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Review

On the front lines of the opioid epidemic: Rescue by naloxone

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ABSTRACT

Naloxone is a specific, high affinity opioid antagonist that has been used to treat suspected or confirmed overdose for more than 40 years. Naloxone use was initially confined to an emergency room setting, but the dramatic rise in opioid overdose events over the past two decades has, with increasing frequency, shifted naloxone use to first responders including police, emergency medical technicians, and the friends and family of overdose victims. The opioids responsible for overdose events have also evolved, from prescription opioids to heroin and most recently, very high potency synthetic opioids such as fentanyl. In 2016, synthetic opioids were linked to more overdose fatalities than either prescription opioids or heroin. In this review, I will discuss the evolution and use of naloxone products by first responders and the development of additional rescue medications in response to the unprecedented dangers posed by synthetic opioids.

1. Overview

The World Health Organization estimated that more than 33 million individuals misused opioids in 2014 (World Drug Report, 2016). Nowhere is this problem more acute than in the United States. Thus, about 4.4% of the adult population (~11.8 million people) misuse (that is, ingest for nonmedical purposes) opioids and based on DSM-V criteria, 2.1 million Americans have a more severe opioid use disorder (OUD) (McCance-Katz, 2018). This public health crisis, often referred to as "the opioid epidemic", continues to draw media attention on an almost daily basis.

While an imperfect barometer of its impact on society, overdose deaths can be viewed as the leading edge of the opioid epidemic. The number of opioid overdose fatalities has increased every year since 2000 (Compton et al., 2016; Skolnick, 2018), and at a much-accelerated rate beginning around 2010. Recent estimates indicate that in 2016, there were more than 42,000 overdose deaths (Hedegaard et al., 2017) in the United States compared to 33,000 fatalities reported the previous year (Rudd et al., 2016). There is no indication that this rate of rise is slowing (Katz, 2017). Moreover, because specific causes of death are very often not identified on death certificates, a recent reanalysis of the Centers for Disease Control (CDC) mortality counts suggests these values systematically underestimate opioid-involved overdose deaths by 20–35% (Ruhm, 2018). Thus, a re-analysis of the 2015 official CDC estimate of 33,091 deaths involving opioids indicates the actual number approached 40,000 (Ruhm, 2018).

Overdose deaths do not provide an adequate representation of the profound societal impact of the opioid epidemic. A detailed description of the multiple, devastating consequences of the opioid epidemic over the past two decades effects is beyond the scope of this review. Nonetheless, some insights can be gleaned by the sheer number of hospital visits associated with opioid use, estimated at over 1.27 million in 2014 (Weiss et al., 2017) as well as the number of infant admissions (estimated at 27 per 1000 admissions) to the neonatal ICU with a diagnosis of neonatal abstinence syndrome (Tolia et al., 2015). The "all in" costs of the opioid epidemic (ranging from lost worker productivity to increased healthcare and criminal justice costs) were estimated at $115 billion in 2017. Based on current use patterns and mortality rates, it will cost another $500 billion by 2020 unless significant measures are taken (Rhyan, 2018). Perhaps most remarkable is *the reduction in overall life expectancy in the U.S. reported in 2015*, with opioid overdose deaths the principal contributor to this decline. (Dowell et al., 2017)

2. Evolution of the opioid epidemic

The patterns of opioid misuse are changing. Examining the nature of these changes is instructive when attempting to understand how the opioid epidemic has evolved. In the mid-late 20th century, the great majority (~80%) of individuals entering treatment programs for substance abuse reported heroin as the first opioid used. At the beginning of 21st century, this pattern had shifted almost 180°, with approximately 75% of heroin users reporting the first opioid used was a prescription drug (Cicero et al., 2014). Multiple studies conducted during the first decade of this millennium are consistent with this rather remarkable shift in initial misuse, away from heroin to prescription opioids (reviewed in Compton et al., 2016). Misuse of prescription

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opioids as the primary driver of the opioid epidemic is further evidenced by a report that the incidence of heroin use is 19-fold higher in individuals with a prior history of nonmedical use of prescription opioids compared to people reporting no previous nonmedical use (Muhuri et al., 2013).

