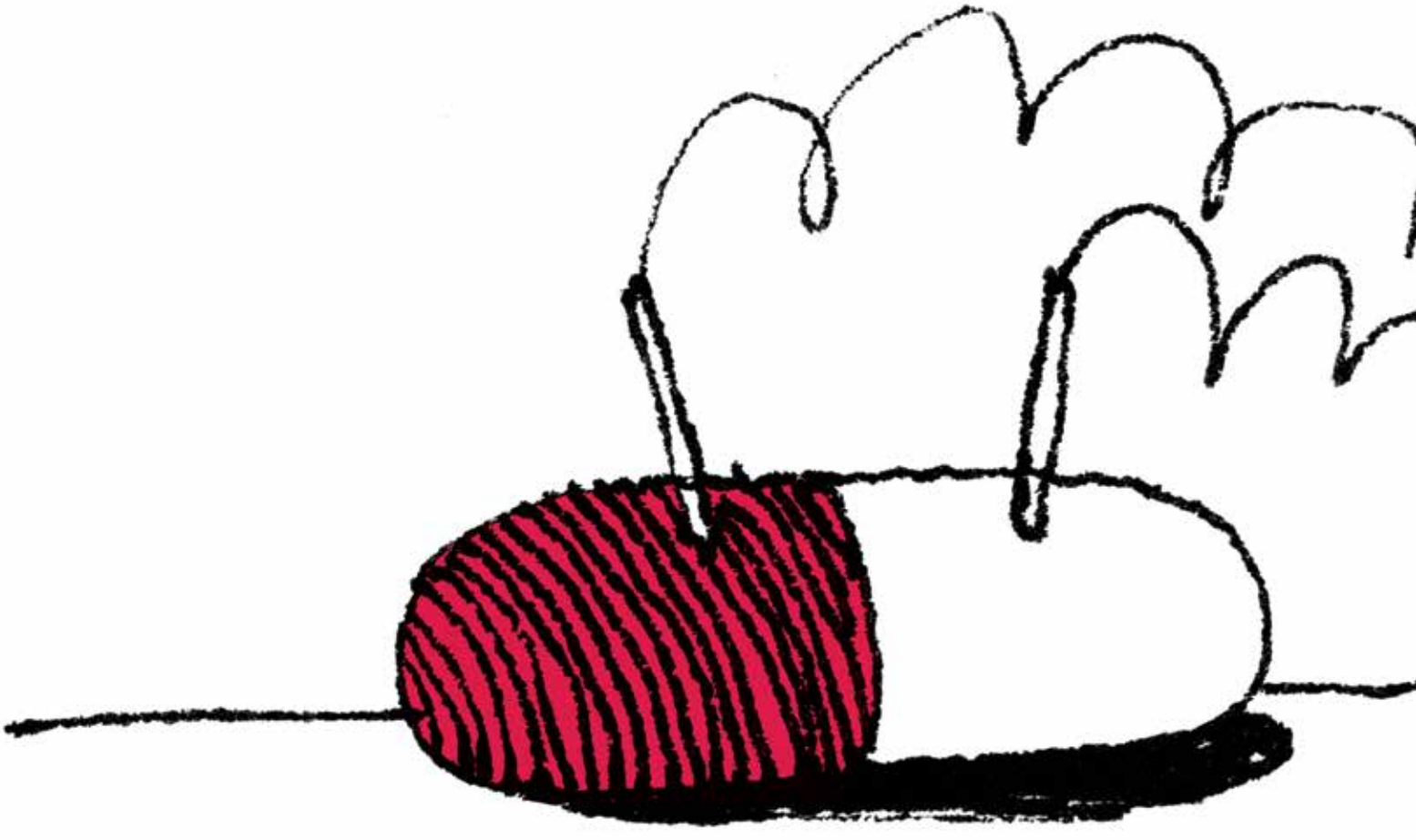
ABUSE DETERRENT FORMULA



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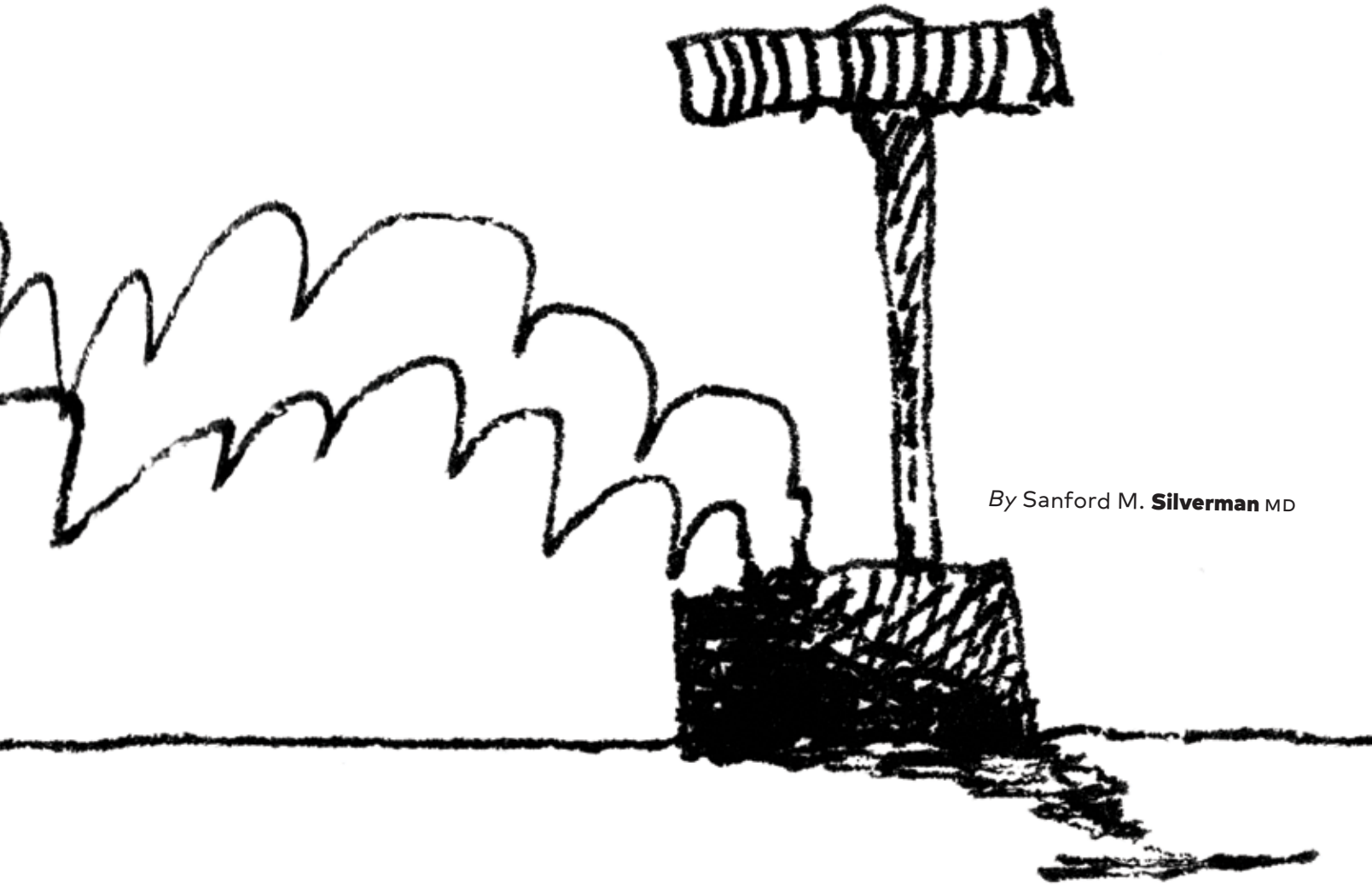

By Sanford M. **Silverman** MD

THE PROBLEM

Prescription drug abuse is the fastest growing problem in the US. According to the Center for Disease Control (CDC) enough opioid pain relievers were sold in 2010 "to medicate every adult in the United States with the equivalent of a typical dose of 5 mg of hydrocodone every 4 hours for 1 month."[1] In 2011 there were 41,340 deaths from prescription drug poisonings, over 17,000 involving opioids. Prescription drug overdose was the leading cause of injury death in 2012. Among people 25 to 60 years old, prescription drug overdose caused more deaths than motor vehicle traffic crashes. The drug overdose death rate has more than doubled from 1999 through 2013.[2-6]

Diversion

Diversion is defined as the intentional removal of a medication from legitimate and dispensing channels.[7] It is common among prescription drugs, where approximately 53% were obtained from a friend or relative, and 83.6% of those were from a single physician source.[8]

SOLUTIONS

Regulatory

Several states have imposed laws which limit amounts, doses, and distributions of opioid pain medications for the treatment of noncancer pain.[9–11]

Sublingual buprenorphine is utilized to treat opioid use disorder. On March 29, 2016, the US Department of Health and Human Services (HHS) announced lifting the cap of 100 patients to 200 who can be treated with sublingual buprenorphine for opioid use disorder. As of July 6, 2016, HHS increased this to 275 patients.[12]

The Food and Drug Administration (FDA) proposed a "Safe Use Initiative" in 2009 in which they proposed to identify, using a transparent and collaborative process, specific candidate cases; drugs, drug classes, and/or therapeutic situations that are associated with significant and measurable amounts of preventable harm.[13]

