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REVIEW ARTICLE

Opioid overdose: evidence-based management guidelines and new antidote development

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ABSTRACT

Importance: Opioid overdose is the commonest cause of drug-related deaths worldwide. Naloxone is an effective treatment when instituted early. The emergence of highly potent novel synthetic opioids such as nitazenes and fentanyl analogues has led to a systematic reappraisal of the evidence on management of opioid toxicity with naloxone and development of evidence-based clinical guidelines to reduce opioid-related deaths.

Observations: Guidelines on management of opioid-associated out-of-hospital cardiac arrest recommend standard resuscitation alone in pulseless patients and administration of naloxone if there is uncertainty about the presence of a pulse. For pre-hospital and in-hospital reversal of respiratory depression, intravenous or intranasal naloxone is recommended. Current guidelines recommend a titrated dosing strategy in hospital to reduce the risk of opioid withdrawal. New formulations of intranasal naloxone have been approved to facilitate take-home naloxone and community-based naloxone distribution programmes to reduce opioid-related deaths. Nalmefene and buprenorphine are existing licensed drugs which are being considered as alternatives to naloxone for toxicity from long-acting opioids. Several new experimental antidotes are currently in development to counter the threat from novel synthetic opioids.

Conclusions: Naloxone remains the gold standard antidote for opioid toxicity, both for pre-hospital and hospital use. Further research is required to determine the optimal dose and route of administration. New antidotes are in development but require randomised clinical trials to test their safety and efficacy before they can be implemented in clinical practice.

Keywords: opioid; naloxone; nitazenes; fentanyl; antidotes; drug-related death.

Introduction

Opioids are synthetic or natural substances that stimulate opioid receptors whilst opiates refer to opioids naturally derived from the opium poppy, *Papaver somniferum,* such as heroin. Endogenous and exogenous opioids act as agonists, partial agonists, or agonist-antagonists on four main opioid receptors (μ,κ,δ, opioid receptor like 1 (ORL1)). Mu opioid receptors (MOR) mediate analgesia, sedation, respiratory depression, euphoria, gastrointestinal dysmotility, and physical dependence; Kappa opioid receptors (KOR) mediate analgesia, miosis, diuresis, and dysphoria; delta opioid receptors (DOR) mediate analgesia, inhibition of dopamine release and cough suppression. Opioids can be delivered through a variety of routes (oral, subcutaneous, intravenous, inhalation, sublingual, intranasal, buccal, transmucosal and dermal) which result in varying distribution to the central nervous system depending on their lipid solubility.

Opioids are used in the treatment of pain but are often sold illicitly (drug diversion) and misused for their euphoric effects. The classical triad of opioid toxicity is reduced consciousness, miosis and a reduced respiratory rate with shallow breaths but this may not always be reliable as a similar clinical picture can be seen following intoxication with sedative-hypnotic drugs, hypoglycaemia or head injury[1]. Opioids are often used with other substances such as stimulants which may mask the signs of opioid toxicity. Chronic opioid users may develop tolerance and not exhibit the typical signs of opioid toxicity, such as miosis or respiratory depression. Recent prolonged abstinence (e.g during incarceration) resulting in loss of tolerance significantly increases the risk of death from overdose after prison release[2]. Acute respiratory distress syndrome (non-cardiogenic pulmonary oedema) can occur as a result of rapid reversal with naloxone or the direct effects of the opioid, particularly with heroin and U-47700[3].

Novel highly potent synthetic opioids such as nitazenes and fentanyl analogues have emerged in the UK and European drug market. Nitazenes and fentanyls demonstrate anomalous pharmacological properties, including poor correlation between *in vitro* and *in vivo* potency and measurements of affinity or efficacy, ability to orientate in various ways within the orthosteric binding pocket of the μ opioid receptor (MOR), accessing the orthosteric binding pocket via a lipophilic pathway, potential for arrestin-biased signalling, lower cross-tolerance to heroin *in vivo*, induction of respiratory muscle rigidity and reduced sensitivity to reversal by naloxone compared with other opioid agonists[4].

