Psychopharmacology (2022) 239:2063–2081
https://doi.org/10.1007/s00213-022-06125-5

REVIEW

Treatment of opioid overdose: current approaches and recent advances

Stevie C. Britch[1,2] · **Sharon L. Walsh**[1,2,3,4,5]

Received: 25 September 2021 / Accepted: 18 March 2022 / Published online: 7 April 2022

Abstract

Background The USA has recently entered the third decade of the opioid epidemic. Opioid overdose deaths reached a new record of over 74,000 in a 12-month period ending April 2021. Naloxone is the primary opioid overdose reversal agent, but concern has been raised that naloxone is not efficacious against the pervasive illicit high potency opioids (i.e., fentanyl and fentanyl analogs).

Methods This narrative review provides a brief overview of naloxone, including its history and pharmacology, and the evidence regarding naloxone efficacy against fentanyl and fentanyl analogs. We also highlight current advances in overdose treatments and technologies that have been tested in humans.

Results and conclusions The argument that naloxone is not efficacious against fentanyl and fentanyl analogs rests on case studies, retrospective analyses of community outbreaks, pharmacokinetics, and pharmacodynamics. No well-controlled studies have been conducted to test this argument, and the current literature provides limited evidence to suggest that naloxone is ineffective against fentanyl or fentanyl analog overdose. Rather a central concern for treating fentanyl/fentanyl analog overdose is the rapidity of overdose onset and the narrow window for treatment. It is also difficult to determine if other non-opioid substances are contributing to a drug overdose, for which naloxone is not an effective treatment. Alternative pharmacological approaches that are currently being studied in humans include other opioid receptor antagonists (e.g., nalmefene), respiratory stimulants, and buprenorphine. None of these approaches target polysubstance overdose and only one novel approach (a wearable naloxone delivery device) would address the narrow treatment window.

Keywords Naloxone · Opioid overdose · Overdose reversal · Nalmefene · Fentanyl overdose

Introduction

The opioid epidemic in the USA began in the late 1990s and has recently entered the third decade of increasing opioid overdose deaths. On October 16, 2017, the US federal government declared the opioid epidemic a public health emergency (Hargan 2017). Estimates suggest that the opioid crisis has cost the US economy more than $1 trillion from 2001 to 2017 when considering costs related to productivity, health and child care, family assistance, criminal justice, and education (Altarum 2018; Rhyan 2017). Opioid overdose was responsible for less than 10,000 deaths in 1999 but increased to nearly 50,000 by 2019 (National Institute on Drug Abuse 2021) and opioids accounted for the majority (69.5%) of total drug overdose deaths in 2018 (Hedegaard et al. 2020). Although there was a slight decline in opioid overdose deaths in 2018, in 2019, opioid overdose deaths increased again (from 46,802 in 2018 to 49,860 in 2019) (Hedegaard et al. 2020; National Institute on Drug Abuse 2021). These numbers spiked even further during the COVID-19 pandemic, reaching new all-time highs; data indicate that the 12-month period leading up to April 2021 had more than 100,000 drug overdose deaths and over 74,000 opioid overdose deaths (Ahmad et al. 2021; O'Donnell et al.

✉ Sharon L. Walsh
Sharon.Walsh@uky.edu

[1] Center On Drug and Alcohol Research, University of Kentucky, Lexington, KY 40508, USA

[2] Department of Behavioral Science, University of Kentucky, Lexington, KY 40536, USA

[3] Department of Pharmacology, University of Kentucky, Lexington, KY 40536, USA

[4] Department of Pharmaceutical Sciences, University of Kentucky, Lexington, KY 40536, USA

[5] Department of Psychiatry, University of Kentucky, Lexington, KY 40509, USA

2021). It is likely, were it not for the availability of naloxone, that the number of opioid overdose deaths would be higher, but it is difficult to quantify the number of lives saved by naloxone because of the lack of a unified data system.

The opioid epidemic has exhibited three distinct waves due to (1) prescription opioids, (2) heroin, and (3) fentanyl and fentanyl analogs (F/FAs). Opioid overdose deaths due to prescription opioids climbed steadily from the start of the opioid epidemic in the late 1990s to 2011, marking the first wave of the opioid epidemic (Paulozzi et al. 2011). Opioid prescription volume increased between 1992 and 2011 but has decreased substantially (43%) since 2011 (Aitken and Kleinrock 2019). Still, prescription opioid overdose deaths have remained high; 17,029 people died from a prescription opioid overdose in 2017 and these numbers declined to 14,139 in 2019 (National Institute on Drug Abuse 2021). Overdose deaths involving heroin rose during the second wave; 3036 deaths were attributed to heroin in 2010 and this number increased to a peak of 15,469 deaths in 2016 (National Institute on Drug Abuse 2021; Rudd et al. 2014). Since 2016, there has been a slight decrease in overdose deaths involving heroin (14,029 heroin-involved deaths were reported in 2019) (National Institute on Drug Abuse 2021). The third wave marks perhaps the most rapid increase in opioid overdose deaths. Opioid overdose deaths due to high potency opioids such as F/FAs have spiked more than tenfold since 2013; there were 3105 overdose deaths in 2013 and 31,335 deaths just 5 years later (Hedegaard et al. 2020). Concerns have been raised that intranasal naloxone commonly distributed in communities (i.e., Narcan®) may be insufficient for the treatment of F/FA overdose (France et al. 2021; Kim et al. 2019; Lynn and Galinkin 2018); these concerns arise from (1) case studies and retrospective analyses, (2) pharmacokinetics, and (3) pharmacodynamics. The present narrative literature review discusses the utility of naloxone and the current advances and new technologies that may provide additional treatment options for opioid overdose symptoms. This review also closely assesses the methodological details of the observational reports to evaluate their value for informing the efficacy of naloxone against F/FA overdose. The focus of this review is primarily on case studies, controlled clinical trials, and epidemiological evidence; please see France et al. (2021) for a thorough review of the relevant preclinical literature.

Naloxone

History and pharmacology

In the 1950s, the opioid receptor antagonists nalorphine and levallorphan were used to reverse opioid-induced respiratory depression; however, when administered alone, these drugs could also cause respiratory depression (Foldes et al. 1969; Thomas and Tenney 1955). Naloxone hydrochloride was developed in the 1960s and was the first opioid receptor antagonist capable of reducing opioid-induced respiratory depression without producing opioid receptor agonist effects. The FDA approved naloxone in 1971 (U.S. Food and Drug Administration, NDA 016,636), and it is now the most widely used opioid overdose reversal agent. Naloxone was almost exclusively administered in the hospital setting by trained clinical professionals until 1996 when the Chicago Recovery Alliance program became the first opioid overdose prevention program to distribute naloxone to the community (Any Positive Change 2021).

Naloxone is a semisynthetic, lipophilic, competitive, non-selective opioid receptor antagonist that reverses and blocks opioid-induced effects (e.g., analgesia, respiratory depression). Naloxone can be administered via various routes, the time to maximum plasma concentration (t_{max}) of naloxone is about 2–3 min when administered IV, 10–20 min when administered IM, and 15–30 min when administered IN (Adapt Pharma Operations Limited 2019; McDonald et al. 2018; Ryan and Dunne 2018; Tylleskar et al. 2017). Naloxone has an elimination half-life ($t_{1/2}$) of 1–2 h when administered IN or IM (Adapt Pharma Operations Limited 2019; Tylleskar et al. 2017), while IV fentanyl has an elimination half-life of 4.4–9.7 h (Ahonen et al. 2000; Bentley et al. 1982). The short half-life of naloxone relative to many opioid receptor agonists may lead to the recurrence of respiratory depression during an overdose event and require that multiple doses of naloxone be administered (Carpenter et al. 2020; Fareed et al. 2015; Kitch and Portela 2016; Lyttle et al. 2012; Raja et al. 2017; Rogers et al. 2016; Wilde et al. 2020; Zuckerman et al. 2014) (see Table 2).

While naloxone is generally considered safe and effective, one of the most common risks regarding naloxone administration is precipitation of abrupt onset opioid withdrawal in those who are physically dependent on opioids (Evans et al. 1973; Loimer et al. 1992; Wikler et al. 1953). Higher naloxone doses are associated with a higher incidence of opioid withdrawal symptoms (Purssell et al. 2021), which may have implications for the utility/acceptability of higher dose formulations. More rarely, cardiovascular effects can also be seen in people who inject high doses of opioids or use stimulants (Cuss et al. 1984; Hunter 2005; Lameijer et al. 2014; Merigian 1993; Osterwalder 1996).

One concern about the efficacy of naloxone to treat a real-life overdose event is that multiple intoxicating substances, in addition to opioids, may also be present and may contribute to the overdose event (e.g., stimulants, benzodiazepines, alcohol, etc.). The complex pharmacology of polysubstance overdose can pose serious challenges for overdose treatment. Only one non-opioid overdose reversal agent is available for commonly misused psychoactive drugs; flumazenil is

approved for the reversal of benzodiazepine overdose. However, flumazenil should only be administered in a hospital setting because it can cause potentially serious side effects (e.g., seizures) and can worsen overdose involving both stimulants or antidepressants and benzodiazepines (Burr et al. 1989; Penninga et al. 2016). In a real-life situation, drugs contributing to a polysubstance-related overdose are typically unknown and the risks of naloxone administration are outweighed by the risk of death from respiratory depression due to opioid overdose.

Currently, the FDA has approved labeling for generic naloxone in the clinical setting which states that initial doses of 0.4 to 2 mg of IM naloxone are appropriate and that naloxone administration can be repeated to a maximum dose of 10 mg (Adapt Pharma Operations Limited 2016). Other products have been developed for use by medical and non-medical personnel. Narcan®, developed by Adapt Pharma (acquired by Emergent BioSolutions in 2018), was approved by the FDA in 2015 and is available as a 4 mg/0.1 mL IN spray (Adapt Pharma Operations Limited 2019; Center for Drug Evaluation and Research 2015). Evzio® was manufactured and distributed by Kaléo Inc.; it was originally FDA-approved as a 0.4 mg/0.4 mL IM/SC autoinjector but received approval at a higher dose of 2 mg/0.4 mL in 2016 (Center for Drug Evaluation and Research 2016; Kaleo Inc. 2014; Kalei Inc. 2016). However, this product was removed from the market in 2020 (U.S. Food and Drug Administration 2021c). More recently, the FDA granted approval of Teva Pharmaceutical's generic naloxone 4 mg/0.1 mL IN spray in 2019 (U.S. Food & Drug Administration 2019), which became available in December 2021 despite ongoing litigation with Adapt Pharma. Within that same month, Sandoz launched a generic naloxone 4 mg/0.1 mL IN spray with approval by Emergent BioSolutions (PRNewswire 2021). Unfortunately, the entry of these generic formulations onto the market does not provide the hoped-for increase in access that would accompany substantive financial discounts. Teva Pharmaceutical's generic product is 5% less than the Narcan® wholesale price and Sandoz's product is 6.5% less than Narcan® (Dunleavy 2022). Additionally, at this point, it is not clear that these new generic products will offer a public health discount that is currently available for Narcan®, which reduces the price by ~ 40% (Dunleavy 2022).