In 2012, the FDA also proposed and implemented REMS (Risk Evaluation and Mitigation Strategy) for extended release/long acting (ER/LA) opioids for the treatment of chronic noncancer pain.[14] This new REMS required ER/LA opioid analgesic companies to make training available for healthcare professionals who prescribe ER/LA opioid analgesics on proper prescribing practices and to distribute educational materials to prescribers and patients on the safe use of these pain medications. The ER/LA opioid REMS is at no cost to the practitioner and is currently voluntary for prescribing ER/LA for noncancer pain. However, the TIRF (Transmucosal Immediate Release Fentanyl) REMS is *mandatory* for prescribers of these products.[15] TIRF products are FDA approved and restricted to the treatment of breakthrough cancer pain.

Guidelines

Various organizations have published guidelines for the use of opioids in the treatment of noncancer pain. These are quite similar in their recommendations, and in fact the consensus from these organizations is that the level of evidence when utilizing chronic opioid therapy for the treatment of noncancer pain is fair and at times lacking.[16–18]

The CDC has compiled opioid guidelines for primary care physicians treating noncancer pain.[19] The rationale being that primary care physicians manage a significant amount of chronic pain and have little training to do so. Across medical specialties it is believed that addiction is a common consequence of prolonged use, and that long-term opioid therapy often is overprescribed for patients with chronic noncancer pain.

> **The goal is to *deter* abuse, realizing it is impossible to *prevent* abuse.**

Opioids With Abuse Deterrent Formulations (ADFS)

The FDA's Abuse-Deterrent Opioids—Evaluation and Labeling Guidance for Industry, released in 2015, establishes the rationale and methodology for the development of ER/LA opioids that contain abuse deterrent properties.[20] The goal is to *deter* abuse, realizing it is impossible to *prevent* abuse. Many opioid products are manipulated (crushed, snorted, injected, etc) to facilitate abuse. Since ER/LA opioids contain a large amount in a single delivery system(s), they are a favorite target of abusers. In short, the goal of an abuser is to convert an ER/LA opioid into an immediate release (IR) one. ADFs are intended to make manipulation more difficult or to make abuse of the manipulated product less attractive or less rewarding.

Opioid products can be abused in a variety of ways. Amongst them include being swallowed whole, crushed and swallowed, crushed and snorted, crushed and smoked, or crushed, dissolved and injected. It should be noted that the most common form of abuse is the oral (nonmanipulated) route, which is not addressed by ADFs.

ADFs can be categorized as follows:

❶ **Physical/chemical barriers**—Physical barriers can prevent chewing, crushing, cutting, grating, or grinding of the dosage form. Chemical barriers, such as gelling agents, can resist extraction of the opioid using common solvents like water, simulated biological media, alcohol, or other organic solvents. Physical and chemical barriers can limit drug release following mechanical manipulation, or change the physical form of a drug, rendering it less amenable to abuse.

❷ **Agonist/antagonist combinations**—An opioid antagonist can be added to interfere with, reduce, or defeat the euphoria associated with abuse. The antagonist can be sequestered and released only upon manipulation of the product. For example, a drug product can be formulated such that the substance which acts as an antagonist is not clinically active when the product is swallowed, but becomes active if the product is crushed and injected or snorted.

❸ **Aversion**—Substances can be added to the product to produce an unpleasant effect if the dosage form is manipulated or is used at a higher dosage than directed. For example, the formulation can include a substance irritating to the nasal mucosa if ground and snorted.

❹ **Delivery system** (including use of depot injectable formulations and implants)—Certain drug release designs or the method of drug delivery can offer resistance to abuse. For example, sustained-release depot injectable formulation or a subcutaneous implant may be difficult to manipulate.

❺ **New molecular entities and prodrugs**—The properties of a new molecular entity (NME) or prodrug could include the need for enzymatic activation, different receptor binding profiles, slower penetration into the central nervous system, or other novel effects. Prodrugs with abuse deterrent properties could provide a chemical barrier to the *in vitro* conversion to the parent opioid, which may deter the abuse of the parent opioid. New molecular entities and prodrugs are subject to evaluation of abuse potential for purposes of the Controlled Substances Act (CSA).

❻ **Combination**—2 or more of the above methods could be combined to deter abuse.

Premarketing Studies

The FDA suggests 3 categories of study in order to obtain approval for abuse deterrence.

