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The Opioid Epidemic: Crisis and Solutions

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Abstract

The widespread abuse of prescription opioids and a dramatic increase in the availability of illicit opioids have created what is commonly referred to as the opioid epidemic. The magnitude of this epidemic is startling: About 4% of the adult US population misuses prescription opioids, and in 2015, more than 33,000 deaths were attributable to overdose with licit and illicit opioids. Increasing the availability of medication-assisted treatments (such as buprenorphine and naltrexone), the use of abuse-deterrent formulations, and the adoption of US Centers for Disease Control and Prevention prescribing guidelines all constitute short-term approaches to quell this epidemic. However, with more than 125 million Americans suffering from either acute or chronic pain, the development of effective alternatives to opioids, enabled at least in part by a fuller understanding of the neurobiological bases of pain, offers the best long-term solution for controlling and ultimately eradicating this epidemic.

1. SCOPE OF THE EPIDEMIC

Over the past two decades, the United States has seen a dramatic rise in the use and misuse of opioids. Currently the most widely prescribed class of drugs in the United States, an estimated 245 million prescriptions (not including refills) for opioids were dispensed in 2014 (1). The diversion and misuse of prescription opioids, a resurgence in heroin use, and the recent increase in the abuse of illicit, high-potency synthetic opioids such as fentanyl have fueled what is now generally known as the opioid epidemic. Both the magnitude and the manifestations of this epidemic are startling: More than 4% of the adult population (>10 million Americans) currently misuse prescription opioids (2). The most visible manifestation of the opioid epidemic is the rising number of overdose deaths, estimated at more than 33,000 in 2015 (3). Perhaps more disturbing is the dramatic rise in fatalities attributed to heroin and, more recently, fentanyl and its analogs. Overdose deaths due to heroin increased by more than 20% between 2014 and 2015, and overdose deaths attributable to synthetics (other than methadone) such as fentanyl increased by more than 72% (3). Less expensive and often more accessible than prescription opioids, these illicit opioids have now taken center stage as a serious public health concern (4, 5). Observational studies indicate that the great majority of heroin users initially misused prescription opioids. The incidence of heroin users reporting prior nonmedical use of opioids is 19 times higher than that of heroin users who did not report previous nonmedical use (6). This trend represents a significant shift in the pattern of opioid misuse; in the 1960s, more than 80% reported heroin was the first opioid used (7).

The more than 33,000 overdose deaths (3) and the more than 750,000 emergency department visits linked to opioid misuse are highly publicized aspects of this epidemic (8), yet its other aspects, although they receive far less attention, are nonetheless consequential. For example, between 2004 and 2013, there was an almost 4-fold increase (from 7 to 27 per 1,000 admissions) in infant admissions to the neonatal intensive care unit with a diagnosis of neonatal abstinence syndrome (9). Increases in the incidence of infectious diseases such as hepatitis C and HIV can often be traced to injection drug use, much of it fueled with illicit opioids (10, 11). A more detailed discussion of these and other societal burdens imposed by this epidemic, covering criminal activities, the years of worker productivity lost to opioid misuse, and more, is beyond the scope of this review.

2. ORIGINS OF THE EPIDEMIC

If increases in the number of opioid overdose deaths (**Figure 1**) are used as an imperfect means of tracking the opioid epidemic, then its antecedents are rooted in two seemingly unrelated events that occurred in the late 1990s. The first was the American Pain Society's efforts in the mid- to late 1990s to recognize pain as the fifth vital sign. This approach was embraced by both the Veterans Health Administration and the Joint Commission on Accreditation of Healthcare Organizations in 2000. These efforts stress a patient's rights to the assessment and management of pain. A consequence of this well-intentioned approach was to liberalize the prescribing of opioids for chronic, noncancer pain. This increased availability of prescription opioids is one factor contributing to increases in misuse (12). Ironically, driven in large part by growing concerns over the opioid epidemic, the American Medical Association recently recommended that pain be removed as the fifth vital sign (13).

The movement to adopt pain as the fifth vital sign coincided with the approval of a sustained-release formulation of oxycodone (OxyContin®). In its first year on the market (1996), OxyContin had annual sales of approximately $48 million, increasing to $1.1 billion by 2000 (14). By 2010, sales of OxyContin rose to $3.1 billion, representing approximately 30% of the total analgesic market. The dramatic rise in the use of a branded, sustained-release formulation in a market crowded with