What circumstances led to a dramatic increase in the misuse of prescription opioids over the past two decades? On a superficial level, the rising number of opioids prescribed in the United States (rising between an estimated 85 million in 1994–245 million in 2014) (Volkow and McLellan, 2016) increases the opportunity for diversion and misuse (Compton and Volkow, 2006). However, a more fundamental question is: why did the number of prescriptions for opioids increase by 3-fold during this period? The primary triggers can be traced to two events that occurred in the mid-to-late 1990s: the first was an effort by the American Pain society to recognize pain as the "5th vital sign." This well-intentioned initiative stressed a patient's right to have his/her pain assessed and managed, resulting in a more liberal approach to prescribing opioids for chronic, non-cancer pain conditions.

Coincident with efforts to recognize pain as the 5th vital sign, the FDA approved (1996) a sustained release formulation of oxycodone (OxyContin®). In less than 4 years, Oxycontin® sales rose to over $1 billion. By 2010, sales rose to $3.1 billion, or about 30% of the total analgesic market share. By any measure, this was spectacular, even more so considering this is a well-established market space with highly effective and relatively inexpensive generic competitors. Aggressive marketing and promotion was most certainly a major contributor to its commercial success. Nonetheless, during a 5-year period (1997–2002) during which OxyContin® sales rose about tenfold for the treatment of non-cancer pain, there were also significant increases in the prescribing of other opioids. For example, when expressed as grams consumed/100,000 population, oxycodone (including generics), fentanyl, and morphine use increased by 402%, 226%, and 73%, respectively (Van Zee, 2009). Part of this increase was likely catalyzed by the medical establishment adopting pain as the "5th vital sign". In 2016, driven in large part by the opioid epidemic, the American Medical Association recommended removing pain as the "5th vital sign" (Anson, 2016).

Misuse of prescription opioids generally begins when medications are taken by mouth, but often leads to injection and insufflation in order to speed delivery to the central nervous system, leading to a more intense rewarding ("high") effect (Volkow and McLellan, 2016). In 2010, Oxycontin® was reformulated in order to deter abuse by injection and insufflation, and multiple marketed opioids now incorporate abuse deterrent features (e.g. the medicine will form a gel when crushed; incorporating an opiate antagonist). While overdose deaths due to prescription opioids continue to increase (Fig. 1), 2011 marked the beginning of an upsurge in heroin related fatalities. Because abuse deterrent formulations are less likely to be diverted, this well-intentioned effort may have inadvertently contributed to the rise in heroin associated overdose deaths (Dart et al., 2015; Evans et al., 2018), and beginning in 2013, to a marked rise in the misuse of high potency "synthetics" (non-morphinans) such as fentanyl (Fig. 1).

2.1. The rise of high potency "synthetics"

While overdose deaths due to both prescription opioids and heroin continue to increase, fentanyl and fentanyl analogs are now responsible for more fatalities (> 20,000 in 2016) than any other opioid (Fig. 1). Multiple factors contribute to the dangers posed by these molecules (collectively termed "synthetics"). Unlike both naturally occurring (e.g. morphine) and semi-synthetic opiates (e.g. heroin, oxycodone), synthetics are piperidine-based (Fig. 2), obviating both the need to grow opium poppies and the labor required to collect, harvest and process the opium paste to produce heroin. The chemistry of fentanyl is simple compared to opiates, and this is reflected in its cost: it has been estimated that the cost of a kg of illicit fentanyl is roughly $3500 compared to $65,000 for heroin (Frank and Pollack, 2017). Fentanyl is ~50-fold more potent than heroin (Volkow and Collins, 2017) and ~20-fold less expensive to produce. Advantaged by these economics, drug dealers are incentivized to switch from heroin to synthetics. Most synthetics are imported from China and Mexico (United States Drug Enforcement Administration, 2017), and the potency of these compounds facilitates easy transport: a 40 g tin of fentanyl that can be sent in the mail or slipped in a shirt pocket is equivalent to ~ 1 kg of heroin.

