Joint RCEM and NPIS best practice guideline: assessment and management of acute opioid toxicity in adults in the emergency department

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ABSTRACT

The Royal College of Emergency Medicine Toxicology Special Interest Group in collaboration with the UK National Poisons Information Service and the Clinical Toxicology Department at Guy's and St Thomas' NHS Foundation Trust has produced guidance to support clinicians working in the ED with the assessment and management of adults with acute opioid toxicity. Considerations regarding identification of acute opioid toxicity are discussed and recommendations regarding treatment options and secondary prevention are made. There is a focus on making recommendations on the best available evidence.

PREFACE

The Royal College of Emergency Medicine (RCEM) best practice guideline (BPG) was produced by members of the RCEM Toxicology Special Interest Group, the UK National Poisons Information Service and clinicians from the Clinical Toxicology Department at Guy's and St Thomas' NHS Foundation Trust. BPGs use a multimodal search strategy to produce guidance for areas of clinical controversy where little robust evidence exists or areas of particular concern or anxiety to fellows and members.[1] This BPG was originally published online in May 2024.

KEY RECOMMENDATIONS

1. In acute opioid toxicity, the aim of naloxone administration should be reversal of respiratory depression and maintenance of airway protective reflexes, not full reversal of unconsciousness. (Recommendation level C)
2. Adverse effects from naloxone are more likely to occur when excessive doses of naloxone are used. (Recommendation level B)
3. Generally, patients should be observed for at least 4 hours after the last dose of naloxone and for at least 6 hours after the suspected time of opioid use. The length of the observation period may need to be adjusted from this standard depending on the duration of the effect of the opioid(s) taken. (Recommendation level C)
4. The treatment of patients who have experienced a non-fatal overdose provides a valuable opportunity to provide brief intervention, onward referral to drug liaison services and to promote engagement with community services. (Recommendation level B)

A key to the strength of recommendations taxonomy is given in table 1.

SCOPE

The scope of this guideline is limited to the initial management, in the ED, of acute opioid toxicity related to the use of illicit opioids, and/or misuse (non-medical use), or deliberate self-poisoning (overdose) of prescription and over-the-counter opioids. It is *not applicable* for opioid toxicity in patients taking prescribed opioids for palliative care/cancer pain (follow guidance on TOXBASE for management of these patients), or for managing acute opioid toxicity in settings other than EDs.

BACKGROUND

Acute opioid toxicity is a common reason for presentation to EDs in the UK and constitutes a significant burden on emergency health services. Presentations are more common at weekends, in the late evening and at night, but can occur at any time of the day.[2]

Across Europe, opioids are the drugs most frequently encountered in acute drug toxicity presentations to the ED (heroin in particular, but presentations involving other opioids, including methadone, are also common).[2 3] In relation to other class A drugs, 1 085 000 people aged 16–59 years old in England and Wales reported use of any class A drug in the last year; 64 000 of these were opioids including heroin or methadone.[4]

Acute opioid toxicity has a high potential for significant mortality. Opioid-related drug deaths are common, averaging 60 per week in Great Britain in 2022.[5–7] In Scotland, the rate of drug poisoning deaths was 2.7 times as high as the UK average in 2022 and opiates/opioids were implicated in 82% of all drug misuse deaths.[8] Increasing trends in mortality related to prescription opioid misuse have also been noted since 2013 across Europe.[9]

There have been an increasing number of new psychoactive substance (NPS) reported in Europe in recent years. Since 2009, a total of 74 NPS opioids have been identified on the European drug market; these are often found in products purported to be heroin and so users may not be aware that they are using these novel opioids.[10] These synthetic NPS opioids are often highly potent and/or longer acting than heroin, meaning that a typical street dose can pose an increased risk of life-threatening acute opioid toxicity, particularly as users may not be

Table 1 The strength of recommendations taxonomy[28]

Strength of recommendation	Definition
A	Recommendation based on consistent and good-quality patient-oriented evidence
B	Recommendation based on inconsistent or limited-quality patient-oriented evidence
C	Recommendation based on consensus, usual practice, opinion, disease-oriented evidence and case series for studies of diagnosis, treatment, prevention or screening

aware that they are being exposed to a novel opioid when using drugs such as heroin.[10]

There have been several outbreaks of severe acute opioid toxicity and deaths relating to novel opioids such as fentanyls and nitazenes (eg, isotonitazene which has twice the potency of fentanyl) in recent years.[11] These have led to spikes in drug-related deaths in England in 2017, 2021 and 2023,[12] prompting local and national concern and making the management of opioid toxicity in the ED even more relevant today.