Fentanyl is a highly lipid soluble synthetic opioid which is 100-fold more potent than morphine and 50-fold more potent than heroin. Over 500 fentanyl analogues of widely varying potency exist, including pharmaceutical fentanyls such as remifentanil and fentanyl analogues not approved for human medical use such as acetylfentanyl, carfentanil, ocfentanil and furanylfentanyl[5]. Benzimidazole opioids, also known as nitazenes, are a class of synthetic opioids with an unusual benzimidazole structure, that were synthesized in the 1950s as potential analgesic medications with agonist activity at the MOR with a potency several hundred times that of morphine but have never been used clinically due to their profound risk of respiratory depression and death[6]. Modifications at the 4-position of the benzyl structure with replacement of the ethoxy group by other small ether groups (e.g methoxy, propoxy and isopropoxy) leads to compounds with significant opioid agonist activity, with the isopropoxy form of etonitazene (isotonitazene) being the most potent at around 500 times the potency of morphine (Figure 1). 2-benzyl benzimidazole opioids, including isotonitazene, are highly lipid soluble and likely to cross rapidly into the brain[7]. The apparent rate of agonist dissociation from the MOR varies between compounds with rapid dissociation seen with morphine, alfentanil and fentanyl and slow dissociation with isotonitazene, etonitazene, ohmefentanyl and carfentanil[8]. Other novel non-fentanyl synthetic opioids include: brorphine which has a benzimidazolone scaffold that distinguishes it from a fentanyl analogue[9]; desomorphine (street name Krokodil), a semi-synthetic narcotic drug often homemade using codeine, gasoline, iodine and red phosphorus (from matchboxes) and is 10-fold more potent than morphine[10]; acyl piperazine opioids (cinnamylpiperazines; AP-series opioids) which contain a piperazine core linked to a cinnamyl moiety e.g 2-methyl-AP-237, AP-237 (bucinnazine), AP-238, and para-methyl-AP-237; MT-45 and its analogues ;benzamide and 2-phenylacetamide opioids (U-series opioids e.g U-47700)[11].

Opioid use disorder and overdose is a growing concern worldwide, accounting for over 100,000 deaths annually and is the leading cause of death in adults aged 25-64 in the US[12,13]. In 2023, opioids were involved in over 2500 drug-related deaths in the UK, mostly due to morphine, heroin and methadone[14], over 80000 deaths in the US[15] and over 5000 deaths in the European Union[16]. Following the emergence of new synthetic opioids, deaths involving illegally manufactured fentanyls more than doubled from 2019 to 2022 in the US. In the UK, 179 deaths were reported involving one or more nitazenes confimed analytically between June 2023 and May 2024[17] and outbreaks of fatal and non-fatal poisoning from potent synthetic opioids such as the fentanyl derivative carfentanil and nitazene opioids, have been reported in Europe and US[16,18] causing increasing concern about the potential harm to public health[19].

The aim of this article is to review recently published guidelines on the management of opioid toxicity both in the pre-hospital and hospital settings, focusing on the clinical evidence for the optimal use of naloxone to reverse opioid toxicity and reduce opioid-related deaths. We also provide an overview of new antidotes at various stages of development to meet the challenges of an evolving opioid overdose epidemic.