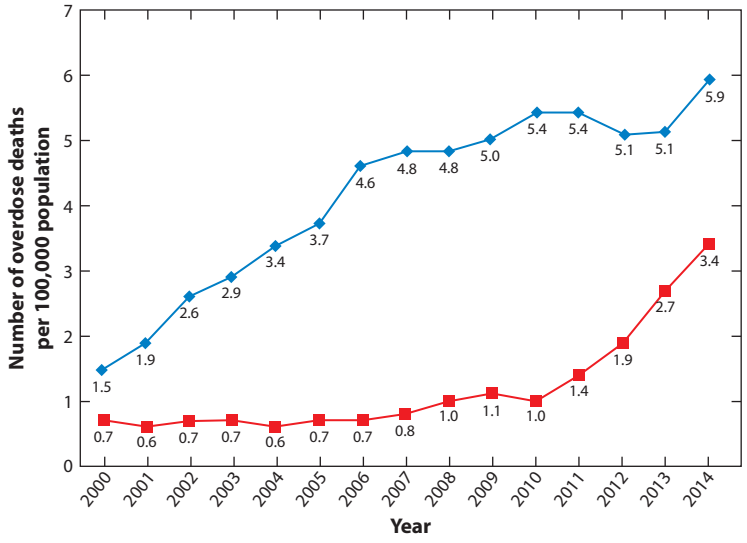

Figure 1

Age-adjusted rates of death related to prescription opioids (*blue diamonds*) and heroin drug poisoning (*red squares*) in the United States, 2000–2014. Modified with permission from Compton et al. (6).

generics is remarkable and merits additional comment. Perhaps fueled by the growing movement to adopt pain as the fifth vital sign, Purdue Pharma marketed and promoted OxyContin aggressively. Between 1997 and 2002, prescriptions for OxyContin to treat noncancer pain increased by about 10-fold. During this period, significant increases were also seen in the prescribing of other opioids for the treatment of noncancer pain. For example, when expressed on the basis of grams consumed/100,000 population, increases of 226%, 73%, and 402% were reported in the use of fentanyl, morphine, and oxycodone (including OxyContin), respectively (14). Although several studies demonstrated that immediate-release oxycodone administered four times daily exhibited similar efficacy and safety to OxyContin administered every 12 h (15, 16), by 2001, OxyContin had become the most frequently prescribed branded opioid for treating moderate to severe pain (14). In 2000, the highest marketed dose of OxyContin was increased from 80 mg to 160 mg; the highest strength was approved specifically for opioid-tolerant patients. The availability of high doses of this potent opioid likely contributed to its popularity for misuse. Although delayed absorption was believed to reduce its abuse liability, the original formulation of OxyContin could be crushed and subsequently either snorted or injected. By 2004, OxyContin had become the most widely abused prescription opioid (17).

Injection and insufflation remain the preferred routes for opioid misuse, resulting in a rapid delivery to the brain with intense rewarding effects (1). In an effort to deter abuse via injection and snorting, OxyContin was reformulated in 2010. The US Food and Drug Administration (FDA) has issued a guidance on the development of abuse-deterrent technologies (18), and at least five marketed opioids now carry abuse-deterrent labeling. Dart et al. (19), tracking fatalities linked to prescription opioids and heroin, suggest that the marked rise in heroin use is associated with the reformulation of OxyContin. Thus, the increased availability of abuse-deterrent formulations has had an unintended consequence: a resurgence in the abuse of less expensive and more available alternatives, including heroin and illicit synthetics such as fentanyl.

3. IMMEDIATE SOLUTIONS

3.1. Abuse-Deterrent Opioid Formulations

First introduced in 2010, multiple extended-release/long-acting commercially available opioids incorporating abuse-deterrent features are now available. These formulations use either physical (e.g., a viscous gel is formed when crushed) or chemical (e.g., a low dose of an opioid antagonist is incorporated in the formulation and released upon crushing) deterrents that discourage misuse by injection and insufflation. However, these products do not deter misuse when taken by the intended (oral) route of administration. Multiple second-generation formulations in various stages of development employ fundamentally different technologies to deter abuse. For example, NKTR-181 is an opioid agonist that has been chemically modified to slow its rate of entry into the central nervous system (20). This compound is currently in Phase III trials with an indication for moderate to severe chronic low back pain (21). NKTR-181 has been reported to have a lower abuse liability than opioids in self-administration studies using both rats and nonhuman primates (20). Another novel approach, albeit at a much earlier stage of development, also employs chemical modification of opioids. The modified opioid is liberated when activated by trypsin in the small intestine. In addition to studies demonstrating that these modified opioids cannot be liberated by in vitro manipulation, studies in dogs indicate that oral administration of multiple doses is not dose proportional, which may limit the potential for both oral abuse and overdose (22). Currently, neither generic nor immediate-release opioids have abuse-deterrent labeling, whereas all abuse-deterrent formulations are branded. This presents an economic dilemma, limiting the use of abuse-deterrent formulations to insurance providers and individuals willing to pay for the significantly higher costs of these formulations.

3.2. Medication-Assisted Therapies

Individuals diagnosed with an opioid use disorder (OUD) have multiple therapeutic options. However, pharmacological approaches to treating OUDs have not fundamentally changed in over 15 years. Methadone, first introduced in the 1960s, remains an integral part of the armamentarium for the treatment of OUDs, with at least 330,000 individuals currently enrolled in maintenance methadone programs, and remains available (other than as an analgesic) only through licensed clinics. Current recommendations for methadone maintenance recommend 12 months of therapy as a minimum, and some individuals stabilized on methadone maintenance appear to benefit for years (23).