IDENTIFICATION OF OPIOID TOXICITY

Acute opioid toxicity typically causes the triad of (1) drowsiness (central nervous system depression), (2) respiratory depression (hypoventilation and reduced respiratory rate) and (3) pupillary miosis.

Other symptoms and signs may be present and can include the following[13]:

- Nausea and vomiting
- Neuropsychiatric features including nightmares, anxiety, agitation, euphoria, dysphoria, depression, paranoia and hallucinations
- Urticaria and pruritus
- Convulsions
- Hypotension and bradycardia
- Hypothermia secondary to environmental exposure

Commonly, opioids are co-ingested with alcohol or other drugs that can exacerbate respiratory depression (benzodiazepines and GABA-ergics such as pregabalin),[14] or with other drugs that result in mixed toxicity (sympathomimetics such as crack cocaine or synthetic cannabinoid receptor agonists)[2] which may mask the typical opioid toxidrome and/or result in additional adverse effects.

The severity and duration of opioid toxicity will vary depending on the amount of opioid used, the potency of the opioid(s), the opioid tolerance of the individual and the route of use (oral, inhalation and/or intravenous).

Urine drug screening has *no* role in the immediate clinical management of patients presenting to the ED where acute opioid toxicity is clinically considered. The diagnosis of an opioid toxidrome is clinical and should be based on history, symptoms and signs. Naloxone can be a useful diagnostic agent in a patient with drowsiness and significant respiratory depression. In cases where there is uncertainty regarding the presentation, discussion with a clinical toxicologist via the UK National Poisons Information Service is recommended.

MANAGEMENT

Naloxone is widely accepted as the antidote for opioid toxicity. It acts as a mu-opioid receptor antagonist. Naloxone can have a role not only to treat opioid toxicity, but also as a therapeutic trial in those with respiratory depression and suspected opioid toxicity. The preferred route of use for naloxone in the ED is intravenous, but it can also be administered intramuscularly, intranasally[15] or intraosseously[16]—these routes should generally *only* be considered in the ED for patients in whom intravenous access is difficult or not possible. It should be noted that the intramuscular and intranasal routes of administration are associated with a longer time to peak blood concentrations of naloxone. We actively discourage giving intramuscular naloxone alongside intravenous naloxone, or intramuscular naloxone prior to discharge of patients with acute opioid toxicity.