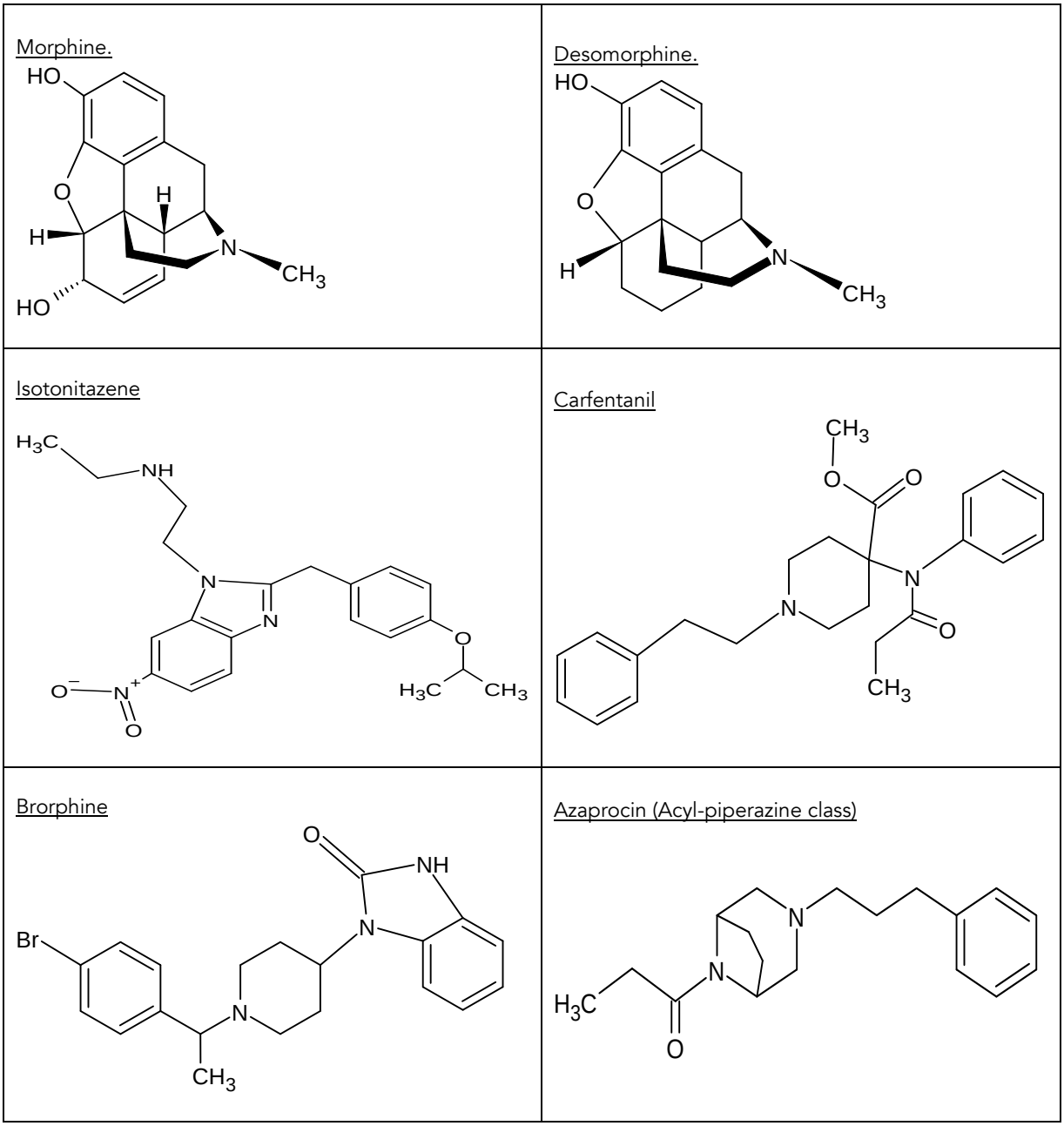

Figure 1. Chemical Structures of Selected Opioids.

Naloxone

Naloxone is a non-selective, competitive, μ receptor antagonist with greater receptor affinity than exogenous opioids. Naloxone is highly lipophilic and therefore rapidly distributes throughout the central nervous system with a time of onset to action of seconds to minutes after intravenous administration. Despite being available in clinical practice for over 50 years, there have been few published studies on the pharmacokinetics of naloxone by different routes until the past decade and these have been comprehensively reviewed by Saari et al.[20]. Bioavailability of naloxone after oral and rectal administration is 1-2% and 15% respectively, thus naloxone must be administered parenterally via intravenous (IV), endotracheal, intramuscular (IM), intraosseous (IO), subcutaneous (SC) and/or intranasal (IN) route. Naloxone has a rapid onset of action, reaching maximal serum concentration within 2 minutes after IV administration, 10 minutes after IM, and 15–30 minutes after IN. Naloxone distributes to the central nervous system and equilibrates with the plasma within minutes. Naloxone is extensively metabolized in the liver to inactive metabolites with a serum elimination half-life of 30–90 minutes which is shorter than the half-life of many opioids, requiring careful monitoring and repeat dosing when necessary. If other routes such as endotracheal, intramuscular, intraosseous are used then onset of action may be 5-10 minutes, or even longer if the patient is hypotensive. This is clinically important in situations such as cardiac arrest and may alter the duration of resuscitation efforts.

Formulations available in the UK and EU include naloxone 0.4 mg/mL and 2mg/2mL for intravenous injection and naloxone 1.26 mg/0.1 mL and 1.8 mg/0.1mL for intranasal administration. In the United States, the FDA-approved naloxone formulations include naloxone nasal sprays (2, 3, 4 and 8 mg), prefilled naloxone injection devices for intramuscular (IM) or subcutaneous (SC) use, and generic naloxone for IV, IM or SC use. The 3 mg and 4 mg intranasal atomised spray formulated in 0.1 mL were approved in 2023 for over-the-counter, non-prescription use in response to the need to reduce opioid-related deaths. The Evzio auto-injector has been withdrawn but the Zimhi auto-injector is a prefilled syringe containing 5 mg/0.5 mL naloxone for IM injection into the anterolateral aspect of the thigh, through clothing if necessary[21]. A pharmacokinetic study comparing the bioavailability of 5 mg IM naloxone in a prefilled syringe compared to 2 mg IM naloxone in an auto-injector showed higher Cmax and AUCs with the higher dose. This may be desirable for reversing opioid toxicity caused by the more potent synthetic opioids[22].

Adverse effects of naloxone include severe withdrawal in opiate-dependent patients. Nausea, vomiting, sweating, tachycardia, tremor, hyperventilation and hypertension may occur. Rarely, cardiac effects may occur, particularly in patients who are in pain controlled by opioids and have pre-existing cardiac disease: hypo-or hypertension, pulmonary oedema, atrial and ventricular fibrillation and cardiac arrest. There are rare reports of convulsions following the use of naloxone. A systematic review of 49 case reports of pulmonary oedema after naloxone administration for reversal of opioid toxicity found that pulmonary oedema can occur irrespective of dose but the median dose of naloxone was 4 mg for out-of-hospital opioid overdoses[23].

Although animal and human studies show a clear dose-dependent response in naloxone reversal of opioid-induced respiratory depression, the optimal dosing, formulation and route of administration of naloxone remains controversial. The emergence of potent synthetic opioids has led to a re-examination of naloxone as higher doses may be required to reverse respiratory depression which has to be balanced against the risk of precipitating opioid withdrawal, pulmonary oedema and arrhythmias.

