What naloxone doses should be used in adults to reverse urgently the effects opioids or opiates?

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Summary

Naloxone is a highly effective antidote for opioids and opiates and its use is potentially life-saving in many circumstances. It is used across a range of care settings where opioid and opiate use is common, and for a number of scenarios that range from management of drug misuse and dependence to the provision of palliative care.

However, as with any drug, its use may also pose risks against which the benefits of treatment need to be weighed. Giving too much naloxone can cause acute withdrawal syndrome (AWS) and a return of pain. Other effects, such as cardiac arrhythmias and pulmonary oedema, are also possible which in some circumstances can be potentially life-threatening in themselves. Hence thought needs to be given to the use and dosing of naloxone, and as a result has been subject to NHS England Patient Safety Alerts (1;2).

Regardless of the reason for the exposure to opioids or opiates, urgent or emergency use of naloxone should only ever be considered where there is an immediate threat to life or a diagnosis of respiratory depression (reduced respiratory rate with a corresponding decrease in oxygen saturation). The primary aim of treatment is to reverse the toxic effects of opiates such that patients are no longer at risk of respiratory arrest, airway loss, or other opioid-related complications. The primary aim of treatment **should not** be to restore a normal level of consciousness, and indeed in some circumstances restoring a normal level of consciousness is entirely inappropriate.

Naloxone is given most often by the **intravenous** or **intramuscular** routes. A range of preparations are available in the UK; the majority are licensed to be given via either of these routes (3-9).

Two dosing regimens exist for naloxone. These are: **higher initial dose regimens** and **lower initial dose regimens**. For both, an **initial dose** will often need to be followed by **subsequent doses carefully titrated to effect**. In some circumstances a **continuous naloxone infusion** may also be warranted.

Higher initial dose regimens are used primarily in **emergency situations associated with drug misuse and dependence**; they are **not** normally appropriate in the context of long term opioid therapy. They are characterised by the licensed dose summarised in the BNF:

By intravenous injection, *400 micrograms; if no response after 1 minute, give 800 micrograms, and if still no response after another 1 minute, repeat dose of 800 micrograms; if still no response, give 2 mg (4 mg may be required in a seriously poisoned patient), then review diagnosis; further doses may be required if respiratory function deteriorates (10)*

Similar regimens may also be given by other routes. Intramuscular administration of naloxone can be performed by clinicians or by anyone in an emergency for the management of acute overdose for the purpose of saving a life; a product exists with a licence that covers specifically use in the community (9). The following intramuscular dose is derived from UK Ambulance Services Guidance:

By intramuscular injection, *400 micrograms initially, with further 400 microgram doses given incrementally every 3 minutes until an effect is noted (11)*

Lower initial dose regimens are used **by clinicians** in some circumstances of urgent and emergency use. They have use in **drug misuse and dependence**, in the context of **long term opioid therapy**, and in other circumstances where **tailored reversal** is necessary.

For the emergency management by clinicians of cases of **suspected drug misuse and dependence**, the following is derived from UK Ambulance Services guidance:

By slow intravenous injection, *dilute 2mL of an 800 microgram/2mL formulation of naloxone with 8mL of water for injection or sodium chloride 0.9%; give the resultant solution by slow intravenous injection (1mL [80mcg] at a time) to response to "relieve respiratory depression, but maintain patient in a 'groggy' state" (11)*

In the context of **long term opioid therapy** where return of pain is an issue, lower dose regimens are often appropriate. The following is derived from the Palliative Care Formulary and Palliative Care Guidelines Plus:

By slow intravenous injection, *initial dose of 100–200 microgram stat intravenously, followed by 100 microgram every 2 minutes* until respiratory function is satisfactory *(12-14)*

Even lower doses are also suggested: by ***intravenous injection,*** *20 micrograms* or 80 *micrograms given every two minutes* until respiratory function is satisfactory (12-18)

Continuous naloxone infusions may be of use where involvement of a long-acting opioid is known or suspected and the magnitude of the overdose particularly sizeable. Typical intravenous infusions include initiation of a dose of 60% of the initial IV bolus, given over 1 hour, with subsequent titration to respiratory rate and level of consciousness (12;19).

Background

The opioid and opiate antagonist, naloxone, is a highly effective antidote the use of which is potentially life-saving (20-22). The drug has a role in a wide range of clinical situations and practice contexts, mirroring the broad range of uses of opioids and opiates (11;12;23;24). However, whilst naloxone use is often vital, its use may also introduce potential risks, with these described in various prescribing and other guidance (14;21;22). The particular risks associated with inappropriate naloxone use have been highlighted in two NHS England Patient Safety Alerts (1;2). This alert followed reports to the National Reporting and Learning system and a report to the coroner in relation to a particular case which has now been followed up by a Parliamentary and Health Service Ombudsman report (25;26).

With the background above in mind, this Medicines' Question and Answer seeks to clarify the various dosing regimens available for naloxone in practice, and the factors that should be considered in balancing the need for treatment against the risk of inappropriate use. The document aims both to inform individual practice and to help development of organisational policies in this area. It aims to be useful across the range of settings in which the drug is used.

