ANNUAL REVIEWS

Annual Review of Biomedical Engineering

Prevention of Opioid Abuse and Treatment of Opioid Addiction: Current Status and Future Possibilities

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Annu. Rev. Biomed. Eng. 2019. 21:61–84

First published as a Review in Advance on February 20, 2019

The *Annual Review of Biomedical Engineering* is online at bioeng.annualreviews.org

https://doi.org/10.1146/annurev-bioeng-060418-052155

Keywords

opioid drugs, opioid abuse, abuse-deterrent formulations, abuse-deterrent testing methods, nonprescription opioids

Abstract

Prescription opioid medications have seen a dramatic rise in misuse and abuse, leading regulators and scientists to develop policies and abuse-deterrent technologies to combat the current opioid epidemic. These abuse-deterrent formulations (ADFs) are intended to deter physical and chemical tampering of opioid-based products, while still providing safe and effective delivery for therapeutic purposes. Even though formulations with varying abuse-deterrent technologies have been approved, questions remain about their effectiveness. While these formulations provide a single means to combat the epidemic, a greater emphasis should be placed on formulations for treatment of addiction and overdose to help those struggling with opioid dependence. This article analyzes various ADFs currently in clinical use and explores potential novel systems for treatment of addiction and prevention of overdose.

Contents

1. INTRODUCTION

The Centers for Disease Control and Prevention (CDC) have declared that the United States is in the midst of an opioid overdose epidemic (1). This epidemic is one of the worst American public health crises in recent decades (2). In 2017 alone, almost 50,000 deaths occurred due to opioid overdose (3). While the epidemic began in the 1990s, the total number of opioid-related deaths from 2001 to 2016 is greater than 335,000 (4). The opioid crisis in the United States, however, is not new. By 1925, there were reportedly around 200,000 heroin addicts in the United States, and 15% of American soldiers in Vietnam became addicted to heroin (5).

Opioid addiction, abuse, and misuse and opioid-related deaths in the United States have resulted from substantial promotion of the use of prescription opioids by the pharmaceutical industry since around 1996 (6). Tragically, even many newborns are experiencing withdrawal symptoms due to their mothers' opioid use during pregnancy (6, 7). The CDC estimates that the total economic burden of prescription opioid misuse alone is around $80 billion a year (8). The abuse of highly potent synthetic opioids, such as fentanyl (100 times the strength of morphine) and carfentanyl (10,000 times the strength of morphine), has led to an alarming rate of accidental opioid overdose, in particular for first responders, including police officers and paramedics (9, 10). Since the issue of opioid overdose is not limited to drug addicts, avoiding accidental overdose is as important as prevention and treatment of opioid abuse. Development of opioid analgesics with reduced adverse effects is ideal but has been elusive thus far (11).

Prescription opioids must be differentiated from nonprescription opioids (illegal, unregulated sources of opioids). Prescription opioid drugs, manufactured by pharmaceutical companies, are usually designed to deter intended abuse. The abuse-deterrent properties of prescription drugs are present regardless of whether the drugs are obtained through the internet or by unethical and illegal prescribing practices (12). By contrast, nonprescription opioids, which can be obtained on the street illegally, have no mechanisms of deterrence. Furthermore, the strength of such opioids is

not regulated at all, and their abuse cannot be controlled by engineering of the formulations. The current opioid epidemic is driven by street opioids—in particular, heroin and fentanyl—rather than by prescription opioids (13). Fentanyl and other synthetic opioids are the leading cause of overdose deaths in the United States (14). In the city of Akron, Ohio, alone, over a time span of only 3 weeks, 236 overdoses and 14 fatalities were suspected to be due to carfentanyl (15). Thus, dealing with the opioid epidemic requires distinction of the two different sources of opioid drugs.

2. MISUSE, ABUSE, AND DIVERSION OF PRESCRIPTION OPIOIDS

Opioid-use disorder (OUD) differs from opioid dependence and addiction. A patient with OUD may develop tolerance and withdrawal symptoms if the opioid dose is decreased, but does not show maladaptive behavior (16). Abuse is defined as the intentional nontherapeutic use of a drug to achieve a desirable effect, while misuse describes the intentional therapeutic use of a drug in an inappropriate way (17).

Modern pain management relies heavily on prescription opioid analgesics, the abuse or misuse of which has led to serious and worsening public health problems (18). Morbidity and mortality associated with nonmedical use of prescription opioids have been continuously increasing (19). Abuse of opioid medications is intended mainly to achieve a feeling of euphoria, rather than pain relief. There is an urgent need to develop abuse-resistant formulations that can prevent individuals from abusing, misusing, or diverting prescribed opioid analgesics. Developing truly abuse-resistant formulations, however, has been difficult. To date, the US Food and Drug Administration (FDA) does not allow any clinically used abuse-deterrent formulation (ADF) to claim abuse or tamper resistance in its labeling (20). Thus, pharmaceutical companies and regulatory authorities have focused on developing ADFs that discourage abuse of the drug for the sole purpose of getting high, while simultaneously addressing undertreated pain (21, 22).

Most abuse of prescription opioids occurs through administration of physically manipulated formulations by alternate routes, such as intranasal and pulmonary (e.g., smoking) administration or injection, for faster absorption of the active ingredient. The most common modes of physical manipulation are chewing, crushing, grating, and grinding, sometimes followed by ethanol extraction, for subsequent snorting (nasal insufflation) or intravenous injection. Most ADFs are designed to deter such physical manipulation for opioid drug abuse. **Figure 1** shows common methods of opioid abuse, such as physical manipulation of formulations to convert them into powder for smoking, snorting, or chewing. Such manipulation is also employed to extract opioids using water or organic solvent for intravenous administration.

Prescriptions of opioid drugs must continue to meet the extensive need for effective pain relief, and safe opioid prescriptions can be achieved by ADFs that make physical manipulation more difficult and abuse of the manipulated product less attractive or rewarding (18, 23). Introduction of ADFs has resulted in a decrease in abuse, therapeutic errors, and diversion of extended-release opioid drugs (24). There is evidence that abuse of a reformulated opioid drug becomes lower than that for the original opioid drug, especially through nonoral routes of administration, such as injection, snorting, and smoking (25). The benefits are always accompanied by risks. No ADF is perfect, and a drug with an abuse-deterring property may give rise to the false assumption that it will not be abused.