The NIH has previously called for higher dose naloxone products due to the rise in opioid overdose deaths (Volkow and Collins 2017). In 2021, the FDA approved two higher dose naloxone products: KLOXXADO™ (Hikma Pharmaceuticals) received FDA approval in April 2021 and became available on the market in August 2021. This product delivers 8 mg IN naloxone, double the highest dose available in the previous products (Hikma Specialty USA Inc. 2021; U.S. Food and Drug Administration 2021a). Some have voiced concerns that an 8 mg IN naloxone spray may be too high and potentially harmful (Hill et al. 2022). ZIMHI™ (Adamis Pharmaceuticals), a product that delivers 5 mg IM or SC naloxone, also received FDA approval in October 2021 and is expected to be available on the market in early 2022 (Global Newswire 2021; U.S. Food and Drug Administration 2021b).

Efficacy against fentanyl and fentanyl analogs

The efficacy of naloxone to reverse opioid-induced respiratory depression has been well-known for over 50 years. Some clinical studies have demonstrated naloxone reversal of respiratory depression induced by morphine, morphine-6-glucuronide (Olofsen et al. 2010), and buprenorphine (van Dorp et al. 2006). A double-blind study of patients in the emergency department for suspected opioid overdose reported that naloxone was a safe and efficacious treatment (Kaplan et al. 1999). Another randomized trial of 172 patients with suspected opioid overdose found that 72.3 and 77.5% of patients responded within 10 min of pre-hospital IN and IM naloxone administration, respectively (Kerr et al. 2009). One study reported that roughly 66% of patients who received naloxone before arriving at the hospital had a Glasgow Coma Score greater than 14 (indicating the patient is fully awake and alert) and that these patients were less likely to require additional medical intervention (Fidacaro et al. 2019).

It is important to understand the efficacy of naloxone as a reversal agent for F/FA overdose given the recent rise in illicit F/FA overdose deaths. We were unable to find any rigorously controlled prospective clinical studies directly examining the dose–response of naloxone for the treatment of illicit F/FA overdose in humans. The FDA has not recommended a minimal naloxone dose for administration by a layperson but has advised that products developed for bystander use should achieve a minimum exposure that is similar to 0.4 mg IM naloxone with a similarly rapid onset (Adapt Pharma Operations Limited 2016).

Morphine, fentanyl, and naloxone share some pharmacokinetic characteristics, but a notable exception is their lipophilicity. The lipophilicity of naloxone (logP = 2.09) is greater than morphine (logP = 0.89–1.07), but lower than fentanyl (logP = 4.28) (National Library of Medicine 2021a; National Library of Medicine 2021b; National Library of Medicine 2021c). The high lipophilicity of fentanyl results in rapid distribution; the distribution half-life of fentanyl has been reported at 1.36–2.5 min after IV administration and ~ 6.5 min after IN administration (Bentley et al. 1982; Foster et al. 2008). Rapid distribution of F/FAs and movement across the blood–brain barrier may contribute to the rapidity of F/FA overdose. In an emergency overdose situation, the window of time that naloxone administration will effectively reverse F/FA overdose

may be very narrow compared to other opioids. In one report 75% of people interviewed ($n = 64$) in Massachusetts who witnessed, received, or administered naloxone due to a fentanyl overdose reported that overdose symptoms occurred within "seconds to minutes" (Somerville et al. 2017). This study also reported that records of those who died from fentanyl overdose indicated that 90% of overdose decedents were pulseless when EMS arrived and 36% of these overdose cases occurred within "seconds to minutes" after drug use (Somerville et al. 2017). Another study found that healthy patients undergoing a surgical procedure experienced changes in their respiratory pattern and heart rate 15–30 s after receiving 0.25–0.8 mg fentanyl IV (Grell et al. 1970). This narrow window of time in which an overdose needs to be identified and treated with naloxone is a significant concern that differs from other commonly misused opioids (e.g., heroin).

Another concern with F/FAs centers around non-morphine-like effects that occur at relatively low doses, specifically the rapid onset of diaphragm and muscle wall rigidity and vocal cord closure, a clinical effect termed "wooden chest syndrome." One clinical study of fentanyl as a supplement to N_2O-O_2 in 584 patients requiring anesthesia reported that a fentanyl dose of 0.25 mg consistently produced chest wall rigidity within 60–90 s, and this effect persisted for 8–15 min (Grell et al. 1970). Other studies have reported fentanyl-induced chest wall rigidity in patients scheduled for open-heart surgery, with no concurrent administration of N_2O. In these studies, 90–100% of patients administered fentanyl (19–50 µg/kg) experienced chest wall rigidity (Comstock et al. 1981; Hill et al. 1981; Kentor et al. 1980). Two studies have also reported that F/FA-induced muscle rigidity occurred in the vocal cords, resulting in vocal cord closure (Bennett et al. 1997; Scamman 1983). Preclinical studies have suggested that naloxone is incapable of treating F/FA-induced muscle rigidity (Miner et al. 2021) and that F/FA-induced muscle rigidity may be at least in part due to activity at noradrenergic receptors in addition to µ-opioid receptors (Lui et al. 1993, 1989, 1990, 1995; Weinger et al. 1988). Patients who receive fentanyl anesthesia also typically receive paralytics with mechanical ventilation for akinesia which conveniently prevents wooden chest syndrome and paralytics are listed as a treatment for fentanyl-induced muscle rigidity in the highlights of prescribing information for fentanyl citrate injection (Akorn Inc. 2019). A number of published reports outline concerns about the ability to treat non-opioid receptor-mediated F/FA-induced muscle rigidity during an overdose event (Pergolizzi et al. 2021; Torralva and Janowsky 2019; Volkow 2021). However, the prevalence of wooden chest syndrome and vocal cord closure in people who are experiencing an overdose, the role it plays in F/FA overdose, and naloxone efficacy against wooden chest syndrome are largely unmeasured at this point.

Studies in patients administered fentanyl anesthesia during surgery have reported that naloxone reversed respiratory depression (Takahashi et al. 2004; Tigerstedt 1977). While these data are intriguing, it is difficult to generalize these results to illicit fentanyl overdose scenarios, which can vary widely with respect to the dose administered and specific fentanyl analog. Some retrospective chart reviews, community outbreaks, and surveys have suggested that the incidence of multiple doses of naloxone per overdose event is increasing, while others suggest no change in naloxone dose administration (Table 1). A CDC report interviewed 64 people in Massachusetts who witnessed, received, or administered naloxone due to a fentanyl overdose and found that 83% of respondents reported more than two doses of naloxone were required (Somerville et al. 2017). Available naloxone kits at that time contained 2 mg/2 ml, IN; therefore, if functioning optimally, two doses of naloxone at that time would be equivalent to one dose of the currently used product, Narcan® (4 mg naloxone); however, it is unknown if the jerry-rigged naloxone atomizer used for IN administration during this time was optimized for full delivery. A prospective analysis of 89 patients admitted to the emergency department from July 2016 to July 2017 due to unintentional opioid overdose reported that the average pre-hospital naloxone dose administered was 5.8 ± 5.0 mg (range: 0–26 mg; median: 4 mg). Additionally, only two patients received naloxone in the emergency department after being treated pre-hospital; however, it is important to note that this study excluded people who were incapable of completing the survey (possibly due to opioid overdose signs and symptoms, e.g., sedation) and that the overdoses captured in this study cannot be attributed to F/FAs as urine toxicology was performed on only 7% of patients (Marco et al. 2018). Several case studies of F/FA overdose have been reported in the literature, but it is difficult to draw conclusions from these reports due to numerous caveats, including inconsistent patient treatment and outcomes (see Table 2).

In contrast, in a retrospective study of emergency department records from a fentanyl outbreak (confirmed via medical examiner findings) in Chicago, IL, from April 2005 to December 2006, the average pre-hospital dose of naloxone was 1.53 mg (range: 0.4–4 mg, 81% via IV route and 11% SL), whereas naloxone administration in the emergency department was an average of 3.36 mg (range: 0.4–12 mg). Again, a direct fentanyl-naloxone relationship cannot be established in this study because no blood or urine screens were tested for fentanyl (Schumann et al. 2008). When records of 957 EMS-transported patients suspected of "uncomplicated" (i.e., without comorbid acute medical conditions) fentanyl overdose were retrospectively analyzed, 47.1% had received naloxone from a bystander and 57.2%

Table 1 Community fentanyl outbreaks, retrospective reports, and surveys

Reference	Population/data source	Opioid	Naloxone	Summary Outcomes	Limitations
Avetian et al. (2018)	261 case reports from eight first-responder or community-based organizations	95.4% heroin, 5.2% fentanyl	4 mg IN	1 dose: 65% 2 doses: 32.7% 3–4 doses: 2.4% 98.8% successful reversal of overdose	Type of opioid is "presumed." No blood or urine confirmation of fentanyl or heroin use
Bell et al. (2019)	1072 interviews of people who had used naloxone provided by the Prevention Point Pittsburg program between 2013 and 2016	Allegheny County Medical Examiner's Office data showed increase in the proportion of drug overdose deaths due to F/FAs in the area	0.4 mg IM naloxone was defined as one dose	One dose of naloxone reversed 56.9% of overdose events, after a second dose of naloxone 92.6% of overdose events were reported as reversed	Reports may be from bystanders. No confirmation that fentanyl was involved in any of the cases in which naloxone was used
Bode et al. (2017)	Opioid overdose records in Jackson Memorial Hospital Emergency Department 2015–2016	Unknown	Vials of naloxone/patient ratio in 2015 was 0.89, and in 2016 was 2.33	Between 2015 and 2016 there was a disproportionate increase in naloxone administration compared to opioid overdose events. It is suggested that this effect is due to increased fentanyl overdose in the area	No blood or urine confirmation of fentanyl in overdose cases. No confirmation of increased fentanyl use in the community
Carpenter et al. (2020)	121 people diagnosed with an opioid overdose by a physician in a single ED and had a positive urine drug screen for opioids	Urine drug screens indicated 28 patients were positive for opioids, 23 positive for fentanyl, and 70 positive for both opioids and fentanyl	Mean IV naloxone dose in those where naloxone was deemed effective: 0.58 mg (opioids only), 0.8 mg (fentanyl only), and 0.8 (opioids and fentanyl)	The mean dose of naloxone necessary to reverse opioid overdose was not statistically different between people who used opioids, fentanyl, or both	It is unclear how much naloxone patients received before arrival to the ED
DiSalvo et al. (2021)	Report on 9 patients in their 30's across two EDs with a history of cocaine use (but no history of opioid use)	Several patients reported insufflation of cocaine, 8 patients had positive serum fentanyl (1.1–5 ng/mL) and the 9th declined testing	7 patients who lost consciousness were treated with 1–8 mg naloxone (mean = 4.2 mg) IV or IN by EMS. No naloxone was given in the ED	All patients had recovered respiration by arrival at the ED. Four patients received > 1 dose of naloxone from EMS. Two patients received > 4 mg of naloxone from EMS	Only two patients received > 4 mg naloxone. Doses of fentanyl and serum fentanyl prior to naloxone are unknown. Time from onset of symptoms to naloxone treatment is unknown
Mahonski et al. (2020)	1139 records of suspected opioid overdose from Poison Control Center in Maryland, 2015–2017	Various suspected: heroin (774 cases), oxycodone (48 cases), methadone (16 cases), fentanyl, morphine, hydrocodone, and buprenorphine (16 cases total)	Average 3.12 mg naloxone	The majority of patients received 2 mg naloxone (62.2%) and another 33.2% received 4 mg naloxone. The total dose of naloxone increased between 2015 and 2017, while the reversal rate decreased	Less than 16 cases were suspected of fentanyl overdose. Includes naloxone doses given to people who expired

