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Substance Use Disorders (FG Moeller, Section Editor)

Prescription Opioid Misuse: Effective Methods for Reducing the Epidemic

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Opinion statement

Prescription opioid misuse has been a significant epidemic during the past decade. Formulations of prescription opioids with different mechanisms of abuse-deterrence have been developed or are currently under development. Given that these medications are substantially more difficult to use in an illicit fashion and minimize the potential for euphoria and/or create an aversive experience when over-ingested, they represent an important next step in pharmacological innovation. Immediate decreases in nonmedical use and in associated overdose mortality and adverse events have been observed after a highly abused opioid, OxyContin, was changed into an abuse-deterrent formulation. However, this reduction in OxyContin use may have simply shifted the drug of choice towards other more easily misused opioids, suggesting that a change in formulation alone will not be sufficient in controlling the epidemic. To control prescription opioid misuse requires treating populations with opioid use disorder and preventing the development of opioid abuse or dependence in unaffected populations. Buprenorphine with naloxone has been designed as an abuse-deterrent formulation, while also demonstrating significant efficacy in treating opioid use disorder. Thus, the dissemination of buprenorphine treatment can be a helpful step in reducing the current epidemic. Other strategies to reduce the epidemic include limiting the availability of leftover prescription opioids through drug take back programs, monitoring physician prescriptions through state prescription

monitoring programs, and implementing evidence-based practices in pain management. Increased referral of patients with chronic nonmalignant pain to comprehensive pain rehabilitation programs can also reduce healthcare utilization while improving patient outcomes. Also, routine screening for prescription misuse and referral for addictions treatment must become a standard practice in order to ensure patient safety and create early opportunities for intervention.

Introduction

The early twenty-first century has seen a dramatic rise in the use, misuse, dependence upon, and medical complications arising from prescription opioid medications. According to the US Center for Disease Control (CDC), sales of prescription opioids in 2010 were more than four times those in 1999, increasing to approximately 7.1 kg per 10,000 populations, equivalent to 710 mg per person in the USA [1]. Similarly, the overdose mortality in 2008 almost quadrupled the rate observed in 1999. The admission rate into substance abuse treatment for opioid use disorders in 2009 was almost six times the rate in 1999, and the estimated emergency department (ED) visits from nonmedical use of opioid analgesics increased 111 % during 2004–2008 (from 143,500 to 271,700 visits) [1, 2]. According to the National Survey on Drug Use and Health (NSDUH), in 2013, there were an estimated 4.5 million current (past month) non-medical users of prescription pain relievers (1.7 % of US population), a slight decrease from the previous year's estimate of 4.9 million current users (1.9 %); however, opioids remain second only to cannabis in rates of illicit use and is far above the prevalence of other illicit substances [3]. Non-medical use of prescription opiates among adolescents and young adults also represents a significant problem. Among adolescents, 68 % of intentional exposures to prescription medications were identified to be opioids, and about one-third were suspected suicide attempts, resulting in a mortality rate of 0.1 % [4]. A similar trend in use was identified among college students, with 48 % of this population reporting non-medical use of pain relievers [5]. Sources of opioid prescriptions illicitly obtained and used by adolescents include, in descending order: friends and family through purchase or theft, a single physician, drug dealers, and the internet [6]. Interestingly, evidence suggests that among those diagnosed with opioid use disorder who do not themselves have a medication prescription, approximately half obtain medications from a person with a prescription, suggesting an even greater role of physician as source than previously suspected [7].

Other factors associated with addiction liability of prescription opioids include the individual's underlying motivation for use as well as pharmacologic factors such as route of administration. For example, McCabe et al found that persons who took leftover medications from their own previous prescriptions were using primarily to relieve physical pain, while persons obtaining medications from other sources were more likely to demonstrate prescription opioid abuse and other substance use behaviors [8]. Ultimately, this raises concerns regarding continued access to leftover medications as well as the need to encourage safe disposal of unused prescription medications. In a separate study, Butler et al found the abuse potential of specific opioids was associated with the user's preferred route of administration. The investigators found that patients entering substance abuse treatment (N=59,792) most frequently abused hydrocodone and oxycodone immediate-release (IR) and extended-release (ER), with oxycodone ER carrying the greatest risk for abuse. The investigators also found that route of administration differed between the medications, with hydrocodone being most likely to be abused orally, oxycodone primarily by nasal route (i.e., snorting or inhalation), and morphine most likely being used intravenously [9•], replicating their findings from an earlier study [10]. Importantly, non-oral routes of administration appear to be a progression from oral ingestion and have been associated with a longer duration of abuse [11–14].