2.1. What Is an Abuse-Deterrent Formulation?

According to the FDA, ADFs target the known or expected routes of abuse, such as crushing for snorting or dissolving for injection, for a specific opioid drug substance (26). ADFs are not

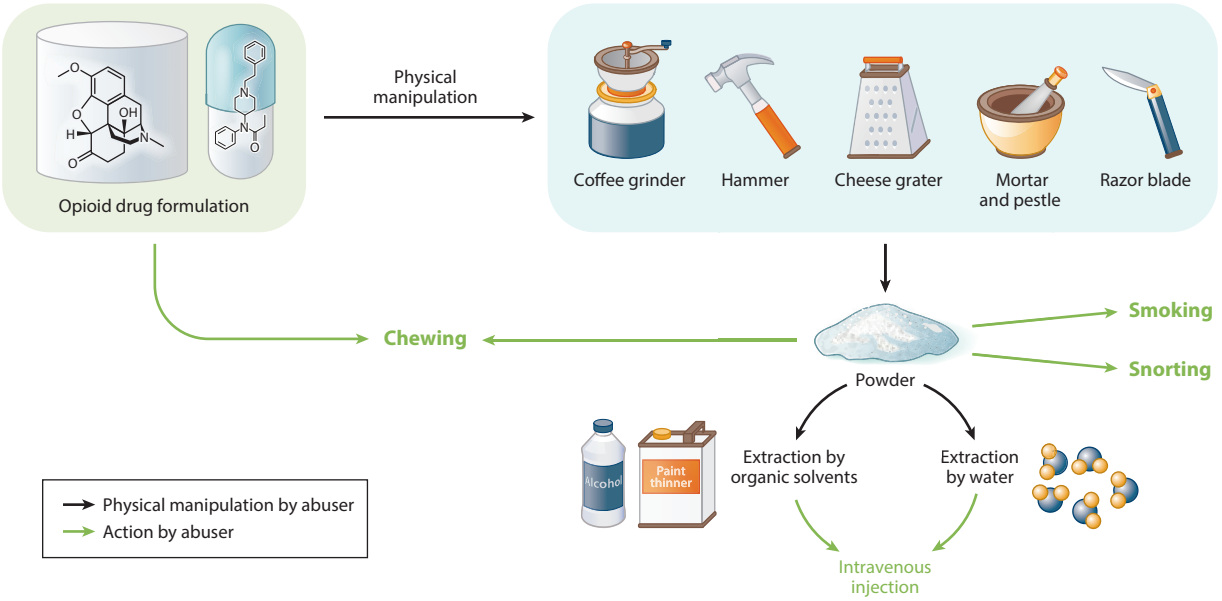

Figure 1

Various ways of abusing opioid formulations in capsule and tablet forms. Current opioid formulations, including abuse-deterrent formulations, can be easily manipulated into powders for abuse by smoking, snorting, and chewing. The powders can be further treated with water or organic solvents to extract opioids for intravenous injection.

abuse or addiction proof but can make abuse more difficult or less rewarding. The FDA supports advances in the relatively new field of abuse deterrence by taking a flexible, adaptive approach to the evaluation and labeling of potential ADFs. Unfortunately, however, currently marketed ADFs do not effectively deter the most common forms of opioid abuse, such as swallowing multiple tablets or capsules intact (26).

ADF approval is based on two guidelines issued by the FDA: "Abuse-Deterrent Opioids—Evaluation and Labeling" (18) and "General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products" (27). These guidelines make recommendations concerning how abuse-deterrent properties should be examined and evaluated. The FDA categorizes abuse-deterrent technologies into seven different approaches: physical/chemical barriers, agonist/antagonist combinations, aversion, delivery systems, new molecular entities and prodrugs, combinations, and novel approaches. Although each of these strategies has merit, none of them used alone may be adequate to reduce (let alone eliminate) the problems of misuse, abuse, and diversion of prescription opioid analgesics. This is simply because there is no way of knowing what methods abusers may come up with for tampering with ADFs. Thus, each approach should be considered a method that simply presents an impediment, discouraging attempts at tampering (22, 28).

If a new opioid formulation demonstrates enough compelling abuse deterrent evidence in any one of these seven approaches in comparison to a non-abuse-deterrent predecessor or a similar product, then the product may be officially labeled an ADF if approved by the FDA. The issue is that the meaning of "deterrent" has typically been used only in comparison with the original formulation, which has no deterrent properties. Thus, even though a given formulation may be effective in delaying opioid abuse in a certain method, many other possibilities for abuse exist; consequently, no ADFs have shown true abuse-deterrent properties. To understand how a formulation can be approved as an ADF, one needs to understand how abuse-deterrent properties are tested.

2.2. In Vitro Testing Methods of Abuse-Deterrent Properties

The abuse-deterrent capabilities of different opioid formulations must be evaluated through appropriate scientific assessment and careful clinical studies using various study designs in several populations, because many different types of individuals are exposed to opioids (29). Clinical studies, however, are extremely costly, and not all new ADFs may necessarily be tested in this manner. The FDA calls for in vitro assessments of various physical and chemical manipulations of the product matrix and the active pharmaceutical ingredient, but there are only key points and recommended studies regarding how these assessments should be designed and conducted.

Reducing misuse of abuse-deterrent products will never be absolute; thus, the extent of abuse deterrence can be understood only in relation to a control comparator (18). The FDA recommends three categories of premarket studies:

- Category 1: laboratory-based in vitro manipulation and extraction studies,
- Category 2: pharmacokinetic studies, and
- Category 3: clinical abuse potential studies (18).

Category 1 studies are designed to evaluate how easily the potential abuse-deterrent properties of a formulation can be defeated or compromised. These properties are usually examined by testing how easy or difficult it is to (*a*) chew (using a formulation without an opioid drug), crush, cut, grate, and grind; (*b*) extract the active ingredient using water, vinegar, ethanol, isopropanol, acetone, and mineral spirits; (*c*) snort the ground particles; (*d*) smoke; and (*e*) draw into a syringe. If a test formulation shows limited nasal administration after product manipulation and/or limited extraction of opioids that can be used for injection, the formulation can be tested in Category 2 pharmacokinetic studies, followed by Category 3 clinical abuse potential studies generally conducted in a drug-experienced, recreational user population (18). In vitro testing is designed to demonstrate only one property (e.g., swelling by incorporated hydrogels, which makes extraction and/or injection more difficult). Therefore, a given ADF may not deter abusers if they apply different methods to defeat the formulation.

Approval of an ADF has been conditional upon satisfactory completion of the three premarketing studies, along with continuous evaluation of the drug's use through postmarketing studies. The manufacturer is also obligated to implement a Risk Evaluation and Mitigation Strategy program, consisting of management and education plans to ensure that the drug's benefits outweigh the risks. The FDA emphasizes that it will take a flexible, adaptive approach to the evaluation and labeling of potentially abuse-deterrent products, since the science and evaluation of abuse-deterrent technologies are in their infancy and constantly evolving (18).

2.3. Current Abuse-Deterrent Formulations

Various abuse-deterrent technologies have been developed over the years, including physical/chemical barriers that make it difficult to crush tablets and extract the opioids, aversive agents that make abuse cause unpleasant adverse effects (e.g., flushing, itching, sweating, chills, headaches), and addition of sequestered antagonists (20, 21, 23, 28, 30–33). As of 2018, the FDA has allowed only eight ADFs to describe abuse-deterrent properties in their labeling (**Table 1**) (26).

