking, inhalation, or injection; while ADF drugs can still be abused by being taken intact orally, ADF versions of extended-release (ER) product may be more difficult to manipulate for immediate release. Strategies being used for ADFs are physical barriers which are aimed at preventing a person from chewing, crushing, cutting, grating, or grinding the drug. Chemical barriers (often used with physical ones) prevent the opiate from being extracted from the excipients or unwanted medications. Agonist/antagonist combinations render the opiate inactive if the product is chewed (an advantage over most ADFs) or otherwise tampered with. Aversive agents, such as niacin, which give the user an unpleasant sensation when the drug is misused, constitute another ADF type, while changes to drug delivery systems are yet another strategy. Under development are formulations which require either chemical or enzymatic transformation within the body in order to release the opioid, as are and combination strategies (applying multiple technologies in a single product). It appears that ADF formulations can reduce abuse of a specific agent but this loss may be offset by increases in the use of other opioids, including heroin. ADF technology is clearly advancing rapidly and providing clinicians and their patients with more choices. The use of ADF technology may enhance safety to those who require around-the-clock opioid analgesia.

Keywords: Opiate; Opioid; Opioid Abuse; Analgesic; Addiction; Abuse Deterrence; Abuse Deterrent Formulations; ADF

Introduction

Opioid abusers typically tamper with opioid products in order to extract the active drug which is then smoked, inhaled, or injected intravenously (IV) [1]. The opioids most likely to be abused are those with long-acting (LA) or extended-release (ER) formulations because each tablet or capsule contains more opioid than their short-acting or immediate-release (IR) counterparts. While most drug abusers prefer the more rapid onset of action typical of IR opioids, the large quantity of opioid in the ER products makes them particularly attractive targets for abuse, especially to those who tamper with the product to extract the active agent for inhalation, smoking, or injection [2]. This involves manipulating the product (typically being able to crush it, pulverize it, or dissolve it in solution for use in a syringe) and may also involve chewing the product in an effort to defeat the ER mechanisms.

Technologies have developed to produce ER opioid formulations designed to resist or deter abuse by making these products harder to crush or dissolve. These so-called abuse-deterrent formulations (ADFs) are now recognized as important tools for the prevention of opioid misuse and abuse, although they cannot completely prevent all abuse and they do not prevent the drugs from being taken intact orally. ADF products first came to market in the early part of this millennium and have since been greatly supported by the U.S. Food and Drug Administration (FDA) which set forth regulations governing their testing and appropriate labeling [3]. Over the years, a variety of ADF strategies have been explored, some of which have reached the market while new technologies are being tested and developed.

The evolution of ADF products has not been without difficulties and controversy. It was feared that the very nature of these products might encourage overprescribing in the mistaken belief that these ADF products made the opioids impervious to abuse [4]. There was an educational curve to be surmounted in that some clinicians were unsure if an ADF product was truly the equivalent of a conventional opioid and if these products must be prescribed differently. Once ADFs became commercially available, the abuser network tried to “hack” them, developing and publishing detailed “recipes” and work-arounds to best extract the active agent [5,6]. Public health officials expressed concern that while an ADF product might reduce abuse of one particular product, it would only cause abusers to migrate to other prescription opioids or even heroin, since there would be no net decrease in abuse [4]. It was feared that in this way ADF products might convert former prescription opioid users into street drug users, which would only exacerbate the problem of prescription opioid abuse.

Large-scale, long-term epidemiological studies will be required to definitively provide evidence as to whether or not ADF products prevent or limit opioid misuse and abuse globally. The FDA has recently issued a document of methodology for the post-market evaluation of ADF products [7]. Further study is also needed to ascertain the value of ADF products in ER formulations compared to IR formulations. For now, ADF products appear to be an important tool in combating the misuse and abuse of all types of prescription opioids.