Buprenorphine, first introduced as an analgesic more than 40 years ago, was approved as a sublingual tablet for the treatment of OUDs in 2002. Naloxone was subsequently incorporated in the formulation to deter parenteral abuse. The introduction of buprenorphine/naloxone (originally branded as Suboxone®) has both dramatically changed the treatment of OUDs and impacted pharmaceutical industry views on developing medications to treat addictions. Substance use disorders (SUDs) have been traditionally viewed as a small and unattractive market for pharmaceutical investment. However, peak US sales of Suboxone prior to patent expiration were well in excess of $1 billion (24). Multiple generic formulations (sublingual tablets and buccal film) of buprenorphine/naloxone are now available. Based on the 2015 Indivior annual report (25), an estimated more than 1.38 million individuals are prescribed some form of buprenorphine/naloxone to treat OUDs. Despite its apparent commercial success, maintaining patients on buprenorphine/naloxone is challenging. Thus, health outcomes research indicates that 57% of patients leave treatment within 2 months, and the vast majority do not remain in treatment beyond 3 months (C. Heidbreder, personal communication). These data are consistent with a single-site,

14-week prospective study comparing buprenorphine maintenance versus a taper regimen: Almost 90% of the cohort on a buprenorphine taper regimen and 33% of patients maintained on buprenorphine did not complete the trial (26).

Obviating the need for a patient to make one or more daily decisions to take a medication by using long-acting formulations is a simple and effective strategy to increase adherence. The approval of buprenorphine implants is the most recent example of this strategy reduced to practice (27). These subcutaneously placed rods sustain buprenorphine levels for six months but require surgery for both insertion and removal and are currently approved only for patients who are maintained on daily doses of ≤8 mg (28). Multiple buprenorphine products are now in late-stage development, including formulations for both weekly and monthly injections (29, 30) that offer the potential for more dosing flexibility without surgery.

Naltrexone has been approved for the treatment of opioid dependence for more than 30 years. Despite its efficacy in blocking the euphoria and reinforcing effects of opioids, the use of oral naltrexone is limited because of low medication adherence. In 2010, the FDA approved a monthly depot injection of naltrexone (Vivitrol®) for relapse prevention. This approval was based on a double-blind, placebo-controlled trial of 250 detoxified patients diagnosed with opioid dependence who had been detoxified for at least 7 days (31). This multisite trial was conducted in Russia, where agonist therapy is not currently permitted. Patients were administered injections of either depot naltrexone or placebo monthly for 6 months together with counseling. The primary endpoint was abstinence between study weeks 5–24, as measured by both urine analysis and self-report. Patients in the depot naltrexone cohort had a significantly higher proportion of abstinent weeks (90%) compared to patients in the placebo arm (35%; $P = 0.0002$). Naltrexone also produced a statistically significant ($P = 0.0042$) increase in the median retention time in the study (168 days) compared with placebo injection (96 days).

Depot naltrexone has the potential to be particularly valuable in the criminal justice system, where the majority of incarcerated individuals with a history of OUDs are already abstinent. Thus, only a small percentage of individuals in the criminal justice system receive medication-assisted therapies (MATs) and are at high risk for both relapse and overdose upon release. Consistent with this hypothesis, a recent study (32) compared monthly injections of depot naltrexone to treatment as usual (consisting of brief counseling and referrals to community treatment programs) in community-dwelling, previously incarcerated adults with a history of opioid dependence. This randomized, open-label study was composed of volunteers who expressed a preference to not receive agonist maintenance therapy. During the 24-week treatment phase, volunteers receiving depot naltrexone had a longer median time to relapse (10.5 weeks versus 5.0 weeks; $P < 0.001$), lower relapse rate (defined in this study as ≥10 days of opioid use/28 days) (43% versus 64% of participants; $P < 0.001$), and a higher percentage of negative opioid urine screens (74% versus 56%; $P < 0.001$) compared to the treatment-as-usual arm. There did not appear to be a sustained carryover effect of naltrexone because the rate of opioid-negative urines was identical in both arms (46%) at about 1 year after cessation of treatment. Nonetheless, despite the relatively modest size of this study (~300 volunteers), no overdose events were reported in the cohort that received depot naltrexone for 24 weeks compared with 7 (including several fatal overdoses) in the treatment-as-usual group ($P = 0.02$).

Because depot naltrexone has also been approved to treat alcohol use disorder, estimating the subpopulation of patients currently receiving depot naltrexone for the treatment of OUD is challenging. Nonetheless, the manufacturer estimates that at any point in time, about 20,000 patients are receiving depot naltrexone for OUD, with an average treatment duration of 3–5 months (E. Ehrich, personal communication). Even as a conservative estimate, the number of patients receiving depot naltrexone is small compared to those receiving either methadone or

buprenorphine. Although the monthly cost of depot naltrexone is significantly higher than that of either methadone or buprenorphine, these high costs appear to be more than offset if total health-care costs are considered (33).