Figure 2 depicts the main concepts of approaches to abuse deterrence. For example, microspheres in a capsule are more difficult to grind and crush. Most ADFs contain hydrophilic polymers that absorb water and swell to form a hydrogel. Hydrogels make it difficult to extract the opioid by water and, more importantly, to administer the drug by intravenous injection. Aversive agents are substances that are added to the formulation and released, if a formulation is physically

Table 1 Examples of current ADFs approved by the FDA

Name (opioid, manufacturer, year)	Abuse-deterrent mechanisms (reference)
Physical and chemical barriers	
OxyContin® (oxycodone HCl, Purdue Pharma, 2013)	This reformulated tablet has increased resistance to crushing, breaking, and dissolution using a variety of tools and solvents. When subjected to an aqueous environment, it gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle (34)
Hysingla® ER (hydrocodone bitartrate, Purdue Pharma, 2014)	This formulation 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, it gradually forms a viscous hydrogel that resists passage through a hypodermic needle (35)
MorphaBond™ ER (morphine sulfate, Inspirion Delivery Technologies, 2015)	This tablet has increased resistance to cutting, crushing, or breaking using a variety of tools. When subjected to a liquid environment, the formulation forms a viscous material that resists passage through a needle (36)
Xtampza® ER (oxycodone HCl, Collegium Pharma, 2016)	This capsule containing microspheres is less susceptible to the effects of grinding, crushing, and extraction using a variety of tools and solvents. It also resists attempts to pass the melted capsule contents or microspheres suspended in water through a hypodermic needle (37)
Arymo® ER (morphine sulfate, Egalet, 2017)	This polymer matrix tablet has increased resistance to cutting, crushing, grinding, or breaking using a variety of tools. When subjected to a liquid environment, it forms a viscous hydrogel that resists passage through a hypodermic needle (38)
RoxyBond™ (oxycodone HCl, Daiichi Sankyo, 2017)	This tablet has increased resistance to cutting, crushing, grinding, or breaking using selected tools. The intact and manipulated tablets resist extraction in selected household and laboratory solvents under various conditions, including selected pretreatments. This formulation forms a viscous material that resists passage through a needle; it is also more difficult to prepare solutions suitable for intravenous injection (39)
Sequestered antagonists	
Targiniq™ ER (oxycodone HCl and naloxone HCl, Purdue Pharma, 2014)	This combination tablet (now discontinued) can be crushed and dissolved in solution, but complete separation or complete inactivation of naloxone from oxycodone was not achieved through various techniques and conditions (40)
Embeda® (morphine sulfate and naltrexone HCl, Pfizer, 2015)	When this pellet-containing capsule is crushed and mixed in a variety of solvents, morphine sulfate and naltrexone HCl, which are sequestered in the core of microcapsules, are simultaneously extracted (41)
Drugs withdrawn from the market	
Troxyca® ER (oxycodone HCl and naltrexone HCl, Pfizer, 2016)	Altering the capsules by crushing, dissolving, or chewing the pellets can release sufficient naltrexone to precipitate withdrawal in opioid-dependent individuals (42)
Vantrela™ ER (hydrocodone bitartrate, Teva, 2017)	This formulation resists crushing, breaking, and dissolution using a variety of tools and solvents and retains some ER properties despite manipulation. When the crushed tablet is subjected to attempts at small-volume extraction, the resulting material becomes viscous and resists passage through a hypodermic needle (43)

Data are from Reference 26. Abbreviations: ADF, abuse-deterrent formulation; ER, extended release; FDA, US Food and Drug Administration.

manipulated, to cause a noxious odor, burning sensation, nausea, emesis, or diarrhea. Opioid antagonists can be loaded inside opioid formulations, and the sequestered antagonist can be released upon tampering to inactivate the opioid agonist.

Each approach has typically been designed to deter only one or two methods of abuse; thus, FDA approval of an ADF does not mean that it is truly resistant to abuse. ADFs may deter abuse to a certain extent, but abuse can still occur. Users have quickly learned to bypass abuse-deterrent properties, which are already extremely narrow (44). The use of physical barriers is the most

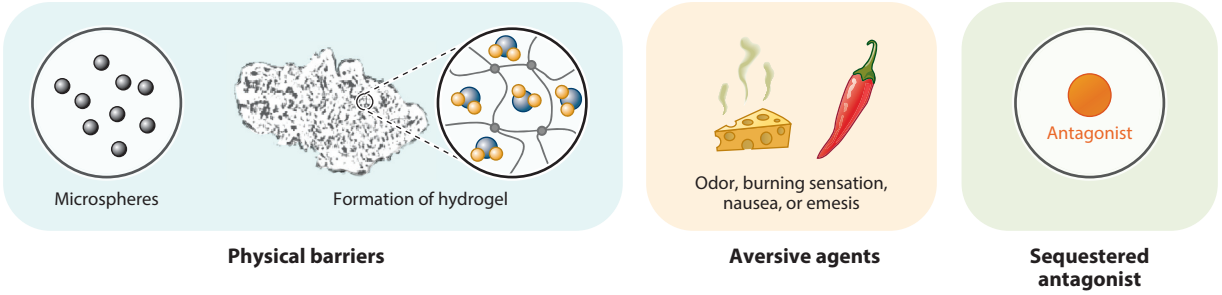

Figure 2

Approaches to abuse deterrence used in opioid drug formulations. Opioid formulations can be prepared in microparticles to deter physical manipulations of dosage forms and/or by adding a gelling agent to hinder opioid extraction. To hinder abuse by smoking, snorting, or chewing, certain agents causing a foul order or a burning sensation can be added, along with agents causing nausea or emesis. An opioid antagonist such as naloxone or naltrexone can be sequestered in a formulation that can be released only if tampered with.

popular approach, followed by the antagonist sequestering method (**Table 1**). Physical barrier formulations are based on some polymers' unique properties of forming hydrogels that resist dose dumping, drug extraction, and use with a syringe. Cross-linked hydrophilic polymers absorb water, causing them to form a hydrogel. Cross-linking can be chemical (i.e., covalent) or physical (e.g., noncovalent). Gel-based tablet formulations turn into a gel that is difficult to draw into a syringe for intravenous administration. These formulations, however, can still be readily exploited through other tampering methods.

Two FDA-approved ADFs, Troxyca® ER and Vantrela™ ER, have been withdrawn from the market (26) because they can be manipulated despite their potential to deter abuse. Sequestering naltrexone, as in Troxyca ER, or naloxone in a formulation designed to deter abuse is reasonable. Naloxone can successfully prevent opioid overdose death, especially as take-home naloxone (i.e., as a preprovision of naloxone to opioid users and family members), which was first proposed in 1996 (45). Thus, sequestering naloxone in a formulation designed to deter abuse is reasonable. The issue, however, is whether it can be foolproof. Troxyca ER was shown to be easily manipulated: It released 90% of its oxycodone from intact pellets into common solvents within 3 h or more, and approximately 60% within 15 min when two other solvents were used (46). Abuse potential of FDA-approved ADFs is always present, and it is simply a matter of time before users find ways to manipulate them for extraction of the opioid analgesics. Vantrela ER was withdrawn because, although it was designed to make intravenous abuse difficult, it can be abused by other routes.

