High-potency benzodiazepine misuse in opioid-dependent patients: use naloxone with care

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ABSTRACT

The misuse of highly potent benzodiazepines is increasing in the UK, particularly among the opioid-using population in Scotland. Differentiating opioid from benzodiazepine toxicity is not always straightforward in patients with reduced level of consciousness following drug overdose. Patients on long-term opioid substitution who present with acute benzodiazepine intoxication and are given naloxone may develop severe opioid withdrawal while still obtunded from benzodiazepines. This situation can be difficult to manage, and these patients may be at increased risk of vomiting while still unable to protect their airway. Fortunately, the short half-life of naloxone means that the situation is generally short-lived. Naloxone should never be withheld from patients with life-threatening respiratory depression where opioids may be contributing, particularly in community and prehospital settings; however, where appropriate clinical experience exists, naloxone should ideally be administered in small incremental intravenous doses with close monitoring of respiratory function. Increased awareness of the potential risks of naloxone in opioid-dependent patients acutely intoxicated with benzodiazepines may reduce the risk of iatrogenic harm in an already very vulnerable population.

CASE VIGNETTE

A 29-year-male on regular methadone is found collapsed in the street. The ambulance crew record a Glasgow Coma Scale (GCS) of 3, respiratory rate of 8 breaths/min, heart rate of 64 beats/min, blood pressure (BP) of 108/64 mm Hg, oxygen saturation of 92% on air, capillary blood glucose of 6 mmol/L, pupils 4 mm and sluggish, and no external evidence of head injury. Oxygen is applied and the patient moved to the ambulance where a dose of 0.4 mg naloxone is administered intramuscularly. On arrival at the ED 20 minutes later, he is agitated, groaning, thrashing about and difficult to contain on the trolley. His GCS is now 7 (E1, V2 and M4), respiratory rate 20 breaths/min, heart rate 90 beats/min, BP 154/90 mm Hg, oxygen saturations 100% on 15 litres of oxygen and capillary blood glucose 6.4 mmol/L. Pupils remain 4 mm and sluggish. During assessment, he begins to vomit and is turned into the lateral position. The ED team prepare for rapid sequence induction of anaesthesia. While drugs are being drawn up, the patient stops thrashing and appears to become deeply asleep. He maintains a respiratory rate of 16 and oxygen saturations of 95% on air, and with deep stimulation, his GCS is 10 (E2, V3 and M5). No further vomiting occurs. Non-invasive capnography shows a normal waveform, respiratory rate of 16 breaths/min and end-tidal carbon dioxide of 4.8 kPa. A CT scan of the head shows no abnormality. A pragmatic decision is taken to nurse him in the lateral position and transfer him to a high-dependency area for close monitoring of respiratory function. Two hours later, he is fully awake and states that he had taken 10 'street Valium' in addition to his usual methadone dose.

Opioids and benzodiazepines are two of the drug classes most familiar to emergency department (ED) clinicians, both as therapeutic agents and drugs of misuse. Both are associated with dependence and have distinct withdrawal syndromes. This paper discusses the potentially dangerous situation that can arise when naloxone administration precipitates opioid withdrawal in a patient acutely intoxicated with benzodiazepines. Data are provided to show why this presentation is likely to become increasingly common in the UK. A case vignette is used to illustrate key features of this presentation and to highlight management options.

The UK has the highest rates of problem opioid use in Europe.[1] The drug-related death rate in Scotland is 12 times the European average,[1] with opioids implicated in 89% of drug-related deaths in 2020.[2] The UK also has one of the largest populations of opioid users enrolled in Opioid Substitution Treatment[1]: in Scotland over 30 400 patients were prescribed methadone or buprenorphine in 2020/2021, more than 1 in every 200 people.[3]

Naloxone was first synthesised in 1960 and rapidly emerged as the leading opioid antagonist due to its high efficacy in reversing opioid-induced respiratory depression.[4] Naloxone is a life-saving drug,[5] and in 2011, Scotland became the first country in the world to roll out a national naloxone programme. A total of 58 000 take-home naloxone kits were issued to persons at risk of opioid overdose or their close contacts between 2011 and 2019.[6]

In the UK, naloxone dosing recommendations are given in the Toxbase database,[7] the guidelines of the Joint Royal Colleges Ambulance Liaison Committee (JRCALC),[8] and the summary of product characteristics (SPC) for two formulations of take-home naloxone (Prenoxad and Nyxoid).[9 10] The indications, routes and doses recommended in these guidelines are compared in table 1.