Abuse-deterrent formulations

Given the widespread concerns regarding misuse and diversion of prescription opioid medications, various abuse-deterrent formulations of these medications with different mechanisms have been released or are currently under development.

Tamper-resistant formulations

One method of achieving abuse-deterrence is through employment of tamper-resistant technologies, since prescription opioids are frequently crushed for snorting or extracted for IV use [9•, 12]. These types of formulations are designed to withstand physical pressure applied to pills, thus making users unable to create a fine powder for either snorting or IV abuse. Additionally, these formulations turn into a gel-like compound when dissolved in water or other solvents, thus making it difficult to extract for IV use. Examples of tamper-resistant formulations include reformulated extended-release oxycodone (ERO), oxymorphone (Opana ER), and Tapentadol (Nucynta ER).

Reformulated extended-release oxycodone

Extended-release oxycodone was first introduced in 1996 and aggressively marketed as an effective pain reliever with substantially reduced addiction potential due to its long-acting pharmacologic properties. However, it quickly became the most widely abused prescription opioid in the USA [15]. As a result, extended-release oxycodone (ERO) was reformulated with tamper-resistant technology and released to market in August 2010.

Since its re-release, numerous studies have examined both its abuse potential and the actual post-marketing outcome regarding its abuse prevalence and overdose-related mortality rates. Extraction of the active compound from reformulated ERO is substantially more difficult [16], and in a study of recreational users ($N=30$), it received the lowest ratings among all opioid products in terms of attractiveness, value, desirability, and likelihood of tampering [17]. In a pharmacokinetics study conducted in healthy controls, Perrino et al found that in contrast to the original formulation of oxycodone (Oxycontin), the crushed reformulated compound demonstrated a lower maximum plasma concentration as well as an increased time to reach maximum plasma concentration. As a result, when the reformulation was crushed, the user experienced a slowed oxycodone release, reduction in euphoric effects, and greater intranasal irritation [18].

Since release of the abuse-deterrent formulation of oxycodone, a number of studies have shown substantial reductions in the rates of oxycodone misuse and diversion. Based upon data from the Survey of Key Informants' Patients (SKIP) program of the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) system, Cicero et al reported significant post-reformulation reductions in both (1) rates of identification of ERO as primary drug of choice

and (2) past month ERO abuse in patients entering treatment; however, the prevalence of heroin use among respondents nearly doubled [19•]. In a later study based upon data from the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO), Butler et al. reported that non-oral abuse of reformulated ERO in individuals assessed for substance abuse treatment was 66 % lower in comparison to previously reported rates of misuse of the original formulation ERO [20]. Further, Havens et al found in a sample of experienced ERO abusers in a rural Kentucky county ($N = 189$) that self-reported rates of past 30-day abuse of reformulated ERO were lower (any route 33 %, 1.9 days/month; snorting 5 %, 0.2 days/month; injecting 0.5 %, <0.1 days/month) than those of oxycodone IR (any route 96 %, 19.5 days/month; snorting 70 %, 10.3 days/month; injecting 51 %, 10.5 % days/month) as well as retrospectively reported rates of abuse of the original formulation of ERO [21].

In addition to observed reductions in the rates of reformulated ERO misuse, the harms associated with ERO also appear to be decreased. Based upon data from the Poison Center Study and Drug Diversion programs of the RADARS System, Severtson et al reported that in the 18-month period following the release of reformulated ERO (October 2010 through March 2012), ERO abuse exposure calls to poison centers decreased 38 %, therapeutic errors decreased 24 %, and diversion reports decreased 53 % [22]. In a separate study examining data from the National Poison Data System (NPDS), Coplan et al reported that following ERO reformulation, calls to poison centers related to abuse exposures decreased 36 %, therapeutic errors decreased 20 %, and accidental exposures decreased 39 %, while calls related to heroin and other single-entity (SE) oxycodone formulations either remained stable or were increased [23]. Based upon the manufacturer's pharmacovigilance database, Sessler et al found that ERO abuse-related overdose deaths (adjusted per 100,000 ERO prescriptions dispensed after the reformulation) decreased 86 % from the year before to the third year after reformulation, while non-fatal ERO adverse events and reported ER morphine fatalities remained unchanged [24].