How ADFs are Used to Thwart Opioid Misuse and Abuse

ADF opioids cannot reduce opioid misuse or abuse if a subject takes the product intact and by mouth. Thus, a patient who might double his dose of opioids on a bad day will not be prevented from doing so by an ADF product. A recreational user will still be able to take a few pills orally. Many abusers take the drug intact by mouth and about 20% to 40% of abusers reported that they took opioids orally but chewed them to release the opioid agent more quickly [2]. Some ADF products that resist crushing or chewing or that release an antagonist when chewed may thwart this particular form of abuse.

However, the more egregious forms of opioid misuse and abuse involve alternative routes of administration such as smoking, inhalation (“snorting”), injection (both intramuscular and IV), and rectally [8]. Many opioid addicts prefer to chew prescription opioids (to defeat the timed-release system), smoke them, snort them, or inject them in an effort to get more drugs into their system faster. In order to abuse opioids in this way, the abuser must be able to extract the active opioid from the product (for example, removing it from the excipients). In the case of ER opioid formulations, the abuser must find a way to effectively dismantle the product’s timed release system. ADF opioids aim to prevent the active agent from being extracted in such a way that it might be smoked, inhaled, chewed, or dissolved and drawn up into a syringe for injection [2].

In recent years, a number of ADF products have been developed, of which a subset has successfully reached the marketplace albeit with limited real-world data due to their relatively recent arrival. Many states in the U.S. have some legal requirements that ADF opioids are included on formularies and are covered by insurance [9]. It is reasonable to assume that other ADF products are in development or on the drawing board. The latest ADF product to come to market is a long-acting oxycodone product. The aim of our review is to review the current ADF offerings and assess this latest product in that context. See table 1.

Brand name	Generic	ADF Mechanism	Year approved	Comment
Hyslinga® ER	Hydrocodone (single-entity)	Physical and chemical	2014	
Embeda®	Morphine	Agonist/antagonist combination	2014	
MorphaBond™	Morphine	Physical and chemical barriers	2015	
Xtampza ER®	Oxycodone	Microspheres	2016	
OxyContin®	Oxycodone	Physical and chemical barriers	2013	Offers the most real-world data on the effect of ADF versus non-ADF
Troxyca ER®	Oxycodone	Agonist/Antagonist combination	2016	
ARYMO™ ER	Morphine	Physical and chemical barriers	2017	
Vantrela™ ER CEP-33237	Hydrocodone	Physical and chemical barriers	2017	
Targiniq	Oxycodone	Agonist/antagonist combination	2017	

Table 1: Abuse-deterrent formulations of ER opioids currently on the market or nearing commercialization [10].

Abuse Liability of ER Opioids

The abuse liability of any prescription opioid depends in part on the nature of the drug (some opioids are better “liked” than others for the quality of the high they impart), the pharmacokinetic properties they possess via a specific route of administration, and their formulation (ER products are generally more desired by abusers than IR products due to higher doses of opioids). In pharmacological terms, abusers want to achieve the highest serum concentration (C_{max}) in the shortest time (T_{max}) [11]. While recreational users and patients who misuse their pain relievers may simply take extra oral tablets and capsules by mouth, altering the route of administration can markedly improve C_{max} and T_{max} values [2]. Before the advent of ADF technologies, abusers might chew the drug, crush it for snorting, or dissolve it in water so it can be drawn into a syringe for IV or IM injection. These approaches generally require separation of the active agent (opioid) from the rest of the pill (excipients and possibly other active ingredients that are not attractive to abusers) or, alternately, removing opioid from a transdermal patch delivery system and/or defeating the timed-release mechanisms. Until the advent of ADF technologies, manipulating prescription opioid products was not particularly difficult.