ADFs may be approved if they demonstrate abuse-deterrent properties as defined in the guidelines on "Abuse-Deterrent Opioids—Evaluation and Labeling" (18). It is not difficult for a drug to meet such requirements. For example, OxyContin® was approved as an ADF because of its resistance to crushing and its ability to form a viscous gel (**Table 1**), with the hope that incremental improvements in the formulation would reduce the incidence of overdose due to abuse and misuse (47, 48). Hysingla® was approved because of its resistance to grinding and insusceptibility to vaporizing (49). The ability of these properties to prevent abuse is limited, however, as there are various ways to overcome them. A user's determination to thwart abuse-deterrent properties cannot be underestimated.

Opana® ER was frequently abused by snorting, as its original formulation was easy to shave down into a powder and snort. Although the new formulation was difficult to snort, it was prone to preparation for intravenous use (44). A consequence of the transition to intravenous use led to an HIV outbreak in Indiana as a result of needle sharing (50). This example shows why ADFs

cannot deter opioid abuse in a meaningful way and may even have harmful consequences. Drug manufacturers, however, continue to tout the value of ADFs in addressing the opioid epidemic. Overall, the value of the ADFs is in question, especially when higher drug costs inhibit access to opioids for patients in need (51), and there is no consensus among experts (52, 53). While the ADFs are only one means for fighting the opioid epidemic, it is important to understand that the use of well-known "generally recognized as safe" polymeric excipients as physical barriers is limited.

2.4. Limitations of Current Abuse-Deterrent Formulations

Early on in the development of ADFs, the FDA was willing to approve ADFs with only minor improvements to their abuse-deterrent properties. It was hoped that, as more ADFs were introduced, some of them would eventually work as intended. As described above, however, each ADF may have only one abuse-deterrent characteristic and, thus, only limited usefulness. In addition, if an ADF is "cracked" by someone who is knowledgeable about chemistry, the information can be posted on the internet for anybody to follow. Detailed visual demonstrations of how to defeat the ADFs can easily be found online.

The limited (if any) efficacy of current ADFs raises an issue regarding whether abuse-deterrent opioid formulations are worth the cost and effort (44). ADFs have been promoted by pharmaceutical companies despite having only a limited ability to deter abuse of opioid drugs, and the fact that ADFs cannot deter all types of abuse has caused the risk of using ADFs to outweigh their benefits. A prominent example is Opana ER. In 2017, the FDA asked the manufacturer of Opana ER, Endo Pharmaceuticals, to remove the ADF version from the market because its risks outweigh any potential benefits (54). This was a relatively rare occurrence, since only about 35 drugs have been removed from the market since the 1930s (55). Overall, the opioid crisis in the United States is getting worse (54).

Prescription opioid formulations are supposed to be prescribed, by a clinician, only for patients who need them. Unfortunately, however, they can easily be obtained on the street. This ready availability allows addicts to take multiple tablets at the same time without tampering with ADFs. Abuse involving ingestion of multiple tablets cannot be deterred by any existing abuse-deterrent technology. Two technologies are now in development to address this problem. They rely on pH-dependent release, causing ingestion of too many tablets to alter stomach pH and inhibit drug release (56, 57). Human variability, acidic drinks (e.g., cola, orange juice), and stomach contents could all present problems for these technologies. In addition, in order to truly prevent overdose deaths by ingestion of multiple tablets, every currently approved opioid drug product would need to be removed from the market and replaced with a product implementing these technologies.

2.5. Challenges to Development of Abuse-Deterrent Formulations

The FDA has issued a guidance that assists and makes recommendations regarding the development and testing of ADFs (27), but does not establish legally enforceable responsibilities. This document sets forth the FDA's current position on abuse-deterrent opioids; because these new technologies are constantly evolving and their true effectiveness is unknown, the FDA's position may evolve as more epidemiological data are collected.

KemPharm's recent drug application for Apadaz™ exemplifies the challenging developmental environment. Apadaz is composed of benzhydrocodone (i.e., a hydrocodone prodrug with one benzoic acid moiety) and acetaminophen. The prodrug approach to abuse deterrence is based on the idea that the prodrug form is "unabusable" because it is pharmacologically inactive until

transformed in vivo. Biotransformation is typically performed enzymatically, depending on the route of administration, and takes much longer to activate if abused via a different route. Certain solvents and/or conditions can transform a prodrug into the active form (e.g., hydrolysis), so although prodrugs are not totally tamper proof, they provide an additional mechanism of deterrence. Apadaz was approved by the FDA in February 2018, but without abuse-deterrent labeling. The original application was not approved, mainly due to concerns regarding abuse through oral and nasal administration (58). Even though this is a novel technology to combat abuse deterrence, the bar to approval for labeling as an abuse deterrent is much higher than initially set.

2.6. Prevention of Abuse by Eliminating Patient Access

The best way to overcome problems associated with prescription opioids is to eliminate patients' access to them completely. Patients could be administered nonoral forms of opioid drugs, such as injections of depot formulations that can release opioids to control and relieve pain. The probability of opioid addiction increases sharply if the opioid drug is used for 5 days or more (59). Ideally, therefore, an injectable depot formulation should deliver an opioid drug only for 5 days or less. Such injectable depot formulations have yet to be developed, however. Advances in controlled drug delivery technologies during the last few decades may enable development of such formulations for specific cases.

An extended-release formulation of morphine sulfate in a lipid-based drug delivery system (DepoMorphine/DepoDur®) was first studied in mice and dogs and is able to deliver and maintain plasma concentrations for up to 1 week in mice (60). DepoFoam®, another lipid-based drug delivery system, is a multivesicular liposome, essentially a honeycomb of internal aqueous compartments formed from lipids (61). Drug release is dictated by erosion and/or reorganization of the lipid membranes. DepoDur was approved by the FDA in May 2004 for single-dose epidural administration for the treatment of pain following major surgery. Although clinical studies have documented the efficacy of DepoDur, most patients receiving DepoDur still requested additional systemic opioids to achieve adequate pain control (61). DepoDur has been discontinued in the United States.

CAM2038, a once-weekly or once-monthly buprenorphine injection formulation, is currently in Phase III studies for chronic pain (62). The delivery system is a liquid crystalline matrix depot, typically a combination of an amphiphilic molecule (e.g., glycerol monooleate or glycerol diooleate), a lipid (e.g., phosphatidylcholine), a solvent (e.g., ethanol), and a drug. After injection and contact with interstitial fluids, water penetrates the liquid crystalline precursor solution, and the solvent diffuses outward, creating a shell around the matrix depot. Drug release occurs first during the restructuring process, along with steady-state drug diffusion once completely transformed, and finally during the degradation of the system.