To provide some structure, the questions and answers the document addresses have been sub-divided as follows:

Question One. What are the indications for naloxone and what are the published dosing regimens?
Question Two. What should be considered when balancing the benefits and risks of different naloxone dosing regimens?

Question One.
What are the indications for naloxone and what are the published dosing regimens?

The indications for naloxone

Appendix 1 summarises the indications stated for naloxone and the doses suggested across a range of different publications and sources. The indications for and use of naloxone are not described uniformly across these sources (3-8;10;12;19;21;27-29).

Fundamentally, the only indication for urgent and emergency use of naloxone is respiratory depression, regardless of the reason for the exposure to opioids or opiates. A diagnosis of respiratory depression should be sought before naloxone is considered; however, in some circumstances, particularly in drug misuse and dependence when the antidote is used by lay persons, the prerogative will be to save a life and a diagnosis may not be possible (9;11;15;27).

The severity of the respiratory depression significantly affects the way in which naloxone should be used. The indications for naloxone can be described as:

i. the reversal of acute opioid or opiate toxicity with severe respiratory depression or arrest;
ii. the reversal of less severe respiratory depression (3;5-8;10;12;19;21;27-29).

Acute opioid or opiate toxicity with severe respiratory depression or arrest may be a result of inappropriate use in patients relatively naïve to opioids or opiates: for example, those with suicidal intent attempting overdose with large quantities of drugs such as codeine and dihydrocodeine (21)(12). Conversely, acute toxicity may occur in those with some period of regular pre-existing opiate and/or opioid use. This can occur in regular opiate drug misusers, in whom evidence of neuro-adaptation or 'physical dependence' may be present (24). An increased risk of toxicity may also develop iatrogenically, with particular risks present in the context of long term opioid therapy for pain (12).

The literature discusses widely the importance of quickly establishing the severity of the respiratory depression (11;14;15;21;30). There are some slight differences in the definition of severe respiratory depression used between emergency medicine and palliative care texts. Ambulance and emergency department guidance classifies severe respiratory depression/arrest similarly. Ambulance guidance suggests assisted ventilation where SpO_2 < 90% (on high concentration oxygen for 30–60 seconds) and respiratory rate is half the normal rate (11). Emergency medicine advice suggests supplemental oxygen or bag-valve-mask ventilation where RR < 10/minute or SpO_2 < 92% (on air) (30). Palliative care sources define severe respiratory depression/arrest as present where RR < 8/minute, with effects on SpO_2 also noted (12;15;17). Where possible, measures of PCO_2 will provide further sensitivity in determining the severity of respiratory depression. Regardless, the severity of the respiratory depression defines the acuteness of the toxicity, subsequent management, and whether or not naloxone is indicated.

Naloxone dosing regimens

Where acute toxicity and a subsequent need for naloxone are established, the literature discusses two different treatment regimens. These can be categorised as **"higher initial dose regimens"** and **"lower initial dose regimens"**. For both, an **initial dose** will often need to be followed by **subsequent doses carefully titrated to effect** (11;12;15;21;22;29). The uses and characteristics of the different dosing strategies are as follows.

- "**Higher initial dose regimens"** are considered of particular value where there is respiratory arrest and significant urgency. The aim is to achieve a fairly pronounced and instant reversal, albeit at the expense of a controlled effect (3-8;10;11;22;28;29). Such regimens are discussed primarily in the literature pertaining to urgent and emergency use, and particularly in the context of the high number of fatal opiate overdoses, and strategies that have been put in place to deal with such (22-24). In previously opioid naïve patients, use of these regimens would not be expected to pose problems (24); however, care must be exercised with use of these regimens in other groups, given the risks of abrupt reversal (discussed below).

- "**Lower initial dose regimens"** are considered of value where the situation is less immediately life-threatening, or where a more controlled effect is desirable. These regimens aim to balance the need to reverse toxicity against the known risks of abrupt reversal. In addition to a lower initial dose, they may be characterised by "watch and wait" periods, with slow incremental dose titration to effect (11;14;17;30). Such regimens are recommended in some situations of emergency use by clinicians (such as in A&E or by paramedics) (11;30), as well as being the mainstay of use in the context of long term opioid therapy (12;13;15;17).

In addition to the severity of the toxicity and the urgency of the situation, the literature also discusses a number of other factors important in determining which regimen should be used. In particular, for drug misusers, factors such as timely access to naloxone and the possible refusal of continued treatment after an initial dose need to be considered (20;23).