OPIOID-ASSOCIATED OUT-OF-HOSPITAL CARDIAC ARREST

Opioid-associated out-of-hospital cardiac arrest (OA-OHCA) occurs primarily in the 20-59 age group compared to OHCA with a presumed cardiac cause which affects mainly patients >60 years of age. OA-OHCA is more likely to occur at home or in a private setting and is less likely to be witnessed and receive bystander cardiopulmonary resuscitation (CPR). A high proportion of patients with OA-OHCA have pulseless electrical activity (PEA) and asystole with <10% presenting with ventricular fibrillation but the reported survival in OA-OHCA of 18.6% is higher than the 11.9% survival rate in OHCA with other causes in the Save Hearts in Arizona Registry and Education[24].

American Heart Association guidelines for management of opioid-associated out-of-hospital cardiac arrest recommend that if the patient is definitely pulseless and receiving standard resuscitation, including assisted ventilation, naloxone is unlikely to be beneficial and standard resuscitation alone is indicated. When it is uncertain whether the patient is pulseless, it is reasonable to administer naloxone along with CPR. When potent synthetic opioids have been used, dose titration of naloxone may be required for patients with central nervous system and respiratory depression but over-antagonism has potential adverse events[24].

A systematic review identified a few studies examining naloxone for undifferentiated or "drug related" cardiac arrest but all had a high risk of bias and no evidence was found to alter these resuscitation guidelines. The authors recommended a clinical trial to investigate the benefit of naloxone for OA-OHCA[25]. Retrospective studies have variably found that drug-related OHCA treated with naloxone was associated with increased survival to hospital discharge (AOR 2.48, 95% CI 1.34–4.58)[26] and not associated with survival to hospital discharge (AOR 1.01, 95% CI 0.46–2.21) or return of spontaneous circulation (ROSC) (AOR 0.43, 95% CI 0.16– 1.20) compared with no naloxone administration[27]. Studies using the prospective non-traumatic OHCA registry in Oregon also variably report that naloxone administration (given prior to ROSC) was not associated with ROSC at emergency department arrival (AOR 1.43, 95% CI 0.64–3.20), survival at hospital discharge (AOR 1.99, 95% CI 0.39–10.30), or survival with favourable neurological outcome (AOR 1.99, 95% CI 0.34–11.55)[28] and that early naloxone administration in patients with non-shockable rhythms was associated with an increased odds of ROSC (AOR 2.14, 95% CI 1.20–3.81), survival to discharge (AOR 4.41, 95% CI 1.78–10.97) and favourable neurological outcomes (AOR 4.61, 95% CI 1.74–12.19) compared to no naloxone[29]. In all of these studies, opioid or other drug exposure confirmation was not reported, which may explain the variable findings.

OPIOID-ASSOCIATED OUT-OF-HOSPITAL RESPIRATORY DEPRESSION/ARREST

Out-of-hospital death from opioid overdose is preventable with timely basic life support and the administration of the drug naloxone to reverse opioid effects. The optimal dosing and route of administration of naloxone in the pre-hospital setting remains unclear despite multiple systematic reviews of this topic[30,31,32]. Evidence-based guidelines for administration of naloxone by pre-hospital emergency medical personnel in the US, informed by these systematic reviews, recommend the intravenous and intranasal routes of administration equally to facilitate titration of dose instead of the intramuscular route due to difficulty with titration, slower time to clinical effect and potential exposure to needles[33].

Usability by the public, police officers and pre-hospital emergency services is a key consideration in the roll-out of pre-hospital naloxone programmes to reduce opioid-related mortality. A usability study showed that IM administration of naloxone using the Evzio auto-injector device was superior to IN administration with respect to speed of administration and success rates with and without training[34]. However, the Evzio device was discontinued in 2020 and it is unclear whether this still applies to new auto-injector devices and intranasal preparations. A retrospective emergency medical services chart review in New Jersey showed that 1971 of 2166 suspected opioid overdose victims survived with 2 mg IN naloxone with no redosing needed[35]. A retrospective, cross-sectional study of 218 adult patients with pre-hospital opioid overdose in 2 neighbouring counties of Southeast Michigan showed that 54 of 124 adult patients in Washtenaw had a positive response to an average initial 1.77 mg IN naloxone dose whilst 39 of 94 adult patients in Oakland county had a positive response to an initial average 0.48 mg IN naloxone dose during the pre-hospital period[36]. In a prospective study in Ohio, police officers were trained to administer an IN 2 mg naloxone kit on suspected opioid overdose victims before the arrival of emergency medical services and successfully revived 52 out of 67 patients[37]. Similar pilot studies have been undertaken in other countries prior to implementation of pre-hospital intranasal naloxone administration.