- Category 1—Laboratory based *in vitro* manipulation and extraction studies
- Category 2—Pharmacokinetic (PK) studies
- Category 3—Human abuse liability studies

Category 1—Laboratory based in vitro manipulation and extraction studies

In vitro studies should assess various simple and sophisticated mechanical and chemical ways a drug could be manipulated, such as by:

- Defeating or compromising the controlled release of an opioid from ER formulations for purposes of abuse by different routes of administration
- Preparing an IR formulation for alternative routes of administration
- Separating the opioid antagonist, if present, from the opioid agonist, thus compromising the product's abuse deterrent properties

Category 2—Pharmacokinetic (PK) studies

The goal of the clinical PK studies should be to understand the *in vivo* properties of the formulation by comparing the PK profiles of the manipulated formulation with the intact formulation and with manipulated and intact formulations of the comparator drugs through one or more routes of administration. For example, an ER/LA ADF product should show the same or nearly the same pharmacokinetics, such as C_{max}, T_{max}, and AUC (area under the curve), as one without ADF.

Category 3—Human abuse liability studies

These studies generally are conducted in a drug experienced, recreational user population. Subjects should generally not be physically dependent and should not be currently seeking or participating in treatment for drug abuse such that participating in the study could make them vulnerable to relapse. These subjects will consume the drug in a double blinded fashion. This is often done via the oral and intranasal routes. The subjects will compare placebo, intact ADF, crushed ADF, and an active comparator (usually an IR formulation).

In typical abuse liability studies, several instruments have been used to measure subjective responses predictive of the likelihood of abuse. These instruments include:

- Visual Analogue Scales (VAS)—used for drug liking, good effects, bad effects, and other drug abuse related effects
- Profile of Mood States (euphoria, "high")
- Unipolar scale: score of 0 to 100 with 0 being no response and 100 being maximum response, usually used to assess "How high are you?"
- Bipolar scale: score of 0 to 100 with 0 being minimal "disliking," 100 being maximal "liking," and 50 being a neutral response neither "liking or disliking"

The VAS should be the primary measure for drug liking because it appears to correlate most directly with potential for abuse. Other measures of particular interest include assessment of likelihood to take the drug again and assessment of overall drug liking.

Category 4—Postmarketing Studies

Category 4 epidemiological studies are designed to measure abuse deterrence (overall and route specific abuse and abuse deterrence) in a large population. To date, no manufacturer has achieved this category labeling for abuse deterrence. How ever, there have been some postmarketing studies for ADF OxyContin® (Purdue Pharma, Stamford, CT).

Coplan et al measured changes in exposure to extended release oxycodone (ERO, OxyContin®) prior to and after its ADF reformulation.[21] They looked at all exposure types (therapeutic errors, abuse, and accidental exposure) for ERO, short acting (SE) oxycodone, and heroin. For all types of exposure, the ERO ADF showed a net *decrease* of 26% over a 3-year period. The SE oxycodone showed a 15% *increase* and the use of heroin *increased* by 37%. Decrease in all types of ERO exposures were greater with increasing dose. Conclusions of this study were:

- Abuse deterrent formulations, with physicochemical barriers appear to be promising at reducing abuse and adverse outcomes from misuse.
- More consistent abuse deterrent properties and addressing heroin availability may be necessary to improvise public health benefit.

Dart et al examined trends in opioid analgesic abuse and mortality in the US from the Researched Abuse, Diversion, and Addiction Related Surveillance (RADARS) System to describe trends between 2002 and 2013 in the diversion and abuse of oxycodone, hydrocodone, hydromorphone, fentanyl, morphine, and tramadol.[22]

The programs gathered data from drug diversion investigators, poison centers, substance abuse treatment centers, and college students. Heroin use was shown to *increase* significantly after the release of ADF OxyContin, while a concomitant *decrease* in ADF OxyContin use was observed. This increase was documented via the National Poison Data System, the American Association of Poison Control Centers, and the National Survey on Drug Use and Health (Substance Abuse and Mental Health Services Administration or SAMHSA.

Butler et al studied abuse rates and routes of administration of reformulated ADF OxyContin.[23] An observational design

"Since extended release long acting opioids contain a large amount in a single delivery system(s), they are a *favorite target* of abusers. In short, the goal of an abuser is to *convert* an ER/LA opioid into an immediate release (IR) one."

compared the prevalence, prescription-adjusted prevalence rates, and ROA (routes of administration) patterns of past-30-day abuse of oral reformulated OxyContin (ORF) in the period after its introduction, to that of OxyContin before introduction.

Abuse patterns for 2 comparator opioid compounds (ER morphine and ER oxymorphone) were assessed during the same pre- and post-ORF periods. The primary route of nonoral abuse of ER oxymorphone is by snorting and of ER morphine is by injecting, thus providing relevant controls for route-specific comparisons.

The study demonstrated a substantial *decrease* in the use of original formulation OxyContin and a *decrease* in the overall usage of both ADF and original OxyContin. The routes of administration showed changes in pre and post ORF. Specifically, there was a net *increase* in oral use of 21.6%, a net decrease in insufflation (snorting) of 27.3%, a net decrease in smoking of 2.2%, and a net decrease of injection of 19.8%.