In a review of tampering, it was determined that the rate at which abusers tampered with opioids varied by product; for instance, 72% of abusers tampered with morphine ER, 63% tampered with oxycodone ER, but only 31% tampered with the fixed-dose combination of oral hydrocodone plus acetaminophen (Vicodin®) [2]. The “better-liked” opioids (oxycodone, hydromorphone, morphine) are more likely to be tampered with than the less-liked opioids (buprenorphine, tramadol). Further, this review found that the most common method for nonmedical use of prescription opioids was oral ingestion, followed by snorting, injection, and smoking-which was the least common method for abusers to use (< 3%) [2]. Rectal routes of administration (“plugging”) are described in the literature, but statistics were not available as to how frequently this method is used. Experienced, long-term opioid abusers and addicts tend to be more likely to inject drugs than more casual or less experienced recreational opioid users [2]. Route of administration likewise varied by drug: oxycodone is injected by 23% to 59% of abusers; morphine is mostly abused by injection (59%). See table 2.

Drug	Oral Ingestion	Inhalation	Injection	Comment
Oxycodone	27% - 89%		23% - 59%	
Oxycodone-acetaminophen (Percocet)	83%	44%	0.5%	Lower abuse potential than most opioids; the acetaminophen content of these pills makes less attractive
Hydrocodone-acetaminophen (Vicodin, Lortab)	Majority			Lower abuse potential than most opioids; the acetaminophen content of these pills makes them unattractive
Morphine	40%	39%	56%	Morphine is a versatile drug in terms of routes of administration for abuse
Hydromorphone			90%	Almost all abuse is by injection
Fentanyl	55%	5%	32%	19% smoke it; some abuse the transdermal or transmucosal formulations
Buprenorphine			0%	While buprenorphine is abused in some parts of the world, its abuse in the US is minimal compared to the other agents
Methadone	72%	10%	8%-11.5%	

Table 2: Preferences of opioid abusers for routes of administration by type of opioid [2,12].

Factors that favor migrating from oral ingestion to a different route of administration include longer duration of opioid abuse, male gender, and living in a rural area [12]. Men and women differ markedly in terms of opioid abuse patterns: the mean age at first use of opioids is younger for men (19.2 ± 8.4 for men versus 25.0 ± 7.9 for women) and for age at which the onset of regular use began (27.3 ± 10.7 vs. 30.0 ± 6.9 , respectively). Men were much more likely to inject opioids (41.7% vs. 16.7%) than women [12].

Opioid abusers seem to progress from oral ingestion of prescription opioids to snorting as the user gains experience and finally to IV injection. Rarely would this sequence be inverted. In fact, taking prescription opioids by routes other than oral ingestion are considered predictors of more severe drug-related problems [13]. Thus, it is possible to some degree to understand what drugs and routes of administration are most attractive to abusers. In general, products that contain a relatively high dose of the active agent (such as ER products) are more likely to appeal to drug abusers than those with small amounts of the agent. Drugs like oxycodone, morphine, hydromorphone are more appealing than drugs like buprenorphine or tramadol. Therefore, ADF products should deter abuse by chewing, inhalation, smoking, and injection.

Mechanisms of Abuse Deterrence

A variety of ADF technologies and strategies have evolved and continue to evolve. The FDA currently recognizes seven different strategies, one of these is deemed “novel approaches” and leaves the door open for yet to be developed future technologies [14]. Physical barriers may be included in the drug and are aimed at preventing a person from chewing, crushing, cutting, grating, or grinding the drug. Chemical barriers-which can be used along with physical barriers-are those that make it extremely difficult to extract the opioid agent using common solvents.

Another technique pairs the opioid agonist (the drug desired by abusers) with a sequestered or non-sequestered antagonist. These coformulations release the antagonist when the drug is tampered with, thus negating the drug’s pleasurable effects.

Aversive agents (such as niacin) can be incorporated into the product with the goal of making it unpleasant to manipulate or ingest the drug. For example, an aversive agent may irritate the delicate mucus membranes of the nose if the drug is snorted.

Changes to drug delivery systems can make it more challenging to abuse an opioid. For example, opioids that are delivered via a depot system or as a long-acting injectable resist abuse.

Although not yet on the market, the notion of a prodrug or a novel molecular structure has been discussed by pharmaceutical companies. The concept is that the opioid is delivered in an oral formulation which requires either chemical or enzymatic transformation within the body to release the opioid. The other categories recognized by the FDA for ADF products are combination strategies (applying multiple technologies in a single product) and novel approaches [14].