The piperidine-based structure of fentanyl is also highly conducive to derivatization. Dozens of fentanyl analogs have been described in the literature, and the U.S. Drug Enforcement Administration has seized multiple analogs, including 4-fluoroisobutrylfentanyl, 3-methylfentanyl, acrylfentanyl, acetylfentanil, and carfentanil (United States Drug Enforcement Administration, 2017). Typical of the challenges inherent in limiting the availability of this highly mutable class of illicit compounds is acetylfentanyl, a simple fentanyl congener (Fig. 2). First synthesized in the 1960s, this compound is not approved for medical, veterinary, or other obvious industrial use. Acetylfentanyl is a potent opioid that can be made in three steps from readily available materials (Katselou et al., 2016) and has been linked to overdose deaths in the U.S., Europe, and Japan (Katselou et al., 2016). However, because

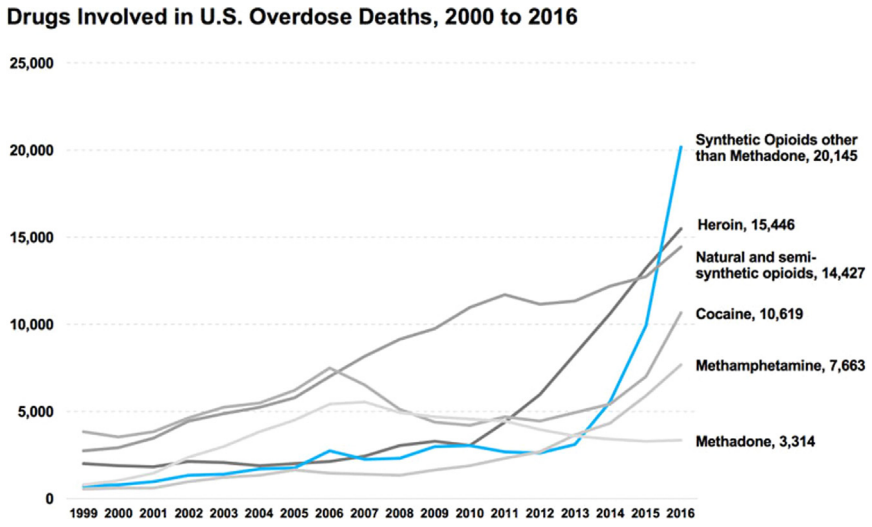

Fig. 1. Opioids involved in U.S. overdose deaths, 2000–2016 (source: National Institute on Drug Abuse website; https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates (Last accessed May 2018).

Fig. 2. The fentanyl molecule is highly mutable. There are multiple loci on the fentanyl molecule which makes it highly amenable to derivatization. Upper panel (left to right): fentanyl, 3-methylthienylfentanyl, acetylfentanyl. Lower panel carfentanil, 3-methylfentanyl, lofentanil.

acetylfentanyl is not generally analyzed in forensic toxicology laboratories, it is difficult to either fully appreciate or assess its contribution to the rising rate of opioid-related fatalities.

Fentanyl and its derivatives are inherently dangerous by dint of their potencies; it is a reasonable assumption that illicit synthetics are not diluted with pharmaceutical accuracy or precision. The lethal dose of fentanyl is ~ 2–3 mg (United States Drug Enforcement Administration, 2017) and based on this estimate, a lethal dose of carfentanil is ~20–30 μg. These lipophilic molecules are absorbed through the skin, mucous membranes, and lungs, which also raises the potential for unintentional exposure to incapacitating, if not lethal doses (United States Drug Enforcement Administration, 2017). Not only are the high potencies of synthetic opioids problematic, but the long half-lives of several derivatives (8–10 h), including fentanyl itself (Kharasch, 2015), further complicates medical management of overdose.

Fentanyl is often mixed with heroin in order to increase the potency of the latter (Zezima, 2018; Yeginsu, 2018). A recent preclinical study (Solis et al., 2017) reported that substituting heroin with 10% fentanyl resulted in a dramatic enhancement of brain hypoxia compared to the intravenous administration of the original quantity of either heroin or fentanyl. This apparent synergism could contribute to the increasing number of overdose deaths linked to fentanyl. Other pharmacodynamic factors may also contribute to the lethal effects of fentanyl. Schmid et al. (2017) recently reported that the "therapeutic window" (expressed as the analgesic ED_{50}/respiratory depression ED_{50}) of fentanyl in mice is 2–4 fold lower than morphine. This lower therapeutic window obtains using different measures of both analgesia (hot plate, tail flick) and respiratory depression (% oxygen saturation, breath rate). Consistent with these data, the authors demonstrated that on binding to μ opioid receptors, fentanyl preferentially signals through βarrestin2, a class of scaffolding protein that modulates subsequent signaling through G proteins (Schmid et al., 2017). It is this property of fentanyl (and perhaps its analogs) to preferentially signal through βarrestin2 that may in part explain its potency in producing respiratory depression, the *sine qua non* of opioid intoxication (Boyer, 2012). Ironically, grounded on studies describing an atypical pharmacological profile (including less respiratory depression) of opioids such as morphine in genetically engineered mice lacking βarrestin2, there are now efforts to develop safer analgesics that bind to opioid receptors but preferentially signal through G proteins. This concept, known as functional selectivity or biased agonism (Rankovic et al., 2016) has led to the clinical evaluation of compounds that exhibit less respiratory depression compared to traditional opiates while maintaining good analgesia (Soergel et al., 2014).