Two randomized controlled trials in Australia compared out-of-hospital IN (2 mg at 2 different concentrations) versus IM naloxone (2 mg) administration. Compared with IM naloxone (2 mg), lower-concentration IN naloxone (2 mg/5 mL) was associated with a lower likelihood of

spontaneous respiration within 8 minutes (63% vs. 82%; OR, 0.38 [CI, 0.18 to 0.81]), a higher likelihood of repeated dosing (26% vs. 13%; OR, 2.4 [CI, 1.0 to 5.7]), longer time to a respiratory rate greater than 10 breaths/min (8 vs. 6 minutes; P = 0.006), decreased likelihood of a GCS score greater than 11 at 8 minutes (57% vs. 72%; OR, 0.52 [CI, 0.27 to 1.0]) and decreased risk for agitation and irritation (2.4% vs. 14%; RR, 0.19 [CI, 0.04 to 0.83])[38]. A randomised controlled trial comparing 2mg IM naloxone and 2mg higher concentration IN naloxone (2mg/mL) showed no significant difference in adequate response (defined as effective and spontaneous respiration at a rate ≥10 breaths/min or a Glasgow Coma Scale [GCS] score ≥13) within 10 minutes (72% vs. 78%; adjusted odds ratio [OR], 0.7 [95% CI, 0.3 to 1.5]), mean response time (8.0 vs. 7.9 minutes), or risk for agitation or violence (6.0% vs. 7.9%; relative risk [RR], 0.77 [CI, 0.25 to 2.3]). However, IN naloxone was associated with increased likelihood of repeated dosing (18% vs. 4.5%; adjusted OR, 4.8 [CI, 1.4 to 16])[39]. The different results between these 2 RCTs may have arisen from the different concentrations of intranasal naloxone used as the maximum volume absorbed in each nostril is around 0.5 mL, and therefore the bioavailability of naloxone is reduced with lower concentrations, suggesting that the formulation of IN naloxone is important for efficacy. This is supported by a double-blind, double-dummy randomized clinical trial where the 104 subjects randomized to IM 0.8 mg naloxone administration were less likely to require a rescue dose of naloxone compared with 93 subjects randomized to IN 0.8 mg/1mL naloxone administration (8 [8.6%] vs 24 [23.1%]; odds ratio, 0.35; 95% CI, 0.15-0.66; P = .002). Time to respiratory rate of at least 10 and time to Glasgow Coma Scale score of at least 13 were increased in the group receiving IN naloxone compared with the group receiving IM naloxone[40]. In a study of 201 participants with opioid overdose (heroin suspected in 196) in the pre-hospital setting in Norway, IN naloxone (1.4 mg/0.1 mL) was less effective than 0.8 mg IM naloxone in terms of the primary outcome of return to spontaneous respiration rate of ≥10 breaths/minute within 10 minutes (risk difference 17.5% (95% CI, 8.9%-26.1%)[41]. Additional naloxone was required more commonly in the IN group (19.4% (95% CI, 9.0%-29.7%).

The 2 cohort studies comparing IN (2 mg dose, concentration not reported) and IV naloxone (dose range 0.4 - 2 mg) had a high risk of bias but found few differences between the 2 routes[42,43]. One cohort study comparing IM and IV naloxone found no difference (94% vs. 95%; RR, 1.0 [CI, 0.94 to 1.1]) in the likelihood of a positive response (defined as GCS score ≥14 and respiratory rate ≥10 breaths/min within 5 minutes of administration)[44]. Another cohort study comparing SC and IV naloxone reported a longer time from administration to a respiratory rate of at least 10 breaths/min (5.5 vs. 3.8 minutes; P = 0.001) with SC naloxone but no difference in time from arrival at the patient's side to a respiratory rate of at least 10 breaths/min (9.6 vs. 9.3 minutes; P = 0.67). SC naloxone was associated with a lower likelihood of a need for multiple doses than IV naloxone (15% vs. 35%; RR, 0.42 [CI, 0.25 to 0.71])[45].

Although the systematic reviews identified a few randomised controlled trials and cohort studies comparing different administration routes of naloxone, there are no clinical studies of the benefits/harms of differences in timing of repeated dosing of naloxone or of titration of naloxone until resumption of spontaneous respiratory effort versus return to consciousness. A head-to-head comparison of different naloxone doses or formulations administered by the same route in the pre-hospital setting has not been performed, in particular, there are no randomised controlled trials of the highly concentrated reformulations of naloxone (1.26 or 1.8mg/0.1 mL) approved in the EU or (2, 3, 4 or 8 mg/0.1 mL) in the US.

OPIOID-ASSOCIATED TOXICITY IN HOSPITAL EMERGENCY DEPARTMENTS

Despite the extensive use of naloxone for opioid reversal, the optimal dosing and route has not been formally investigated in well-conducted studies. A best practice guideline by Royal College of Emergency Medicine (RCEM) in April 2024 (Guideline for the Assessment and Management of Acute Opioid Toxicity in Adults in the Emergency Department) recommend a naloxone dosing strategy based on the severity of poisoning with a starting dose of 0.4 mg followed by rapid dose escalation every 60 seconds in patients who are peri-arrest versus a starting dose of 0.1- 0.2 mg with careful titration in other patients.(Figure 2) These guidelines recommend intravenous administration of naloxone as the preferred route due to the rapid onset of action and it allows

careful titration to the desired clinical effects, while preventing unwanted effects. The IM or IN routes are recommended when IV access is difficult. When repeated doses are likely to be required, an IV naloxone infusion may be started at an hourly infusion rate equal to around 60% of the doses that were required to adequately reverse respiratory depression and titrated to the desired clinical effect. Once the respiratory rate is stable, the infusion should be continued at the same rate for at least 4 hours before titrating it down by 25% of the maximum infusion rate every 1-2 hours until it is stopped[46].