A naltrexone implant developed in Russia was reported to deliver medication for up to 2 months. A study of 306 opioid-addicted patients who recently underwent detoxification compared this 1-g implant to both oral naltrexone and placebo using a double-dummy design. Using this design, patients receiving the naltrexone implant also received oral placebo; patients in the oral naltrexone (50-mg) arm also received a dummy (placebo) implant, and patients in the placebo arm received both placebo tablets and a dummy implant. At study end (6 months), 52.9% (54 of 102 patients) receiving the naltrexone implant remained in treatment and relapse-free compared to 15.7% of patients administered oral naltrexone and 10.8% of patients in the placebo arm, respectively (34). These subcutaneous naltrexone implants are surgically implanted but are biodegradable and, unlike the recently approved 6-month buprenorphine implants, do not require removal. It is not known if these implants will eventually be approved by the FDA, but strategies that promise long-term naltrexone therapy merit further testing to provide additional treatment options for patients with a history of OUDs.

Although multiple therapeutic options exist to treat OUDs, based on both the average duration a patient remains in treatment and the risks inherent in administering opioids on a chronic basis, these are imperfect options. However, because both methadone and buprenorphine/naloxone are generic, to be commercially successful, a novel therapy would have to demonstrate a significant advantage in one or more treatment dimensions. Such advantages could include better efficacy in preventing relapse (i.e., sustaining abstinence), ease of administration to achieve a therapeutic goal [that is, facilitate (and maintain) abstinence without the need for either a taper or withdrawal regimen], and/or a better safety profile than current therapies.

3.3. Naloxone Distribution to Treat Opioid Overdose

Parenteral naloxone has been approved to treat opioid overdose for over 45 years, but beginning in the late 1990s, there have been efforts to distribute improvised intranasal naloxone kits and overdose training materials to first responders, including potential bystanders (35). Currently, the majority of morbidity and mortality incidents appear to be accidental overdoses with prescription opioids (36), with dosage the most consistent factor associated with increased risk of overdose, especially with concurrent use of sedative-hypnotics (37). Nonetheless, distribution of these improvised naloxone kits and training on use have been driven by the harm-reduction community and primarily confined to individuals with OUDs and the friends and family of individuals at risk (38). Improvised overdose reversal kits generally consist of 1-2 syringes, each containing 2 ml of naloxone (most often 1 mg/ml; a 0.4 mg/ml strength is also used), and a mucosal atomizing device. One ml is delivered to each nostril; a second dose is recommended if there is no response to the first dose. Both the peer-reviewed (39) and patent (5) literature suggest that administering naloxone with these improvised devices results in plasma concentrations well below those attained using the minimum recommended (0.4 mg) parenteral dose. The optimal volume for intranasal drug delivery is generally considered to be less than 0.2 ml/nostril (40), so a significant amount of naloxone delivered in a volume of 1 ml may be lost by either swallowing or running out of the nostril (39). Moreover, several lots of the mucosal atomizing device were recalled in late 2016 (41) because of complaints that these devices delivered a stream of fluid rather than an atomized plume. Nonetheless, multiple reports (42–44) have described successful reversal of opioid overdose using these improvised devices despite a high error rate in both the assembly and proper intranasal administration, even when individuals received training in the week prior (45).

In 2014, the FDA approved an auto-injector (Evzio®) to reverse overdose. This device delivers an intramuscular dose of 0.4 mg of naloxone (46). The following year, the FDA approved Narcan® nasal spray, a concentrated formulation of naloxone that delivers 4 mg in 0.1 ml (47). This intranasal formulation results in maximum plasma concentrations (C_{max}) approximating a 2-mg intramuscular injection (the highest recommended starting dose of naloxone), with a rapid onset of action (48). In January 2017, the FDA approved a 2-mg dose of this product (49). Although improvised devices continue to be used, especially in the harm-reduction community, these devices may not deliver sufficient naloxone to reverse more potent opioids such as fentanyl (5, 50), and reporting bias may result in underestimating treatment failures (51). The initial recommended parenteral doses of naloxone, which are grounded on hospital-based care, are between 0.4 and 2 mg. Prompted in part by the additional hazards posed by an increased availability of heroin and synthetics such as fentanyl (4, 5), in October 2016, an FDA advisory committee recommended by a narrow margin to increase the minimum standard for exposure provided by naloxone delivery devices. Consistent with this recommendation, the FDA recently approved a 2-mg Evzio autoinjector that delivers a C_{max} approximately 5-fold higher than the original device approved in 2014. Although naloxone products are currently available by prescription only, with the encouragement of the US Department of Health and Human Services (52), all but three states now have some form of legislation that is intended to increase access to naloxone. Moreover, recent US Centers for Disease Control and Prevention (CDC) prescribing guidelines for opioids in chronic pain (53) recommend coprescribing naloxone to patients at increased risk for overdose, such as individuals receiving $\geq$50 morphine mg equivalents per day, when benzodiazepines are prescribed together with opioids, and to patients with a history of overdose.