Naloxone causes few side effects in opioid-naïve patients, but patients with opioid dependence can

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Table 1 Comparison of recommendations from Toxbase, JRCALC, and the SPC for Prenoxad and Nyxoid

	Toxbase[7]	JRCALC[8]	Prenoxad SPC[9]	Nyxoid SPC[10]
Listed indications	Reversal of the effects of opioid poisoning, in particular, respiratory and CNS depression.	Reversal of acute opioid or opiate toxicity for respiratory arrest or respiratory depression Unconsciousness, associated with respiratory depression of unknown cause, where opioid overdose is a possibility	In patients where breathing does not appear to be normal In patients where breathing is normal, but the patient is unrousable or suspected to be unconscious	Known or suspected opioid overdose as manifested by respiratory and/or CNS depression
Route	Intravenous recommended Can be given intramuscularly if intravenous access not possible or delayed	Intravenous or intraosseous recommended Can be given intramuscularly, subcutaneously or intranasally if intravenous/intraosseous route not available, or clinician not trained to administer drugs intravenously/intraosseously	Intramuscular	Intranasal
Initial dose	For severe opioid-induced respiratory depression: 0.4 mg intravenously In patients at risk of acute withdrawal, for example, chronic opioid use: 0.1–0.2 mg intravenously No specific recommendation for intramuscular route	For respiratory arrest/respiratory depression: 0.4 mg intravenously For adults who may be opiate dependent: 0.1 mg intravenously at a time, titrating to response For intramuscular/subcutaneous route: 0.4 mg For intranasal route: 0.4 mg	0.4 mg	1.8 mg
Goal	Aim for reversal of respiratory depression and maintenance of airway protective reflexes, not full reversal of unconsciousness.	Titrate to relieve respiratory depression but maintain patient in 'groggy' state.	Repeat every 2–3 min until an ambulance arrives or the patient begins breathing normally/regains consciousness.	Repeat after 2–3 min if necessary to relieve respiratory depression.

Comparison is restricted to recommendations for adult patients.
CNS, central nervous system; JRCALC, Joint Royal Colleges Ambulance Liaison Committee; SPC, summary of product characteristics.

experience severe withdrawal symptoms after naloxone administration.[4] The dose of naloxone that will precipitate opioid withdrawal in an individual patient is dependent on many factors (such as which opioids have been taken and when, degree of opioid dependence and route of naloxone administration)[11] and is notoriously difficult to predict. Outcomes reported in the literature reflect this unpredictability. For example, one series of 15 patients with predominantly methadone-induced respiratory depression required a median dose of only 0.08 mg naloxone intravenously to restore adequate ventilation, and two patients receiving this dose developed symptoms of opioid withdrawal.[12] In a recent series of 197 patients with predominantly heroin-induced respiratory depression who received a standardised dose of 1.6 mg naloxone intramuscularly, adequate ventilation was restored in 97% of presentations; withdrawal occurred in 39%, severe agitation in 7% and vomiting in 3%.[13] The optimal dosing and route of naloxone administration continue to be debated.[14]

Benzodiazepines have traditionally been associated with less severe overdoses and far less deaths than opioids. However, recent years have seen a dramatic rise in the use of novel, highly potent benzodiazepines in the UK.[2] The 2020 European Drug Report noted that 'in Scotland, criminal groups are known to be involved in the large-scale illicit manufacture and distribution of fake benzodiazepine medicines. Typically made to look like 10-milligram diazepam tablets, and known as 'street Valium', these fakes often contain new or uncontrolled benzodiazepines'.[1] Hospital stays due to sedative/hypnotics increased fivefold in Scotland between 2009/2010 and 2019/2020,[15] and benzodiazepines were implicated in 73% of drug-related deaths in 2020—the majority of these involving potent illicit benzodiazepines such as etizolam.[2]

Concurrent use of benzodiazepines and opioids is common, with the majority of illicit benzodiazepine users in Scotland also using opioids.[16] This presents a challenge for clinicians when assessing the unresponsive patient with suspected drug overdose: is this opioid toxicity, benzodiazepine toxicity or a combination of both, and does the patient have a background of dependence on either drug class?