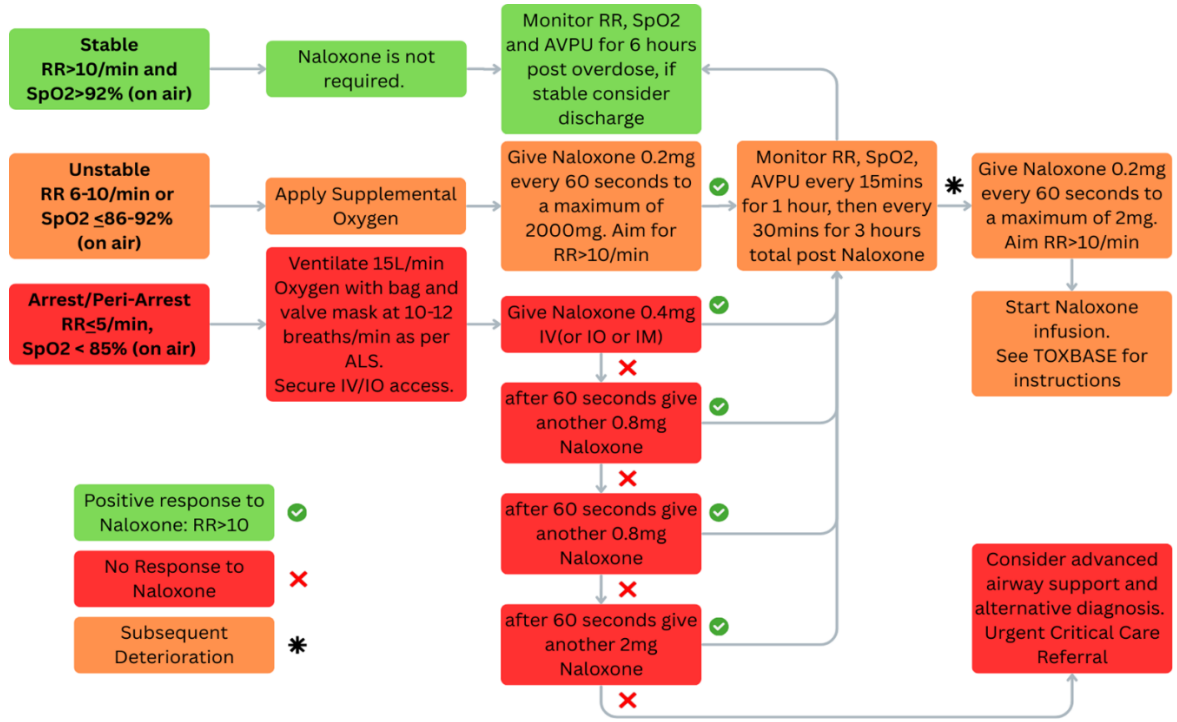

Figure 2. Treatment Algorithm for Opioid Overdose in Adults in Emergency Departments

A retrospective chart review of 121 subjects at a single emergency department in Atlanta revealed that naloxone was given IV in 62%, IN in 38%, IM in 25% and intraosseous (IO) in 1%, with successful opioid reversal in 93% of cases at a median initial dose of 0.8 mg IV. Opioid withdrawal occurred in 11% of patients at a median naloxone dose of 0.6 mg IV[47]. In another retrospective cohort study of 84 adults presenting to 2 different Emergency Departments (ED) with opioid intoxication and received IV naloxone (initial dose 0.4 mg vs 1-2 mg), opioid toxicity was successfully reversed in 18 of 42 patients with 0.4 mg IV without the need for additional doses of naloxone. The time to recurrence of opioid toxicity after naloxone administration was not dependent on the first dose of IV naloxone administered[48].

A randomised clinical trial conducted in an Iranian ED setting, found that adequate response (defined as a level of consciousness of "lethargic" or "conscious" after treatment) was more likely after intranasal naloxone (0.4 mg/2 mL) than intravenous naloxone (0.4 mg) (100% vs. 60%; RR, 1.7 [CI, 1.3 to 2.1]) and agitation was less common after intranasal naloxone. (0% vs. 24%; RR, 0.04 [CI, 0.002 to 0.66])[49].

A recent double-blinded randomised placebo-controlled trial conducted in patients with suspected opioid poisoning and respiratory depression in Australia randomised patients to receive either IM naloxone 1.6 mg or saline placebo followed by IV naloxone as needed. Reversal of respiratory depression at 10 min was similar between groups. Recurrence of respiratory depression was reduced significantly with fewer naloxone infusions and fewer naloxone doses administered in the IM group. Opioid withdrawal was slightly increased in the IM naloxone group compared to the placebo group but not significantly[50]. It is unclear whether the patients included in this study are generalizable to the patient population outside Australia but it is possible that the longer duration of activity and lower peak concentration achieved with IM naloxone may be helpful in reducing opioid withdrawal and recurrence of respiratory depression.