Table 1 (continued)

Reference	Population/data source	Opioid	Naloxone	Summary Outcomes	Limitations
Marco et al. (2018)	Survey of adult patients in the ED for opioid overdose between 2016 and 2017	Unknown. Patients reported a history of heroin (75%), cannabis (13%), and methamphetamine (11%) use	Average 5.8 mg pre-hospital naloxone	The range of naloxone was 0–26 mg, but this was self-reported and excluded people who were incapacitated	Excluded people who were incapable of completing the survey (possibly due to opioid overdose signs and symptoms). Overdose cannot be contributed to F/FA urine toxicology was performed on only 7% of patients
Massey et al. (2017)	20 emergency responses due to opioid overdose within 53 h in West Virginia	Reported use of heroin in 14 patients. Toxicology showed opioids in 6 patients (not performed in 12 patients)	Various doses (0–4 mg) and routes of administration (IN, IV, and IM)	All patients recovered with naloxone treatment	Only four patients had confirmed F/FA via a public safety investigation. F/FA confirmation was not conducted in the other 17 patients
Merlin et al. (2017)	2166 records of suspected opioid overdose and naloxone administration between 2014 and 2016, from RescueNet Zoll (Bloomfield, CO; largest EMS service provider for New Jersey)	Unknown	Various	91% of patients recovered after a single dose of IN naloxone, 9% received a second dose, and 2.4% received a third dose	It is unclear what the range of cumulative naloxone doses were or if more than 4 mg naloxone was ever administered
Nielsen et al. (2020)	Ambulance patient care records of illicit opioid use, 2013–2018 in Victoria, Australia	Various, including suspected fentanyl	Various doses and routes of administration	Odds ratios for having an effective response from naloxone did not significantly differ across opioid types	It is unknown if larger doses of naloxone were given to people overdosing on fentanyl vs other opioids
Rowe et al. (2019)	Drug Overdose Prevention and Education Project (DOPE), California Electronic Death Reporting System records, and San Francisco Fire Department Records of EMS, 2014–2015	Community outbreak of "China White" powder sold as heroin, tested by mass spectrometry as fentanyl	Various, unknown doses and routes of administration	During this community fentanyl-outbreak there was an increase in naloxone reversals by community bystanders (DOPE records), but no increase in overdose deaths involving opioids or fentanyl, and no increase in EMS incidents involving naloxone	Doses of naloxone given to people who overdosed on fentanyl vs other opioids is unknown
Schumann et al. (2008)	Chicago-based ED records and Cook County Medical Examiner's Office records, 2005–2006	Heroin and suspected fentanyl	EMS/bystander administration: 1.53 mg naloxone average (range: 0.4–4 mg) ED administration: 3.36 mg naloxone average (range: 0.4–12 mg) Various routes of administration	Average dose of naloxone given is lower than currently available products. Only one of 55 patients received more than 8 mg naloxone in the ED	Unclear if naloxone dose calculations include people who expired No toxicology confirmation of fentanyl for patients seen in the ED

Table 1 (continued)

Reference	Population/data source	Opioid	Naloxone	Summary Outcomes	Limitations
Scheuermeyer et al. (2018)	1009 records of suspected fentanyl overdose from a Vancouver, British Columbia ED, Sept-Dec 2016	Suspected fentanyl	Median 0.4 mg naloxone administered by EMS (unknow route) Unknown dose and route of naloxone in the ED	Naloxone was administered by EMS or bystander in 546/1009 cases. Only 18 patients received naloxone in the ED, and none expired in the ED	No toxicology confirmation of fentanyl for patients; See Santos et al. (2019)
Somerville et al. (2017)	64 interviews of adults in Massachusetts who had witnessed or experienced an opioid overdose in the past 6 months and used illicit opioids in the past 12 months, 2014–2016	Suspected fentanyl	Typically dose in that area was 2 mg IN naloxone	83% reported more than 2 doses of naloxone were required to reverse suspected fentanyl overdose	No toxicological confirmation of fentanyl overdose. It is unclear what doses of naloxone were needed to reverse suspected fentanyl overdose
Tomassoni et al. (2017)	Report on 12 patients across two emergency departments within 6 h for suspected opioid overdose	Suspected fentanyl: 11 patients tested positive for fentanyl; one patient was not tested	Total dose range of 0.5–6 mg 0–6 mg naloxone administered by EMS via various routes of administration 0–2 mg IV naloxone administered	Three patients expired. Two were dead on arrival to the ED, one expired from multiorgan failure 3 days later Naloxone doses were not larger than currently available products	Only 4 of 12 patients received more than 4 mg naloxone, one of which was dead on arrival

Table 2 Case studies on naloxone effects against highly potent opioid receptor agonist overdose

Reference	Patient demographics	Opioid receptor agonist	Naloxone dosing	Summary outcomes	Limitations
Armenian et al. (2017)	41-year-old female with a history of opioid misuse, seen in the emergency department (ED)	13 min post-arrival serum tested positive for fentanyl (15.2 ng/mL), U-47700 (7.6 ng/mL), and hydrocodone (107.6 ng/mL). Patient reported oral ingestion	0.4 mg IV naloxone given two min after arrival to the ED	The patient woke after receiving naloxone and was able to answer questions. A single dose of naloxone was sufficient to reverse overdose symptoms	Other substances were also present in the patient's serum drug screen, including acetaminophen, benzoylecgonine, gabapentin, and sertraline
Bardsley (2019)	32-year-old male with a history of heroin abuse, seen in the ED	Suspected carfentanil	12 mg naloxone total; 4 mg IN naloxone upon arrival to ED and 8 mg IV naloxone (given in 2 mg increments)	Patient recovered and left against medical advice 70 min after resuscitation. Multiple doses of naloxone were required	Patient reported using unknown IV opioids, which they thought to be heroin. No confirmation of F/FA use
	26-year-old female with a history of heroin abuse, seen in the ED	Suspected carfentanil	10 mg naloxone total; 2 mg IN naloxone upon arrival to ED and 8 mg IV naloxone HCL (given in 2 mg increments)	Patient recovered and was discharged after 3 h. Multiple doses of naloxone were required	Patient reported using unknown IV opioids, which they thought to be heroin. No confirmation of F/FA use
Barrueto et al. (2004)	21-year-old female	Oral fentanyl (steeped a 100 µg/h fentanyl patch in hot water and drank the resulting solution)	0.4 mg IV naloxone administered in the ED	Patient recovered with one dose of naloxone	No toxicology confirmation of fentanyl. Unusual ingestion method
Coleman et al. (2009)	33-year-old healthy female in active labor at 38 weeks gestation	45 µg intrathecal sufentanil was given in error (typical dose is 5 µg)	520 µg over 60 min postpartum	Patient complained of pruritus, but no changes in consciousness, respirations, or oxygen saturation occurred	Patient was in active labor, did not experience respiratory depression, and had no history of substance use
Çoruh et al. (2013)	76-year-old male undergoing bronchoscopy and endobronchial transbronchial needle aspiration of paratracheal lymph node	250 µg IV fentanyl	0.2 mg IV naloxone	Patient developed chest wall rigidity and decreased oxygen saturation which was "rapidly" resolved with one dose of naloxone	No history of opioid use disorder
Fareed et al. (2015)	Male patient with a history of opioid use disorder and heroin use	Patient reported relapse with heroin use twice (unknown route of administration). Urine drug screen between uses was fentanyl positive, but not at time of overdose event	The patient received one "dose" of IN =naloxone at home, from bystander, and was momentarily alert. He received a second dose of naloxone (unknown administration route) by EMS, and a third dose of naloxone (unknown dose and route) was administered in the ED	The patient recovered but was admitted to a psychiatric unit for several days post overdose and received treatment for opioid use disorder	It is unclear how much naloxone the patient received. The fentanyl positive urine drug screen occurred prior to the overdose event and it is unclear if the same drug source was used before and after the drug screen; there is no confirmation of fentanyl in the patient's system at the time of overdose

Table 2 (continued)

Reference	Patient demographics	Opioid receptor agonist	Naloxone dosing	Summary outcomes	Limitations
Kitch and Portela (2016)	72-year-old male, seen in the ED	IN heroin	4 mg naloxone total: 2 mg IN administered by law enforcement and two doses of 1 mg IV administered by EMS	Patient was intubated and admitted to the ICU. Extubated after several hours and discharged home 3 days later	No physiological testing to confirm presence of F/FAs. Law enforcement laboratory testing of heroin from an unknown scene showed fentanyl, it is unclear if this test was conducted on the drugs found at the overdose scene of the patients in this report or if the sample was from other heroin overdose events in that community during that time. One of these reports is of IN extended-release oxymorphone
	23-year-old male with a history of heroin use, seen in the ED	IV heroin	4 mg IN total: 2 doses of 2 mg IN naloxone both administered by law enforcement	Patient was alert upon arrival to the ED, observed for 4 h and discharged home	
	21-year-old male, seen in the ED	Heroin (unknown route)	2 mg IN administered by law enforcement	Patient was alert upon arrival to the ED, observed for 4 h and discharged home	
	42 or 43-year-old male history of IV drug use, seen in the ED	IN extended-release oxymorphone (one tablet)	2 mg IN administered by law enforcement	Patient was alert upon arrival to the ED, observed for 5 h and discharged home	
Lyttle et al. (2012)	15-year-old girl seen in the ED, deliberate overdose	6 mg transdermal fentanyl: 5 fentanyl patches at 100 µg/h for 12 h	IM naloxone administered by EMS (unknown dose) In the hospital she received two "doses" of IV naloxone followed by a naloxone infusion of 6 µg/kg/h, which was increased to 12 µg/kg/h for 24 h	After a single dose of naloxone by EMS the patient regained consciousness and had improved respiration, but respiration declined upon arrival to the ED. Naloxone administered in the ED only temporarily improved respiration, until a high dose naloxone infusion was given for 24 h. Patient was discharged after 9-days in a psychiatric unit	Patient had no history of opioid use disorder and overdose was intentional. The fentanyl dose the patient was exposed to was very large, much higher than what is often seen with accidental overdose
Marquardt and Tharratt (1994)	36-year-old male seen in the ED	Patient heated contents of fentanyl patch and inhaled the smoke	2 mg IV Narcan® administered by EMS	Patient had a respiratory rate of 6 breaths/m, after receiving a single dose of naloxone and arriving at the ED respiratory rate was 18 breaths/m. Patient was discharged home same day	Only a single dose of naloxone was needed to reverse fentanyl overdose. No blood analysis was conducted to determine blood fentanyl concentration
Nath et al. (2009)	28-year-old male undergoing laparoscopic nephrectomy	150 µg IV fentanyl	200 µg IV over 5 min	Patient developed pulmonary edema post naloxone administration	The pulmonary edema discovered post-fentanyl and naloxone makes it difficult to determine the efficacy of naloxone to treat fentanyl vs the side effects of naloxone. No history of opioid use disorder