4. LONGER-TERM, INNOVATIVE APPROACHES

4.1. Biologics

Biologics, including vaccines and monoclonal antibodies, represent a nontraditional approach to the treatment of OUDs (54). Biologics utilize a pharmacokinetic rather than pharmacodynamic approach to therapy; antibodies generated in response to a vaccine, or exogenously administered monoclonal antibodies, bind the abused opioid to reduce (and ideally, prevent) its entry into the central nervous system. In a patient population in which medication adherence is problematic (55, 56), a vaccine or monoclonal antibody allows a patient to make fewer good decisions (in the ideal, a vaccination followed by periodic boosters) to remain in treatment compared to one (or more) decisions daily to remain adherent to a conventional therapy. The specificity of a biologic does not preclude a patient from receiving structurally unrelated molecules as therapy (e.g., a heroin vaccine would not interfere with a traditional MAT such as methadone), nor will it prevent the misuse of either these or other opioids.

The concept of developing an opioid vaccine is not novel; the first description of a vaccine reducing the reinforcing effects of heroin in a nonhuman primate was reported more than 40 years ago (57). There are multiple barriers to developing a highly effective vaccine targeted against an opioid. First, unlike a vaccine targeted at, for example, a bacterial protein, low-molecular-weight molecules such as heroin and oxycodone are not antigenic. Thus, to develop an effective vaccine, the targeted opioid must be chemically modified to enable covalent coupling to a substrate recognized as foreign by the immune system. In addition, the demands placed on a small-molecule vaccine are far greater than those placed on a traditional vaccine from both a temporal and quantitative perspective. For example, intravenous injection of a 40-mg heroin bolus (a dose that would not be lethal in a tolerant individual) represents approximately 6×10^{19} molecules delivered within

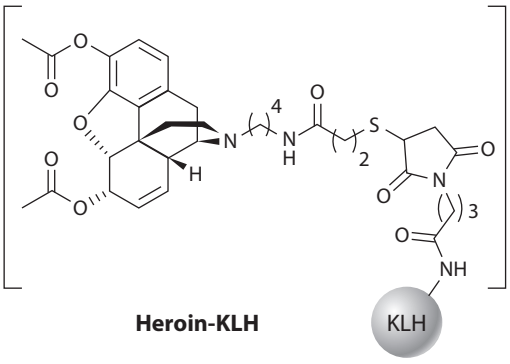

Figure 2

Rendering heroin antigenic through covalent attachment to KLH. Three vaccinations of this immunoconjugate (50 μg) with an alum/CpG adjuvant to mice on days 0, 14, and 28 shifted the antinociceptive potency of heroin between 9.5-fold (hot plate test) and 13.9-fold (tail immersion test) on day 46. From Bremer et al. (58). Abbreviations: CpG, cytosine-guanine oligodeoxynucleotide; KLH, keyhole limpet hemocyanin.

seconds. Antibodies raised to an effective heroin vaccine must be able to bind these molecules within seconds to a few minutes, whereas circulating antibodies raised by a vaccine to an infectious agent (e.g., influenza) would generally encounter orders of magnitude fewer virus particles that can be neutralized over a time frame of minutes to hours.

Design of an effective heroin vaccine is further complicated by its rapid metabolism to 6-acetylmorphine and morphine. Vaccine design strategies include modification of the heroin molecule at the bridehead nitrogen and linking this to keyhole limpet hemocyanin through thiol-maleimide coupling (**Figure 2**). The vaccine generated using this strategy shifted the analgesic ED_{50} of heroin by approximately 10-fold in mice immunized three times over a 28-day period (58). Matyas et al. (59) have approached the rapid metabolism of heroin by replacing the labile acetyl moieties on the 3 and 6 positions with more stable acetamide moieties. This heroin analog is then linked to tetanus toxoid through the bridgehead nitrogen. Traditional vaccines have used alum as an adjuvant for almost 100 years, but both heroin vaccines described here supplement alum with novel adjuvants (a potent TLR9 agonist and liposomes containing monophosphoryl lipid A, respectively) that result in higher antibody titers compared to alum. Very recently, Bremer et al. (60) described a fentanyl vaccine designed using the same basic principles described by this group to design a heroin vaccine (58). This vaccine, administered three times to mice over a 28-day period, produced significant reductions (up to 33-fold) in the analgesic potency of fentanyl and several fentanyl analogs. The mutability of the fentanyl molecule presents an additional challenge for the development of a commercial vaccine. Another recent report (61) described vaccines directed against oxycodone and hydrocodone. These vaccines produced significant (6–10-fold) reductions in the potency of oxycodone and hydrocodone, respectively, in both the hot plate and tail flick tests. Both vaccines also dramatically increased the serum half-lives of these opioids (consistent with high-affinity binding of hydrocodone and oxycodone to the antibodies generated by these vaccines) and increased the survival rate of mice challenged with subcutaneous doses of oxycodone and hydrocodone, respectively.

The opioid epidemic has engendered both interest and federal funding for vaccine development. Although preclinical studies are encouraging, no antiopioid vaccines have reached the clinic. This is a dynamic epidemic, with shifting preferences and availabilities of illicit opioids. This poses an additional commercial risk because of the potential for researchers to develop a vaccine

directed against an opioid that may no longer be a focus of misuse by the time the vaccine reaches the market. Moreover, clinical experience with other small-molecule (cocaine and nicotine) vaccines has shown that multiple immunizations administered over several months were necessary to produce meaningful antibody titers (62, 63). This lag in onset, the apparent requirement for multiple immunizations, and a changing array of target molecules present significant challenges to private-sector development.