3. Evolution of naloxone as a rescue medication

Naloxone was first approved by the United States Food and Drug Administration (FDA) in 1971 for the treatment of opioid overdose. This high affinity, competitive opioid antagonist is listed as an 'essential medicine' by the World Health Organization. Originally approved for parenteral administration, naloxone was largely confined to an emergency room setting (Boyer, 2012) where dose titration, generally via the intravenous route, can be employed to reverse the clinical signs of opioid intoxication (including respiratory depression and stupor) whilst minimizing symptoms of acute withdrawal in opioid-dependent individuals.

However, with increasing frequency, naloxone use has shifted from the emergency room to first responders such as police, emergency medical technicians, and the friends and family of overdose victims. In April of 2018, the United States Surgeon General took the extraordinary step of issuing an advisory urging "…..*patients currently taking high doses of opioids as prescribed for pain, individuals misusing prescription opioids, individuals using illicit opioids such as heroin or fentanyl, health care practitioners, family and friends of people who have an opioid use disorder,*

and community members who come into contact with people at risk for opioid overdose…" to know how to use naloxone and keep it within reach." (Adams, 2018).

Administering an injection is problematic for many first responders. In efforts largely driven by the harm reduction community, improvised intranasal naloxone "kits" have been distributed and used to reverse opioid overdose for more than two decades. Initially, distribution of these kits and the training required to assemble and use the device was generally limited to individuals with an opioid use disorder and the friends and family of individuals at risk of an overdose (Doe-Simkins et al., 2014). These improvised overdose reversal kits usually consist of 1–2 syringes, each containing 2 ml of naloxone (1 mg/ml), and a mucosal atomizing device. After assembly, 1 ml is delivered to each nostril; a second dose is recommended if there is no response within 3 min of the first dose. Plasma concentrations produced by administering a 2 mg dose (1 mg to each nostril) using an improvised intranasal device fall well below those produced by the minimum (0.4 mg) recommended parenteral dose of naloxone (Morrone, 2016). The recommended volume of fluid delivered to each nostril is significantly higher than the optimum for intranasal delivery (< 0.2 ml/nostril) (Grassin-Delyle et al., 2012), so much of the delivered spray may either run out of the nostril or down the throat. Furthermore, in a human factors usability study of an improvised device, there was a very high error rate associated with assembly and use, even when individuals received training from a nurse prior to a second attempt at assembly and use (Edwards et al., 2015). While there have been multiple reports describing successful rescues with improvised devices, it has been hypothesized that reporting bias could result in an underestimation of treatment failures (Zuckerman et al., 2014; Strang et al., 2016). Moreover, the studies reporting high rescue rates with improvised nasal naloxone kits (Doe-Simkins et al., 2014; Chou et al., 2017; Lynn and Galinkin, 2018) appeared prior to the dramatic increase in the availability and misuse of potent synthetic opioids.

The first FDA product approved (2014) for use by first responders was an auto-injector delivering an IM dose of naloxone (0.4 mg/0.4 ml) (Food & Drug Administration, 2014). A usability study (Edwards et al., 2015) showed that > 90% of subjects could correctly use this device to administer a naloxone injection with no prior training. This dose was approved based on the historical recommended starting doses of naloxone (0.4–2 mg), with data largely derived from hospital-based care. However, the rapid increase in overdose fatalities due to high potency synthetic opioids resulted in an FDA advisory committee recommending an increase in the minimum recommended starting dose of naloxone in 2016 (Food & Drug Administration, 2016) Consistent with this recommendation, the FDA subsequently approved an auto-injector delivering a 2 mg IM dose.