Table 2 (continued)

Reference	Patient demographics	Opioid receptor agonist	Naloxone dosing	Summary outcomes	Limitations
Raheemullah and Andruska (2019)	62-year-old male with chronic hepatitis C and 20 year history of IV heroin use, seen in the ED	Patient reported heroin use. Urine drug screen opioid positive, blood drug screen acrylfentanyl positive	2 mg IN naloxone administered by EMS	Patient's respiratory rate improved from 3 breaths/m to 6 breaths/m after naloxone treatment. Patient was then intubated without further naloxone treatment. Patient was treated in ICU for 12 days	Patient was treated with fentanyl by EMS for intubation and was further sedated with propofol and fentanyl. Treatment of opioid overdose with additional opioids rather than naloxone makes interpretation of naloxone efficacy challenging
Raja et al. (2017)	36-year-old-male with a history of opioid use disorder and IV heroin use, seen in ED	Patient reported 1 g IV heroin mixed with fentanyl across two injections separated by 3.5 h	One dose IN naloxone administered by bystander a second dose IN naloxone administered by first responders from fire department	Patient's consciousness improved and respiratory rate improved from 4 breaths/m to 16 breaths/m several minutes after the second dose of IN naloxone and placement of an oropharyngeal airway. Upon arrival to the ED patient was alert and	There is no confirmation of fentanyl use. Urine drug screen conducted 16 h post-ED admission was negative for all drugs of abuse
Rogers et al. (2016)	36-year-old male, seen in ED	Patient reported using inhaled acetyl fentanyl via e-cigarette vaping device and oral consumption of acetyl fentanyl mixed with alcoholic beverages	6 mg IV naloxone total: 2 mg IV naloxone administered by EMS, 2 doses of 2 mg IV naloxone administered in the ED	Patient's consciousness and respiratory rate improved after the first dose of naloxone. Mental status had declined upon arrival to ED, but recovered with a second dose of naloxone, and fully recovered after a 3rd dose of naloxone	No laboratory confirmation of acetyl fentanyl
Ryan and Meakin (1989)	25-day-old neonate male, weighing 3.9 kg undergoing surgery for pyloric stenosis	26 µg/kg fentanyl was given in error (intended dose was 2 µg/kg)	Bolus 40 µg IV naloxone, followed by increasing doses up to 200 µg IV naloxone. An additional 200 µg IV naloxone bolus was given followed by IV infusion of naloxone at 200 µg/h for 24 h	Patient had minimal reflex responses with "no respiratory effort" and spontaneous breathing started after the first 200 µg dose of naloxone	Patient was a neonate that received, due to error, a high fentanyl dose. Not representative of overdose in an adult with a history of opioid use disorder

Table 2 (continued)

Reference	Patient demographics	Opioid receptor agonist	Naloxone dosing	Summary outcomes	Limitations
Slingsby et al. (2019)	15-month-old female, seen in ED	Father reported possible buprenorphine ingestion, urine toxicology positive for fentanyl but negative for buprenorphine	IV naloxone bolus followed by IV naloxone infusion (unknown doses)	Naloxone improved consciousness and respiration	Fentanyl dose and route of administration is unknown. Not representative of overdose in an adult with a history of opioid use disorder
	7-month-old female, seen in ED	Urine toxicology positive for fentanyl	None	Patient was not given fentanyl because it was initially suspected that her symptoms were due to infections etiology	Patient did not receive naloxone. Patient also tested positive for coronavirus. Not representative of overdose in an adult with a history of opioid use disorder
	26-month-old-female, seen in ED	Urine toxicology positive for fentanyl	Unknown if naloxone was administered	Patients' symptoms resolved and she appeared normal in the ED	Patient did not receive naloxone. Not representative of overdose in an adult with a history of opioid use disorder
	23-month-old female, seen in ED	Urine toxicology was positive for fentanyl	IV naloxone bolus (unknown dose)	Patient improved with naloxone treatment	Not representative of overdose in an adult with a history of opioid use disorder. Dose of naloxone is unknown
Wahl and Gault (2021)	34-year-old male seen in the ED	Reported to have ingested 75 mcg/hr fentanyl patch	IM naloxone (800 mcg) by EMS. 50 mg oral naloxone tablet and 400 mcg IV naloxone was administered in the ED	Patient improved with naloxone treatment	No toxicology confirmation of fentanyl
Wilde et al. (2020)	25-year-old male with a history of opioid use, seen in the ED	IN fentanyl spray reported, but blood analysis negative for fentanyl. Liquid chromatography-high resolution quadrupole time-of-flight mass spectrometry showed the presence of chclopropylfentanyl	0.8 mg naloxone total: two doses of 0.4 mg naloxone administered by ED physician	Patient improved with naloxone treatment	Patient tested positive for multiple psychoactive substances, including cocaine, cannabinoids, and LSD
Zuckerman et al. (2014)	26-year-old-male with a history of opioid abuse	Patient masticated two 25 µg fentanyl patches. Blood toxicology was positive for fentanyl	3.8 mg naloxone total: 2 mg IN naloxone, followed by 1 mg IV naloxone administered by EMS. 0.8 mg IV naloxone (two × 0.4 mg doses) administered in the ED	Naloxone treatment by EMS improved the patient's respiratory rate improved from 6 breaths/m at the scene to 20 breaths/m upon arrival to the ED but declined and required two more naloxone doses. Patient was admitted for one day	Patient did not require more naloxone than what is provided in current products

of patients received naloxone from EMS, with the average naloxone dose administered by EMS being 0.4 mg, parenteral. Additionally, 18.2% of patients received naloxone from both a bystander and EMS. However, no analyses were performed to confirm if F/FAs were involved in the overdose episodes (Scheuermeyer et al. 2018). Finally, one recent retrospective emergency department chart review reported that there was no significant difference in the amount of IV naloxone required to reverse overdose symptoms in 121 patients who had urine drug screens test positive for fentanyl, other opioids, or both fentanyl and other opioids (Carpenter et al. 2020).

Collectively, these various reports from emergency departments and emergency medical services do not support the contention that naloxone is incapable of reversing a F/FA overdose. Interpretation of these reports is limited by a lack of data reported regarding total or incremental naloxone doses, routes of administration, and qualitative or quantitative serum and urine toxicology reports; inclusion of decedents in analysis; and exclusion of patients with severe opioid overdose symptoms (i.e., unable to complete a survey due to overdose symptoms). The doses of naloxone administered in these studies, if reported, are often reported as averages or ranges, which can be misleading if one patient required a substantially higher dose of naloxone than others. When toxicology reports are included, they are often qualitative (i.e., positive/negative within a specified cutoff), which provides little information about the actual concentration of the opioid agonist and its contribution to the overdose event. Additionally, EMS and ED opioid reversal protocols may be locally standardized, which could drive dosing practices, but these are rarely available alongside empirical data. Even when these protocols are reported, the opioid(s) responsible for an overdose may be novel or unknown, omitted from reports, or detected in combination with other drugs. These issues make drawing conclusions about naloxone's ability to reverse F/FA overdose nearly impossible from the extant literature. More research is needed to fully understand the relationship between F/FAs and overdose reversal by naloxone. Overall, there is an absence of quality data supporting the conclusion that currently available naloxone products are ineffective at treating illicit F/FA overdose.

Recent advances in overdose treatments and technologies

Nalmefene

Nalmefene is a μ-opioid receptor antagonist capable of reversing opioid overdose signs and symptoms, including respiratory depression. Revex®, an injectable nalmefene product, was approved by the FDA in 1995 for the reversal of opioid overdose signs and symptoms but was removed from the market by Baxter Healthcare Corporation in 2008 due to "business reasons," not safety or efficacy concerns (Abram 2017). A meta-analysis of eight randomized controlled trials comparing nalmefene (10–100 mg/day for 1–52 weeks) to placebo or active control in patients with substance use or impulse control disorders reported no evidence that nalmefene was associated with increased risk of serious adverse events, suggesting nalmefene is safe (Johansen et al. 2017). However, those taking nalmefene were 3.22 times more likely to withdraw from the study due to unwanted side effects/adverse events, these side effects are outweighed when nalmefene is administered acutely during an emergency overdose event.

Nalmefene has a considerably longer half-life (8–11 h) than naloxone (1–2 h), which may be beneficial against many opioid receptor agonists that also have a longer half-life (Dixon et al. 1987; Gal and Difazio 1986; Glass et al. 1994; Konieczko et al. 1988). Two randomized double-blind studies of six healthy men each reported that nalmefene (2 mg IV or 50 mg oral) pretreatment prevented subjective and respiratory effects for up to 8 h and 48 h, respectively, when challenged with 2 μg/kg of fentanyl (a dose commonly used during surgical procedures and for postoperative pain) (Gal and Difazio 1986; Gal et al. 1986; Prescriber's Digital Reference 2021). One study directly compared naloxone and nalmefene (1, 2, 4, or 8 μg/kg of either drug) reversal of fentanyl (IV infusion to obtain 1.5 ng/mL plasma concentration) and reported both antagonists were equipotent at reversing opioid-induced respiratory depression (Glass et al. 1994). This study also reported that nalmefene clearance was approximately 2.5-fold slower and the elimination half-life nearly two times longer than naloxone (Glass et al. 1994).

Unfortunately, nalmefene has a slow absorption rate when given intranasally; a study in healthy adults reported that IN nalmefene had a T_{max} of 2 h (Krieter et al. 2019). As such, the FDA granted fast-track designation of injectable nalmefene to Purdue Pharma L.P. in 2019 (Purdue Pharma 2019), but no IN products have been approved. Opiant Pharmaceutical is currently developing and testing an IN nalmefene formulation, OPNT003. A recent study by the sponsor reported that dodecyl maltodise, an absorption enhancement agent used in other approved pharmacotherapies (e.g., Tosymra®), significantly improves the bioavailability of IN nalmefene (Krieter et al. 2019). The formulation of dodecyl maltoside + nalmefene had a T_{max} of 15 min, while nalmefene alone had a T_{max} of 2 h. Additionally, the combination of dodecyl maltodise and nalmefene produced maximum plasma concentrations more than double that of nalmefene alone, and at 15 min post-administration the plasma concentration of nalmefene was nearly 12-fold greater in those who received dodecyl maltodise + nalmefene (Krieter et al. 2019).