Perhaps the most important ADF target is the prevention of opioid abuse by injection. Injection is the route of administration favored by experienced opioid abusers, addicts, street drug users, and younger rather than older abusers. Injection is a very dangerous route of administration in that it is associated with serious adverse outcomes and is more associated with addiction, morbidity, and mortality than any other route of administration [15,16].

The FDA has issued guidance with respect to abuse-deterrent (AD) properties and can authorize AD labeling of products that meet those standards [14]. At the time of publication, six ADF opioids have been approved and more are under consideration [10]. The FDA has established four main types of testing for novel ADF products which apply to both extended-release and immediate-release products [17-19]. See table 3.

Type of study	Goal	Test parameters	Details	Category
Premarket studies designed to determine if the ADF product will reduce misuse and abuse				
<i>In vitro</i> manipulation and extraction	Can AD mechanism be defeated and allow user to extract a sufficient yield of usable drug?	Premarket, lab testing	Physical manipulation of product, yield, and quality of extracted drug (small enough particle size for snorting, syringeability)	1
Route-specific pharmacokinetic study of manipulated and intact product	What are pharmacokinetic products of manipulated drug?	Premarket, usually tested on healthy volunteers who are administered naltrexone	The abuse quotient is calculated as the extent and rate of increase of serum drug concentrations based on C_{max} and T_{max} values. In some cases, further testing to determine the effect of food and/or alcohol on pharmacokinetics may be carried out.	2
Route-specific clinical abuse potential studies	How much do experienced subjects "like" these products?	Premarket, often randomized, double-blind controlled studies with experienced opioid users	Drug liking is measured on 100-point visual analog scales; subjective measures are taken as well as pupillometry (objective test)	3
Post-market studies to determine the real-world impact of the ADF product				
Real-world abuse reductions	Does this ADF actually reduce abuse in the real world?	Post-market, relies on systematic data collection from electronic records, poison control centers, drug treatment centers, and so on	Only reformulated Oxycontin has sufficient available data for this level of testing; over time, other ADF products will be able to conduct this sort of analysis as well	4

Table 3: FDA testing types for ADF in order to meet ADF labeling requirements.

“Dose dumping” refers to the property of alcohol to precipitate the rapid release of opioid from certain extended-release opioid formulation [20]. Alcohol dose dumping is an important consideration in drug testing as many who abuse opioids are polydrug abusers and may consume alcohol concurrently with opioids or may mix opioids with alcohol [21-23]. Dose-dumping studies and studies that explore whether an opioid can be extracted from a product, dissolved, and drawn into a syringe (“syringeability”) are important ADF goals as well.

Current Opioid ADF Formulations

Hydrocodone ER (Hyslinga®)

Hyslinga® ER (Purdue Pharma, LP, Stamford, CT) is a single-entity hydrocodone product in an extended-release formulation intended to be taken once a day for moderate to severe pain that requires round-the-clock analgesia [24,25]. It holds the distinction of being the first single-entity hydrocodone product that could label itself ADF under the FDA guidelines [26].

This product uses proprietary RESISTEC® technology to create an extended-release formulation that is difficult to manipulate [25]. The abuse deterrence involves the inclusion of polyethylene oxide polymers and a process that makes the tablets crush resistant and difficult to dissolve. If an attempt is made to dissolve the tablet, the result is a viscous liquid that cannot be aspirated into a syringe. In studies, hydrocodone ER (20 to 120 mg) resisted crushing, breaking, grinding, and disintegration using a variety of solvents [25].

In a drug likeability study, subjects (n = 40) were randomized in a double-blind, five-treatment crossover study to receive 60 mg of hydrocodone orally, 60 mg of extended-release hydrocodone tablet (Hyslinga® ER) to be taken orally, 60 mg of Hyslinga® ER to be chewed, 60 mg of Hyslinga® ER to be milled into fine particles, or placebo [27].