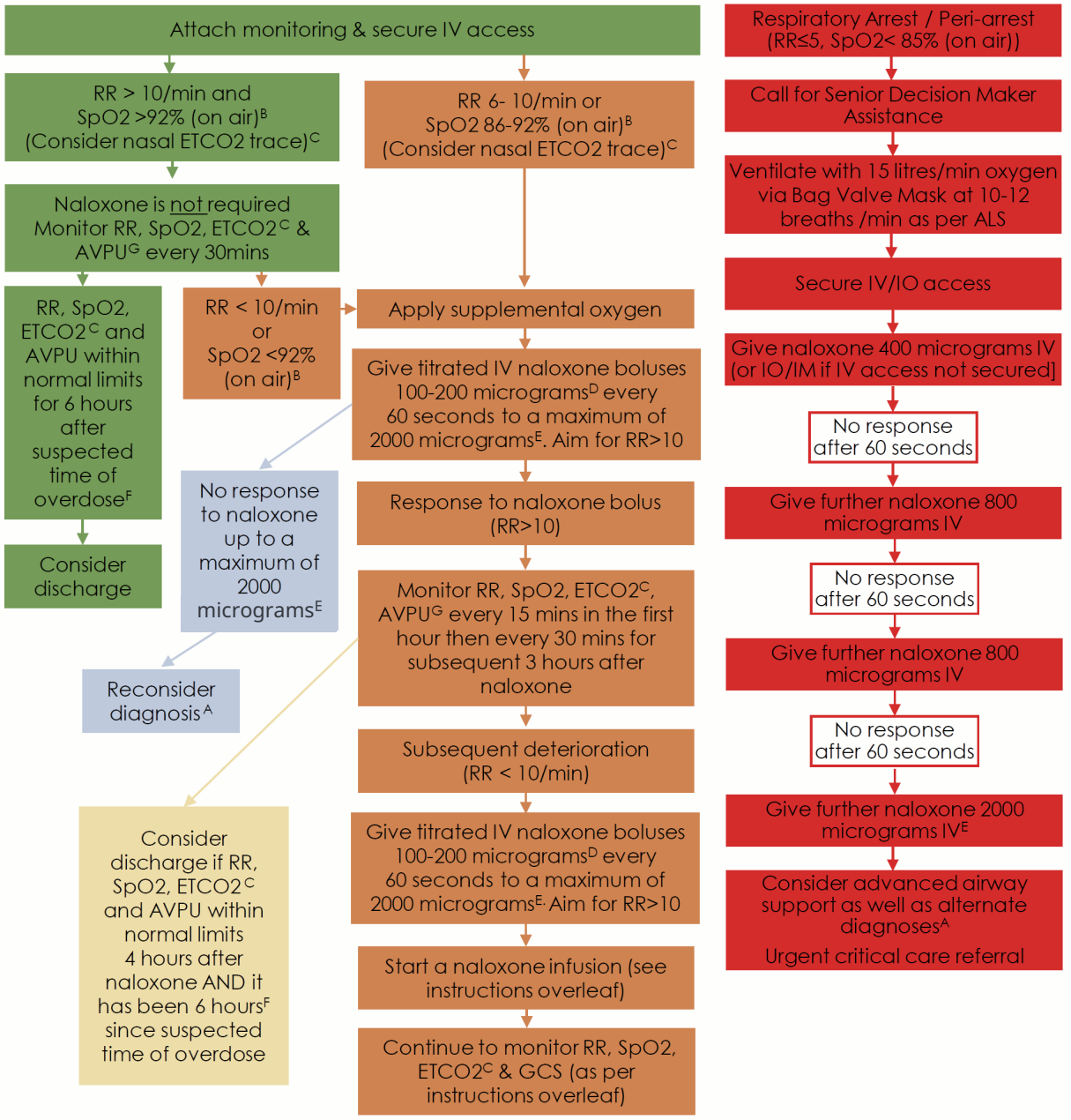
Figure 1 summarises the management of patients with suspected acute opioid toxicity in the ED. It is important to note that the recommended dosing of naloxone depends on the circumstances of exposure and severity of respiratory depression. In the hospital setting, smaller intravenous doses are preferable for initial (non-respiratory arrest) treatment as this enables the clinician to ascertain the dose required to reverse respiratory depression while also avoiding the risk of acute iatrogenic opioid withdrawal.[17] This is key as although opioid reversal leading to acute iatrogenic opioid withdrawal is not typically life-threatening, it may be compounded by overzealous opioid reversal unmasking stimulant toxicity in individuals who have used opioids with stimulants such as cocaine or methamphetamine. Features of acute opioid withdrawal are listed in table 2. Measures to control an agitated patient in this situation, such as chemical or physical restraint or paralysis and intubation, may have negative consequences and carry significant risk for both patients and staff.[18] The process of acute opioid withdrawal is often distressing to patients and may cause patients to avoid accessing healthcare.[19] The importance of avoiding acute opioid withdrawal to reduce negative patient experiences and provide an opportunity for secondary prevention in a calm setting cannot be overstated.

In acute opioid toxicity, the aim of naloxone administration should be reversal of respiratory depression and maintenance of airway protective reflexes, *not full reversal of unconsciousness*. Although level of consciousness (eg, alert, verbal, pain, unresponsive; GCS) can be useful to monitor, therapeutic targets should be an RR of over 10 breaths/min and oxygen saturation of greater than 92% on room air (in the absence of pre-existing respiratory disease such as chronic obstructive pulmonary disease where target saturation may routinely be 88–92%). Additionally, if available and where clinicians are experienced with its use, nasal end-tidal carbon dioxide monitoring can be used as an adjunct to the clinical assessment of ventilatory status to aid decision-making.

Naloxone is generally well tolerated, but reported adverse effects of naloxone include nausea, vomiting, sweating, tachycardia, tremor, hyperventilation and hypertension; these effects are more likely to occur when excessive doses of naloxone are used, reinforcing the importance of using titrated doses of naloxone to avoid inducing acute opioid withdrawal related to opioid reversal.[20 21] Less commonly, cardiac adverse effects may occur, particularly in patients who are taking opioids for pain relief and have pre-existing cardiac disease: hypotension or hypertension, pulmonary oedema, atrial and ventricular fibrillation and cardiac arrest have been reported. However, these adverse effects may have resulted from non-cardiogenic pulmonary oedema related to the opioid rather than an unwanted effect of the naloxone. Finally, there are rare reports of convulsions following the use of naloxone; however, a causal link has not been shown and there is the potential that these convulsions may have been related to drugs co-used with opioids rather than to

Figure 1: Management of suspected acute opioid toxicity in adults in the ED[A]

(this should NOT be used for opioid toxicity in patients taking prescribed opioids for cancer pain)