Taken together, these data suggest that nalmefene is safe and well-tolerated. In contrast to naloxone, the long half-life of nalmefene is similar to or greater than that of many opioid receptor agonists. Although nalmefene alone has poor IN bioavailability, new data suggest a combination formula with dodecyl maltoside may obviate this issue and show promise for a novel opioid overdose reversal agent.

Respiratory stimulants

There is some interest in utilizing non-opioid respiratory stimulants to treat respiratory depression caused by opioid overdose. While this work is largely still in the preclinical stage (for a thorough review of the preclinical literature see Imam et al. 2020), a few clinical reports have examined respiratory stimulants (potassium channel blockers, N-methyl-D-aspartate receptor antagonists, ampakines, and analeptics), albeit with little-to-no evidence of utility during a real-life overdose event. 4-Aminopyridine, a potassium channel blocker, was the first reported to reverse respiratory depression caused by IV fentanyl (Sia and Zandstra 1981). However, 4-aminopyridine can have considerable side effects, including dysesthesias and dizziness (Blight and Henney 2009; Hayes et al. 2003). An analysis of clinical studies examining 4-aminopyridine reported that paranesthesia and dizziness occurred in roughly 34% of people (Jensen et al. 2014). Other side effects reported in this meta-analysis included, among others, nausea and vomiting, anxiety, difficulty walking, abdominal pain, hyperkalemia, and seizures; these side effects could limit the potential utility of 4-aminopyridine during an illicit opioid overdose event. More recently, studies reported that IV GAL021 (Galleon Pharmaceuticals Corp.), a calcium-activated potassium channel blocker was able to reverse alfentanil-induced respiratory depression, with few adverse events (Roozekrans et al. 2015, 2014). However, GAL021 may not be ideal during an opioid overdose event due to its short half-life and a decrease/ceiling in its efficacy to treat opioid-induced respiratory depression (Roozekrans et al. 2015). Taken together, these studies do not provide strong support for the use of potassium channel blockers for the treatment of opioid overdose. Ampakines have also been investigated as opioid overdose reversal agents; RespireRx Pharmaceuticals Inc. pursued the development of ampakines after one double-blind, placebo-controlled, crossover study in 16 men reported that pretreatment with the ampakine CX717 partially *prevented* alfentanil-induced respiratory depression (Oertel et al. 2010). In a phase 2a clinical trial a similar ampakine, CX1739, antagonized respiratory depression induced by a remifentanil infusion but did not prevent respiratory depression when a bolus of remifentanil was administered (RespireRX Pharmaceuticals Inc. 2016), suggesting that CX1793 would not be a preferred treatment for opioid overdose. A single double-blind, placebo-controlled study reported that doxapram caused small reductions in alfentanil-induced respiratory depression (Roozekrans et al. 2017). Finally, the N-methyl-D-aspartate receptor antagonist esketamine improved remifentanil-induced respiratory depression in one double-blind, placebo-controlled study (Jonkman et al. 2018). However, esketamine may not be ideal as an overdose treatment due to its documented psychomimetic effects (Jonkman et al. 2018). While these developments with respiratory stimulants to treat opioid overdose are intriguing, overall clinical evidence in support of respiratory stimulants as an opioid overdose treatment is lacking. Many of the stimulants examined thus far have substantial side effects that limit their ability to be used in the field. Additionally, studies have only used IV administration of respiratory stimulants, a route that is unlikely to be used by bystanders to an overdose event. Finally, it is unclear if respiratory stimulants will interact with other substances that may contribute to the overdose event (e.g., cocaine, benzodiazepines, alcohol, etc.) or have sufficient activity to reverse the effects of supratherapeutic opioid doses typically seen in overdose.

Buprenorphine

Buprenorphine is a μ-opioid receptor partial agonist that is currently approved by the FDA for the treatment of opioid use disorder and as an analgesic. There are three reports of bystanders using buprenorphine to reverse opioid overdoses when naloxone was not readily available. One report indicated that a bystander used an IV dose of a transmucosal formulation (8 mg buprenorphine/2 mg naloxone) to reverse a heroin overdose, but the overdose reversal may be attributed to naloxone in this case (Yokell et al. 2012). However, in another case report, a bystander reported that he successfully used sublingual buprenorphine/naloxone on a person experiencing a heroin overdose (Welsh et al. 2008). Naloxone has poor bioavailability when administered sublingually or orally, due to a large first-pass effect, suggesting that buprenorphine was the primary reversal agent in this case (Smith et al. 2012). Finally, a man was administered buprenorphine in the emergency department for an overdose involving several substances (150 mg methadone syrup, 200 mg fluoxetine, and 20 mg clonazepam) (Zamani and Hassanian-Moghaddam 2017). Although the patient responded to buprenorphine, the development of apnea led medical providers to switch to naloxone for the remainder of the treatment. In addition to these case reports, a phase 2 open-label controlled clinical trial compared buprenorphine and naloxone treatment of methadone overdose (Zamani et al. 2020). This study reported that several patients required high doses and prolonged infusions of naloxone to reverse methadone-induced sedation, resulting in high

rates of side effects (e.g., withdrawal) attributed to naloxone. Additionally, patients who received buprenorphine had more "complete responses" with less recurrence of respiratory depression than patients who received naloxone. There are several concerns with this study though, as described by Mégarbane et al. (2020), including the mild opioid poisoning (i.e., Glasgow Coma Scores of 13–15 and respiratory rate of 10–16 breaths/min) of these patients and the high doses of naloxone. It is also important to consider that buprenorphine may be less effective at reducing high efficacy μ-opioid agonist effects in people who have developed tolerance and/or physical dependence on opioids. While the available data support naloxone efficacy over buprenorphine in overdose reversal, the observation that buprenorphine (a low efficacy agonist) can reduce the effects of high efficacy μ-opioid agonists, at some doses, is well documented and, in some circumstances or locations, buprenorphine may be available when naloxone is not. That said, we are not aware of any development efforts that are currently underway to utilize buprenorphine as an overdose treatment due to the potential diversion of buprenorphine (e.g., see review by Lofwall and Walsh 2014) and the superiority of naloxone over buprenorphine.

Wearable naloxone delivery device

Many barriers may prevent bystander naloxone administration during an opioid overdose. One major concern with F/FAs is the short time frame in which an overdose event occurs (thereby limiting the window for naloxone administration). A recent multi-city study reported that nearly half of people who use opioids reported that they usually used drugs while alone (Park et al. 2019). To combat fatal opioid overdose occurring while alone (with a narrow treatment window as seen with F/FAs), researchers from Purdue University recently designed an "automatic antidote delivery device (A2D2)," a wearable device that, in theory, would identify respiratory depression via ECG and magnetically activate a naloxone containing subcutaneous implant to release the opioid receptor antagonist (Dhowan et al. 2019). A preliminary proof-of-concept study of this device reported that the A2D2 product is capable of releasing 1.9 mg of powdered acetaminophen in one min when manually activated. To our knowledge, this prototype device has not been tested with naloxone or activated by an ECG signal of respiratory depression. Additionally, the study also found drug leakage after 1000 h, suggesting that the product may need to be replaced frequently. This device is a creative approach to addressing an issue many people who use opioids may experience. In a survey of 97 people who use opioids, 76% reported that they would be willing to wear a device that automatically administers a reversal agent when an overdose is detected (Kanter et al. 2021). However, the implementation of a wearable device has barriers including potential market price, patient interest, and insurance coverage, and extensive preclinical and clinical testing is still needed before this product will be able to reach the market. NIDA is currently funding research on several wearable devices, including biosensors that notify emergency personnel and are paired with either a wearable or implantable automatic naloxone delivery device. Another currently funded study is developing a wrist monitor and smartphone application to automatically administer IM naloxone. These devices are in early development, and no results have been published.

Summary and conclusions

Naloxone is the most widely used opioid overdose reversal agent. The FDA has approved initial doses of 0.4 to 2 mg of IM naloxone in the clinical setting and repeated administration to a maximum dose of 10 mg is appropriate (Adapt Pharma Operations Limited 2016). Intranasal products that are currently available to the public include Narcan® (4 mg IN spray), KLOXXADO® (8 mg IN spray), and generic naloxone (4 mg IN spray), and ZIMHI™ (5 mg IM or SC) is expected to be available in early 2022. Clinical studies have demonstrated that naloxone is a safe and efficacious treatment for opioid overdose reversal. However, several concerns have been raised in the literature regarding the ability of naloxone to reverse F/FA overdose (France et al. 2021; Kim et al. 2019; Lynn and Galinkin 2018). Retrospective analyses and case studies have given rise to some of these concerns, but many of these studies lack toxicological confirmation of F/FA use and do not provide naloxone dose or administration route. Additionally, some studies include people who have expired while others exclude people who are unable to answer questions. These studies have numerous limitations (see Tables 1 and 2) and overall provide limited evidence that naloxone is ineffective at treating F/FA overdose. Another concern with F/FA overdose is non-opioid receptor-mediated effects, such as wooden chest syndrome. However, the rate at which wooden chest syndrome occurs in people who use drugs and are experiencing an overdose, as well as the role of wooden chest syndrome in overdose is largely unknown. The major concern regarding naloxone treatment of F/FA overdose is based on the pharmacokinetics of fentanyl which result in a narrow window of time during which naloxone can be administered for reversal of overdose. These studies provide a complex picture of the extant evidence regarding naloxone's efficacy against F/FAs but also reflect substantial success in naloxone reversal of F/FA overdoses. Prospective studies of overdose reversal that collect accurate dosing information in the field are

extremely challenging to conduct and are largely absent from the literature.

Recent advances in opioid overdose treatments have attempted to address several of these concerns. The use of an absorption enhancer may shorten the T_{max} and increase the bioavailability of IN nalmefene and is currently under development (Krieter et al. 2019). The benefit of nalmefene (compared to naloxone) is its long duration of action, which may prevent the re-occurrence of respiratory depression that can occur with long-acting opioid receptor agonists, such as fentanyl. However, patient acceptance of a long-acting opioid receptor antagonist is a concern. Other alternatives to naloxone that are in the early stages of development include respiratory stimulants. However, the potential for side effects and unknown interactions with other illicit substances that could be contributing to the overdose event are major concerns with respiratory stimulants. A few case reports and one pilot study have also indicated that buprenorphine can be used as a treatment for opioid overdose.

Nalmefene, buprenorphine, and respiratory stimulants all are incapable of addressing perhaps the most prominent issue with treating F/FA overdose: the narrow treatment window. There is recent interest in the development of a wearable naloxone delivery device that could theoretically overcome the narrow treatment window with F/FA overdose. Only one wearable device product has undergone a proof-of-concept study, but this device still requires extensive development before reaching the market and will need to overcome several factors, such as patient interest, cost, and insurance coverage.

Funding This work was supported by National Institute on Drug Abuse grants R01 DA016718 (Dr. Walsh) and T32 DA035200 (Dr. Britch). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Declarations

Conflict of interest Sharon Walsh serves on a Scientific Advisory Board for Opiant Pharmaceuticals and as an advisor for Pocket Naloxone.