The first intranasal (IN) naloxone product meeting FDA criteria was approved in November 2015 (Food and Drug Administration, 2015). The basis of approval for this product is illustrated in Fig. 3. IN doses of 2, 4, and 8 mg produced maximum plasma concentrations (C_{max}) exceeding an approved (0.4 mg) intramuscular (IM) dose, used as a comparator. Plasma concentrations produced by this concentrated IN formulation (0.1 ml/nostril) were dose proportional between 2 and 8 mg (Krieter et al., 2016). The time to reach maximum plasma concentration (T_{max}) following IN dosing ranged between 20 and 30 min, not significantly different from the IM comparator (Krieter et al., 2016). At the earliest time point studied (2.5 min), plasma naloxone concentrations after IN administration of 2–8 mg were higher than following a 0.4 mg IM dose. The plasma half-life of IN naloxone was ~2 h within this dose range (compared to ~1.3 h following IM injection). In human use studies, > 90% of subjects were able to perform the 2 critical tasks (inserting the device in a nostril and delivering a dose of medication) considered necessary for rescue with no prior training or guidance provided (Krieter et al., 2016). Based on the bioavailability of IN naloxone relative to IM (~50%), the 4 mg dose has a pharmacokinetic profile resembling a 2 mg IM dose. This 4 mg IN dose was the initial product strength approved (Krieter et al., 2016), with both the FDA and several European countries (McDonald et al., 2017) subsequently approving a 2 mg dose.

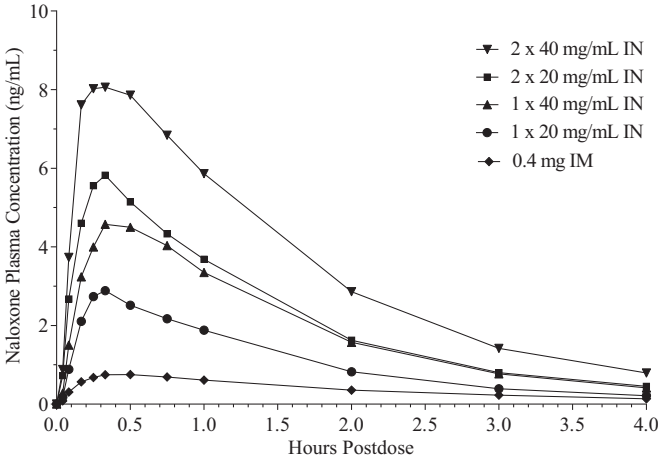

Fig. 3. Plasma concentrations of naloxone following intranasal or intramuscular administration. Intranasal naloxone was administered to healthy volunteers in a volume of 0.1 ml to either one or both nostrils as described in Krieter et al. (2016). This figure is derived from the data in Krieter et al. (2016).

While neither the auto-injector nor nasal spray enables titration of an opioid overdose with the precision of an infusion (Boyer, 2012), both can be quickly and easily administered by individuals with little or no training. These devices also eliminate the potential for transmission of Hepatitis C and HIV (that are often linked to injection drug use) via needle stick injury. While intended for use by non-medically trained personnel, U.S. federal law mandates that naloxone can only be dispensed with a prescription. In order to navigate this apparent paradox, every state currently has some variant of a naloxone access law that allows individuals to obtain naloxone through either a pharmacy or health care provider. Often, this is accomplished by a state (or local) public health official issuing a "standing order" that permits pharmacists to dispense naloxone as a prescription to individuals on request (Substance Abuse and Mental Health Services Administration, 2018).

Each overdose is unique: the ability of a competitive opioid antagonist like naloxone to effect a rescue is dependent upon multiple factors including the type(s) and quantities of opioid(s) involved, the presence of other CNS depressants (alcohol, benzodiazepines) that can potentiate opioid-induced respiratory depression, the interval between overdose and attempted rescue, and the victim's level of tolerance to opioids. While the efficacy of naloxone at reversing the pharmacological actions of opioids is well established (Kaplan et al., 1999; reviewed in Boyer, 2012), field assessment of FDA approved naloxone devices (auto-injector and nasal spray) by first responders are only now emerging. A recent study (Avetian, 2017) describing the efficacy of the 4 mg naloxone nasal spray (NNS) was based on case report data provided by both first-responder and community-based organizations. The challenges obtaining this type of data are illustrated by the authors' attempts to enlist organizations willing to participate in the survey. More than 150 organizations were contacted, but only eight had collected (and were willing to provide) documented, quantitative data on attempted overdose reversals. These data, collected by organizations from a small (7) sampling of states, were obtained (April-August 2016) shortly the after introduction of NNS. Survival outcome was reported for 245/261 cases; successful reversals were reported in 242/245 cases. First responder reports of response times to reversal were subjective. Nonetheless, of the 170 successful rescues reporting time to response, 73.5% (125/170) occurred in ≤ 5 min. The types of opioids (and other CNS depressants) misused were Included in the questionnaire, but this information was not confirmed by subsequent analyses. In cases when the opioid was identified, the great majority of overdose incidents