"Higher initial dose regimens" for acute toxicity with severe respiratory depression/arrest

As discussed, in urgent situations where abrupt reversal of toxicity is the predominant consideration, higher dose regimens are appropriate. The licensed intravenous and intramuscular doses fall under this definition, as do a number of other stated doses (3-8;10;11;22;28;29). Administration of naloxone using such doses may occur via a number of routes: intravenous, intramuscular, sub-cutaneous, intra-osseous, and intranasal administration are all possible (11;22). Large dose intravenous, intramuscular, and subcutaneous regimens are licensed (3-8;10). The BNF provides a helpful summary of the intravenous regimen (10):

By intravenous injection, 400 micrograms; if no response after 1 minute, give 800 micrograms, and if still no response after another 1 minute, repeat dose of 800 micrograms; if still no response, give 2 mg (4 mg may be required in a seriously poisoned patient), then review diagnosis; further doses may be required if respiratory function deteriorates

Dosing guidance in other publications (for example to Ambulance Services, from the Resuscitation Council, and from Drug Misuse and Dependence experts) sticks broadly with the licensed intravenous regimens, but tends to recommend marginally longer (2–4 minute) intervals between repetition of doses (11;21-23). It should be noted that naloxone has a short plasma half-life (1–2 hours) and its pharmacokinetics are such that it is not retained in the brain for significant periods following administration (31). Its duration of action is thus short (31) and as a result frequent re-dosing may be required, particularly for larger overdoses.

In addition to intravenous doses, the *intramuscular dose is 400 micrograms initially, with further 400 microgram doses given incrementally every 2–3 minutes until an effect is noted* (9;11). Where practicable, the site of injection should be varied for repeated intramuscular doses (11). Intra-osseous (11) and sub-cutaneous (3-8) administration are also possible.

For the management of acute overdose for the purpose of saving a life, anyone can administer naloxone and from 2015 it also became exempt from prescription only medicines requirements when supplied by a drug service commissioned by the NHS, a local authority or Public Health Agency (24;32). A product exists with a licence that specifies use in community settings; this product is presented in a pre-filled syringe (9;32). Where naloxone administration may be performed by anyone for the purpose of saving a life, training would be expected to complement provision (33).

"Lower initial dose regimens" for acute toxicity with respiratory depression

In most circumstances, the higher dose regimens described above will be safe and efficacious in reversing the effects of overdose in drug misuse and dependence (20). However, the need for high initial dose treatment as well as its continuation needs to be balanced against the risks of acute withdrawal syndrome and sympathetic excess (a fuller discussion of the risks of abrupt withdrawal is provided below). That these risks exist means use of naloxone is not without consequences even in the context of drug misuse and dependence (30). The treatment risks, of course, need to be considered against the risk of death without naloxone, but they may warrant the use of lower dose regimens in cases of emergency, particularly where respiratory depression is

less severe or where a more controlled and tailored partial reversal is otherwise considered advantageous (for example, where there are risks to health care professionals) (11).

Lower dose regimens are also particularly warranted in the context of long term opioid therapy where return of pain is a potential issue (12;13;15;17). A specific dose is licensed post-operatively (10).

The particular recommended regimens are as follows.

In an emergency that is managed by emergency care personnel, guidance for ambulance trusts suggests that a controlled effect can be achieved by *diluting 2mL of an 800 microgram/2mL formulation of naloxone with 8mL of water for injection or sodium chloride 0.9%, and the solution then administered by slow intravenous injection (1mL (80mcg) at a time)* to response, repeated every 3 minutes, to "relieve respiratory depression, but maintain patient in a 'groggy' state" (11). Similarly, a 2005 review of the literature in the Emergency Medicine Journal suggests *an initial dose of 100 micrograms, repeated every minute as necessary but titrated to response* (to achieve respiratory rate >10/minute; GCS 13–14; and absence of acute withdrawal syndrome) (30).

Palliative care advice suggests similar, and in some cases even smaller dose regimens for patients on **long term opioid therapy.** There is a lack of consensus on dosing regimens in this context and difference in guidance exist (10;26;34). The Palliative Care Formulary and Palliative Care Guidelines Plus, for example, give *an initial dose of 100–200 microgram stat intravenously, followed by 100 microgram every 2 minutes* until respiratory function is satisfactory (12-14). However even lower doses are also suggested: *20 micrograms* or *80 micrograms given every two minutes* until respiratory function is satisfactory (12-18).

These above doses are not specified in the manufacturers product literature but a dose is licensed specifically for **postoperative respiratory depression** (3-6;8); the BNF states (10):

By intravenous injection, 100–200 micrograms (1.5–3 micrograms/kg); if response inadequate, give subsequent dose of 100 micrograms every 2 minutes; alternatively, subsequent doses can be given by intramuscular injection every 1–2 hours.

With regard to this licensed dose, in practice there is little difference between it and the unlicensed doses summarised previously for respiratory depression in circumstances where controlled reversal is required. Therefore in practice, for any patient where a more tailored effect needs to be achieved, a lower initial dose extended regimen (such as those described) should be considered regardless of the cause of the respiratory depression.

Ongoing emergency treatment and the role of continuous naloxone infusions

For both higher and lower initial dose regimens for acute toxicity, continuous titrated use of naloxone may be required and in some cases a continuous infusion warranted.