References

Abram AK (2017) Determination that REVEX (nalmefene hydrochloride injection), 0.1 milligram base/milliliter and 1.0 milligram base/milliliter, was not withdrawn from sale for reasons of safety or effectiveness. U.S. Food and Drug Administration. https://www.federalregister.gov/d/2017-23952

Adapt Pharma Operations Limited (2016) FDA advisory committee on the most appropriate dose or doses of naloxone to reverse the effects of fife-threatening opioid overdose in the community settings. https://www.fda.gov/media/100409/download

Adapt Pharma Operations Limited (2019) Narcan nasal spray package insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208411s001lbl.pdf

Ahmad FB, Rossen LM, Sutton P (2021) Provisional drug overdose death counts. Center for Disease Control and Prevention, National Center for Health Statistics. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

Ahonen J, Olkkola KT, Hynynen M, Seppälä T, Ikävalko H, Remmerie B, Salmenperä M (2000) Comparison of alfentanil fentanyl and sufentanil for total intravenous anaesthesia with propofol in patients undergoing coronary artery bypass surgery. Br J Anaesth 85:533–540. https://doi.org/10.1093/bja/85.4.533

Aitken M, Kleinrock M (2019) Medicine use and spending in the U.S. a review of 2018 and outlook to 2023. https://www.iqvia.com/insights/the-iqvia-institute/reports/medicine-use-and-spending-in-the-us-a-review-of-2018-and-outlook-to-2023

Akorn Inc. (2019) Highlights of prescribing information, fentanyl citrate injection. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/016619s043lbl.pdf

Altarum (2018) Economic toll of opioid crisis in U.S. exceeded $1 trillion since 2001. Altarum. https://altarum.org/news/economic-toll-opioid-crisis-us-exceeded-1-trillion-2001

Any Positive Change (2021) Chicago Recovery Alliance Services. https://anypositivechange.org/cra-services/

Armenian P, Olson A, Anaya A, Kurtz A, Ruegner R, Gerona RR (2017) Fentanyl and a novel synthetic opioid U-47700 masquerading as street “norco" in central california: A Case Report. Ann Emerg Med 69:87–90. https://doi.org/10.1016/j.annemergmed.2016.06.014

Avetian GK, Fiuty P, Mazzella S, Koppa D, Heye V, Hebbar P (2018) Use of naloxone nasal spray 4 mg in the community setting: a survey of use by community organizations. Current medical research and opinion 34:573–576. https://doi.org/10.1080/03007995.2017.1334637

Bardsley R (2019) Higher naloxone dosing may be required for opioid overdose. Am J Health Syst Pharm 76:1835–1837. https://doi.org/10.1093/ajhp/zxz208

Barrueto F Jr, Howland MA, Hoffman RS, Nelson LS (2004) The Fentanyl Tea Bag Vet Hum Toxicol 46:30–31

Bell A, Bennett AS, Jones TS, Doe-Simkins M, Williams LD (2019) Amount of naloxone used to reverse opioid overdoses outside of medical practice in a city with increasing illicitly manufactured fentanyl in illicit drug supply. Subst Abus 40:52–55. https://doi.org/10.1080/08897077.2018.1449053

Bennett JA, Abrams JT, Van Riper DF, Horrow JC (1997) Difficult or impossible ventilation after sufentanil-induced anesthesia is caused primarily by vocal cord closure. Anesthesiology 87:1070–1074. https://doi.org/10.1097/00000542-199711000-00010

Bentley JB, Borel JD, Nenad RE Jr, Gillespie TJ (1982) Age and Fentanyl Pharmacokinetics. Anesth Analg 61:968–971

Blight AR, Henney HR 3rd (2009) Pharmacokinetics of 14C-radioactivity after oral intake of a single dose of 14C-labeled fampridine (4-aminopyridine) in healthy volunteers. Clinical therapeutics 31:328–335. https://doi.org/10.1016/j.clinthera.2009.02.004

Bode AD, Singh M, Andrews J, Kapur GB, Baez AA (2017) Fentanyl laced heroin and its contribution to a spike in heroin overdose in Miami-Dade County. Am J Emerg Med 35:1364–1365. https://doi.org/10.1016/j.ajem.2017.02.043

Burr W, Sandham P, Judd A (1989) Death after Flumazepil. BMJ 298:1713–1713. https://doi.org/10.1136/bmj.298.6689.1713-a

Carpenter J, Murray BP, Atti S, Moran TP, Yancey A, Morgan B (2020) Naloxone dosing after opioid overdose in the era of illicitly manufactured fentanyl. J Med Toxicol 16:41–48. https://doi.org/10.1007/s13181-019-00735-w

Center for Drug Evaluation and Research (2015) Approval Package for: Application Number: 208411Orig1s000. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208411Orig1s000Approv.pdf

Center for Drug Evaluation and Research (2016) Approval Package for: Application Number: 209862Orig1s000. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/209862Orig1s000Approv.pdf

Coleman L, Carvalho B, Lipman S, Schmiesing C, Riley E (2009) Accidental intrathecal sufentanil overdose during combined spinal-epidural analgesia for labor. Int J Obstet Anesth 18:78–80. https://doi.org/10.1016/j.ijoa.2008.10.001

Comstock KM, Carter GJ, Moyers RJ, Stevens CW (1981) Rigidity and hypercarbia associated with high dose fentanyl induction of anesthesia. Anesth Analg 60:362–363. https://doi.org/10.1213/00000539-198105000-00018

Çoruh B, Tonelli MR, Park DR (2013) Fentanyl-induced chest wall rigidity. Chest 143:1145–1146. https://doi.org/10.1378/chest.12-2131

Cuss FM, Colaço CB, Baron JH (1984) Cardiac arrest after reversal of effects of opiates with naloxone. Br Med J (clin Res Ed) 288:363–364. https://doi.org/10.1136/bmj.288.6414.363

Dhowan B et al (2019) Simple minimally-invasive automatic antidote delivery device (A2D2) towards closed-loop reversal of opioid overdose. J Control Release 306:130–137

DiSalvo P, Cooper G, Tsao J, Romeo M, Laskowski LK, Chesney G, Su MK (2021) Fentanyl-contaminated cocaine outbreak with laboratory confirmation in New York City in 2019. Am J Emerg Med 40:103–105. https://doi.org/10.1016/j.ajem.2020.12.002

Dixon R, Gentile J, Hsu HB, Hsiao J, Howes J, Garg D, Weidler D (1987) Nalmefene: safety and kinetics after single and multiple oral doses of a new opioid antagonist. J Clin Pharmacol 27:233–239. https://doi.org/10.1002/j.1552-4604.1987.tb02191.x

Dunleavy K (2022) Teva, Sandoz have launched Narcan generics, but Emergent's branded option should still thrive: analysts. https://www.fiercepharma.com/pharma/teva-and-sandoz-s-generics-have-launched-but-emergent-s-narcan-still-likely-to-thrive

Evans LEJ, Swainson CP, Roscoe P, Prescott LF (1973) Treatment of drug overdosage with naloxone a specific narcotic antagonist. The Lancet 301:452–455. https://doi.org/10.1016/S0140-6736(73)91879-5

Fareed A, Buchanan-Cummings AM, Crampton K, Grant A, Drexler K (2015) Reversal of overdose on fentanyl being illicitly sold as heroin with naloxone nasal spray: a case report. Am J Addict 24:388–390. https://doi.org/10.1111/ajad.12230

Fidacaro GA, Patel P, Carroll G, Bartimus H, Hunter K, Hong R (2019) Do patients require emergency department interventions after prehospital naloxone? J Addict Med. https://doi.org/10.1097/ADM.0000000000000563

Foldes FF, Duncalf D, Kuwabara S (1969) The respiratory, circulatory, and narcotic antagonistic effects of nalorphine, levallorphan, and naloxone in anaesthetized subjects. Can Anaesth Soc J 16:151–161. https://doi.org/10.1007/bf03005795

Foster D, Upton R, Christrup L, Popper L (2008) Pharmacokinetics and Pharmacodynamics of Intranasal Versus Intravenous Fentanyl in Patients with Pain after Oral Surgery. Ann Pharmacother 42:1380–1387. https://doi.org/10.1345/aph.1L168

France CP et al (2021) Countermeasures for preventing and treating opioid overdose. Clin Pharmacol Ther 109:578–590. https://doi.org/10.1002/cpt.2098

Gal TJ, Difazio CA (1986) Prolonged antagonism of opioid action with intravenous nalmefene in man. Anesthesiology 64:175–180. https://doi.org/10.1097/00000542-198602000-00008

Gal TJ, Difazio CA, Dixon R (1986) Prolonged blockage of opioid effects with oral nalmefene. Anesthesiology 65:A344. https://doi.org/10.1097/00000542-198609001-00342

Glass SAP, Jhaveri MR, Smith RL (1994) Comparison of potency and duration of action of nalmefene and naloxone. Anesth Analg 78:536–541. https://doi.org/10.1213/00000539-199403000-00021

Global Newswire (2021) Adamis received FDA approval for ZIMHI. https://www.globenewswire.com/en/news-release/2021/10/18/2315581/32832/en/Adamis-Receives-FDA-Approval-for-ZIMHI.html

Grell LF, Koons AR, Denson SJ (1970) Fentanyl in anesthesia: A Report of 500 Cases. Anesth Analg 49:523–532. https://doi.org/10.1213/00000539-197007000-00003

Hargan ED (2017) Determination that a public health Emergency Exists. https://www.phe.gov/emergency/news/healthactions/phe/Pages/opioids.aspx

Hayes KC, Katz MA, Devane JG, Hsieh JT, Wolfe DL, Potter PJ, Blight AR (2003) Pharmacokinetics of an immediate-release oral formulation of Fampridine (4-aminopyridine) in normal subjects and patients with spinal cord injury. J Clin Pharmacol 43:379–385. https://doi.org/10.1177/0091270003251388

Hedegaard H, Minino AM, Warner M (2020) Drug overdose deaths in the United States, 1999-2018. https://www.cdc.gov/nchs/data/databriefs/db356_tables-508.pdf#page=3

Hikma Specialty USA Inc. (2021) Highlights of prescribing information, Kloxxado. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212045s000lbl.pdf

Hill BA, Nahrwold LM, De Rosayro MA, Knight RP, Jones MR, Bolles ER (1981) Prevention of rigidity during fentanyl–oxygen induction of anesthesia. Anesthesiology 55:452–454. https://doi.org/10.1097/00000542-198110000-00021

Hill LG, Zagorski CM, Loera LJ (2022) Increasingly powerful opioid antagonists are not necessary. Int J Drug Policy 99:103457. https://doi.org/10.1016/j.drugpo.2021.103457

Hunter R (2005) Ventricular tachycardia following naloxone administration in an illicit drug misuse. J Clin Forensic Med 12:218–219. https://doi.org/10.1016/j.jcfm.2005.01.011

Imam M, Kuo A, Smith M (2020) Countering opioid-induced respiratory depression by non-opioids that are respiratory stimulants [version 1; peer review: 2 approved] F1000Research 9 https://doi.org/10.12688/f1000research.21738.1