4.2. Small Molecules

Preclinical studies indicate multiple, nonopioidergic approaches to treating OUDs are also effective in reducing the rewarding effects and cue reactivity to other abused substances such as cocaine and tobacco (64, 65). These approaches target circuits that play critical roles in cognition, motivation, and drug reward (64–66). For example, D3 antagonists, long viewed as potential medications both to treat cocaine use disorder (64) and for smoking cessation (67), attenuate heroin self-administration and block both the acquisition and expression of conditioned place preference induced by heroin (68). Similarly, lorcaserin, a 5-hydroxytryptamine type 2c agonist approved to treat obesity, attenuates nicotine self-administration and relapse in multiple animal models (66) and, in a Phase II study, was recently reported to produce a dose-dependent abstinence signal in smokers (69). Lorcaserin was recently reported to suppress oxycodone self-administration and cue-induced reinstatement in rats (70) at doses that are effective in blocking nicotine self-administration (66). Additional clinical studies with both classes of molecule are needed to determine if these mechanisms have a place in the treatment of OUDs and, if so, how to create incentives for private-sector investment given the formidable barriers to developing medications to treat SUDs (24, 71).

5. LONGER-TERM, STRATEGIC SOLUTIONS

At the root of the opioid epidemic is what can justifiably be termed the pain epidemic. An estimated more than 125 million American adults suffer from either acute or chronic pain (72). Despite an obvious need and apparent market opportunity for better pain therapeutics, the dramatic rise in opioid abuse intersects a retreat from neuroscience research and development by the pharmaceutical sector (73). Pain therapeutics, often either integrated or closely aligned with neuroscience programs, have been impacted by these reductions. In 2008, the pharmaceutical sector's collective pain portfolio was estimated to comprise in excess of 150 drug candidates in various stages of development (73). However, the exit of many pharmaceutical companies (including Abbot, AstraZeneca, and GlaxoSmithKline) from pain research and development reduced the number of candidates in this pipeline, often diverting these resources to other therapeutic areas advantaged by tools exemplified by animal models with high predictive validity; the means to readily assess target engagement in vivo; and biomarkers that can diagnose and stratify patients for a clinical trial, monitor disease progression, and, ultimately, be used as a surrogate of drug efficacy. Moreover, redeployment of resources to other therapeutic areas has a negative, trickle-down effect on academia and small biotechnology companies, which traditionally look to partners for both expertise and capital to translate novel targets and compounds into products.

Although a comprehensive discussion of the current pain portfolio is beyond the scope of this review, basic research findings over the past two decades have led to the discovery and development of powerful analgesics that appear to lack some of the limiting side effects of prototypic opioids. Studies using both μ opiate receptor antagonists and transgenic mice have provided compelling evidence that μ receptor activation mediates the analgesic as well as the undesirable (tolerance,

respiratory depression, and reduced gastrointestinal motility) effects of opioids (74, 75). These data suggest that increasing the selectivity for μ relative to other (κ, δ) opioid receptors would not result in an analgesic lacking the limiting side effects associated with prototypic opioids such as morphine and oxycodone. This selectivity principle had guided the design of opioid analgesics since the identification of opioid receptors in the 1970s. However, a fuller understanding of the signal transduction pathways associated with G protein–coupled receptors, including μ receptors, led to the demonstration that ligands binding to these receptors can exhibit bias, preferentially signally through distinct intracellular pathways while not coupling to others (76). Multiple lines of evidence indicate that a biased μ receptor ligand (μ receptors signal through both $G_{i/o}$ and β-arrestin pathways) could result in a novel pharmacology. For example, in β-arrestin 2 knockout mice, morphine analgesia was enhanced (77) while constipation and respiratory depression were reduced compared to wild-type animals (78). These findings led to the hypothesis that a ligand preferentially coupling μ opioid receptors to G proteins compared to β-arrestins (that is, a G protein-biased ligand) could mimic the pharmacological profile of morphine observed in β-arrestin 2 knockout mice (79). TRV130 is structurally unrelated to opiates and preferentially couples to G proteins with a higher affinity (EC_{50} = 8 versus 50 nM) and an efficacy only slightly lower than that of morphine (**Figure 3**). In contrast, its efficacy at recruiting β-arrestin 2 is <20% that of morphine. Consistent with findings in β-arrestin 2 knockout mice, TRV130 is a potent and effective analgesic in multiple pain models with far less respiratory depression and gastrointestinal slowing than morphine (79). The effects of TRV130 have now been independently confirmed and extended by Manglik et al. (80), who identified another G protein–biased agonist, PZM21. In contrast to TRV130, PZM21 was an effective analgesic in supraspinal (hot plate)– but not spinal (tail flick)–mediated pain. However, at analgesic doses, PZM21, like TRV130, led to far less respiratory depression than morphine and significantly less constipation than morphine. These authors (80) also noted that unlike morphine, neither TRV130 nor PZM21 produced a significant conditioned place preference, a test often used to predict abuse liability. These latter findings are inconsistent with studies in knockout mice suggesting that a G protein–biased drug would be at least as rewarding as morphine (81, 82). Clearly, a G protein–biased analgesic as effective as morphine with