The same routes of administration of comparator ER/LA opioids (oxymorphone and morphine) were also examined. For oxymorphone there was a net *decrease* in oral consumption by 8.1%, a net *increase* in insufflation by 7%, a net *increase* in smoking by 1.7%, and a net *increase* of injection by 7%. Morphine showed no real significant changes.

Cicero et al also looked at heroin usage postrelease of reformulated OxyContin.[24] They found a significant rise in heroin usage and a concomitant decrease in OxyContin usage. 70% of respondents indicated a switch to heroin, approximately 24% to other oxycodone products, and less than 15% to other opioids. Respondents were college students and a subset that was willing to give up their anonymity and participate in the interview based Researchers and Participants Interacting Directly (RAPID) program. Among these 88 participants who indicated experience using pre-ADF and ADF OxyContin, the residual level of abuse reflected the following 3 phenomena:

❶ Transition from nonoral routes of administration to oral use: 38 participants (43%)
❷ Successful efforts to defeat the ADF mechanism leading to a continuation of inhaled or injected use: 30 participants (34%)
❸ Exclusive use of the oral route independent of formulation type: 20 participants (23%)

Product insert (PI)—Section 9.2: Abuse

Section 9.2 in the PI of any opioid product discusses abuse potential. It also denotes whether the product has abuse deterrent properties as conveyed through Category 1–3 studies required by the FDA.

Current ADFs Available

Embeda®

Embeda® (Pfizer, NY) is an ER/LA ADF of morphine. Specifically, it uses an antagonist (naltrexone) mixed with the active drug (morphine), which if crushed or manipulated releases and reduces the euphorigenic or rewarding effect of morphine. The beads use a proprietary technology of sequestered naltrexone that will not release with normal oral consumption but will after crushing or other physical manipulation. Category 3 studies show significantly less liking and euphoria of crushed Embeda consumed orally and intranasally as compared to both placebo and active comparators (ER morphine and IR morphine).[25–28]

OxyContin®

OxyContin® is an ER/LA oxycodone product that utilizes technology which provides significant resistance to crushing or grinding. The residual produced after such manipulation is difficult to syringe due to the formation of a gelatinous mass when liquid is added. OxyContin has abuse deterrent properties as denoted in section 9.2 of the PI.[29]

In Vitro Testing

In vitro category 1 studies were performed to evaluate the success of different extraction methods in defeating the ER formulation. Results support that, relative to original OxyContin, there is an increase in the ability of ORF to resist crushing, breaking, and dissolution using a variety of tools and solvents. The results of these studies also support this finding for ORF relative to an IR oxycodone. When subjected to an aqueous environment, ORF gradually forms a viscous hydrogel (ie, a gelatinous mass) that resists passage through a needle.

Clinical Liability Studies

In a randomized, double blind, placebo controlled, 5 period crossover pharmacodynamic study, 30 recreational opioid users with a history of intranasal drug abuse received intranasally administered active and placebo drug treatments. The 5 treatment arms were finely crushed ORF 30 mg tablets, coarsely crushed ORF 30 mg tablets, finely crushed original OxyContin 30 mg tablets, powdered oxycodone HCL 30 mg, and placebo. Drug liking was measured on a bipolar drug liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking and 100 represents maximum liking. Response to whether the subject would take the study drug again was also measured on a bipolar scale of 0 to 100 where 50 represents a neutral response, 0 represents the strongest negative response ("definitely would not take drug again") and 100 represents the strongest positive response ("definitely would take drug again"). 27 of the subjects completed the study. Incomplete dosing due to granules falling from the subjects' nostrils occurred in 34% (n=10) of subjects with finely crushed ORF, compared with 7% (n=2) of subjects with finely crushed original OxyContin and no subjects with powdered oxycodone HCL.[29]

The intranasal administration of finely crushed ORF was associated with a numerically lower mean and median drug liking score and a lower mean and median score for "take drug again" compared to finely crushed original OxyContin or powdered oxycodone HCL.[29]

Targiniq®

Targiniq® is an ER/LA oxycodone product that utilizes an antagonist (naloxone) mixed with the opioid. Specifically, it uses an oxycodone:naloxone ratio of 2:1. The naloxone undergoes extensive first pass effect after oral consumption and has minimal to no effects, which allows the oxycodone to provide therapeutic analgesia. If manipulated and subsequently insufflated or injected, the naloxone antagonizes the effects of the oxycodone, thus reducing the reward and likeability to the abuser.