Jensen HB, Ravnborg M, Dalgas U, Stenager E (2014) 4-Aminopyridine for symptomatic treatment of multiple sclerosis: a systematic review. Ther Adv Neurol Disord 7:97–113. https://doi.org/10.1177/1756285613512712

Johansen KGV, Tarp S, Astrup A, Lund H, Pagsberg AK, Christensen R (2017) Harms associated with taking nalmefene for substance use and impulse control disorders: A systematic review and meta-analysis of randomised controlled trials. PloS One 12:e0183821. https://doi.org/10.1371/journal.pone.0183821

Jonkman K et al (2018) Esketamine counters opioid-induced respiratory depression. Br J Anaesth 120:1117–1127. https://doi.org/10.1016/j.bja.2018.02.021

Kaleo Inc. (2014) Highlights of prescribing information, EVZIO. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205787orig1s000lbl.pdf

Kaleo Inc. (2016) Highlights of prescribing information, EVZIO. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209862lbl.pdf

Kanter K et al (2021) Willingness to use a wearable device capable of detecting and reversing overdose among people who use opioids in philadelphia. Harm Reduct J. https://doi.org/10.21203/rs.3.rs-151919/v1

Kaplan JL et al (1999) Double-blind, randomized study of nalmefene and naloxone in emergency department patients with suspected narcotic overdose. Ann Emergency Med 34:42–50

Kentor ML, Schwalb AJ, Lieberman RW (1980) Rapid high dose fentanyl induction for CABG. Anesthesiology 53:S95

Kerr D, Kelly AM, Dietze P, Jolley D, Barger B (2009) Randomized controlled trial comparing the effectiveness and safety of

intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. Addiction 104:2067–2074. https://doi.org/10.1111/j.1360-0443.2009.02724.x

Kim HK, Connors NJ, Mazer-Amirshahi ME (2019) The role of take-home naloxone in the epidemic of opioid overdose involving illicitly manufactured fentanyl and its analogs. Expert Opin Drug Saf 18:465–475. https://doi.org/10.1080/14740338.2019.1613372

Kitch BB, Portela RC (2016) Effective use of naloxone by law enforcement in response to multiple opioid overdoses. Prehosp Emerg Care 20:226–229. https://doi.org/10.3109/10903127.2015.1076097

Konieczko KM, Jones JG, Barrowcliffe MP, Jordan C, Altman DG (1988) Antagonism of morphine-induced respiratory depression with nalmefene. Br J Anaesth 61:318–323. https://doi.org/10.1093/bja/61.3.318

Krieter P, Gyaw S, Crystal R, Skolnick P (2019) Fighting fire with fire: development of intranasal nalmefene to treat synthetic opioid overdose. J Pharmacol Exp Ther 371:409–415. https://doi.org/10.1124/jpet.118.256115

Lameijer H, Azizi N, Ligtenberg JJM, Ter Maaten JC (2014) Ventricular tachycardia after naloxone administration: a Drug Related Complication? Case Report and Literature Review Drug Saf Case Rep 1:2–2. https://doi.org/10.1007/s40800-014-0002-0

Lofwall MR, Walsh SL (2014) A review of buprenorphine diversion and misuse: the current evidence base and experiences from around the world. J Addict Med 8:315–326. https://doi.org/10.1097/adm.0000000000000045

Loimer N, Hofmann P, Chaudhry HR (1992) Nasal administration of naloxone for detection of opiate dependence. J Psychiatr Res 26:39–43. https://doi.org/10.1016/0022-3956(92)90014-f

Lui PW, Chang GJ, Lee TY, Chan SH (1993) Antagonization of fentanyl-induced muscular rigidity by denervation of the coerulospinal noradrenergic pathway in the rat. Neurosci Lett 157:145–148. https://doi.org/10.1016/0304-3940(93)90723-x

Lui PW, Lee TY, Chan SH (1989) Involvement of locus coeruleus and noradrenergic neurotransmission in fentanyl-induced muscular rigidity in the rat. Neurosci Lett 96:114–119. https://doi.org/10.1016/0304-3940(89)90252-8

Lui PW, Lee TY, Chan SH (1990) Involvement of coerulospinal noradrenergic pathway in fentanyl-induced muscular rigidity in rats. Neurosci Lett 108:183–188. https://doi.org/10.1016/0304-3940(90)90728-r

Lui PW, Tsen LY, Fu MJ, Yeh CP, Lee TY, Chan SH (1995) Inhibition by intrathecal prazosin but not yohimbine of fentanyl-induced muscular rigidity in the rat. Neurosci Lett 201:167–170. https://doi.org/10.1016/0304-3940(95)12162-5

Lynn RR, Galinkin J (2018) Naloxone Dosage for Opioid Reversal: Current Evidence and Clinical Implications. Ther Adv Drug Safe 9:63–88. https://doi.org/10.1177/2042098617744161

Lyttle MD, Verma S, Isaac R (2012) Transdermal fentanyl in deliberate overdose in pediatrics. Pediatr Emerg Care 28:463–464. https://doi.org/10.1097/PEC.0b013e31825358b4

Mahonski SG, Leonard JB, Gatz JD, Seung H, Haas EE, Kim HK (2020) Prepacked naloxone administration for suspected opioid overdose in the era of illicitly manufactured fentanyl: a retrospective study of regional poison center data. Clin Toxicol (phila) 58:117–123. https://doi.org/10.1080/15563650.2019.1615622

Marco CA, Trautman W, Cook A, Mann D, Rasp J, Perkins O, Ballester M (2018) Naloxone use among emergency department patients with opioid overdose. J Emerg Med 55:64–70. https://doi.org/10.1016/j.jemermed.2018.04.022

Marquardt KA, Tharratt RS (1994) Inhalation abuse of fentanyl patch. J Toxicol Clin Toxicol 32:75–78. https://doi.org/10.3109/15563659409000433

Massey J et al (2017) Opioid overdose outbreak - West Virginia, August 2016. MMWR Morb Mortal Wkly Rep 66:975–980. https://doi.org/10.15585/mmwr.mm6637a3

McDonald R et al (2018) Pharmacokinetics of concentrated naloxone nasal spray for opioid overdose reversal: Phase I healthy volunteer study. Addiction 113:484–493. https://doi.org/10.1111/add.14033

Mégarbane B, Chevillard L, Vodovar D (2020) Naloxone should remain the appropriate antidote to treat opioid overdose. Crit Care 24:173. https://doi.org/10.1186/s13054-020-2835-5

Merigian KS (1993) Cocaine-induced ventricular arrhythmias and rapid atrial fibrillation temporally related to naloxone administration. Am J Emerg Med 11:96–97. https://doi.org/10.1016/0735-6757(93)90074-l

Merlin MA et al (2017) Incidence of naloxone redosing in the age of the new opioid epidemic. Prehosp Emerg Care 21:682–687. https://doi.org/10.1080/10903127.2017.1335818

Miner NB, Schutzer WE, Zarnegarnia Y, Janowsky A, Torralva R (2021) Fentanyl causes naloxone-resistant vocal cord closure: A platform for testing opioid overdose treatments. Drug Alcohol Depend 227:108974. https://doi.org/10.1016/j.drugalcdep.2021.108974

Nath SS, Tripathi M, Pandey C, Rao B (2009) Naloxone-induced pulmonary edema: a potential cause of postoperative morbidity in laparoscopic donor nephrectomy. Indian J Med Sci 63:72–75. https://doi.org/10.4103/0019-5359.49240

National Institute on Drug Abuse (2021) Trends and statistics in overdose death rates. https://www.drugabuse.gov/drug-topics/trends-statistics/overdose-death-rates

National Library of Medicine (2021a) PubChem compound summary for CID 3345, fentanyl. https://pubchem.ncbi.nlm.nih.gov/compound/Fentanyl

National Library of Medicine (2021b) PubChem compound summary for CID 5284596, naloxone. https://pubchem.ncbi.nlm.nih.gov/compound/Naloxone

National Library of Medicine (2021c) PubChem compound summary for CID 5288826, morphine. https://pubchem.ncbi.nlm.nih.gov/compound/5288826

Nielsen S et al (2020) Comparing rates and characteristics of ambulance attendances related to extramedical use of pharmaceutical opioids in Victoria, Australia from 2013 to 2018. Addiction 115:1075–1087. https://doi.org/10.1111/add.14896

O'Donnell J, Tanz LJ, Gladden RM, Davis NL, Bitting J (2021) Trends in and Characteristics of Drug Overdose Deaths Involving Illicitly Manufactured Fentanyls — United States, 2019–2020. https://www.cdc.gov/mmwr/volumes/70/wr/mm7050e3.htm?s_cid=mm7050e3_w#suggestedcitation

Oertel BG et al (2010) Selective antagonism of opioid-induced ventilatory depression by an ampakine molecule in humans without loss of opioid analgesia. Clin Pharmacol Ther 87:204–211. https://doi.org/10.1038/clpt.2009.194

Olofsen E, Van Dorp E, Teppema L, Aarts L, Smith TW, Dahan A, Sarton E (2010) Naloxone reversal of morphine- and morphine-6-glucuronide-induced respiratory depression in healthy volunteers: a mechanism-based pharmacokinetic–pharmacodynamic modeling study. Anesthesiology 112:1417–1427. https://doi.org/10.1097/ALN.0b013e3181d5e29d

Osterwalder JJ (1996) Naloxone–for intoxications with intravenous heroin and heroin mixtures–harmless or hazardous? A Prospect Clin Study J Toxicol Clin Toxicol 34:409–416. https://doi.org/10.3109/15563659609013811

Park J et al (2019) Willingness to use safe consumption spaces among opioid users at high risk of fentanyl overdose in Baltimore Providence, and Boston. J Urban Health 96:353–366. https://doi.org/10.1007/s11524-019-00365-1

Paulozzi LJ, Jones CM, Mack KA, Rudd RA (2011) Vital signs: overdoses of prescription opioid pain relievers—United States, 1999–2008. MMWR MorbMortal Wkly Rep. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6043a4.htm

Penninga EI, Graudal N, Ladekarl MB, Jürgens G (2016) Adverse events associated with flumazenil treatment for the management of suspected benzodiazepine intoxication—a systematic review with meta-analyses of randomised trials Basic. Clin Pharmacol Toxicol 118:37–44. https://doi.org/10.1111/bcpt.12434

Pergolizzi JV Jr, Webster LR, Vortsman E, Ann LeQuang J, Raffa RB (2021) Wooden chest syndrome: The Atypical Pharmacology of Fentanyl Overdose. J Clin Pharm Ther 46:1505–1508. https://doi.org/10.1111/jcpt.13484

Prescriber's Digital Reference (2021) fentanyl - Drug Summary. https://www.pdr.net/drug-summary/Fentora-fentanyl-2330

PRNewswire (2021) Sandoz launches authorized generic of Narcan® (naloxone hydrochloride) Nasal Spray 4 mg in US to help reverse opioid overdose, expanding access during surge in overdose deaths. https://www.prnewswire.com/news-releases/sandoz-launches-authorized-generic-of-narcan-naloxone-hydrochloride-nasal-spray-4-mg-in-us-to-help-reverse-opioid-overdose-expanding-access-during-surge-in-overdose-deaths-301450103.html