A. Always consider alternate diagnoses, investigations should include BM, VBG, paracetamol concentration ± CT Head
B. Interpret saturations with caution in those with pre-existing respiratory disease such as COPD
C. If available (and clinicians are experienced in its use), nasal ETCO2 can be used as an adjunct to the clinical assessment of ventilatory status to aid decision making, but it should be interpreted with caution in those with pre-existing respiratory disease and in context of the history and clinical signs
D. Initial naloxone bolus doses should be 100 micrograms, if the patient does not respond to four 100 microgram boluses, subsequent bolus doses should be 200 micrograms. Draw up 1x 400 microgram naloxone vial in a 10mL syringe and make up to 10mL with saline. A 100 microgram bolus will be 2.5mL and a 200 microgram bolus will be 5mL.
E. Those with severe toxicity or exposed to highly potent opioids may require larger doses of naloxone (more than 4 mg)
F. If a patient reports, or the clinician suspects, use of a longer acting opioid such as methadone or an NPS opioid the observation period should be extended up to 12 hours.
G. Whilst it is useful to monitor level of consciousness (AVPU, GCS), the aim of naloxone administration should be reversal of respiratory depression and maintenance of airway protective reflexes, not full reversal of unconsciousness.

This is a suggested pathway for management and not a mandatory standard of care. Clinicians (particularly senior decision-makers with sufficient anaesthetic training) may choose use alternative approaches, including oxygenation with permissive hypercapnia, or lower bolus doses of naloxone, and tolerate lower respiratory rates than suggested here.

Figure 1 Management of suspected acute opioid toxicity in adults in the ED.[A] AVPU, alert, verbal, pain, unresponsive; BM, capillary blood glucose; COPD, chronic obstructive pulmonary disease; $ETCO_2$, end-tidal carbon dioxide; IM, intramuscular; IO, intraosseous; IV, intravenous; NPS, new psychoactive substance; SPO_2, oxygen saturation; VBG, venous blood gas.

Table 2 Features of acute opioid withdrawal

Features of acute opioid withdrawal	
Yawning	Coughing
Sneezing	Runny nose
Lacrimation	Hypertension
Tachycardia	Dilated pupils
Diarrhoea	Cool, clammy skin
Fine muscle tremor	Nausea
Irritability	Restlessness
Anxiety	

naloxone.[22] Clinically, it is difficult to ascertain whether many of the reported adverse effects of naloxone actually relate to co-used drugs or the opioid toxicity itself.

COMMENCING A NALOXONE INFUSION

As noted in figure 1, incremental intravenous boluses of naloxone (100–200 micrograms every 60 s) should be administered until the RR is greater than 10 breaths/min. Patients may require large doses of up to 2000–4000 micrograms, but it is important that naloxone is given in small incremental doses to decrease the risk of acute withdrawal syndrome related to opioid reversal. Following an initial response, if the patient subsequently deteriorates and requires further intravenous boluses of naloxone to maintain adequate ventilation, they will require a naloxone infusion.

It is recommended starting with an hourly infusion rate of naloxone of 60% of the total dose(s) of naloxone that were required to adequately reverse the respiratory depression during the second dosing of naloxone.

With high-dose infusions, be aware that the syringe may need replacing relatively soon, and it may be appropriate to provide a follow-on prescription at the same time as the initial prescription.

Preparation: mix 4 mg (10×400 micrograms/1 mL vials) of naloxone with 30 mL of 0.9% sodium chloride solution (dextrose can be used as an alternative), to provide a final 40 mL volume with a concentration of 100 micrograms/mL, for infusion using an intravenous pump.

Administration: table 3 gives indicative starting infusion rates in micrograms/hour and mL/hour of prepared solution.

MONITORING OF PATIENTS ON A NALOXONE INFUSION

Once commenced, the naloxone infusion should be titrated to the desired clinical effect. Patients on naloxone infusions require frequent observation, initially every 15 min for first hour after the infusion is started and then every 30 min. If a patient on a naloxone infusion shows signs of respiratory depression (RR of less than 10 breaths/min, oxygen saturation on room air of less than 92% and/or a concerning end-tidal carbon dioxide trace), further intravenous boluses of 100–200 micrograms naloxone should be given every 60 s up to a maximum of 2000 micrograms to achieve an RR of over 10 breaths/min. The infusion rate/hour can then be increased by 60% of the total bolus dose of naloxone that was required. If a patient on a naloxone infusion begins to show signs of acute opioid withdrawal syndrome, the infusion rate should be decreased, generally by 50% in the first instance, but if the patient is significantly agitated, the naloxone infusion can be stopped temporarily; the infusion can be restarted after 30–60 min, at 50% of the previous infusion rate/hour, once the withdrawal settles. If the naloxone infusion dose/rate is changed, more frequent monitoring should recommence with observations every 15 min for the first hour and every 30 min thereafter.