The basis for continuous treatment relates to naloxone's pharmacokinetics. The drug has a short half-life, whilst those of opiates and opioids vary more (with methadone, for example, having a comparatively long half-life) (23;35). In addition, its distribution is such that it is present in significant quantities in the brain immediately following administration, but is then rapidly re-distributed to the serum (30;31). The other potentially important factor here relates to pharmacokinetic differences between opioids—agonists with high μ-opioid-receptor affinity (e.g. buprenorphine) may particularly require continuous infusions for example (35).

Thus for some opioids or opiates (e.g. those with a particularly long half-life, or high receptor affinity), or where overdoses are particularly large with any opioid or opiate, an continuous naloxone infusion may be required to prevent a lapse into sedation following initial treatment of acute toxicity (5;7;21). Typical intravenous infusions include initiation of a dose of *60% of the initial IV bolus, given over 1 hour*, with subsequent titration to respiratory rate and level of consciousness; a solution of *concentration 2 mg in 500mL of sodium chloride 0.9% or glucose 5% is normally used* (12;19).

Question Two.
What should be considered when balancing the benefits and risks of different naloxone dosing regimens?

As discussed, naloxone is a potentially life-saving drug when used in settings ranging from emergency scenarios associated with drug misuse and overdose, in circumstances of long term opioid therapy, and post-operatively. It is used by a large variety of individuals: its relatively unique legal status means anyone can administer the drug for the purpose of saving a life (24;32); and it is also used by health care professionals across a range of disciplines (in emergency medicine, palliative care and anaesthesia). However, balancing the benefits and risks is not straightforward—there are a number of potential regimens, and determining which is appropriate needs to consider the risks both in giving too much and in giving too little (30;35). A consideration of the factors below needs to be borne in mind when determining which regimen to use, particularly in the context of drug misuse and dependence where there is a potential choice between higher and lower dose regimens.

The risks of giving too much naloxone when it is not required are well documented. Acute withdrawal syndrome (AWS) from opioids can have both unpleasant and potentially more serious effects (30;35). Vomiting, agitation, shivering, sweating, tremor, and tachycardia may occur; delirium and aggression are also relatively common (33;36). These effects are not in themselves life-threatening (other than vomiting where it affects aspiration) although they are of course highly undesirable, particularly in the context of long term opioid therapy where complete reversal is inappropriate (15;35). Most concerning is the potential for acute withdrawal to cause a sympathetic excess, with resultant pulmonary oedema and ventricular arrhythmia, with these effects being potentially life threatening in themselves (2;11;21;25;30;33). As such the use of naloxone is cautioned in patients with pre-existing heart disease (10;27;28).

In drug misuse and dependence the literature suggests that in opioid misusers, life-threatening withdrawal reactions can occur in as many 1% of cases of naloxone administration (37). More recent data suggests this figure may be far smaller (38); although conversely the issue may be compounded in poly-drug misusers, with case reports suggesting particular risks in those taking concomitant cocaine (39;40). However, the case for conservative regimens in this group needs to be set in context:

- Mortality rates in the range of 1-2% per year are estimated for high risk drug users in Europe, with opioid users 5 to 10-times more likely to die than their peers of the same age group and gender (41). Of the deaths across England and Wales, 1786 deaths were linked to opioids in 2014 (41). Strategies to prevent such deaths will clearly be multi-faceted (20) and a detailed exposition of this area is beyond the scope of this paper. With reference to the use of naloxone in preventing deaths, it is worth noting that the majority of overdoses occur in private homes and are witnessed (20). Hence widespread naloxone distribution to lay responders is recommended as are the availability of a range of formulations and presentations (20;24). In areas where such programmes have been instigated, use of naloxone in this way has had an effect on reducing the proportion of drug-related deaths related to opioids (although this is an area requiring more study) (42) and to further facilitate uptake, naloxone has now been classified exempt from prescription requirements when supplied under schemes. In this scenario then, there are clear risks in not enabling access to naloxone at appropriate doses (32).
- In addition, at an individual patient level, conservative regimens may introduce the risk of re-narcosis (given naloxone's short half-life), particularly where individuals refuse further treatment and/or leave care settings against professional advice (23). Where possible and considered necessary, the short acting nature of naloxone should be made clear to individuals, and the high risk of life-threatening sedation when the antidote wears off explained (23).

In **long term opioid therapy**, considerations of use in this context are different. In this setting the use of naloxone should be considered a last resort because of the risk of pain returning and its implications. The initial approach to a suspected opioid toxicity should be to establish an accurate medication history of current opioid therapy (26;43). In many instances where it is not possible to rouse patients, omitting doses of or reducing sedative drugs will likely be more appropriate. Only where there is a clear diagnosis of respiratory depression, should naloxone be considered; the Palliative Care Formulary suggests that treatment is only necessary where respiratory rate is <8 breaths/minute, and there is a reduced level of consciousness (12;14).