There is concern that overdose with more potent novel synthetic opioids may require higher doses

of naloxone than are currently recommended to reverse respiratory depression. However, a review of case reports and case series indicate that naloxone remains an effective antidote for nitazene poisoning with effective reversal of opioid toxicity at a median 1.2 mg dose of parenteral naloxone in the hospital setting and a median dose of 0.8 mg in the pre-hospital setting. However, persistence of opioid effects requiring prolonged naloxone infusion occurred in 20% of patients, which may be a manifestation of their pharmacological property of slow dissociation from the MOR[51].

As a result, there has been a renewed effort to develop higher dose formulations of naloxone and new antidotes which are more potent opioid antagonists and more long-acting than naloxone. The opioid epidemic has also led to the implementation of take-home naloxone as secondary prevention in emergency department attenders with opioid overdose[52] as well as implementation of community-based naloxone distribution programs which have been shown to be effective in preventing opioid overdose deaths[53].

Novel antidotes

NALMEFENE

Nalmefene, a 6-methylene analogue of naltrexone, is an opioid antagonist that prevents or reverses the effects of opioids (including respiratory depression, sedation, and hypotension). Nalmefene has a longer duration of action than naloxone and has no opioid agonist activity.

In an open-label, randomized, crossover study in healthy volunteers comparing the reversal of remifentanil-induced respiratory depression by intranasal (IN) naloxone hydrochloride (4 mg) to IN nalmefene (2.7 mg), both nalmefene and naloxone produced a time-dependent reversal of remifentanil-induced reductions in minute volume measured 2.5-20 min post administration. At 5 min post-administration, increases in minute volume was significantly higher with nalmefene (5.75 L/min vs 3.01 L/min; $P < .0009$). Both nalmefene and naloxone were well-tolerated by healthy volunteers[54]. In another study, IM nalmefene (1 mg) achieved reversal of fentanyl-induced respiratory depression with a time to onset and a magnitude of reversal that is similar to, or better than, that achieved with standard-of-care naloxone products (IM naloxone 2 mg and IN naloxone 4 mg)[55].

The US FDA approved nalmefene injection and intranasal spray for the complete or partial reversal of opioid drug effects in 2023[56]. The intranasal spray is for the emergency management of known or suspected opioid overdose, and is the first approval of nalmefene for both healthcare and community use. Oral nalmefene is licensed for the treatment of alcohol dependence but the parenteral formulations are not licensed or currently recommended as an alternative to naloxone in the UK or EU. The rapid onset of action may prove particularly valuable in overdose with potent novel synthetic opioids and further studies in patients with opioid overdose are required to establish its safety and efficacy.

BUPRENORPHINE

Buprenorphine is a long-acting, high potency partial agonist at the MOR and is licensed as an opioid substitution treatment for opioid use disorder. In a study comparing IV buprenorphine (10 µg/kg in 28 patients and 15 µg/kg doses in 28 patients) and IV naloxone (titrated dose) in 29 patients with methadone-induced respiratory depression, 55/56 patients who received IV buprenorphine had rapid reversal of respiratory depression, which persisted for at least 12 h whilst IV naloxone was effective in 28/29 patients, but often required very high titrated doses (thus delaying time to response) and prolonged infusion. Intubation (8/29 vs 5/56) and opioid withdrawal (15/29 vs 7/56) were less common with buprenorphine. There were no serious complications or deaths in those receiving buprenorphine. The 15 µg/kg buprenorphine dose appeared to provide a longer duration of action, but precipitated withdrawal more frequently than the 10 µg/kg dose. This small study in methadone overdose suggest that buprenorphine may be a safe and effective substitute to naloxone in patients taking opioids with a long half-life but further studies are required to determine the optimal dose[57].

FENTANYL IgG

The US Food and Drug Administration (FDA) has granted fast track designation for CSX-1004, an investigational therapy for prevention of fentanyl-related overdose. CSX-1004 is a human IgG1 monoclonal antibody specific for fentanyl and fentanyl analogues and works by sequestering fentanyl molecules as they enter the bloodstream, effectively neutralizing them in the blood before they reach the brain and preventing them reaching

their site of action. This is in the early stages of development[58].

METHOCINNAMOX

Methocinnamox is a long-lasting, pseudo-irreversible (non-covalent binding), potent, MOR antagonist but is a competitive antagonist at kappa and delta opioid receptors. Following a single subcutaneous injection, peak concentration occurs 15–45 min after injection with a half-life of 70 minutes and a duration of action of thirteen days. Methocinnamox is effective in reversing acute opioid overdose and prevents subsequent overdose for up to two weeks with minimal adverse effects in animal models. It is now being researched for opioid use disorder and opioid overdose[59].

NEGATIVE ALLOSTERIC MODULATORS

Negative allosteric modulators (NAM) of the opioid receptor bind away from the primary binding site and induce a conformational change, leading to potentiation of the effect of naloxone when it binds to the opioid receptor[60].