Differentiating opioid and benzodiazepine toxicity in the setting of illicit drug use is not straightforward. The miosis typical of opioids may be absent with coingestion of other drugs or following significant brain hypoxia.[17 18] The more familiar benzodiazepines tend not to cause profound respiratory depression except in massive overdose, but novel benzodiazepines may be much more potent: clonazolam, currently circulating in Scotland, is 50 times more potent than diazepam and can cause deep sedation at doses as low as 0.5 mg.[19]

Does the increasing use of highly potent benzodiazepines in the opioid-dependent population alter the risks and benefits of naloxone administration? The traditional view of precipitated opioid withdrawal is that it is 'unpleasant but not life-threatening'.[17] The case vignette, however, illustrates a scenario in which real danger may exist. In this case, the patient was on opioid substitution therapy (thus opioid-dependent) and had taken his daily dose of methadone. He had then ingested a quantity of benzodiazepines of unknown nature and strength and had become unresponsive as a result of benzodiazepine toxicity. Since naloxone does not reverse benzodiazepines, the effect of naloxone in this patient was to precipitate acute opioid withdrawal by reversing his methadone, while he remained significantly obtunded from the effects of benzodiazepines. His GCS of 3 'improved' to 7, but he was now agitated, groaning and thrashing with the pain of opioid withdrawal. Most dangerously, he was now vomiting while potentially unable to protect his airway.

A similar situation can arise if opioid withdrawal is precipitated in a patient intoxicated with other sedating drugs, such as gabapentinoids or antidepressants. In Scotland, however, the high prevalence of illicit benzodiazepines makes this by far the likeliest cause.

Surprisingly little literature exists on the phenomenon of concurrent sedative/hypnotic toxicity and opioid withdrawal. A few older reviews of 'coma cocktails' discuss the risk of precipitated opioid withdrawal in patients obtunded from other causes,[5 20] but contemporary case reports involving highly potent benzodiazepines appear to be lacking.

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In this context, when and how should naloxone be given to balance the risks? The answer depends on the setting in which naloxone administration is being considered and what other management options are available to providers at the time. The Prenoxad SPC has the most liberal indications for naloxone (table 1): as well as patients who are not breathing normally, administration is recommended 'where breathing is normal but the patient is unrousable or suspected to be unconscious'.[9] A relatively high dosing regime (0.4 mg intramuscular every 2–3 min) is recommended. Since lay responders cannot be expected to make a detailed assessment of respiratory depression and have limited options for monitoring and supporting ventilation, early and liberal use of naloxone in this setting seems appropriate regardless of the risk of withdrawal or the presence of benzodiazepines, as there may be a very narrow window of opportunity to save life.

JRCALC offers more nuanced recommendations on naloxone administration for trained prehospital clinicians.[8] Naloxone is recommended only in the presence of respiratory depression and not for the reversal of coma alone, and intravascular (intravenous or intraosseous) administration is recommended when possible. Importantly, clinicians are advised that in patients at risk of opioid withdrawal, naloxone should be given in doses of 0.1 mg at a time, titrated 'to relieve respiratory depression but maintain the patient in a 'groggy' state'. If vascular access cannot be gained, then an initial intramuscular, subcutaneous or intranasal dose of 0.4 mg is recommended.

In the author's experience, some prehospital crews are more liberal with naloxone than JRCALC recommends, at times administering it to adequately ventilating patients with the explicit aim of waking them up. Aside from exposing clinicians to danger if these patients become agitated in the back of an ambulance, this strategy may be particularly risky in opioid-dependent patients with benzodiazepine intoxication who are at increased risk of vomiting while still obtunded. Having said this, detailed assessment of ventilatory status may be difficult in the field, and missing respiratory depression is likely to be worse than overtreating it. Therefore, depending on the skills and resources of the prehospital team, more liberal use of naloxone may be at times appropriate.

It is in the ED setting that there is most room for a careful approach to the use of naloxone, particularly if there is uncertainty as to whether a patient is predominantly benzodiazepine or opioid toxic.