This ADF hydrocodone product was shown to be effective in reducing pain and improving function in patients with moderate to severe chronic noncancer in non-neuropathic pain over 52 weeks (20 to 120 mg) [28]. A subset of patients with osteoarthritis (OA) from this study (n = 307) were evaluated for a 52-week maintenance period with the result that the drug was considered well tolerated and offered clinically meaningful pain control [29].

Hydrocodone ER (Vantrela®)

Vantrela® ER (Teva Pharmaceuticals, Petah Tikva, Israel) is an extended-release, single-entity hydrocodone bitartrate tablet in an abuse-deterrent formulation. It is available in 15, 30, 45, 60, and 90 mg strengths and is designed to be taken every 12 hours for round-the-clock pain control [30]. This product has not yet been cleared by the FDA for market release at the time this article was prepared.

Abuse-deterrent studies found that the formulation resisted chemical and physical manipulations and could help deter the conversion of its ER formulation to an immediate-release formulation. The product resisted cutting, chopping, crushing, milling, and grinding efforts and hydrocodone could not be extracted using a number of solvents. Intact tablets could be dissolved in certain solvents and would result in a liquid that could be aspirated into a syringe, but the drug yield of this liquid is poor. Manipulating the tablets may result in a yield of higher quality hydrocodone, but the resulting material is a very viscous liquid with little drug and poor syringeability [30]. The abuse-deterrent mechanism of Vantrela was developed in cooperation with the FDA. While it is still possible to extract the active agent in this product, the extraction methods that produce the highest yield of opioid also result in low purity of the drug [30].

When this product is manipulated with the intent to abuse it by mouth or intranasally, its active agent has a lower C_{max} and a longer T_{max} than non-ADF products, which in theory should make it less likeable to abusers [30]. As this product is new, abuse deterrent properties have not yet been confirmed in post-marketing studies.

Hydrocodone ER (Zohydro®)

Zohydro® ER (Zogenix) was the first single-entity hydrocodone product approved for the U.S. market and this original approval did not allow for ADF labeling. Consequently, it is not appropriate to consider this product as an ADF in the same light as the other products. How-

ever, this product now contains specific excipients that form a viscous gel when the tablets are crushed or dissolved [31]. It is anticipated that ADF labeling may be granted in the future [25].

Morphine ER (Embeda®)

Embeda® ER (King Pharmaceuticals, Bristol, TN) is a capsule of tiny extended-release morphine pellets with a sequestered core of naltrexone, an opioid antagonist [32]. If the capsule is taken by mouth as prescribed, the morphine is released gradually from the pellets and is metabolized by the body, while the sequestered naltrexone core passes intact through the body [32]. The ratio of morphine to naltrexone pellets is 100:4 [33]. Attempts to crush, chew, dissolve, or otherwise manipulate the capsule release the naltrexone and block the desirable euphoric effects of morphine.

Post-marketing studies find that the safety profile of Embeda® ER is similar to that of other morphine ER products. Tampering may result in withdrawal symptoms or other responses atypical of opioid abuse [34,35].

Morphine ER (ARYMO™)

Arymo™ ER (Egalet Corporation, Wayne, PA) is an extended-release, abuse-deterrent formulation of oral morphine. It utilizes proprietary Guardian Technology and an injection molding process to make the product so dense and extremely hard that it is difficult to chew, crush, or grind. When dissolved in an attempt to inject it, the product converts to a gel-like substance with poor syringeability [36,37]. In a single-center drug likeability study, 46 recreational opioid users had significantly lower drug liking for the ADF Arymo product compared to a comparator non-ADF product [38]. In a study of dissolution profiles for the ADF product, there was no evidence of dose dumping when the product was placed in alcohol although higher alcohol concentrations resulted in more prolonged dissolution times (40% ethanol, 100 mg tablet) [39].