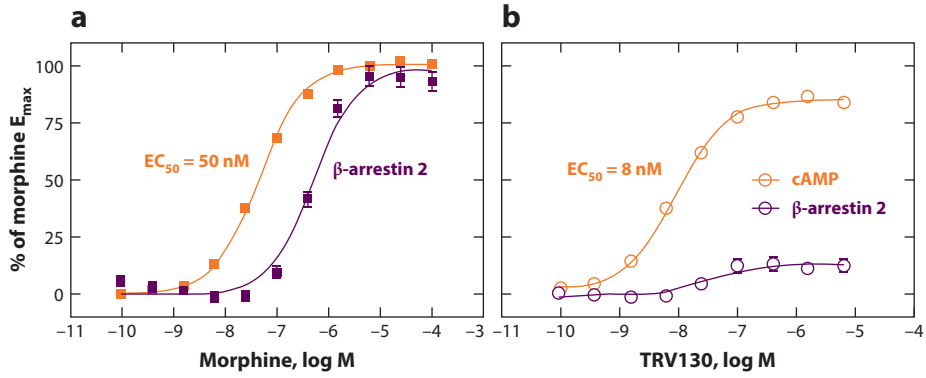

Figure 3

TRV130 is a G protein–biased ligand at human μ opioid receptors. Compared with morphine (*a*), TRV130 (*b*) has similar G protein coupling efficacy (*orange*) with significantly reduced recruitment of β-arrestin 2 (*purple*). These studies were performed in HEK cells expressing human μ opioid receptors. Modified with permission from Dewire et al. (79). Abbreviations: cAMP, cyclic adenosine monophosphate; E_{max}, maximum efficacy compared to morphine; EC_{50}, drug concentration producing 50% of the maximum response.

an improved safety profile, including the potential for reduced tolerance (81) and abuse liability (80), could dramatically alter the course of the opioid epidemic.

Preclinical data demonstrating that TRV130 is a potent analgesic have been confirmed in the clinic. In a randomized, placebo- and active-controlled trial, intravenous administration of TRV130 (2–3 mg every 3 h) provided a profound reduction in pain comparable to morphine (4 mg every 4 h) in patients with moderate to severe pain in the 48 h following bunionectomy (83). The tolerability of TRV130 was similar to that of morphine; TRV130 produced dose-dependent increases in nausea at frequencies comparable to those produced by morphine. In healthy volunteers, TRV130 exhibited statistically significantly smaller reductions in hypercapnia-induced ventilatory drive compared to morphine (84), and in the Viscusi et al. (83) report, TRV130 had a smaller (albeit not statistically significant) effect than morphine in reducing oxygen saturation. These measures can be viewed as surrogates of respiratory depression, which indicates clinical data with TRV130 are consistent with a body of preclinical data demonstrating that G protein–biased ligands have a lower liability for respiratory depression than opioids. The incidence of constipation was low among all groups in this study (83), including patients receiving 4 mg of morphine every 4 h, so the clinical translation of this aspect of ligand bias remains to be confirmed. Based on information on the sponsor's website (**http://www.trevena.com**), TRV130 is currently in Phase III trials; Phase I studies are under way for an orally bioavailable follow-on biased agonist.

Another potentially transformative finding for pain therapeutics is a report that molecules selectively activating truncated 6-transmembrane (6-TM) splice variants of the μ opioid receptor are analgesic but lack the side effects typically associated with opioids, such as respiratory depression and reduced gastrointestinal motility (85). Perhaps most important, the prototypic molecule of this class, the naltrexone derivative iodobenzoylnaltrexamide (IBNtxA), does not appear to produce either physical dependence (no precipitated withdrawal following 10 days of administration) or a conditioned place preference (indicative of reinforcing properties) compared to morphine (85). The analgesic activity of IBNtxA has now been confirmed in a wide variety of acute and chronic (inflammatory and neuropathic) pain models, and its analgesic effects are not manifested in mutant mice that lack exon 11 of the *Oprm1* gene (86); this exon is apparently required for all known 6-TM splice variants. Although they are still in the early days of development, 6-TM–containing opioid receptors represent a new target for pain therapeutics, with a markedly different pharmacological profile of compounds acting at this target.