Discussion

Basic life support and administration of naloxone remains the cornerstone of treatment with early use associated with increased survival following opioid overdose. The optimal route and dosing of naloxone administration in different settings remain unclear and recent systematic reviews and evidence-based guidelines have attempted to summarise the existing studies which are often observational in nature and subject to a high risk of bias. Despite the large number of out-of-hospital opioid-related deaths, the evidence for the use of naloxone in pre-hospital cardiac arrest is poor and better designed studies are required to inform resuscitation guidelines.

Although the pharmacokinetics of naloxone favour the wider use of the IM delivery route in pre-hospital management by non-medical responders, this is best performed using an auto-injector device. The Evzio auto-injector device in the US was priced at $600 and required submission of prior authorisation for refund by insurers. Aggressive sales tactics led to a $12.7m fine from the US department of justice and withdrawal of the device from the market. The Zimhi 5mg auto-injector device is priced at around $150 in the US and is not available in Europe. The high dose of naloxone may increase the risk of opioid withdrawal and such a device may be best reserved for non-civilian use as a medical countermeasure for deliberate opioid release in chemical warfare. In addition, it is unlikely that intramuscular naloxone auto-injector device will become available for widespread use at a competitive price compared to currently available IN naloxone formulations. Intranasal formulations of naloxone have become available much more cheaply to facilitate early administration by pre-hospital and non-medical responders. Current evidence suggests that high concentration intranasal naloxone formulations are as effective as intramuscular naloxone but is more likely to require repeated dosing. Whilst intranasal delivery is likely to remain the standard for pre-hospital non-medical responders due to cost and ease of administration, the optimal dose to minimise adverse effects is not known, particularly when long-acting opioids such as methadone or novel potent synthetic opioids are involved.

For in-hospital management of opioid toxicity, the intravenous route is preferred to allow for careful titration to effect to reduce the risks of opioid withdrawal. Current guidelines recommend a starting dose of 100-200 micrograms in patients with respiratory depression. In the authors' experience, a starting dose of 200 micrograms intravenously is easier to administer in an emergency due to the formulation of the naloxone for injection as a 400 micrograms/mL vial. However, in patients receiving regular opioids for palliative care, a more cautious titration of naloxone may be required, starting at a dose of 40 micrograms. Another clinical scenario encountered in emergency departments is the illegal smuggling of opiates by "body packing" with sealed drug-filled packets swallowed by drug smugglers ("mules") and defecated at the destination. Body packers are at risk of delayed or prolonged toxicity as a result of package rupture resulting in release of large amounts of pure undiluted (uncut) opiate, often heroin. The management of body-packers is outside the scope of this article and is covered more extensively by specific management guidelines[61].

The high potency of new synthetic opioids and their slow dissociation kinetics from the MOR gave rise to initial concerns about the effectiveness of naloxone as an antidote, but clinical experience with patients intoxicated with nitazenes has shown that naloxone remains effective at reversing toxicity

but a higher proportion of patients require a naloxone infusion. Nevertheless, new synthetic opioids which are non-competitive agonists at the MOR may emerge, when very high doses of naloxone may be needed or naloxone may not be effective. This concern has led to research efforts into new antidotes for opioid toxicity. In small studies, nalmefene and buprenorphine are promising for management of overdoses with long-acting opioids such as methadone but require formal evaluation in large randomised controlled trials before they can be recommended as alternatives to naloxone[62,63]. Other highly experimental approaches include the development of drug-specific monoclonal antibodies, long-lasting μ opioid receptor non-competitive antagonists and allosteric modulators that can be used synergistically with naloxone to potentiate its effect.

Secondary prevention strategies targeted at opioid users admitted to hospital following overdose including referral for opioid substitution treatment and provision of take-home naloxone have been shown to reduce opioid-related deaths. The evolving international opioid overdose crisis with the emergence of new potent synthetic opioids which can be produced in clandestine laboratories and easy to acquire cheaply on internet sites creates a public health hazard with the potential for increased morbidity and mortality associated with their use. A coordinated global monitoring system together with primary prevention and harm reduction strategies are required to address this global public health problem.

Conclusions

Opioid-related deaths from overdose is a growing problem worldwide and the emergence of novel potent synthetic opioids has given new impetus to development of guidelines for management of opioid toxicity out-of-hospital and in emergency departments. Naloxone remains the gold standard treatment and new intranasal and intramuscular formulations have become available recently to facilitate pre-hospital administration. The intravenous route is preferred in hospital to allow careful titration to clinical effect without precipitating opioid withdrawal. New antidotes are in development but will require carefully designed randomised clinical trials to determine their safety and effectiveness.

Conflict of Interest Statement:

AK declares no conflict of interest. RT has received a honorarium from BMJBestPractice to author an article on management of opioid overdose and was a member of the guideline development group of the Royal College of Emergency medicine guideline on management of opioid overdose in UK emergency departments.

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AK and RT contributed equally to drafting the manuscript. RT made substantial revisions to the manuscript and provided senior oversight of its production. All authors contributed to the critical revision of the manuscript for important intellectual content. Both authors gave final approval of the version to be published.

Ethics Approval and Consent to Participate

Not applicable.

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