Morphine ER (ADER, MorphaBond™)

Morphine ADER (MorphaBond) is an extended-release, ADF morphine product. It relies on an injection-molding process to create a product that is very dense and hard and resists crushing, chewing, pulverizing, and dissolving [40]. Crushed intranasal morphine ADER resulted in a 40% decrease in E_{max} compared to non-ADF morphine ($p < 0.0001$) but E_{max} values were similar when crushed intranasal non-ADF morphine was compared to intact oral Morphine ADER. Overall, Morphine ADER got lower scores for drug liking and good effects compared to non-ADF morphine [40].

Oxycodone ER (Reformulated OxyContin®)

In 2010, Purdue Pharma introduced a reformulated version of oxycodone (OxyContin) [41]. Using data obtained from the Poison Center Program, Drug Diversion Program, Opioid Treatment Program, Survey of Key Informant Patients Program and StreetRx Program of the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) system, the rates of abuse and diversion of OxyContin were compared prior to reformulation and then for every quarter after reformulation through the second quarter of 2015. The rates of abuse and diversion decreased significantly for each quarter after reformulation with durable results to five years [4]. An initial increase in the abuse of other opioids was observed when the reformulation was first introduced, but then decreased to a lesser extent than the abuse of OxyContin. One year after the reformulation was introduced, the street price for the reformulated OxyContin product was 36% lower than the original product [4], suggesting this product was perceived by abusers and addicts as less desirable.

It must be noted that a certain number of abusers persisted in using OxyContin even after reformulation, using three main strategies. The largest subset of those loyal to the reformulated ADF oxycodone transitioned from non-oral to oral use (43%) and another subset (23%) had only taken the drug orally and simply persisted in their preferred route of administration; for these individuals, the ADF mechanism was irrelevant. About a third of those who abused ADF oxycodone (34%) had found workable methods of defeating the ADF mechanism and extracting enough of the drug to inhale or inject [42].

Originally, oxycodone controlled-release (CR) formulation entered the market in 1995 and was labeled to provide pain control over 12 hours with controlled delivery of the active agent. At the time, it was believed that this product would not be particularly appealing to drug abusers in that a slow-release product did not provide the high C_{max} and “rush” desired by users and the product has a relatively slow T_{max} . Opioid abusers found that the high quantities of opioid in these tablets could be extracted and then inhaled, smoked, or injected for a rapid onset of action, or “rush”. By 2010, a new version of OxyContin (Purdue Pharma) came to market in response to this problem. Although this new product was designed to prevent abuse, it was not labeled as an ADF; however, it was much more difficult to crush or dissolve than the original product [43]. Nevertheless, dedicated “hackers” experimented with ways to defeat the mechanisms.

The reformulation is based on long-chain molecules that make the product more difficult (if not impossible) to crush. Unlike some other ADF products, the reformulated oxycodone is not extremely hard but is more plastic-like and although somewhat malleable, it is not possible to crush it or grind it into powder. When the new formulation is combined with water, the result is a viscous liquid with poor syringeability [44].

Oxycodone ER (Troxyca®)

Troxyca® ER (Pfizer, Inc., New York, NY) is an extended-release oxycodone formulation with sequestered naltrexone in an agonist/antagonist mechanism. This mechanism is labeled to help prevent abuse when the product is crushed or when it is taken intact orally [45]. The product is a capsule with oxycodone pellets surrounding sequestered naltrexone at the core. If the product is crushed, the naltrexone is released and counters the desired effects of the oxycodone [46].

Oxycodone ER (Targiniq®)

Targiniq® ER (Purdue Pharma, Stamford, CT) is an extended-release oxycodone formulation which uses naloxone, an opioid antagonist, as an abuse-deterrent mechanism. If this product is crushed, dissolved, chewed, or ground, the naloxone is released and blocks the desired opioid effects. It should be noted that if the naloxone is released in this way, it may precipitate withdrawal symptoms in patients who are addicted to the drug [32]. This product has been cleared for market release in the United States by the FDA but has not yet been marketed commercially.

Oxycodone ER (Xtampza®)

Oxycodone with DETERx technology (Xtampza® ER, Collegium Pharmaceuticals, Inc., Canton, MA) is an extended-release ADF oxycodone product, which is composed of individual microspheres (about 300 μm in diameter) of oxycodone dispersed in a hydrophobic matrix so that the oxycodone is present as a salt with myristic acid. The microspheres are waxy and retain their physiochemical properties even if the product is tampered with [47].