Purdue Pharma (2019) FDA grants competitive generic therapy (CGT) designation to Purdue Pharma's investigational nalmefene HCl injection for the emergency treatment of known or suspected opioid overdose. https://purduepharma.com/news/2019/04/24/fda-grants-competitive-generic-therapy-cgt-designation-to-purdue-pharmas-investigational-nalmefene-hcl-injection-for-the-emergency-treatment-of-known-or-suspected-opioid-overdose/

Purssell R et al (2021) Comparison of rates of opioid withdrawal symptoms and reversal of opioid toxicity in patients treated with two naloxone dosing regimens: a retrospective cohort study. Clin Toxicol 59:38–46. https://doi.org/10.1080/15563650.2020.1758325

Raheemullah A, Andruska N (2019) Fentanyl analogue overdose: Key Lessons in Management in the Synthetic Apioid Age. J Opioid Manag 15:428–432. https://doi.org/10.5055/jom.2019.0531

Raja AS, Miller ES, Flores EJ, Wakeman SE, Eng G (2017) Case 37–2017. A 36-year-old man with unintentional opioid overdose. N Engl J Med 377:2181–2188. https://doi.org/10.1056/NEJMcpc1710563

RespireRX Pharmaceuticals Inc. (2016) RespireRx Pharmaceuticals Inc. announces data for CX1739 clinical study in opioid induced respiratory depression. http://respirerx.com/respirerx-pharmaceuticals-inc-announces-data-for-cx1739-clinical-study-in-opioid-induced-respiratory-depression/

Rhyan CN (2017) The potential societal benefit of eliminating opioid overdoses, deaths, and substance use disorders exceeds $95 billion per year. https://altarum.org/sites/default/files/uploaded-publication-files/Research-Brief_Opioid-Epidemic-Economic-Burden.pdf

Rogers JS, Rehrer SJ, Hoot NR (2016) Acetylfentanyl: An Emerging Drug of Abuse. J Emerg Med 50:433–436. https://doi.org/10.1016/j.jemermed.2015.10.014

Roozekrans M, Olofsen E, van der Schrier R, Boom M, Mooren R, Dahan A (2017) Doxapram-mediated Increase in Cardiac Output Reduces Opioid Plasma Concentrations: A Pharmacokinetic/Pharmacodynamic-Pharmacokinetic/Pharmacodynamic Modeling Study in Healthy Volunteers. Clin Pharmacol Ther 102:115–122. https://doi.org/10.1002/cpt.601

Roozekrans M, Olofsen E, van der Schrier R, van Gerven J, Peng S, McLeod J, Dahan A (2015) Reversal of opioid-induced respiratory depression by BK-channel blocker GAL021: A pharmacokinetic-pharmacodynamic modeling study in healthy volunteers. Clin Pharmacol Ther 97:641–649. https://doi.org/10.1002/cpt.99

Roozekrans M, van der Schrier R, Okkerse P, Hay J, McLeod JF, Dahan A (2014) Two studies on reversal of opioid-induced respiratory depression by BK-channel blocker GAL021 in human volunteers. Anesthesiology 121:459–468. https://doi.org/10.1097/aln.0000000000000367

Rowe C, Wheeler E, Stephen Jones T, Yeh C, Coffin PO (2019) Community-based response to fentanyl overdose outbreak, San Francisco, 2015. J Urban Health 96:6–11. https://doi.org/10.1007/s11524-018-0250-x

Rudd RA et al. (2014) Increases in heroin overdose deaths—28 states, 2010 to 2012. MMWR MorbMortal Wkly Rep. Center for Disease Control and Prevention. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6339a1.htm

Ryan JP, Meakin G (1989) Fentanyl overdose in a neonate: use of naloxone infusion. Anaesthesia 44:864–865. https://doi.org/10.1111/j.1365-2044.1989.tb09119.x

Ryan SA, Dunne RB (2018) Pharmacokinetic properties of intranasal and injectable formulations of naloxone for community use: a systematic review. Pain Management 8:231–245. https://doi.org/10.2217/pmt-2017-0060

Santos C, Adam A, Calello D, Nelson L (2019) Safety of a brief emergency department observation protocol for patients with presumed fentanyl overdose. Ann Emerg Med 73:99–100. https://doi.org/10.1016/j.annemergmed.2018.10.024

Scamman FL (1983) Fentanyl-O2-N2O rigidity and pulmonary compliance. Anesth Analg 62:332–334

Scheuermeyer FX et al (2018) Safety of a brief emergency department observation protocol for patients with presumed fentanyl overdose. Ann Emerg Med 72:1-8.e1. https://doi.org/10.1016/j.annemergmed.2018.01.054

Schumann H, Erickson T, Thompson TM, Zautcke JL, Denton JS (2008) Fentanyl epidemic in Chicago, Illinois and surrounding Cook County. Clin Toxicol 46:501–506. https://doi.org/10.1080/15563650701877374

Sia RL, Zandstra DF (1981) 4-Aminopyridine reversal of fentanyl-induced respiratory depression in normocapnic and hypercapnic patients. Br J Anaesth 53:373–379. https://doi.org/10.1093/bja/53.4.373

Slingsby B, Moore JL, Barron CE (2019) Infant and toddler ingestion of illicit fentanyl: a case series. Clin Pediatr (phila) 58:1449–1451. https://doi.org/10.1177/0009922819877870

Smith K, Hopp M, Mundin G, Bond S, Bailey P, Woodward J, Bell D (2012) Low absolute bioavailability of oral naloxone in healthy subjects. Int J Clin Pharmacol Ther 50:360–367. https://doi.org/10.5414/cp201646

Somerville NJ et al. (2017) Characteristics of fentanyl overdose — Massachusetts, 2014–2016 Morbidity and Mortality Weekly Report 66:382–386 https://doi.org/10.15585/mmwr.mm6614a2

Takahashi M, Sugiyama K, Hori M, Chiba S, Kusaka K (2004) Naloxone reversal of opioid anesthesia revisited: clinical evaluation and plasma concentration analysis of continuous naloxone infusion after anesthesia with high-dose fentanyl. J Anesth 18:1–8. https://doi.org/10.1007/s00540-003-0214-4

Thomas DV, Tenney SM (1955) The effect of levorphan and levallorphan on the respiratory mechanism of normal man. J Pharmacol Exp Ther 113:250–255

Tigerstedt I (1977) Antagonism of fentanyl with naloxone during N2O+O2+ halothane anaesthesia Acta anaesthesiologica. Scandinavica 21:470–480. https://doi.org/10.1111/j.1399-6576.1977.tb01248.x

Tomassoni AJ et al (2017) Multiple fentanyl overdoses - New Haven, Connecticut, June 23 2016. MMWR Morb Mortal Wkly Rep 66:107–111. https://doi.org/10.15585/mm6604a4

Torralva R, Janowsky A (2019) Noradrenergic mechanisms in fentanyl-mediated rapid death explain failure of naloxone in the opioid

crisis. J Pharmacol Exp Ther 371:453–475. https://doi.org/10.1124/jpet.119.258566
Tylleskar I, Skulberg AK, Nilsen T, Skarra S, Jansook P, Dale O (2017) Pharmacokinetics of a new, nasal formulation of naloxone. Eur J Clin Pharmacol 73:555–562
U.S. Food & Drug Administration (2019) FDA approves first generic naloxone nasal spray to treat opioid overdose. https://www.fda.gov/news-events/press-announcements/fda-approves-first-generic-naloxone-nasal-spray-treat-opioid-overdose
U.S. Food and Drug Administration NDA 016636. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=016636
U.S. Food and Drug Administration (2021a) FDA approves higher dosage of naloxone nasal spray to treat opioid overdose. FDA. https://www.fda.gov/news-events/press-announcements/fda-approves-higher-dosage-naloxone-nasal-spray-treat-opioid-overdose
U.S. Food and Drug Administration (2021b) FDA approves naloxone injection to counteract opioid overdoses. https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-naloxone-injection-counteract-opioid-overdoses
U.S. Food and Drug Administration (2021c) Orange book: Approved Drug Products with Therapeutic Equivalence Evaluations. https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=209862#17222
van Dorp E et al (2006) Naloxone reversal of buprenorphine-induced respiratory depression. Anesthesiology 105:51–57. https://doi.org/10.1097/00000542-200607000-00012
Volkow ND (2021) The epidemic of fentanyl misuse and overdoses: challenges and strategies. World Psychiatry 20:195–196. https://doi.org/10.1002/wps.20846
Volkow ND, Collins FS (2017) The role of science in addressing the opioid crisis. N Engl J Med 377:391–394. https://doi.org/10.1056/NEJMsr1706626
Wahl G, Gault A (2021) Reversal of Ingested Fentanyl Patch Toxicity with Oral Naltrexone in Remote Australia: Case Report. Clin Toxicol (phila) 59:854–855. https://doi.org/10.1080/15563650.2021.1882682
Weinger MB, Cline EJ, Smith NT, Blasco TA, Koob GF (1988) Localization of brainstem sites which mediate alfentanil-induced muscle rigidity in the rat. Pharmacol Biochem Behav 29:573–580. https://doi.org/10.1016/0091-3057(88)90022-6
Welsh C, Sherman SG, Tobin KE (2008) A case of heroin overdose reversed by sublingually administered buprenorphine/naloxone (Suboxone). Addiction 103:1226–1228. https://doi.org/10.1111/j.1360-0443.2008.02244.x
Wikler A, Fraser HF, Isbell H (1953) N-Allylnormorphine: effects of single doses and precipitation of acute abstinence syndromes during addiction to morphine; methadone or heroin in man (post addicts). J Pharmacol Exp Ther 109:8–20
Wilde M, Sommer MJ, Auwärter V, Hermanns-Clausen M (2020) Acute severe intoxication with cyclopropylfentanyl, a novel synthetic opioid. Toxicol Lett 320:109–112. https://doi.org/10.1016/j.toxlet.2019.11.025
Yokell MA, Zaller ND, Green TC, McKenzie M, Rich JD (2012) Intravenous use of illicit buprenorphine/naloxone to reverse an acute heroin overdose. J Opioid Manag 8:63–66. https://doi.org/10.5055/jom.2012.0098
Zamani N, Buckley NA, Hassanian-Moghaddam H (2020) Buprenorphine to reverse respiratory depression from methadone overdose in opioid-dependent patients: a prospective randomized trial. Crit Care 24:44. https://doi.org/10.1186/s13054-020-2740-y
Zamani N, Hassanian-Moghaddam H (2017) Intravenous buprenorphine: a substitute for naloxone in methadone-overdosed patients? Ann Emerg Med 69:737–739. https://doi.org/10.1016/j.annemergmed.2016.12.024
Zuckerman M, Weisberg SN, Boyer EW (2014) Pitfalls of Intranasal Naloxone. Prehosp Emerg Care 18:550–554. https://doi.org/10.3109/10903127.2014.896961