Two other buprenorphine injectable systems have been approved by the FDA: a Probuphine® (buprenorphine) implant, a 6-month subdermal implant (12, 63), and Sublocade® (buprenorphine), a 1-month drug–poly(lactide-*co*-glycolide) (PLGA) mixture in organic solvent that rapidly solidifies in tissue (Atrigel®). Currently, no extended-release buprenorphine product is approved for both OUD and pain. Buprenorphine has not been widely used for the treatment of chronic pain, and questions have been raised about a potential "ceiling effect" or bell-shaped curve observed for analgesia in preclinical studies (64).

Controlled delivery with injectable polymeric systems offers enormous potential, as these systems are able to provide various loading and release profiles for multiple types of drug substances. Pain, and its subsequent treatment, is somewhat subjective. On some days a patient may feel worse

than on other days, and thus may need an extra dose to help ease the pain. Implantable, long-acting systems suffer in this area, as they typically cannot deliver an extra dose as necessary.

2.7. Opioid Delivery Devices

Few opioid delivery devices are presently in development. Such a device differs from a controlled opioid delivery formulation in that the device can include a sensor for detecting pain, a processor for transforming the signal into an action of delivering an opioid drug, and an actuator that releases the proper amount of opioid. Opioid delivery devices are difficult to make, as incorporating the three components and drug reservoir in a system small enough for implantation is not easy. More importantly, implanting such a device requires surgery followed by removal after use. External devices such as subcutaneous pumps allow a patient to control the dose and timing only when pain occurs, but they are useful only in a hospital setting.

Ingestible drug delivery devices are in development. Clinicians can track these devices to ensure that they are used appropriately and at the correct time, and that no more than one tablet is taken during an appropriate interval (65). The idea of a "smart" tablet device is not new, but hurdles exist with regard to regulatory approval, manufacturing, and cost. Currently, minimal data on real-world applications of such ingestible drug delivery devices are available.

3. ABUSE OF NONPRESCRIPTION OPIOIDS

Various ADFs have been introduced in the hope of preventing or deterring individuals from abuse, misuse, and diversion of prescribed opioid analgesics (21, 22, 66, 67). Their effectiveness in reducing abuse, however, has been minimal, as described above. More importantly, nonprescription opioid drugs are readily available. The abuse of (and addiction to) opioids is a serious global problem that affects the health and social/economic welfare of all societies (68). Furthermore, readily available highly potent opioids (e.g., fentanyl, carfentanyl) from illicit sources have led to numerous accidental opioid overdoses, including for first responders (10). Any exposure to potent opioids through the skin, nose, eye, or mouth or via inhalation can cause serious damage to the body. Thus, problems related to opioid overdose are not limited to opioid addicts.

Preventing the use of nonprescription opioids and other illegal drugs requires national and international efforts. History has shown that the war on illegal drugs is difficult to win. While the fight against illegal drugs must continue, treatment and prevention of opioid addiction and overdose must be pursued.

4. TREATMENT AND PREVENTION OF OPIOID ABUSE

To date, efforts to combat the opioid epidemic have focused on downstream efforts (i.e., treating persons addicted to opioids) (69). Upstream strategies that emphasize prevention, especially in rural areas, must also be implemented, as opioid-related mortality is especially high in certain rural areas of the United States (69).

4.1. History of Opioid Addiction Treatment

Treatment of opioid dependency using medication is known as opioid pharmacotherapy or opioid replacement therapy (70). Common pharmacotherapy agents include opioid agonists (e.g., methadone), partial agonists (e.g., buprenorphine), and opioid antagonists (e.g., naltrexone) (71, 72). Structured opioid agonist therapy with buprenorphine, buprenorphine/naloxone, or methadone at a licensed program is highly beneficial in the treatment of patients with pain or with

opioid addiction (12). Buprenorphine is highly effective in treating opioid addiction, and it is also effective in treating neonatal abstinence syndrome (73). The most significant risk of opioid pharmacotherapy using opioid agonists is overdose. There is also a risk of diversion of opioid agonists into illicit channels (70). One way to avoid overdose and diversion is to use injectable, long-acting formulations, such as a buprenorphine implant (6-month duration) approved by the FDA in May 2016 and a buprenorphine depot injection (monthly administration) approved in November 2017 (74). One study showed that extended-release naltrexone is as effective as buprenorphine/naloxone in maintaining short-term abstinence from heroin and other illicit substances (75). The monthly injectable naltrexone formulation also showed effectiveness in opioid relapse when tested in criminal justice offenders (76). In 2018, the FDA approved Lucemyra™ (lofexidine hydrochloride), the first nonopioid drug used to mitigate opioid withdrawal symptoms (77). The effectiveness of such new nonopioid treatment drugs can be enhanced by incorporating them into long-acting formulations.

Implants and depot injection formulations need to be flexible in terms of dosage, duration of action, and partial agonist/antagonist combinations. The irreversibility of long-acting formulations concerns many patients; thus, it would be beneficial to provide options for shorter durations of action that can be shortened or lengthened as patients make progress. Long-acting formulations may also not be desirable, as they may cause patients to remove their implants if they feel the need to use street drugs (78).

Opioid antagonists block the effects of opioid analgesics and reverse their actions quite effectively. There are three pure opioid antagonists (naloxone, nalmefene, and naltrexone) that bind to opioid receptors with high affinity and without intrinsic activity to block the effects of opioid analgesics, displace agonists, and reverse their actions (79, 80). Naloxone is commonly used as an effective opioid antagonist. Naloxone can reverse opioid-induced respiratory depression (and other opioid effects) caused by overdose (80, 81). Since naloxone has a very short half-life of ∼1 h (80), many patients revert to the overdosed state after the effect of naloxone wears off, necessitating multiple administrations.

Naltrexone has been used routinely, safely, and effectively for the last two decades (82). Extended-release naltrexone and oral naltrexone therapy had higher discontinuation rates than did buprenorphine (83). Naltrexone must be taken daily for long periods of time—months or years. Poor adherence to treatment is a common problem, which can be alleviated by long-acting depot formulations. A study of the mechanism of action of naltrexone as a treatment for opioid dependence found that naltrexone blocks opioid receptors, leading to extinction of drug-taking behavior, and attenuates cravings for opioids, in particular cue-induced cravings (84). This observation explains why patients rarely try to override the blockade by naltrexone with excess doses of opioids (84). Naltrexone blocks opioid highs and therefore is used mainly to prevent relapse in opioid addiction. This suggests that naltrexone could also be used as a preventative tool for potential opioid addiction.

4.2. Advantages of Long-Acting Naltrexone Depot Formulations

Oral daily administration of 50 mg naltrexone hydrochloride is known to block dependence to various opioid drugs for 24 h (**Figure 3**) (85, 86). The fact that 50 mg of oral naltrexone is effective for 24 h means that the effective naltrexone concentration in the plasma may be lower than 1 ng/mL (**Figure 3**). Naltrexone is known to block all agonist effects, as long as the serum naltrexone concentration is at or above the conventional minimum effective range of ∼1–2 ng/mL (82).