Even then, other measures to stimulate and encourage the respiratory rate may be effective (manual resuscitation using a bag-valve-mask for example). Where such strategies fail and naloxone is definitely required, the aim of treatment should be to reverse respiratory depression rather than to achieve wakefulness (15;34). Conservative dosing regimens therefore have a particular place in this area of practice (12;18) and the aim is to achieve satisfactory respiratory function without compromising pain control. Subsequent pain management plans and potential referral to palliative care is vital in this setting (14;15;26).

One other complication in determining an appropriate naloxone regimen is that variability in response is in part due to the relatively selective nature of opioids and opiates at the three receptor sub-types (μ-, δ-, and κ-) compared to the non-selective antagonist action of naloxone (30;31). The result is that an effective naloxone dose can vary greatly dependent on the opioid or opiate type and the amount of agonist that has been ingested or injected (30). Where overdoses are particularly sizeable, huge doses may be required; where they are smaller, required naloxone doses will be too.

In summary, naloxone is used in a variety of different care settings: at home, by ambulance staff, in hospital, and in palliative care environments (10-12). Its use is both potentially life-saving, but also associated with particular risks that may vary dependent on the context of care and other factors. The comparative lack of consensus on dose regimens (as described above) is therefore understandable. A pragmatic approach to the development of individual and organisational policies on the management of opioid toxicity and the associated dosing regimens is warranted, and should be mindful of the benefits of reversal and the potential for adverse consequences too. Due to the number of different dosing regimens, individual and organisational policies are likely to be complex. A simple flowchart summarising the recommended regimens at the start of any policy will ensure clinicians have ready access to the essential information in an emergency situation. It would also be useful to ensure related policies, e.g. end of life care, pain management policies are cross referenced with the naloxone policy.

Limitations

This question and answer was limited by the limitations of the evidence-base in this area which mainly consists of observational studies and reports as opposed to studies with more controlled design. The question and answer therefore took a consensus driven approach, seeking to develop a summary of the issues that was acceptable to a range of parties. This question and answer does not therefore purport to provide a systematic review of the literature, but rather a discussion of key publications and their implications.

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Search strategy

Embase:

((*NALOXONE/ AND ("NARCOTIC ANALGESIC AGENT"/ OR ("OPIATE AGONIST"/ OR BUPRENORPHINE/ OR DIAMORPHINE/ OR MORPHINE/ OR OXYCODONE/ OR PETHIDINE/) OR METHADONE/ OR FENTANYL/ OR ALFENTANIL/ OR REMIFENTANIL/ OR PETHIDINE/)) AND ("DRUG OVERDOSE"/ OR ("DRUG THERAPY"/ OR "DRUG DOSE REGIMEN"/))) [DT 2015-2017]
("DRUG THERAPY"/ OR "DRUG DOSE REGIMEN"/) AND (*NALOXONE/ AND ("CHRONIC PAIN"/ OR "PALLIATIVE THERAPY"/))

Medline:

((*NALOXONE/ AND (exp "ANALGESICS, OPIOID"/ OR (remifentanil).af OR (pethidine).af)) AND ("DRUG OVERDOSE"/ OR ("DRUG ADMINISTRATION SCHEDULE"/ OR "DRUG THERAPY"/))) [DT 2015-2017] [Languages English] [Humans]
((*NALOXONE/ AND ("DRUG ADMINISTRATION SCHEDULE"/ OR "DRUG THERAPY"/)) AND ("CHRONIC PAIN"/ OR "PALLIATIVE CARE"/)) [DT 2015-2017]

Appendix 1

Naloxone dosing: description of indications and doses used in formularies and other guidance sources

Information source	Description of indication (s)	Dosing regimen (s) stated for adults	Other information of note
British National Formulary 68 (10)	Overdosage with opioids	*By intravenous injection,* 400 micrograms; if no response after 1 minute, give 800 micrograms, and if still no response after another 1 minute, repeat dose of 800 micrograms; if still no response, give 2 mg (4 mg may be required in a seriously poisoned patient), then review diagnosis; further doses may be required if respiratory function deteriorates *By intramuscular injection,* (into deltoid region or anterolateral thigh) in a non-medical setting, adult 400 micrograms repeated at intervals of 2–3 minutes (in subsequent resuscitation cycles if patient not breathing normally) until consciousness regained, breathing normally, medical assistance available, or contents of syringe used up	Since naloxone has a shorter duration of action than many opioids, close monitoring and repeated injections are necessary according to the respiratory rate and depth of coma. When repeated administration of naloxone is required, it can be given by continuous intravenous infusion instead and the rate of infusion adjusted according to vital signs. Naloxone will immediately reverse opioid-induced respiratory depression but the dose may have to be repeated because of the short duration of action of naloxone; however, naloxone will also antagonise the analgesic effect.
	Reversal of postoperative respiratory depression	*By intravenous injection*, 100–200 micrograms (1.5–3 micrograms/kg); if response inadequate, give subsequent dose of 100 micrograms every 2 minutes; alternatively, subsequent doses can be given by intramuscular injection every 1–2 hours	