Not surprisingly, the reductions in rates of misuse and diversion of ERO have sparked additional clinical study of its underlying pharmacological mechanism, with evaluation of whether this method could be employed with other opioid compounds. Recently, a phase III clinical trial sponsored by Purdue Pharma LP of ER hydrocodone (hydrocodone bitartrate (HYD)), which utilizes an identical, polymer matrix chemical platform as ERO, was completed; however, results of this study have not yet been disseminated (NCT01400139 at clinicaltrial.gov). Altogether, the ERO formulation represents an effective strategy for reducing both nonmedical use of oxycodone and medical complications stemming from misuse.

Extended-release oxymorphone (Opana ER)

Extended-release oxymorphone (Opana ER, Endo Pharmaceuticals Inc.) is a crush-resistant formulation of oxymorphone embedded in hard polyethylene oxide (PEO), approved by FDA on Dec 9, 2011 and made commercially available in 2012. This reformulation, oxymorphone ER-PEO, has been shown to resist crushing by spoons, pill crushers, and hammers as well as resistance to extraction by a test battery of solvents [25]. In a study meant to assess the medication's ability to withstand tampering, Vosburg et al asked drug users to

attempt preparation of reformulated oxymorphone according to their usual patterns, and then measured the resulting particle size and yield of active drug ingredient [26]. The investigators found that the oxymorphone ER-PEO was more difficult to crush into particles suitable for insufflation or injection, and 92 % of participants reported unwillingness to insufflate and 84 % unwilling to inject the tampered products. Despite these findings, however, there have been incidents of misuse of oxymorphone ER-PEO as well several reports of medical complications, such as stroke, seizures, and a thrombotic thrombocytopenic purpura-like illness when the medication is used intravenously [27–29].

Extended-release tapentadol (Nucynta)

ER tapentadol (Nucynta® ER, Ortho-McNeil-Janssen Pharmaceuticals, Inc.) is another formulation utilizing the polyethylene oxide (PEO) matrix. Vosburg et al demonstrated this new formulation had minimum yield of product when tampered with by experienced opioid-dependent individuals [30]. Of note, only 16–24 % of participants were willing to use this medication by snorting in comparison to 100 % of those who expressed willingness to use the original formulation of ER Oxycontin via the same method.

Osmotic extended-release oral delivery system (OROS) hydromorphone (Exalgo)

OROS hydromorphone (Exalgo®, Mallinckrodt Pharmaceuticals, Inc.) was approved by the FDA in 2010 as a treatment for moderate to severe chronic pain of lasting duration, specifically for those in whom tolerance to opioids has already developed [31–33]. OROS technology consists of an osmotically active bilayer core enclosed in a semipermeable tablet shell membrane, which is considered as tamper-deterrent, because the tablet is difficult to crush and the active ingredient cannot be extracted for injection [34]. To date, no clinical studies regarding the abuse potential of OROS hydromorphone are available [35].

Controlled-release oxycodone (Remoxy ER)

Controlled-release oxycodone (Remoxy ER, CRO), a reformulation featuring a high-viscosity hard gelatin capsule, was designed to resist tampering and cannot be extracted with a needle [36]. Setnik et al demonstrated reduced drug liking and abuse potential when CRO, taken whole or chewed, was compared to orally administered oxycodone IR and crushed oxycodone ER [37]. Additionally, Butler et al reported an estimated pre-marketing attractiveness of CRO close to Talwin NX (pentozine combined with naloxone) and significantly different from ER oxycodone (OxyContin, Purdue Pharmac LP), Oxycodone/acetaminophen, (Percocet, Endo Pharmaceuticals) and hydrocodone/acetaminophen (Vicodin, Abbott Laboratories) [38]. However, the FDA declined to approve CRO in June 2011 [39].