The microsphere design assures that the oxycodone retains its long-acting characteristics even if the capsule is crushed or chewed. Since this product retains its long-acting formulation even when the product is crushed, there is no labeling warning that crushing or chewing the product could result in a potentially fatal overdose. This particular formulation is suitable for use via a nasogastric or gastrostomy tube or, for patients with dysphagia, may be sprinkled on food or into a cup to facilitate ingestion. This will not affect the product’s long-acting formulation [48]. In a randomized, open-label, active-controlled, crossover study of 38 healthy subjects (five treatments of 40 mg oxycodone ER), Xtampza® (both intact and crushed) was compared to the new oxycodone ER (intact or crushed) and oxycodone IR (crushed only). When crushed or taken orally, Xtampza was able to retain its ER properties, while crushed OxyContin® ER changes to a pharmacokinetic profile that more closely resembles that of oxycodone IR [49]. This suggests that the ADF mechanism of Xtampza may be more robust and resilient than that of OxyContin ER and that it may also confer safety to patients who do not seek to abuse their medication but may crush pills to make them easier to swallow.

This particular product is associated with lower peak plasma concentrations compared with oxycodone IR. In an open-label, active-controlled, crossover study, 38 healthy subjects received five treatments of oxycodone 40 mg with a standardized, high-fat, high-calorie meal: (1) Xtampza (intact), (2) Xtampza (crushed), (3) OxyContin (intact), (4) OxyContin (crushed), and (5) oxycodone IR (crushed) [49]. Crushed and intact Xtampza were bioequivalent and crushing had no effect on the T_{max} value, but crushed OxyContin, bioequivalent to oxycodone IR, had higher peak plasma oxycodone concentrations than intact OxyContin. Crushed OxyContin also had a shorter T_{max} which at 3.25 hours was similar to oxycodone IR [49]. This study suggests that Xtampza maintains its abuse-deterrent properties even when crushed, which may make it less attractive to potential abusers who wish to tamper with the drug.

Products in Development

While ADFs on the market today resist or deter abuse by grinding, chopping, milling, or pulverizing (for smoking or inhalation) or dissolution (for injection), it is still possible to abuse the drug by taking the products orally, intact. Thus, many ADF products deter snorting, smoking, and injection of the drugs (routes of administration favored by more hardcore abusers), they can still be taken orally. The role of prodrugs in developing even more robust ADF products seems promising. The concept is that the oral product is inactive until it is ingested, whereupon the digestive enzymes work on the product and initiate the release of the opioid. The product itself is inert and if injected or snorted would remain inert, as the digestive enzymes are located exclusively in the gastrointestinal (GI) tract. There are currently products in the pipeline utilizing this design (hydromorphone and oxycodone products) [44].

Do ADF Products Reduce Abuse?

In a study that relied on self-administered surveys from 2,566 opioid-dependent patients with data gathered from 2009 to 2012, OxyContin was the primary drug of abuse for 35.6% of subjects prior to the reformulation, when it dropped to 12.8% in 21 months ($p < 0.001$). It thus appears that the ADF formulation reduced the attractiveness of this popular gent for abusers. However, this loss may have been offset by increases in the use of other oxycodone products, hydrocodone, and other opioids. When asked if they had used oxycodone to “get high in the past 30 days at least once” the use of ADF oxycodone dropped from 47.4% (before reformulation) to 30.0% ($p < 0.001$) but in the same period, heroin use almost doubled. A subset of patients in this survey were interviewed ($n = 103$) and 100% said they preferred the original oxycodone product to the ADF version [43]. About a quarter (24%) said they had figured out ways to defeat the formulation [43].