involved heroin (~95%) with fentanyl reportedly involved in ~5% of cases. However, heroin is often adulterated with synthetics, so this number may not be an accurate reflection of fentanyl-related poisonings. One dose of NNS was reported to produce a reversal in 65% of cases, two doses were required in 32.7% of cases, and about 2.5% of cases required ≥ 3 doses. There were a significant number of cases reporting the use of other CNS depressants: ~28% indicated a concurrent use of benzodiazepines and/or alcohol. Verbatim descriptors (rather than Standard Medical Dictionary for Regulatory Activities [MEDRA] terms) were used to report events following rescue with NNS naloxone. The symptoms of opioid withdrawal following naloxone administration are well described (Kaplan et al., 1999; Boyer, 2012); events consistent with withdrawal were reported in about 38% of cases, including withdrawal (14.3%), nausea and vomiting (14.3%), and irritability or anger (10.2%). Nonetheless, 62.2% of the cases reported 'no event'. This survey of first responder and community-based organizations indicates a high rate of successful rescue with NNS. Very high rescue rates were also reported with improvised intranasal devices (reviewed in Chou et al., 2017; Lynn and Galinkin, 2018) despite the low bioavailability of naloxone administered in large volumes (Morrone, 2016).

The ability of naloxone to reverse the signs of fentanyl-induced narcosis (including respiratory depression) is also well established in both the operating room and emergency department (Glass et al., 1994; Kaplan et al., 1999; Boyer, 2012). However, multiple anecdotal reports suggest that fentanyl may be "too strong" for naloxone (Mattingly, 2017; Blau, 2018). The current National Institute on Drug Abuse (2016) position on this issue states: "Overdoses of fentanyl…may require higher doses [of naloxone] to successfully reverse the overdose".

4. Alternative pharmacotherapies to treat opioid overdose?

Because of the complexity of an opioid overdose and the difficulty obtaining accurate rescue data, the quantity of naloxone that must be administered by first responders to reverse a suspected overdose with a synthetic remains empirical and symptom driven. However, the mismatch between the half-lives of naloxone (~ 2 h; Krieter et al., 2016) and many fentanyl derivatives (e.g. fentanyl, 8–10 h; carfentanil, 7.7 h; sufentanil, 6–9 h) (Kharasch, 2015) can complicate the medical management of overdose. Thus, the short half-life of naloxone can require redosing to prevent relapse if the overdose involves a long-acting opioid. This potential for re-narcotization following an initial reversal with naloxone has been discussed in the peer reviewed literature for over 20 years (Kaplan and Marx, 1993; Wang et al., 1998; Kaplan et al., 1999). Re-narcotization can be life threatening, especially if an overdose victim either refuses transportation to a hospital following rescue or is discharged following a brief emergency room stay; an opioid antagonist with a longer half-life could minimize this potential for relapse following rescue. The need for a longer acting opioid antagonist is perhaps most acute in rural areas that constitute ~72% of U.S. land mass (and contain roughly 15% of the population, over 46 million individuals), where access to an emergency department could be delayed for several hours.

4.1. Other opioid antagonists

Nalmefene, an opioid antagonist structurally related to naltrexone, was approved as an injection to treat opioid overdose (Food and Drug Administration, 1995), and is currently approved in the many countries (outside of the U.S.) to treat alcohol use disorders. Nalmefene was withdrawn from the U.S. market in 2008 due to low sales, with no significant safety issues (Federal Register, 2017). It has a significantly longer half-life (8.2–10.8 h) (Dixon et al., 1986; Food and Drug Administration, 1995;) than naloxone (1–2 h; Krieter et al., 2016; McDonald et al., 2017). Nalmefene was generally administered as an intravenous bolus, but could also be given either intramuscularly (IM) or subcutaneously (SC) if venous access could not be established at parenteral doses between 0.5 and 2 mg (Food and Drug Administration, 1995).