Information source	Description of indication (s)	Dosing regimen (s) stated for adults	Other information of note
Martindale (28)	Known or suspected opioid overdosage	The initial dose of naloxone hydrochloride is 0.4 to 2 mg given *intravenously* and repeated if necessary at intervals of 2 to 3 minutes. If no response has been seen after a total dose of 10 mg then the diagnosis of overdosage with drugs other than opioids should be considered. If the intravenous route is not feasible the *intramuscular* or *subcutaneous* route can be used. When sustained opioid antagonism is needed, an *intravenous infusion* may be used. Dosage regimens have not been well established, and the rate of infusion must be titrated according to the patient's response.	Hypertension, pulmonary oedema, and cardiac arrhythmias including ventricular tachycardia and fibrillation have been reported after the postoperative use of naloxone, generally in patients with pre-existing heart disease undergoing cardiac surgery. However, there have also been reports in healthy patients, including some fatalities. Hypotension, bradycardia, and precipitation of focal seizures have been reported in patients given high-dose naloxone for acute ischaemic stroke. Ventricular fibrillation has been seen in an opioid addict given naloxone to reverse the effects of diamorphine. However, this patient was later shown to have hepatic cirrhosis and alcoholic cardiomyopathy and the UK National Poisons Information Service noted that it had never been informed of such a suspected adverse reaction despite being contacted in about 800 cases of opioid poisoning each year. In a later report severe adverse effects were noted in 6 of 453 subjects given naloxone to reverse diamorphine intoxication. The effects were: asystole (1 case), generalised convulsions (3 cases), pulmonary oedema (1 case), and violent behaviour (1 case).
	Postoperatively to reverse central depression resulting from the use of opioids during surgery	A dose of 100 to 200 micrograms (corresponding to 1.5 to 3 micrograms/kg) may be given *intravenously* at intervals of 2 to 3 minutes, titrated for each patient in order to obtain an optimum respiratory response while maintaining adequate analgesia. If further doses are needed after 1 to 2 hours, they may be given by *intramuscular injection* or *intravenous infusion* for a sustained effect; infusions should be titrated according to response.	

Information source	Description of indication (s)	Dosing regimen (s) stated for adults	Other information of note
AHFS Drug Information (27)	Known or suspected opiate overdosage	The usual initial adult dosage of naloxone hydrochloride is 0.4–2 mg IV, administered at 2- to 3-minute intervals if necessary; if no response is observed after a total of 10 mg of the drug has been administered, the depressive condition may be caused by a drug or disease process not responsive to naloxone. Some experts state that some adults with massive opiate overdosage may require titration to higher doses of naloxone hydrochloride. In patients with chronic opiate addiction, a lower dose of naloxone should be used and slowly adjusted to minimize adverse cardiovascular effects and withdrawal symptoms. Continuous IV infusions of naloxone hydrochloride may be most appropriate in patients who require higher doses, continue to experience recurrent respiratory or CNS depression after effective therapy with repeated doses, and/or in whom the effects of long-acting opiates are being antagonized. For continuous IV infusion, 2 mg of naloxone hydrochloride may be diluted in 500 mL of 0.9% sodium chloride or 5% dextrose injection to produce a solution containing 0.004 mg/mL (4 mcg/mL). The rate of IV infusion should be titrated in accordance with the patient's response.	Naloxone should be used with caution in patients with pre-existing cardiovascular disease or in those receiving potentially cardio-toxic drugs, since serious adverse cardiopulmonary effects (e.g., ventricular tachycardia and fibrillation, pulmonary edema, cardiac arrest) resulting in death, coma, and encephalopathy have occurred in postoperative patients following administration of naloxone. Naloxone should be given with caution to patients known or suspected to be physically dependent on opiates (including neonates born to women who are opiate dependent), particularly in patients with cardiovascular disease, because the drug may precipitate severe withdrawal symptoms.

Information source	Description of indication (s)	Dosing regimen (s) stated for adults	Other information of note
AHFS Drug Information [continued]	Postoperative opiate depression	When naloxone hydrochloride is used to partially reverse opiate depression following the use of opiates during surgery, the usual initial dosage recommended by the manufacturers is 0.1–0.2 mg IV in adults, given at 2- to 3-minute intervals until the desired response (i.e. adequate ventilation and alertness without substantial pain or discomfort) is obtained. Additional doses may be necessary at 1- to 2-hour intervals depending on the response of the patient and the dosage and duration of action of the opiate administered. Some clinicians have recommended an adult dosage regimen of 0.005 mg/kg administered IV and repeated after 15 minutes if necessary. Alternatively, the initial IV dose may be followed in 15 minutes with an IM dose of 0.01 mg/kg. The manufacturers states that supplemental IM doses of naloxone produce a more prolonged effect than repeated IV doses of the drug. Continuous IV infusions of naloxone in a dosage of 0.0037 mg/kg per hour have also been used in adults to reverse postoperative opiate-induced respiratory depression.	Following the use of opiates during surgery, excessive dosage of naloxone hydrochloride should be avoided, because it may result in excitement, agitation, an increase in blood pressure, and clinically important reversal of analgesia, resulting in nausea, vomiting, sweating, tremor, tachycardia, hypotension, hypertension, and seizures.