Hackers who try to defeat the ADF products sometimes share their tips and tricks online or in internet forums. A Google search for “beat the new oxy” conducted on December 27, 2016 turned up 438,000 results. A study of internet forum posts related to sharing methods for defeating the ADF mechanism of the reformulated oxycodone product found 37 “recipes” for thwarting the ADF, of which investigators recognized 32 as reasonably feasible ($n = 45,936$ posts related to reformulated oxycodone) [50]. In real-world situations, abusers rarely have the dedication to consistently hack difficult products. A survey of drug abusers found the majority will not devote more than 10 minutes to manipulating a product [51].

Using crowdsourced online data via the website StreetRx.com, the price of single-entity oxycodone decreased from 2011 to 2015 [4]. The original formulation decreased from \$1.40 to \$0.61 per milligram from 2011 to 2015 (57% reduction, $p < 0.001$). The geometric mean price of the new ADF OxyContin dropped from \$0.89 to \$0.53 per milligram in the same time period (41% reduction, $p = 0.001$) [4]. After oxycodone was reformulated, the FDA required post-marketing epidemiological studies to evaluate emerging patterns of oxycodone abuse. The new formulation was associated with a 32% drop in the rate of ER oxycodone-related cases at poison control centers and a 15% decline in the rate of poisoning associated with the therapeutic use of ER oxycodone. Oxycodone diversion decreased by half (50%) and the street price of oxycodone dropped 22% [52]. Similar findings occurred in a study of substance abuse patients ($n=140,496$), which observed that oxycodone abuse in this population decreased 33% after the reformulation. Moreover, the rate of non-oral abuse of oxycodone ER dropped by 66% [53].

Discussion

Prescription drug misuse and abuse is a serious public health concern and has reached epidemic proportions [54,55]. It is a problem that defies an easy solution because prescription opioids are much needed by a very large and very vulnerable population of pain patients. Preserving access to opioids to those who need them while balancing the societal concerns to limit opioid prescribing in general has been confounding, but gradually solutions are emerging. Some of these solutions include greater education for prescribers and patients, patient-provider opioid agreements, prescription drug monitoring programs, risk assessment tools, and abuse-deterrent drug formulations [11,33,56-61]. To date, only a handful of products have reached the market with ADF properties, but there appears to be a clear evolution in these products. The earliest ADF formulations contained an aversive agent (such as capsaicin or niacin) that made taking the tampered drug unpleasant [33]. Those products have not gained widespread acceptance.

Newer injection-molding polymer-type products that are very hard and crush resistant have emerged as an important new way to deter abuse. These products are not entirely invulnerable to tampering and they can be abused by oral ingestion, which remains a common means for recreational users to take opioids. Nevertheless, before-and-after data of the release of the reformulated oxycodone product demonstrates the profound effect an ADF can have on drug abuse patterns.

Agonist/antagonist formulations offered the important benefit of helping to resist abuse even by those who wanted to chew the drug for oral ingestion.

The latest innovation on the market is the DeteRx technology used for Xtampza, which consisted of microspheres of ER oxycodone such that the long-acting mechanism could not be defeated. In addition, this product offers the advantage that the capsule could be opened and its microspheres sprinkled on food or dissolved in water for easier ingestion; the microspheres could even be delivered to dysphagic patients via a feeding tube.

ADF technology is clearly advancing rapidly and providing clinicians and their patients with more choices.

Conclusion

ADF products are being used with increasing frequency as one more tool in the fight against the epidemic of opioid abuse. Physical and chemical barriers (often used in combination) make the extraction of the active agent more difficult. Another technique pairs the opioid agonist with an antagonist, so that the agonist combines with the antagonist when the drug is tampered with, negating the drug's pleasurable effects. Encapsulating the active agent in microspheres, aversive agents, and changes to drug delivery systems are other types of ADFs now being prescribed. ADFs currently available are: Hyslinga® ER, MorphaBond™, OxyContin®, (all using physical and chemical barriers), and Embeda®, and Troxyca ER® (agonist/antagonist combinations), and Xtampza ER® (microspheres). ADF products make tampering with the product difficult, in some instances and applications virtually impossible, and continue to evolve.

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