Controlled-release oxycodone/acetaminophen (Xartemis XR)

Utilizing PEO technology, the first tamper-resistant oral combination medication, controlled-release oxycodone/acetaminophen (Xartemis XR, Mallinckrodt Pharmaceuticals, Inc.; CR OC/APAP), received FDA approval and was released in 2014 [40]. In phase I study, CR OC/APAP demonstrated less drug liking and

delayed onset of subjective effects in comparison to intact immediate-release oxycodone/acetaminophen [41]. Importantly, when CR OC/APAP was crushed, a further delay in onset of subjective effects was observed. Interestingly, this formulation possesses both immediate- and extended-release properties, and it is this attribute which results in the delayed onset of action when the medication is crushed, since these portions of the medication are then combined [42].

Other tamper-resistant formulations currently under development

Egalet Corporation currently has under development two formulations of pain medication, a controlled-release morphine compound (Egalet 001) and a tamper-resistant oxycodone compound (Egalet 002), which utilize pharmacologic technology to resist common methods of abuse, such as crushing, snorting, dissolving in order to inject, and alcohol dose dumping [43]. Egalet 001 completed phase II clinical trials in 2008 (NCT00446069 at clinicaltrials.gov), and is currently undergoing phase III trial. From CIMA Labs, Inc., a new formulation of extended-release of hydrocodone using CIMA® Abuse-Deterrence Technology is also in an active stage of development. This medication, which features granulated, polymer-coated hydrocodone molecules which are then compressed into tablets, are designed to control release of hydrocodone when taken orally and to further protect against release if the medication is crushed or taken with alcohol [44]. In phase I study, these hydrocodone extended-release tablets, even when pre-treated with high levels of polymer coating, demonstrated similar pharmacokinetics to immediate-release hydrocodone, allowing for comparable pain relief while increasing tamper-resistance [45].

Opioid switching

There is strong evidence of the significant and immediate decline in misuse of tamper-resistant medications, such as reformulated extended-release oxycodone, as well as associated adverse outcomes; however, at the same time, there have been increasing reports of abuse of other opioids with greater tampering potential, such as heroin or buprenorphine [19•, 23, 25]. Buer et al reported in a small sample of individuals longitudinally followed for substance use ($N=25$) that a shift from misuse of the original formulation of oxycodone (OxyContin®) to misuse of immediate-release oxycodone formulations was observed following release of the reformulated extended-release oxycodone (ERO) [46]. In a larger, sentinel sample of 232,874 adults assessed for substance abuse treatment within NAVIPPRO surveillance system, the prevalence of abuse increased for all prescription opioids as a class as well as for ER opioids, with significantly greater abuse of ER oxymorphone and buprenorphine after the introduction of reformulated ERO in 2010, also indicating possible switching of the opioid of choice [47]. These findings suggest that replacement of a widely prescribed opioid formulation alone may have little impact on overall rates of opioid as a class, since without treatment, opioid-dependent individuals are likely to continue substance misuse unabated.

Abuse-deterrent formulations with aversive components

The second type of abuse-deterrent mechanism of action is to add aversive components. The aversive ingredients in these formulations cause unpleasant, but not serious or fatal, reactions when people overtake the prescribed dose or use alternate, non-oral routes of administration. Examples include immediate-release oxycodone containing niacin (Acurox®, Acura Pharmaceuticals, Inc), immediate-release oxycodone with niacin-free aversive components (Oxecta®, Pfizer, Inc.), and oxycodone/acetaminophen with aversive components (Acuracet®, Acura Pharmaceuticals, Inc.). Although promising, the overall clinical utility and effectiveness of these medications is not yet entirely known. For example, these formulations may prevent misuse by reducing oral overtaking and non-oral use, but they might also limit the effectiveness of pain management when compliant patients require higher medication doses due to development of tolerance. Additionally, it is possible that the physical discomfort caused by the aversive components may not be severe enough to deter abuse in those with severe dependence. All the same, this particular mechanism represents an important and exciting advance in the pharmaceutical management of opioid misuse.