Targiniq ER has abuse deterrent properties according to section 9.2 of the PI.[30]

In Vitro Testing

In vitro category 1 studies were performed to evaluate the success of different extraction methods in defeating the controlled-release formulation of Targiniq ER and separating the oxycodone component from naloxone, a potent opioid antagonist. Laboratory test data demonstrate that Targiniq ER can be crushed and dissolved in solution. However, complete separation or complete inactivation of naloxone from oxycodone was not achieved despite using various techniques and conditions.[30]

Clinical Abuse Potential Studies

In the clinical abuse potential studies described below, drug liking was measured on a bipolar drug liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking and 100 represents maximum liking. Response to whether the subject would take the study drug again was measured on a unipolar scale of 0 to 100 where 0 represents the strongest negative response ("definitely would not take drug again") and 100 represents the strongest positive response ("definitely would take drug again"). Response to subjective feeling of getting "high" was measured on a unipolar scale of 0 to 100, where 0 represents "definitely not" and 100 represents "definitely so."

Study in Nondependent, Opioid Abusers—Intranasal (IN) Administration

In a randomized, double blind, placebo and active controlled, 3 period crossover pharmacodynamic study, 23 nondependent, opioid abusers with moderate experience with opioids received IN administered Targiniq ER 40 mg/20 mg (finely crushed tablets),oxycodone HCL 40 mg powder (active control), and placebo treatments.

IN administration of finely crushed Targiniq ER was associated with statistically significant lower maximum drug liking scores (P<0.001) and statistically significant lower maximum scores for "take drug again" (P<0.001), compared to powdered oxycodone HCL, and was associated with similar mean and median maximum scores for drug liking and "take drug again" compared to placebo treatment.[30]

The *efficacy* of Targiniq ER was evaluated in one 12-week, randomized, double blind, placebo controlled clinical trial in opioid experienced patients with uncontrolled moderate to severe chronic low back pain. A higher proportion of patients treated with Targiniq ER (55%) had at least a 30% reduction in pain score from screening to week 12 compared to placebo patients (41%). Also, a higher proportion of patients treated with Targiniq ER (37%) had at least a 50% reduction in pain score from screening to week 12 compared to placebo patients (25%).[30]

Opana®

Opana® is an ER/LA oxymorphone product that utilizes crush resistant INTAC® technology. Opana *does not* have labeling for abuse deterrent properties in section 9.2 of the product information. There are 2 efficacy studies for low back pain: one for opioid naïve patients and the other for opioid tolerant patients. Both studies showed statistically significant reduction in VAS compared to placebo.[31]

Oxaydo®

Oxaydo® is an IR formulation of oxycodone which uses aversion technology to reduce abuse. Specifically, it is formulated with an inactive ingredient (sodium lauryl sulfate, which is found in soap, shampoo, and other personal hygiene products) that may cause nasal burning and throat irritation when insufflated, to discourage intranasal use.

Oxaydo does not have abuse deterrent properties per section 9.2. In a double blind, active comparator, crossover study in 40 nondependent recreational opioid users, drug liking responses and single-dose safety of crushed Oxaydo tablets were compared with crushed IR oxycodone tablets when subjects self-administered the drug intranasally. The presence of sequence effects resulted in questionable reliability of the second period data. First period data demonstrated small numeric differences in the median and mean drug liking scores, lower in response to Oxaydo than IR oxycodone. 30% of subjects exposed to Oxaydo responded that they would not take the drug again compared to 5% of subjects exposed to IR oxycodone. Study subjects self-administering Oxaydo reported a higher incidence of nasopharyngeal and facial adverse events and a decreased ability to completely insufflate 2 crushed tablets within a fixed time period (21 of 40 subjects). The clinical significance of the difference in drug liking and difference in response to taking the drug again reported in this study has not yet been established. There is no evidence that Oxaydo has a reduced abuse liability compared to IR oxycodone.[32]

Xtampza®

Xtampza® is an ER/LA oxycodone that has physical properties which resist crushing and manipulation. Specifically, the microspheres of Xtampza ER relative to IR oxycodone tablets were less susceptible to the effects of grinding, crushing, and extraction using a variety of tools and solvents. Xtampza ER resisted attempts to pass the melted capsule contents or the microspheres suspended in water through a hypodermic needle.[33]

Xtampza ER has abuse deterrent properties as listed in section 9.2. In an oral abuse liability study, Xtampza ER showed the oral administration of chewed and intact Xtampza ER in the fasted state was associated with statistically lower mean drug liking scores compared with crushed IR oxycodone. However, the differences for Xtampza ER chewed and intact compared with crushed IR oxycodone for the "take drug again" scores were small and not statistically significant.[33]