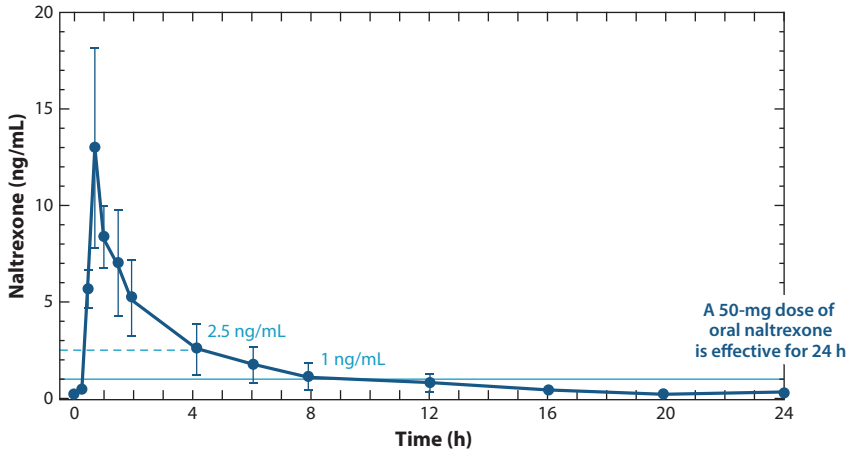

Figure 3

Example profile of plasma naltrexone levels following a 50-mg oral dose in humans (85, 86). The 50-mg oral daily dose has been proven to be clinically effective. The solid blue line represents a naltrexone concentration of 1 ng/mL, achieved 8 h after oral administration, indicating a therapeutically effective level. The dotted blue line represented the target naltrexone concentration in the blood, 2.5 ng/mL.

Naltrexone metabolizes into 6-β-naltrexol, which is also effective. The elimination half-life values for naltrexone and 6-β-naltrexol are approximately 4 h and 13 h, respectively (79, 80, 87). The half-life for naltrexone depicted in **Figure 3**, however, is much shorter than 4 h. The whole-day activity of naltrexone may be dependent on 6-β-naltrexol. A unique advantage of naltrexone is that it does not cause tolerance or dependence, and its discontinuation causes no adverse effects (88). In addition to oral delivery, naltrexone can also be administered by nasal (89) and parenteral (90) routes for immediate response.

While daily oral administration of naltrexone is effective, its use is often accompanied by very low to no adherence to treatment. The retention of subjects in a standardized treatment for oral naltrexone for opioid dependence was only 48.5% at 4 weeks and 9% at 24 weeks (91). This poor adherence issue can be improved through the use of long-acting depot formulations (84, 92, 93). To date, a number of sustained-release preparations of naltrexone have been developed for intramuscular or subcutaneous injection or for surgical insertion (94–96). Development of naltrexone implants and injectable depot formulations began in the mid-1970s, but no formulations became clinically available until 20 years later (82, 86). An initial experimental implant containing 1 g of naltrexone was a large cylinder (9 mm diameter × 20 mm length) that had to be inserted through an incision. It delivered naltrexone for 5–7 weeks. In 2001, naltrexone-containing microparticles made of PLGA were compressed to form pellets with a diameter of 8 mm. Vivitrol®, a PLGA microparticle formulation that delivers 380 mg naltrexone over 1 month, was approved by the FDA for treatment of alcohol abuse in 2006 and for opioid abuse in 2010 (82).

A multicenter, open-label, randomized controlled trial on the comparative effectiveness of self-administered buprenorphine–naloxone sublingual film (Suboxone®) versus monthly intramuscular injections of extended-release naltrexone (Vivitrol) indicated that both medications were equally safe and effective (97). Other studies have shown the efficacy of monthly intramuscular injections of extended-release naltrexone (98). Currently, Vivitrol is the only clinically available formulation, and its efficacy has been well established. However, monthly administration has high attrition rates of 25–36% (93, 99).

4.3. Improvements to Be Made for Long-Acting Naltrexone Depot Formulations

The properties of any future long-acting formulations must be compared with those of Vivitrol. Physicians have been slow to prescribe Vivitrol, despite its clinical effectiveness, for several reasons: high cost of the drug, insufficient infrastructure (e.g., storage facilities, specialized staffing), and lack of access (100). In addition, Vivitrol has the burden of tolerability from repeated high-volume injections (84).

4.3.1. Naltrexone delivery for more than 1 month. Extended naltrexone release has consistently shown better results than oral daily administration (101, 102). The clinical efficacy of Vivitrol, however, has been limited by the requirement of monthly injections, which is associated with high attrition rates after 60 days (93, 99). Thus, a longer-acting (e.g., 2-month) formulation is expected to reduce the rate of relapse and yield more stable patient outcomes over time. Vivitrol is administered as an intramuscular gluteal injection to deliver naltrexone in ~3–4 mL of suspension using a 20-gauge needle (103, 104). Vivitrol comprises 33.7% (380 mg) naltrexone and 66.3% (750 mg) PLGA (103).

Figure 4 presents the pharmacokinetic profile of the 1-month naltrexone formulation. The rationale for making a 2-month formulation using the same amount (380 mg) of naltrexone as in the 1-month formulation is clear. The transient initial peak concentration of naltrexone, occurring approximately 2 h after injection, is followed by the main peak ~2–3 days later (86, 105). Then, naltrexone release slows down over the next 25 days (105, 106). The naltrexone pharmacokinetic profile is generally independent of an individual's weight, creatinine clearance, age, gender, or hepatic function (107).

It is important to understand that the 1-month dose of Vivitrol, 380 mg, is much lower than the cumulative dose of 1-month or oral naltrexone, 1,500 mg. The fact that Vivitrol is effective for 30 days indicates that the minimum therapeutic naltrexone concentration in the blood is approximately 1 ng/mL. In fact, a naltrexone plasma concentration above 1 ng/mL in human volunteers