Immediate-release oxycodone with aversive components

Originally introduced by Acura Pharmaceuticals as oxycodone-niacin (Acurox)), this immediate-release oxycodone formulation containing niacin (vitamin B_3), caused a burning sensation in the nasal passage when crushed and snorted as well as uncomfortable flushing when the medication was overtaken orally [48]. However, the FDA declined to approve oxycodone-niacin in 2010, citing concerns regarding the adverse effects due to niacin; as a result, the medication was reformulated as an immediate-release with niacin-free aversive components (Oxecta®, Pfizer Inc.), which ultimately received FDA approval in 2011 [49]. This approved medication, immediate-release oxycodone with inactive functional excipients (IRO-A), was found in pharmacokinetic study to have similar bioequivalence to both marketed immediate-release oxycodone (Roxicodone) and the IRO-A with niacin formulation, but lacked the flushing adverse effect observed with IRO-A with niacin [50]. In a randomized, double-blind, active-controlled study in nondependent, recreational opioid users aged 18–55 years (N=40), Schoedel et al found that participants receiving crushed IRO-A tablets reported lower scores on drug liking and desire to take the drug again in comparison to those administered crushed IRO (Roxicodone) [51]. The technology utilized with this medication, known as Aversion®, is currently being tested in the combination product, oxycodone/acetaminophen; however, there are no published clinical studies at this time [52].

Opioid agonist/antagonist combination

The third abuse-deterring mechanism is the addition of an opioid antagonist along with the opioid formulation. Within the medication, opioid antagonists can be sequestered and released only when tampering or use by non-oral route of administration occurs.

Extended-release morphine and sequestered naltrexone

In the abuse-deterrent formulation of extended-release morphine and sequestered naltrexone (MS-sNT; Embeda®, Pfizer Inc.), the ratio of morphine sulfate:naltrexone is 100:4 (20 mg/0.8 mg as the lowest dose) [53]. When the medication is crushed or chewed, the sequestered antagonist is released from the core of the capsule, counteracting the euphoric effects of the opioid and even precipitating withdrawal symptoms, in some cases [54, 55]. Importantly, the naltrexone component remains inert if the medication is taken through the oral route and without tampering. In a single-center, randomized, double-blind, crossover study of opioid-dependent males ($N=28$), participants reported significantly less euphoria and drug liking when intravenously administered crushed MS-sNT in comparison to IV morphine alone [56]. Recently, the FDA approved updated labeling for the medication which specifically reflects the abuse-deterrent properties of the medication, and the product is slated to become commercially available in 2015 [57].

Buprenorphine/naloxone and other buprenorphine formulations

Used to treat opioid use disorders in Europe since 1996 and in the USA since 2003, buprenorphine/naloxone (Suboxone®) carries the potential to become the first-line medication to treat opioid dependence due to its favorable side effect profile, reduced abuse potential and availability in office-based settings [58•]. This abuse-deterrent medication was originally formulated as the sublingually administered tablet combination of a high-affinity mu-opioid partial agonist and an opioid antagonist. Given the comparatively poorer oral bioavailability of naltrexone, when the tablet was taken as directed, the partial agonist effect of buprenorphine would predominate, sparing the patient from experiencing the antagonist effect [59]. However, with direct oral ingestion or crush/insufflation of the tablet, the naloxone effect would come to predominate, thus precipitating withdrawal [60]. Likewise, with water or solvent dissolution of the tablet for IM or IV use, naloxone could not be separated from buprenorphine, ensuring the antagonist effect would either diminish the euphoric effects or cause opioid withdrawal [61, 62]. Studies support the decreased addiction liability associated with buprenorphine/naloxone; for example, in a study performed in Finland, a country with significant rates of buprenorphine mono abuse, 80 % of buprenorphine/naloxone abusers reported having a "bad" experience with the combined formulation in comparison to buprenorphine alone. The associated negative experience reduced its demand with the street price of combination tablets being less than half of that of buprenorphine alone [63].

Despite its lower abuse potential, both anecdotal reports and clinical case studies indicate that misuse and diversion of buprenorphine/naloxone for illicit purposes does occur [64, 65]. Additionally, buprenorphine exposure rates among US children have continued to increase since its introduction. One recent epidemiologic study found that 13,600 exposures were recorded through the pharmacovigilance monitoring system, and approximately 36 % of these exposures occurred in children under age 6 years [66]. In relation to these concerns regarding diversion, and in an attempt to increase treatment compliance, three newer formulations of the medication have been developed, (a) sublingual film, (b) buprenorphine depot injection, and (c) buprenorphine

implant. The reformulated sublingual film, introduced in the US in 2010, has gained wider usage due to its faster dissolution on the oral submucosa as well as tamper-resistant packaging to reduce the likelihood of accidental exposures in children [67, 68]. Importantly, in a recent, multi-site, double-blind, double-dummy parallel group trial of buprenorphine/naloxone patients ($N=92$), researchers compared the film with the tablet formulation, and found the two preparations demonstrated comparable dose effects and clinical outcomes [69].