First, it is possible to make a more detailed assessment of ventilatory status. Non-invasive waveform capnography gives a continuous measure of respiratory rate, and the trend in end-tidal carbon dioxide over time can act as an early indicator of ventilatory failure. Blood gas analysis meanwhile provides definitive information on ventilatory status at a given moment in time.

Second, Toxbase explicitly recommends intravenous administration of naloxone to allow for accurate titration (table 1).[7] While patients with a history of injecting drug use can be difficult to cannulate, EDs generally have the lighting, the staff and the advanced tools (such as ultrasound) to be able to achieve vascular access given sufficient time. The perception that naloxone should be administered as quickly as possible to patients with respiratory depression can be challenged: these patients do not die from a lack of naloxone but from a lack of ventilation. If sufficiently experienced staff are present, it may be safer to provide ventilation using a bag–valve–mask device with airway adjuncts while vascular access is obtained than to administer a larger dose of naloxone by another route and risk uncontrolled withdrawal.[11]

Finally, Toxbase recommends titrating boluses of 0.1–0.2 mg naloxone intravenously in patients at risk of opioid withdrawal.[7] However, given that withdrawal can occur with inravenous naloxone doses as low as 0.08 mg, a more cautious approach is to titrate boluses of 0.04 mg intravenously every 2–3 min until adequate spontaneous ventilation is restored, thus aiming to avoid severe opioid withdrawal.[12]

Acknowledging that these patients are more difficult to manage in the prehospital environment, EDs can expect from time to time to receive patients who are predominantly benzodiazepine-toxic but who have received naloxone prehospital and are showing significant opioid withdrawal, as in the case vignette. The first step is to recognise this condition for what it is. It may otherwise be mistaken for partially treated opioid overdose and further naloxone administered, worsening opioid withdrawal without improving GCS. Conversely, when these patients arrive in the ED dangerously agitated and uncooperative, they may actually require rapid tranquilisation. In the author's experience, this is an ideal use for droperidol,[21] allowing clinicians to avoid administering further benzodiazepines. If a benzodiazepine is felt to be necessary, then a short-acting drug such as midazolam should be chosen and given in small increments in an attempt to avoid oversedation.

If recognised, on the other hand, the clinical course of opioid withdrawal with benzodiazepine intoxication can be predicted based on pharmacokinetics. Naloxone is rapidly metabolised and has a duration of action of 20–90 min.[4] This is far shorter than methadone or buprenorphine, but also shorter than almost all benzodiazepines. The opioid withdrawal component is thus likely to be short-lived, and as the naloxone wears off, the patient will return to a much more sleepy and manageable state. Close attention must of course be paid to respiratory function at this stage, and ventilation may need to be supported while decisions are taken on further management. The patient's trajectory will then depend on which benzodiazepines have been taken, when and in what dose. As this information will almost certainly be unknown to the clinician (or indeed the patient), observation in a high-dependency area is likely to be the safest approach.

Could there be a role for flumazenil in these situations? Flumazenil is used much less frequently than naloxone due to the combination of rare but serious side effects (seizures) and the fact that traditional benzodiazepines are less commonly associated with life-threatening respiratory depression. Whether the advent of novel, highly potent benzodiazepines will alter this balance of risks and benefits is not yet clear. Significant respiratory depression may become more common, but users may also be more likely to be benzodiazepine-dependent and therefore precisely the group at highest risk of withdrawal seizures if given flumazenil. For now, administration of flumazenil in unresponsive patients who may be regular benzodiazepine users remains relatively contraindicated.

In summary, the high efficacy of naloxone in restoring ventilation in patients with life-threatening respiratory depression has resulted in its widespread adoption by clinicians and lay responders, with the potential to save a great many lives. However, a dramatic rise in the use of highly potent benzodiazepines among the opioid-using population, particularly in Scotland, means that many opioid-dependent individuals who present unconscious will be acutely intoxicated with benzodiazepines rather than opioids. If these patients are given naloxone, they are at risk of developing opioid withdrawal while still obtunded from benzodiazepines, a potentially dangerous situation. In the community setting, the balance of risks will almost always favour naloxone administration. However, in the prehospital and ED

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settings, depending on the skills and experience available, a more considered approach to naloxone administration may reduce the risk of iatrogenic harm in an already very vulnerable patient population.

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