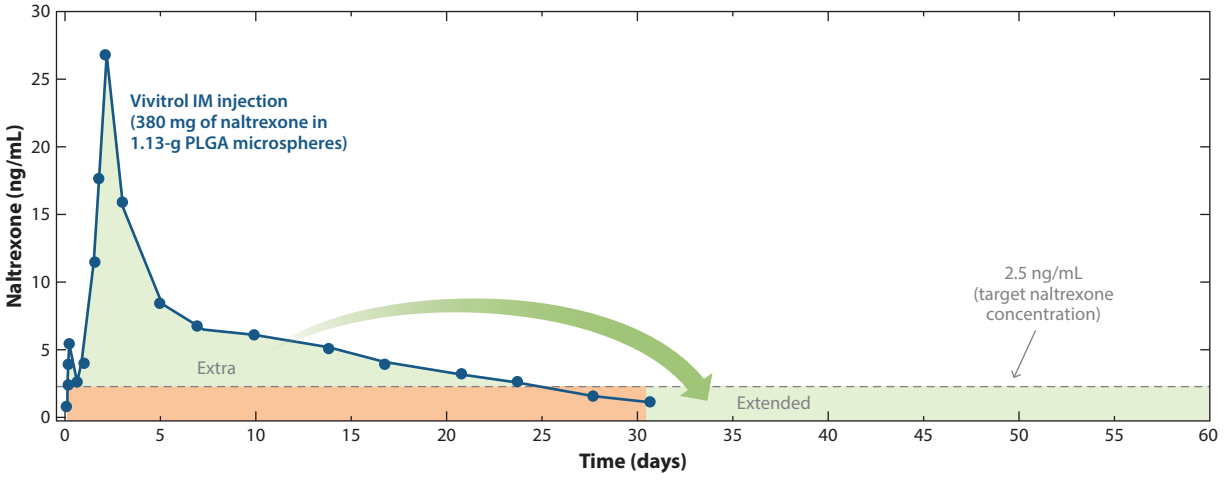

Figure 4

Mean steady-state naltrexone concentration following a single monthly Vivitrol (380-mg dose) intramuscular (IM) injection during the first 30 days (*dark blue circles*) (105, 106). Extra naltrexone (*green shaded area*) can be used to extend the efficacy for another month. The area under the curve (AUC) is exactly half of the total AUC for the 1-month Vivitrol injection. Abbreviation: PLGA, poly(lactide-*co*-glycolide).

who received a single subcutaneous injection of 206 mg of sustained-release naltrexone was effective in reducing the frequency of heavy drinking (108). The naltrexone concentration reaches 1 ng/mL 8 h after oral administration, indicating a therapeutically effective level (**Figure 3**).

Serum naltrexone levels of 2.8 ng/mL were sufficient to block doses of pure diamorphine as high as 500 mg in two patients (109), levels of 2.4 ng/mL completely antagonized 25 mg of heroin (110), and levels of 1–2 ng/mL are sufficient to offer protection from fatal opioid overdose (111, 112). If the target naltrexone concentration in the blood is set to 2.5 ng/mL (**Figure 3**), well above the minimum effective concentration, the excess naltrexone released during the first 20 days or so (**Figure 4**) can be used to extend the duration of naltrexone from 1 month to 2 months. In fact, the area under the curve (AUC) shown in **Figure 4** is exactly half of the total AUC for 1-month Vivitrol; thus, a 2-month formulation with the same total naltrexone dose is feasible. The only question is how one can formulate PLGA microparticles to replace the initial burst release with steady-state release lasting for 2 months. To do so, better-engineered formulations of PLGA microparticles or development of new biomedical devices will be necessary.

4.3.2. Naltrexone formulation with lower cost. The efficacy of Vivitrol is well established, but its clinical application has been slow for several reasons, such as a comparatively complex and time-consuming special ordering process, an hourlong preparation and injection process, and a high cost of approximately $1,200 per monthly dose plus physician and pharmacist fees (113). This price tag is 100 times higher than that of generic oral naltrexone, which costs an average of $11 a month (114). Many patients cannot afford it, and most insurance plans do not cover it. Even for patients with health insurance, deep-muscle Vivitrol injection is treated as a medical procedure, requiring patients to pay their medical deductible first (113). While the cost of Vivitrol may be prohibitive, it is important to note that health care utilization studies have found that use of this drug for the treatment of opioid dependence is associated with fewer hospitalizations than for patients receiving oral opioid dependence therapy, and total health care costs for Vivitrol are similar to those for oral naltrexone or buprenorphine and 49% lower than those for methadone (115, 116).

4.3.3. Naltrexone formulation with less injection pain. Vivitrol is a 4-mL suspension of PLGA microparticles in an aqueous vehicle administered as an intramuscular gluteal injection using a 20-gauge needle (103, 104). The 20-gauge needle (with an outer diameter of 0.902 mm and an inner diameter of 0.584 mm) is necessary due to the microparticles' large size (117). If the size of PLGA microparticles can be reduced to less than 100 μm, a smaller-diameter (e.g., 23- to 25-gauge) needle could be used, which would cause only minimal pain. Such a change in microparticle size could affect the drug release kinetics; therefore, the size change would have to take this factor into account.

5. BIOMEDICAL DEVICES FOR OPIOID ADDICTION TREATMENT

Two of the main adverse effects associated with μ-opioid receptor analgesics are a reduction in respiratory rate and a decrease in air flow (118). The respiratory rate can be significantly reduced even at mild therapeutic dosages and severely depressed with higher doses, leading to respiratory failure. The severity of respiratory depression depends on the type and dose of the opioid (119). For powerful and fast-acting opioids, such as fentanyl, an abuser loses consciousness very quickly, leaving no time to call emergency responders. Users prone to overdose could be pre-equipped with a device that can continually monitor respiration and inform emergency responders if the

respiratory rate becomes dangerously low. Ideally, such a device would not only sense respiration but also deliver a dose of naloxone to counteract the overdosed opioid. Despite the life-saving potential of such devices, none are currently available.

Recently, the FDA launched an innovation challenge to encourage the development of medical devices for detection, treatment, and prevention of addiction, as well as for dealing with diversion and pain treatment (120). The initiative includes diagnostics that can identify patients at increased risk of addiction, treatments for pain without the use of opioid analgesics, and treatments for OUD or symptoms of opioid withdrawal. Biomedical devices, such as brain and spinal cord stimulators to relieve pain and reduce the need to use opioid drugs, can also be used to help reduce the symptoms of opioid withdrawal.

Devices such as implantable drug delivery pumps can be developed and used specifically to deliver opioid-based therapeutics for pain management. Unfortunately, issues can arise with these engineered biomedical devices; the Medtronic SynchroMed™ II and SynchroMed EL are recent examples. These devices were recalled (FDA Class I) due to a software problem that may cause unintended delivery of drugs during a priming bolus procedure (121). The potential bolus dose may lead to serious injury or death. In 2013, Medtronic notified physicians of four potential defects with the pumps, and 14 deaths were associated with SynchroMed (122). While these devices can deliver precise amounts of therapeutics to the intrathecal or epidural space with significantly smaller opioid doses, which may be associated with fewer side effects, they still have potential drawbacks and risks associated with usage. Implantation of these devices requires a surgical procedure, associated with potential surgical complications such as postop infections, errors during the installation/refilling of medication (e.g., injecting into surrounding tissues instead of the pump reservoir) resulting in catastrophic consequences, and finally, potential catheter failures such as fractures or defects that may result in medication flowing out of the defect and the loss of any or most of the therapeutic benefit. Although overall they are reliable, these types of devices require ongoing management and patient care decisions. Future devices should obtain physiological feedback, through the use of physiological sensors or biosensors, to confirm the desired therapeutic effect from drug release, and any effort to make these devices less invasive would greatly benefit patients.