Multiple studies have reported the affinity of nalmefene is higher than naloxone at both native and recombinant μ opioid receptors (Michel et al., 1985; Emmerson et al., 1994; Wentland et al., 2009), but it is unclear if this higher affinity translates to a clinically significant advantage in treating opioid overdose in an emergency room setting (Glass et al., 1994; Kaplan et al., 1999). However, in a preclinical study attempting to model an overdose rescue, Yong et al. (2014) compared the effects of bolus doses of nalmefene and naloxone to reverse carfentanil-induced loss of righting reflex and respiratory depression. Rats were administered 10 μg/kg of carfentanil intravenously and 5 min later, an IM injection of either nalmefene (9.4–150 μg/kg) or naloxone (150 μg/kg). Nalmefene doses as low as 9.4 μg/kg significantly reduced LORR; doses of between 9.4 and 18.8 μg/kg reduced LORR to the same extent as 150 μg/kg of naloxone. A higher dose of carfentanil (20 μg/kg, IV) was used to suppress respiration; nalmefene produced a near complete to complete reversal of respiratory depression (measured by restoration of P_aO_2 and P_aCO_2 to pre-carfentanil levels) at doses between 37.5 and 150 μg/kg within 10 min of injection. Naloxone (150 μg/kg) produced a statistically significant, albeit partial reversal of respiratory depression. Since a single dose of naloxone was used in this study and both compounds are competitive receptor antagonists, these differences may well reflect a higher potency of nalmefene.

Consistent with a higher affinity of nalmefene at μ opioid receptors is its relatively slow in vivo dissociation rate compared to naloxone. In a PET imaging study (Kim et al., 1997) comparing the duration of μ opioid receptor blockade by naloxone and nalmefene in normal volunteers, individuals were dosed with [^{11}C]carfentanil followed by either 2 mg of naloxone or 1 mg of nalmefene administered as an IV bolus. Consistent with previous studies, the plasma half-lives of naloxone and nalmefene were 1.3 and 8.3 h, respectively. However, the half-lives for brain receptor occupancy of naloxone and nalmefene were 2.0 ± 1.6 and 28.7 ± 5.9 h, respectively. This long duration of μ-opioid receptor occupancy by nalmefene was confirmed in a subsequent PET study in normal volunteers using [^{11}C]carfentanil. Oral nalmefene (20 mg) had a plasma half-life of 13.4 h, but a significant occupation (48.4–72%) of brain μ-opioid receptors was detected 50 h later (Ingman et al., 2005).

Multiple opioid antagonists have been described in the peer-reviewed literature, including naltrexone (FDA approved both for treatment of alcohol use disorder and relapse prevention in opioid use disorder) and samidorphan, currently in late stage clinical development (Turncliff et al., 2015). Both of these compounds are high affinity μ opioid receptor antagonists with longer half-lives than naloxone (naltrexone, 3–4 h; (Yuen et al., 1999); samidorphan 7–9 h (Turncliff et al., 2015)) that could potentially be developed to treat opioid overdose. Both PET imaging studies and plasma concentrations relative to naloxone could provide some indication of efficacy, but because the doses required for overdose reversal are not known, the regulatory path for approval to treat opioid overdose could involve pharmacodynamic studies to ensure efficacy, perhaps including field trials.

A high potency, long duration opioid antagonist brings with it the potential for a protracted withdrawal in opioid dependent individuals. There is one report of a double blind, randomized study comparing nalmefene and naloxone in patients admitted to emergency departments (9 centers) with suspected narcotic overdose (Kaplan et al., 1999). In this study, patients were randomized to receive IV doses of nalmefene (1 or 2 mg) or naloxone (2 mg) every 5 min as needed for up to 4 doses, with most patients receiving only one dose of study drug. Post-hoc analysis of patients confirmed as opioid positive demonstrated a rapid and robust reversal of respiratory depression in all treatment arms. No statistically significant differences in withdrawal outcomes were observed among the treatment groups, and no significant overall time-treatment interactions occurred. A similar post-hoc analysis