Information source	Description of indication (s)	Dosing regimen (s) stated for adults	Other information of note
Drug Misuse and Dependence – UK Guidelines on clinical management (23)	Dealing with emergency overdose	Treat opiate overdose with standard resuscitation techniques and with the use of naloxone. Naloxone is given 0.4-2.0 mg parenterally (IV/IM/SC) and this can be repeated after every 3–4 minutes, up to a maximum dose of 10 mg.	It is important to remember the half-life of naloxone is much shorter than methadone and other opioids. This fact should be made clear to patients, particularly in A&E and in other situations where the patient may leave the hospital suddenly. Patients should be helped to understand that they are at risk of re-emergence of life-threatening sedation when the naloxone wears off. Given that some patients may find it difficult to cope with the precipitated discomfort that can occur on administering naloxone, and may choose to leave, it is important that they are helped to understand this risk.
UK Ambulance Service Clinical Practice Guidelines (2013) (11)	Respiratory arrest/extreme respiratory depression – when the urgency of the situation outweighs the need for a controlled effect	Route - IV/IM bolus Concentration – 400 micrograms in 1mL By intravenous or intramuscular injection: 400 micrograms initially, with further 400 microgram doses given incrementally every 3 minutes until an effect is noted Maximum dose 4400 micrograms	Defines severe respiratory depression as: • SpO_2 is <90% on high concentration O_2 • Respiratory rate is <half normal rate • Expansion is inadequate Suggests that naloxone should be considered where respiratory depression develops in cases where an overdose with opiate-type drugs may be possible.

Information source	Description of indication (s)	Dosing regimen (s) stated for adults	Other information of note
UK Ambulance Service Clinical Practice Guidelines (2013) [continued]	Respiratory Depression – when a more CONTROLLED effect is required, e.g. in known or potentially aggressive patients who are suffering respiratory depression rather than arrest	By slow intravenous injection: Dilute 2mL of an 800 microgram/2mL formulation of naloxone with 8mL of water for injection or sodium chloride 0.9%; give the resultant solution by slow intravenous injection (1mL [80mcg] at a time) to response to “relieve respiratory depression, but maintain patient in a ‘groggy’ state”	

Information source	Description of indication (s)	Dosing regimen (s) stated for adults	Other information of note
Medusa injectable medicines guide (19;44)	Suspected opioid overdose or intoxication	*IV injection*: **'HIGHER INITIAL DOSE REGIMEN'** Administer 400 micrograms by IV injection. If no response after 1 minute, give a further dose of 800 micrograms, and if still no response after another 1 minute, repeat dose of 800 micrograms; if still no response, give 2 mg (4 mg may be required in a seriously poisoned patient). If a total dose of 10 mg of naloxone does not produce significant improvement in respiratory function, the diagnosis of opioid- induced or partial opioid induced toxicity should be questioned. Aim for reversal of respiratory depression, not full reversal of consciousness **'LOWER INITIAL DOSE REGIMEN'** Lower doses of 20-100micrograms repeated every 2 minutes as necessary (titrated to response) may be required for patients receiving palliative care and in chronic opioid use. *IV Infusion*: Rate of administration should be titrated in accordance to patient's response to IV bolus and reaction to IV infusion. Usual starting dose is 60% of initial IV bolus infused over 1 hour, then adjusted according to respiratory rate and level of consciousness. *Intramuscular injection*: Give by IM route only if IV administration not possible	

Information source	Description of indication (s)	Dosing regimen (s) stated for adults	Other information of note
	Reversal of CNS and respiratory depression caused by natural or synthetic opioids e.g. post-operatively	*IV injection:* Administer 100-200 micrograms (or 1.5-3 micrograms/kg) by IV injection. If the response is inadequate, subsequent doses of 100 micrograms can be administered at 2 minute intervals by IV injection until satisfactory respiration and consciousness obtained. *IV Infusion using an infusion pump*: Dose and rate of administration should be titrated in accordance to patient's response to IV bolus and reaction to IV infusion. Usual starting dose is 60% of initial IV bolus infused over 1 hour, then adjusted according to respiratory rate and level of consciousness.	
Resuscitation Council Advance Life Support Guidance, version 5 (22)	Opioid poisoning	The route for giving naloxone depends on the skills of the rescuer: IV, IM, SC, endotracheal (ET), and intranasal (IN) routes can be used. The non-IV routes may be quicker because time is saved in not having to establish IV access, which can be extremely difficult in an IV drug abuser. Initial dose of naloxone: 400 mcg IV; 800 mcg IM; 800 mg SC; 2 mg IN; and 1–2 mg ET. Large opioid overdoses require titration to a total naloxone dose of 6–10 mg. The duration of action of naloxone is 45–70 minutes, but respiratory depression may persist for 4–5 hours after opioid overdose. Thus, the clinical effects of naloxone may not last as long as those of significant opioid overdose. Give increments of naloxone until the victim is breathing adequately and has protective airway reflexes.	Acute withdrawal from opioids produces a state of sympathetic excess and may cause complications such as pulmonary oedema, ventricular arrhythmia, and severe agitation. Use naloxone reversal of opioid intoxication with caution in patients suspected of opioid dependence.