Biomedical devices can also be developed to deliver antiopioid drugs. Naloxone has been used effectively in reversing opioid overdose. For overdosed patients, naloxone is used as an injectable or nasal spray. A prefilled autoinjectable naloxone device (Evzio®) makes it easy to quickly administer naloxone into a patient's outer thigh. Nasal spray (Narcan®) is also available. Both are effective but expensive. Narcan costs approximately $150 for two nasal-spray doses, and a two-dose Evzio package is priced at $4,500 (123). Engineers can make these devices robust and lower cost, such that the naloxone formulation is readily available for whoever needs it at any time. Such devices must also be amenable for use by patients' friends and family members without thorough training.

Other potential biomedical devices could be worn by recovering addicts during treatment. Transbuccal administration of naltrexone by an electronically controlled intraoral device for effective blood concentration of naltrexone is under development (124). BuTrans® is a transdermal buprenorphine patch that is used during acute detoxification (31). Similar devices could be developed for potential and recovering addicts to wear at all times so that their respiration can be monitored continuously, triggering the delivery of naloxone or naltrexone as soon as necessary. The success of such devices depends on many factors, particularly the cost of the device. The cost must be low enough for widespread distribution.

Biomedical devices can be developed to help treat opioid withdrawal symptoms without the use of antiopioids. The FDA has approved several biomedical devices that are designed to help patients who are suffering from opioid withdrawal: NSS-2 Bridge® in 2017 and Drug Relief® in 2018. NSS-2 Bridge is a brain-stimulating device that treats symptoms such as joint pain, anxiety,

stomach aches, and insomnia. It is worn behind the ear to stimulate nerves in the brain and spinal cord with four electrodes (125). Drug Relief works in a similar way. It is a wearable auricular neurostimulation device placed behind the ear. Tiny needles inserted in the ear send electrical pulses to alleviate opiate cravings (126). The nerve-field stimulation lasts over 5 days at a time to stabilize patients before treatment with antiopioid drugs such as naltrexone.

6. OPIOID VACCINE

Currently, OUD is treated by opioid replacement therapy utilizing methadone or buprenorphine to reduce withdrawal symptoms or by administration of opioid antagonists such as naloxone and naltrexone. As an alternative, vaccination has been explored for treating substance-use disorders since the early 1970s (127). Vaccination is a promising strategy to promote cessation of opioid abuse and to prevent relapse and potential overdose. In the early 1970s, a morphine vaccine was tested in a single rhesus monkey, and results showed that antibodies against morphine could block the effects of heroin on the central nervous system (127). Around the same time, methadone emerged as the first-line treatment (128), and naltrexone was found to prevent physical dependence on morphine (129). Since then, the vaccination strategy has been set aside as secondary to pharmacotherapies. Recently, amid the opioid epidemic, however, the vaccination approach is attracting renewed attention. Progress in opioid vaccination has been disappointing, with multiple failures of both cocaine and nicotine vaccines in clinical trials due to poor hapten design, poor adjuvant selection, and poor preclinical development (130). Nevertheless, development of clinically viable opioid vaccines has continued, with vaccines against oxycodone and hydrocodone (131, 132) and heroin (130) under development.

Since the opioid crisis began in the 1990s, there have been several new attempts to create an opioid vaccine. OXY-KLH produces high titers of serum antibodies that bind oxycodone in serum (133). An experimental heroin vaccine induced antibodies that prevented the drug from crossing the blood–brain barrier in mice and rats (134). This vaccine also produced antibodies against other commonly misused opioids, including hydrocodone, oxycodone, hydromorphone, oxymorphone, and codeine. A heroin vaccine has been efficacious in preclinical mouse and nonhuman primate models over a wide range of heroin doses (130), with an optimized formulation protecting against a lethal dose of heroin in the mouse model (135) and against heroin contaminated with fentanyl (136).

7. IMPORTANT ISSUES IN THE OPIOID EPIDEMIC

The widespread use of opioids for pain treatment and the opioid crisis are thought to be based on a one-paragraph letter published in the *New England Journal of Medicine* in 1980 (137), which stated that the risk of addiction to opioids was low when used for chronic pain. This letter was based on no credible evidence (138). Purdue Pharma has been promoting the use of its opioid drug, OxyContin, largely on the basis of that letter. Recently, Purdue Pharma was fined $634.5 million following a guilty plea on federal charges of misleading regulators, doctors, and patients about addiction risk (139). The fine appears large, but it is very little compared with the profit that the company made over the years and the damage it has wrought. The false advertisement arose from one goal: profit. Since the introduction of OxyContin, numerous opioid formulations have become available in various forms. The recent advent of ADFs, which started with the good intention of deterring abuse, has not significantly helped counteract the opioid crisis. The US Drug Enforcement Administration will require pharmaceutical companies to provide a legitimate need for opioids to justify their production (140). This is a good policy to prevent

unnecessary production of opioid formulations that can be diverted for illicit purposes. There is no need to produce more opioid drugs than necessary, and the policy of controlling the annual aggregate production quotas is a good start. The idea of the free market should not be applied to the marketing of opioid drugs, as they can destroy the very fabric of society, the current and the future workforce. More than 10 million full-time workers in the United States are known to have a substance-use disorder, and the moral obligation to address opioid addiction effectively has a strong economic imperative (141).

Pain management for patients remains the highest priority, as the current opioid epidemic calls for stricter prescription of opioid drugs. While there are many avenues to pursue in dealing with the epidemic, scientists and engineers can develop new formulations and devices that can prevent abuse and treat addiction. Development of nonaddictive pain medicine would be ideal, but it is years away. Development of antiopioid vaccines is another potentially useful approach, but it is also far from clinical application. These long-term solutions need continuous research and development, but time is running out.

For now, short-term solutions include the use of current techniques to minimize opioid addiction in the first place and to maximize the treatment and prevention of addiction. A practical problem facing the current treatment is the high cost of formulations delivering antiopioid drugs (e.g., naloxone and naltrexone), with price tags ranging from $150 to more than $4,500. New formulation techniques and engineering solutions, which have advanced significantly during the last decade, can be used to make formulations inexpensive enough to be available for anyone, anytime, anywhere. Funding agencies need to support the development of improved formulations by various companies, as competition is the best way of lowering prices.

While investigators strive to develop improved formulations of naloxone and naltrexone for increased access, they also need to carefully consider these drugs' potential unexpected effects, such as an unintentional increase in opioid abuse due to a reduced risk of death and a lack of reduction in opioid-related mortality due to continued abuse by surviving addicts (142). Thus, finding a way to break through the current opioid epidemic crisis requires more than pharmaceutical and technical solutions. Society's view of opioid abuse has to change as well. Many may feel that the current opioid crisis is "someone else's problem." But with the number of addicts and deaths increasing exponentially, the problem may soon affect everyone. An opioid addict is not merely someone on the street—it could be someone we know. We all should provide our support to help those battling addiction.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

The writing of this review was supported in part by CKD Pharmaceutical Corporation and the Ralph W. and Grace M. Showalter Research Trust Fund.

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Annual Review
of Biomedical
Engineering

Volume 21, 2019

Contents

Errata

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