demonstrated similar proportions of adverse events in opioid-positive patients in all three treatment arms: 10% (3/30) in the 1 mg nalmefene group, 26.1% (6/23) in the 2 mg nalmefene group, and 12.5% (3/24) in the naloxone group. The incidence of adverse events increased at the higher dose of nalmefene, but the overall difference was not significant ($p > 0.27$) among treatment arms (Kaplan et al., 1999). While this setting is different from that envisioned for the use of a nalmefene product by first responders, the overall incidence of adverse events reported here is lower than that with 4 mg NNS based on case report data provided by both first-responder and community-based organizations (Avetian et al., 2017). Withdrawal symptoms (e.g. sweating, muscle cramps, piloerection, vomiting, diarrhea), while distressing and unpleasant, are not life threatening (Boyer, 2012). If saving an overdose victim's life is paramount, then the potential for iatrogenic withdrawal symptoms are medically justified when weighed against the risk of a potentially fatal overdose. Prompted by the rising number of overdose deaths linked to synthetic opioids, NIH leadership has recently called for the development of "…stronger, longer-acting formulations of antagonists" (Volkow and Collins, 2017).

4.2. Non-opioid receptor interventions

As part of an intermediate and longer-term plan to counter opioid-induced respiratory depression, NIH leadership (Volkow and Collins, 2017) has also called for the development of other, non-opioid receptor interventions ranging from AMPA receptor potentiators ("AMPAkines") to phrenic-nerve-stimulation devices. There are multiple respiratory stimulants that have been used in a post-operative setting which could potentially be applied to overdose (Golder et al., 2013). However, it appears that at least one AMPAkine (CX717) is in development to reverse opioid-induced respiratory depression (RespireRx Pharmaceuticals, 2016). AMPAkines are positive allosteric modulators (PAMs) that can affect ion channel deactivation or desensitization (or both), resulting in an enhancement of ion flux through AMPA receptor-gated ion channels. AMPAkine enhancement of channel currents requires the presence of transmitter (glutamate); the specific effects of an AMPAkine on channel kinetics are dependent upon its chemotype and the AMPA receptor subtype affected (reviewed in Alt et al., 2006). AMPAkines are thought to modulate central respiratory drive based on evidence that glutamate-mediated neurotransmission (via AMPA receptors) is critical for the generation of respiratory rhythm and is a component of the excitatory inspiratory drive to respiratory motoneurons (Greer and Ren, 2009). Preclinical studies have demonstrated that AMPAkines reverse respiratory depression produced by both GABAergic drugs (propofol, ethanol, barbiturates) and opioids, including fentanyl (Golder et al., 2013; Ren et al., 2009). Ren et al. (2009) reported CX 717 could both protect against and *reverse* fentanyl-induced respiratory depression in rats without affecting analgesia. A Phase I study in normal volunteers is consistent with the potential for CX 717 to reverse opioid-induced respiratory depression (Oertel et al., 2010). In this study, CX 717 (or placebo) was dosed orally, followed by an analgesic dose (target plasma concentration, 100 ng/ml) of a fentanyl analog (alfentanil) that reduced respiratory frequency by ~25% during placebo administration. CX 717 blocked alfentail-induced reductions in respiratory frequency by about 90% ($p < 0.01$), and also significantly reduced alfentanil-induced reductions in blood oxygenation and reductions in response to hypercapnic challenge.

Development of an AMPAkine for use by first responders (perhaps in combination with or following an opioid antagonist) presents a unique set of challenges. Thus, in contrast to use in either the operating room or emergency department, the drug must be delivered in an easy-to-use format that can be used with little or no training. There are volume constraints with devices (auto-injectors, nasal sprays) currently used by first responders which limit potential drug candidates based on potency and solubility. Perhaps even more challenging are the design of clinical trials and potential regulatory hurdles that could require the demonstration of an effect in the presence of an opioid antagonist. Despite these difficulties, the development of adjunctive agents that could be used with opioid antagonists to increase the probability of a successful rescue are viewed as a high public health priority (Volkow and Collins, 2017) and therefore merit further investigation.

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Declaration of interest

I am a full-time employee of Opiant Pharmaceuticals, Inc. Opiant Pharmaceuticals develops medications to treat substance use disorders, including opioid use disorders, and receives royalty and milestone payments from Adapt Pharma, who market a naloxone nasal spray.

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