In an intranasal abuse liability study, approximately 92% (n=33) of subjects had some reduction in drug liking with Xtampza ER relative to crushed immediate-release oxycodone HCL. 78% (n=28) of subjects had a reduction of at least 30% in drug liking with Xtampza ER compared to crushed immediate-release oxycodone HCL, and approximately 58% (n=21) of subjects had a reduction of at least 50% in drug liking with Xtampza ER compared to crushed immediate-release oxycodone HCL.[33]

Hysingla ER®

Hysingla® ER is a once daily hydrocodone ER/LA formulation for chronic pain. It uses the same technology as OxyContin to provide a physical barrier to manipulation. Hysingla ER has abuse deterrent properties per section 9.2 of the PI.[34]

Hysingla ER is formulated with physicochemical properties intended to make the tablet more difficult to manipulate for misuse and abuse, and maintains some extended release characteristics even if the tablet is physically compromised.

> **It should be noted that the most common form of abuse is the *oral* (nonmanipulated) route, which is *not* addressed by ADFs.**

To evaluate the ability of these physicochemical properties to reduce the potential for abuse of Hysingla ER, a series of *in vitro* laboratory studies, pharmacokinetic studies, and clinical abuse potential studies was conducted.

In Vitro Testing

In vitro physical and chemical tablet manipulation studies were performed to evaluate the success of different extraction methods in defeating the ER formulation. Results support that Hysingla ER resists crushing, breaking, and dissolution using a variety of tools and solvents and retains some ER properties despite manipulation. When subjected to an aqueous environment, Hysingla ER gradually forms a viscous hydrogel (ie, a gelatinous mass) that resists passage through a hypodermic needle.

Clinical Abuse Potential Studies in Nondependent Opioid Abusers

Two randomized, double-blind, placebo and active controlled clinical studies in nondependent recreational opioid users were conducted to characterize the abuse potential of Hysingla ER following physical manipulation and administration via the intranasal and oral routes.[31] For both studies, drug liking was measured on a bipolar drug liking scale of 0 to 100 where 50 represents a neutral response of neither liking nor disliking, 0 represents maximum disliking, and 100 represents maximum liking. Response to whether the subject would take the study drug again was measured on a unipolar scale of 0 to 100 where 0 represents the strongest negative response ("definitely would not take drug again") and 100 represents the strongest positive response ("definitely would take drug again").

Intranasal Abuse Potential Study

In the intranasal abuse potential study, 31 subjects were dosed and 25 subjects completed the study. Treatments studied included intranasally administered tampered Hysingla ER 60 mg tablets, powdered hydrocodone bitartrate 60 mg, and placebo. Incomplete dosing due to granules falling from the subjects' nostrils occurred in 82% (n=23) of subjects receiving tampered Hysingla ER compared to no subjects with powdered hydrocodone or placebo.

The intranasal administration of tampered Hysingla ER was associated with statistically significantly lower mean and median scores for drug liking and "take drug again" ($P<0.001$ for both), compared with powdered hydrocodone.[34]

Oral Abuse Potential Study

In the oral abuse potential study, 40 subjects were dosed and 35 subjects completed the study. Treatments studied included oral administrations of chewed Hysingla ER 60 mg tablets, intact Hysingla ER 60 mg tablets, 60 mg aqueous hydrocodone bitartrate solution, and placebo.

"Prodrug ADFs are *precursors* to the active opioid. They are enzymatically bio transformed in the gastro-intestinal tract and therefore *cannot* be abused via inhalation, snorting, and smoking."

The oral administration of chewed and intact Hysingla ER was associated with statistically lower mean and median scores on scales that measure drug liking and desire to "take drug again" ($P<0.001$), compared to hydrocodone solution.[34]

The results of a similar analysis of drug liking for intact Hysingla ER relative to hydrocodone solution were comparable to the results of chewed Hysingla ER relative to hydrocodone solution. Approximately 83% (n=29) of subjects had some reduction in drug liking with intact Hysingla ER relative to hydrocodone solution. 83% (n=29) of subjects had a reduction of at least 30% in peak drug liking scores with intact Hysingla ER compared to hydrocodone solution, and approximately 74% (n=26) of subjects had a reduction of at least 50% in peak drug liking scores with intact Hysingla ER compared with hydrocodone solution. Approximately 17% (n=6) had no reduction in drug liking with intact Hysingla ER relative to hydrocodone solution.[34]

Arymo™ ER®

Arymo™ ER is an extended release morphine sulfate compound that can be administered every 8–12 hours. Arymo ER has physical and chemical properties expected to make abuse by injection difficult.[35]

In Vitro Testing

In vitro physical and chemical manipulation studies were performed to evaluate the ability of different methods to defeat the ER properties. The results of this testing demonstrated that Arymo ER tablets, in comparison to morphine sulfate ER tablets, have increased resistance to cutting, crushing, grinding, or breaking using a variety of tools. When subjected to a liquid environment, the manipulated Arymo ER tablets form a viscous hydrogel (ie, a gelatinous mass) that resists passage through a hypodermic needle.