Generic opioids present a formidable barrier to developing novel analgesics for treating moderate-to-severe acute pain because of both high efficacy and low cost. This profile has been called the "better than the Beatles phenomenon" (87, p. 191). TRV130 will be administered intravenously and used principally in hospitals, competing with generic opioids (such as morphine) for relieving postoperative pain. As a short-term alternative to opioids in the postoperative setting, TRV130 will not have a dramatic impact on reducing the opioid epidemic. However, for the treatment of chronic pain, an analgesic that possesses opioid-like efficacy while lacking one or more of the critical liabilities linked to opioid misuse (including development of tolerance and reinforcing properties) could have a profound, if not transformative, effect on the opioid epidemic. Thus, there is compelling evidence that the incidence of OUDs is related to both dose and duration of administration (88). In a meta-analysis of more than 500,000 patients who had not used opioids in the 6 months prior and with a new diagnosis of any type of chronic noncancer pain, the odds ratio for developing an OUD was 14.9 for patients on chronic (>3 months of use) low-dose opioids and 122.5 for patients on chronic high-dose opioids, respectively. Nonetheless, the evidence for the effectiveness of opioids is not compelling despite their widespread use in the treatment of noncancer chronic pain (1). This is reflected in the National Pain Strategy clinical practice guidelines for managing chronic pain (89) that recommend opioids, albeit with caveats

of insufficient data to guide appropriate patient assessment, selecting the type of opioid, and choosing a dosing strategy. The trend away from using opioids in chronic pain is driven, at least in part, by these risks associated with extended use. This is exemplified in a recent meta-analysis of 229 studies, examining pharmacotherapies for neuropathic pain conditions (including postherpetic neuralgia, peripheral nerve injury, and painful polyneuropathy) (90). Driven principally by concerns of abuse and overdose, opioids are now viewed as third-line therapy (90). Despite number needed to treat (NNT) values of 6–7, monoamine uptake inhibitors and calcium channel blockers were recommended as first-line treatments with a strong endorsement for use. NNT values in this range suggest that for every patient achieving the criterion of pain relief (in these studies, generally a 30–50% reduction in pain scores or a moderate degree of pain relief), 5–6 would receive less (including the possibility of no) benefit. The low efficacy of nonopioid alternatives has also been reported in other pain conditions. For example, NNT values for medications such as milnacipran and pregabalin, approved to treat fibromyalgia, range from 6 to 9 to effect a moderate reduction in pain relief (91, 92).

6. INTEGRATING POLICY AND LONG-TERM SOLUTIONS

Because a very high proportion of current heroin users first misuse prescription opioids (6), formulations that present barriers to misuse should begin to check the opioid epidemic. Policy changes, including recommendations contained in the National Pain Strategy (89), new CDC guidelines (53) informing prescribers on best practices for using opioids in chronic pain, and expanding prescription drug monitoring programs, should further contain the epidemic.

However, if the opioid epidemic is inextricably linked to the pain epidemic, which will assuredly grow as our population ages, then the most effective solution to this problem is accelerating the development of more effective therapeutics. Both the size of the chronic pain market and the relatively low efficacy of currently approved nonopioids make a compelling case for both the need and an economic opportunity to develop effective alternatives, even in the absence of an opioid epidemic.

Novel therapeutics will ultimately emerge from a fuller understanding of pain biology, enabled in part by transformative technologies such as the ability to solve the three-dimensional crystal structure of proteins and perform target interrogation in silico. This was exemplified by the rapid identification of biased μ agonists described by Manglik et al. (80). Adoption of other transformative technologies, including induced pluripotent stem cells (iPSCs) and CRISPR, can result in more efficient target validation through the development of animal models with better translational fidelity and better designed clinical studies made possible by patient selection and stratification. An example of how such technologies may be used in patient selection comes from a rare form of inherited erythromelalgia (IEM). IEM patients experience burning pain sensations in the extremities that can be triggered by either mild heat or increases in body temperature. This chronic pain condition is the result of gain-of-function mutations in the *SCN9A* gene encoding the $Na_v1.7$ sodium channel subtype. In a small clinical trial, an $Na_v1.7$ antagonist (PF-05089771) reduced heat-induced pain in these patients (93). Remarkably, sensory neurons derived from patient iPSC cell lines were able to mimic the hyperexcitability and aberrant responses to heat observed in the clinic, demonstrating the potential for using iPSC cell lines to either stratify or select patients in pain studies. Notably, the discoveries leading to the identification of $Na_v1.7$ as a target for the development of novel analgesics were made over 20 years ago (94). Similarly the concept of biased μ opioid receptor agonism, which led to the discovery and development of compounds such TRV130, stems from research published in the late 1990s (77, 81).

Independent of the benefits accrued by ending the opioid epidemic, the societal costs of pain exceed the annual combined costs of heart disease, diabetes, and cancer (95). If a fuller

understanding of pain biology is key to the development of innovative therapeutics, then investment in both basic and clinical pain research must increase. Pain research represented less than 3% of the US National Institutes of Health (NIH) budget between 2012 and 2015, with no increases projected at least through 2017 (96). Furthermore, when viewed as NIH expenditures per affected person, chronic pain research is funded at a level <10% of that expended on diabetes, <5% of that expended on Alzheimer's disease, and <0.1% of that expended on cancer research (95). Fundamental structural changes, including centralized NIH funding for pain research through a single center or institute and economic incentives (e.g., patent term extension) for developing truly innovative pain therapeutics may, in the long term, be the most effective means of accelerating the development of safer and more effective analgesics and ending the opioid epidemic.

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