Table 3 Recommended starting infusion rates for naloxone infusions

Total initial bolus dose required for response	Starting infusion rate (micrograms/hour)	Starting infusion rate (mL/hour)
200 µg	120	1.2
400 µg	240	2.4
600 µg	360	3.6
800 µg	480	4.8
1000 µg	600	6.0
1200 µg	720	7.2
1400 µg	840	8.4
1600 µg	960	9.6
1800 µg	1080	10.8
2000 µg	1200	12.0

µg, microgram.

Stopping a naloxone infusion

After commencing a naloxone infusion, unless there is evidence of recurrence of toxicity or acute withdrawal, the infusion should continue at the same rate for at least 4 hours before starting to titrate the infusion down. It should then be downtitrated by 25% of the maximum infusion rate every 2 hours while the patient continues to undergo close observation for signs of recurrence of toxicity or acute withdrawal.

It is unlikely that the titration of a naloxone infusion down will be done within the ED unless there are significant delays in organising admission.

A naloxone infusion should not generally be stopped at night (midnight–06:00) unless the patient is experiencing features of acute opioid withdrawal syndrome because recurrence of acute toxicity may be more difficult to routinely detect overnight if the patient is sleeping.

Discharge following the use of naloxone

Patients treated with naloxone and responding with normal observations and mental state may be discharged after an appropriate observation period. Ideally, patients should be observed for at least 4 hours after the last dose of naloxone and for at least 6 hours after the suspected time of opioid use. However, the length of the observation period may need to be adjusted from this standard depending on the duration of the effect of the opioid(s) taken. If a patient reports using a longer-acting opioid or the clinician suspects this (eg, methadone or an NPS opioid), the observation period may need to be extended up to 12 hours.

SECONDARY PREVENTION

One longitudinal study in the USA found that at 12 months following a non-fatal opioid overdose, patients died at approximately 24 times the rate of the general population.[23] Causes of death included drug use-associated diseases, HIV, chronic respiratory diseases, viral hepatitis and suicide.

During a presentation to the ED secondary to acute opioid intoxication and/or overdose, emergency clinicians should always consider the opportunities for brief intervention, onward referral to drug liaison services and encourage engagement with existing community services.

Brief intervention can be provided in the form of verbal or written advice (see online supplemental appendix 1: messages for people who use drugs). Clinicians should be aware of the local drug liaison services in their area and encourage engagement with routes to opiate substitution therapy.

Provision of take-home naloxone varies depending on local commissioning arrangements, but increasingly both in-hospital and community drug services can provide take-home intramuscular or nasal naloxone products,[24] and provide the associated training to administer them. This is an intervention known to reduce drug-related deaths.[25 26]

Finally, presentations with acute opioid toxicity should be used as opportunities to consider bloodborne virus testing in this high-risk cohort as well as homelessness referral if applicable. EDs in England have a legal duty to refer someone who they believe to be experiencing homelessness or to be threatened with becoming homeless within 56 days, to a local housing authority of their choice.[27]

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Disclaimer The college recognises that patients, their situations, emergency departments and staff all vary. This guideline cannot cover all possible scenarios. The ultimate responsibility for the interpretation and application of this guideline, the use of current information and a patient's overall care and well-being resides with the treating clinician.

Competing interests MB—unpaid member of RCEM Toxicology Advisory Group. RG has no declarations of interest. DMW is a member of the UK Advisory Council on the Misuse of Drugs and an expert advisor to the European Monitoring Centre for Drugs and Drug Addiction and the United Nations Office on Drugs and Crime. He is also a clinical coordinator at the UK National Confidential Enquiry into Patient Outcomes and Death (NCEPOD), and on the editorial board of the *Journal of Medical Toxicology*. His work on these guidelines was independent of his roles with these organisations. RT—his work on these guidelines was in his role as director of NPIS (Newcastle). CH is an editor for the *Emergency Medicine Journal*, has received payments from Elsevier for educational articles, has been reimbursed for travel expenses by RCEM and is a recipient of grants from the Centre for Precision Cell Therapy for the Liver. His work on these guidelines was in his role as a member of the RCEM Toxicology Special Interest Group. PID is an adviser to the UK Advisory Council on the Misuse of Drugs, the European Monitoring Centre for Drugs and Drug Addiction the United Nations Office on Drugs and Crime, and the WHO. He is also a commissioner to the UK Commission Human Medicines, on the senior editorial board of *Clinical Toxicology*, and is the president elect of the European Association of Poisons Control Centres and Clinical Toxicologists. His work on these guidelines was independent of his roles with these organisations.

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