The depot formulation of buprenorphine (Norvex™) utilizes a biodegradable polymer microcapsule technology for subcutaneous injection of 58 mg of buprenorphine mono for the treatment of opioid use disorder [70]. The injection provides an opioid blockade effect of approximately 6 weeks duration [70]. In a small double-blind, placebo-controlled, randomized clinical trial of participants with opioid use disorder ($N=15$), depot buprenorphine demonstrated effectiveness in suppressing withdrawal symptoms and attenuated the effects of exogenous opioid challenge in comparison to placebo [71].

The buprenorphine implant (Probuphine®, Titan Pharmaceuticals) delivers a constant, low level of medication for up to a 6-month time period. Utilizing a long-term drug delivery system, a small, solid "rod" made from a polymer matrix of ethylene vinyl acetate and the equivalent of 80 mg of buprenorphine, the rod is placed subdermally and later removed at the end of the treatment period. Because of the matrix technology of the implant, it is difficult to retrieve the medication from the rod, discouraging patient attempts to remove the implant [72]. One open-label study and two randomized, placebo-controlled studies of the buprenorphine implant demonstrated its effectiveness in treating opioid dependence, with participants receiving the medication showing a higher percentage of opioid-free urine samples and minimal withdrawal symptoms almost comparable to those observed with sublingual buprenorphine [73–75]. However, long-term efficacy of these two formulations for maintenance therapy needs further investigation.

Other strategies to reduce the prescription opioid epidemic

Necessarily, in addition to the development of abuse-deterrent formulations, other factors, such as provider prescribing patterns, patient education, and access to substance abuse treatment, must be addressed in order to ensure a lasting impact upon prescription opioid misuse. An important first priority is to balance the availability of prescription opioids for pain management without increasing the supply of medications diverted for nonmedical use. In this regard, regulations and health policy have been shown to be influential factors [76, 77]. Additionally, prescription monitoring programs have been associated with lower prescription volume [78], reductions in poison center intentional exposures and opioid treatment admission [79], and overdose mortality from prescription opioids [76]. However, there are concerns that prescription monitoring programs primarily result in a shift in prescribing practices, rather than decreased abuse rates [80, 81]. Leftover medications have been shown to be a huge resource for prescription opioid abuse [82], and there is widespread unsafe storage and disposal of unused prescription opioids obtained from emergency departments [83], thus take-back programs for unused prescription medications need to be in place [84]. Responsible clinical practice in pain

management and risk stratifications have been shown to be effective in preventing prescription opioid diversion and abuse [85–87]. Specialized, comprehensive pain rehabilitation programs utilizing a multidisciplinary approach and incorporating modalities such as behavioral therapy as well as physical and occupational therapies in conjunction with non-opioid pharmacological treatment have been found to be a cost effective strategy which could further reduce healthcare burden and improve patient functioning and quality of life [88, 89]. Changes in policy and reimbursement strategies may help to incentivize further creation and widespread integration of these services and enhance their impact upon the prescription opioid epidemic by reducing both supply of and demand for pain medications. Lastly, increasing the access to substance abuse treatment will be crucial to curb the epidemic, and effective medication treatments, such as buprenorphine, need to be more widely disseminated.

Conclusions and future steps

The creation of a cadre of opioid formulations which effectively manage pain without adverse events or the potential for prescription opioid abuse potential would be ideal, but remains unlikely for the foreseeable future. Given current limitations, both pharmacological and non-pharmacological strategies are necessary to curb the prescription opioid epidemic. Newly developed abuse-deterrent formulations may quickly decrease the prevalence of misuse of certain prescription opioids, as demonstrated in the example of OxyContin. However, these novel medications, including tamper-resistant formulations, formulations with aversive components, and formulations with opioid antagonists, cannot single-handedly cure the epidemic. Ultimately, the advent of compounds with decreased likelihood of abuse must be combined with public health and policy measures (i.e., prescription monitoring programs), patient and physician education, and increased addictions treatment services in order to create opportunities for widespread change.

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Compliance with Ethics Guidelines

Conflict of Interest
Xiaofan Li declares that he has no conflict of interest.

Daryl Shorter declares that he has no conflict of interest.
Thomas Kosten declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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