Oral Clinical Abuse Potential Study

An oral abuse potential study was conducted in 39 subjects who were nondependent recreational opioid users; 38 subjects completed the study. Treatment arms included manipulated Arymo ER 60 mg tablets (taken with juice), intact Arymo ER 60 mg tablets (taken with juice), crushed 60 mg morphine sulfate ER tablets (mixed in juice), and placebo. The study demonstrated that the oral administration of manipulated Arymo ER resulted in a statistically lower mean drug liking score than the oral administration of crushed morphine sulfate ER tablets. However, the difference between manipulated Arymo ER and crushed morphine sulfate ER tablets for "take drug again" was not statistically significant, indicating that the difference in drug liking scores was not clinically meaningful.

Prodrug ADFs

Prodrug ADFs are precursors to the active opioid. They are enzymatically bio transformed in the gastrointestinal tract and therefore cannot be abused via inhalation, snorting, and smoking. Benzhydrocodone hydrochloride (KP201) is a prodrug of hydrocodone (in combination with acetaminophen) and was developed by KemPharm (KP201/APAP) as a potential ADF.[36] KP201 was tested in healthy individuals and confirmed by a group of opioid-naïve subjects in clinical studies.[37,38] Three human clinical abuse potential studies showed that KP201/APAP produced a significantly lower C_{max}, a delay in T_{max}, a decreased total exposure to hydrocodone, and a

lower incidence of hypoxia at high doses, as compared to a hydrocodone bitartrate and APAP combination for both intranasal and oral administration.[36,39] The manufacturer received new drug application approval and priority review from FDA in February 2016.[40]

ADFs With Unique Delivery Systems

Another potential strategy for deterring opioid abuse is the development of new delivery systems, such as subcutaneous implants and depot injections that provide sustained and gradual opioid release. The buprenorphine transdermal delivery system (BTDS; Butrans®, Purdue Pharma)[41] utilizes a molecule (buprenorphine) with a high affinity for the μ-receptor. As a partial agonist, buprenorphine is a logical choice as an agent for abuse deterrence due to its lack of euphorigenic effects.

Implants could be used to treat patients with comorbid chronic pain and substance abuse, which accounts for 32% of chronic pain patients who require prescription opioids.[42,43] The first subdermal implant of buprenorphine (Probuphine®, Titan Pharmaceuticals) was approved by FDA in May 2016 for the maintenance treatment of opioid dependence.[41] This product provides continuous low dosing of buprenorphine for up to 6 months, obviating the need for daily medication and safeguarding against illicit drug use.[44–46] Although this product is approved for the treatment of opioid dependence, theoretically the same technology could be utilized in the treatment of chronic pain.

Pharmacokinetic data suggests that implant buprenorphine produces lower peak plasma concentrations than sublingual administration.[47] A small study of heroin dependent abusers showed that implant buprenorphine resulted in fewer positive urine tests for opioids, less withdrawal symptoms, and fewer craving events after 6 months.[48] An unpublished Phase III trial demonstrated after 6 months that implant buprenorphine was noninferior to sublingual buprenorphine/naloxone in maintaining clinical stability, with no evidence of illicit opioid use (63.2% vs 53.9%, P=0.21).[48] The monthly cost of such a product is high (approximately $1000), which could be an obstacle to its use.[49]

Conclusion

ADFs are now mandated by the FDA for all pharmaceutical manufacturers of ER/LA opioids. They are part of a broader REMS strategy to mitigate overdose deaths and morbidity associated with prescription opioid use. It is important to note that ADFs do not replace REMS but are an integral component.

The use of ADFs is to protect the public and is not necessarily designed for individual patient use. In fact, if a pain practitioner suspects or diagnoses a patient with a substance used disorder, then controlled substances should not be prescribed for pain. Instead a treatment regime for chemical dependency should be implemented.

One may consider ADFs for opioids as "the child guard cap," which currently exists for all prescription pharmaceuticals (and many over the counter as well). The concept that medications contain an abuse deterrent formulation to protect others in addition to our own patients is really a public health solution to a growing epidemic. These technologies are expensive, and society (and government) must decide who will pay for them and determine whether they are mandated for use or simply recommended. Potential cost savings have demonstrated for substituting reformulated OxyContin for generic oxycodone ER. Several studies in a comprehensive review have assessed the economic impact of reduced abuse, drug overdose rates, and utilization after instituting reformulated OxyContin.[50,51]

The prescription drug epidemic is being fought on multiple fronts. ADFs are just one weapon in that war. ◘

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