Information source	Description of indication (s)	Dosing regimen (s) stated for adults	Other information of note
Oxford Handbook of Acute Medicine (21)	Opiate overdose	Overdosing with opiates usually occurs in regular drug users where the most commonly abused agent is diamorphine (heroin). The suggested dose is 400 mcg in IV boluses given at 2-3 minute intervals, until the patient is rousable and any evidence of respiratory depression corrected. Doses up to 2 mg may be required, but if no response is seen at this level diagnosis of opiate overdose should be suspected.	Avoid giving sufficient naloxone to completely reverse the effect of opiate in an opiate-dependent subject. This is likely to precipitate an acute withdrawal reaction. If this occurs and hypertension is marked (diastolic >120mmHg) then give diazepam (5–10 mg initially IV), and if it persists, commence IV labetalol (50 mg stat followed by IVI until BP is controlled). NB: marked hypertension, acute pulmonary oedema and VT/VF have been observed in non-addicts given naloxone to reverse the effects of high therapeutic doses of opiates for pain.
On-line Palliative Care Formulary (12)	Opioid overdose in immediately life-threatening situation (i.e. unconscious patient with minimal/no respiratory effort)	Assess each dose after 1 minute and if no response, move to the next dose: • Start with 400 microgram, then 800 microgram, then 800 microgram, to a total of 2–4 mg • If no response to 2–4 mg consider an alternate diagnosis	Higher doses required when reversing the effects of buprenorphine, because of its higher receptor affinity. Possibility of pulmonary oedema discussed, particularly if there is unexpected breathlessness and hypoxia after naloxone and oxygen. Careful titration using lower doses of naloxone should be used to avoid a severe acute withdrawal syndrome and, in those receiving opioids for analgesia, severe pain and hyperalgesia.

Information source	Description of indication (s)	Dosing regimen (s) stated for adults	Other information of note
	Severe but not immediately life-threatening respiratory depression (iatrogenic overdose in patients receiving opioid analgesia but can also be applied to overdose from drug misuse)	Suggests that treatment is only necessary where respiratory rate is <8 breaths/min in a patient with a reduced level of consciousness. In such circumstances, give 100 microgram intravenously every 2 minutes until respirations are satisfactory. Even lower doses are suggested (based on American guidance): 20 microgram intravenously every 2 minutes until respirations are satisfactory. Titrate the dose against respiratory function (i.e. to achieve a respiratory rate ≥ 8 breaths/min and no cyanosis) and *not* the level of consciousness.	
Palliative Care Guidelines Plus (13)	Reversal of opioid induced respiratory depression	Suggests the following dose titrated to response (intravenous/intramuscular/subcutaneous): Give an initial dose of 100-200 micrograms stat, followed by 100 microgram every 2 minutes if response inadequate.	Use with caution; larger than recommended naloxone doses can reverse analgesia, leading to intense pain/distress. They may result in hypertension, arrhythmias, pulmonary oedema and cardiac arrest. Follow local/BNF guidance Consult specialist advice if needed.
	Management of iatrogenic opioid overdose (adapted from www.palliativedrugs.com)	Suggests that treatment is only necessary where respiratory rate is <8 breaths/min, and the patient is barely rousable/unconscious and/or cyanosed. In such circumstances, small 20 microgram doses are recommended to be given every two minutes until respiratory status is satisfactory.	Use with caution; larger than recommended naloxone doses can reverse analgesia, leading to intense pain/distress. They may result in hypertension, arrhythmias, pulmonary oedema and cardiac arrest. Follow local/BNF guidance

Information source	Description of indication (s)	Dosing regimen (s) stated for adults	Other information of note
Scottish Palliative Care Guidelines (18)	Reversal of life threatening respiratory depression due to opioid analgesics	Suggests that treatment only necessary where respiratory rate < 8 respirations/minute, and oxygen saturation<85%, patient cyanosed. Administer 80 micrograms as a slow IV bolus every 2 minutes until respiratory rate satisfactory (>8 respirations/minute)	Total antagonism will result in severe pain with hyperalgesia and, if physically dependent, severe physical withdrawal symptoms and marked agitation. Opioid withdrawal syndrome: anxiety, irritability, muscle aches, nausea and vomiting; can include life-threatening tachycardia and hypertension. Cardiac arrhythmia's, pulmonary oedema and cardiac arrest have been described.
UK National Poisons Information Service – Toxbase.org (29)	Severe opiate-induced respiratory depression following acute overdose	Give and initial dose of 400 micrograms If no response after 60 seconds, give a further 800 micrograms Is still no response after another 60 seconds, give another 800 micrograms If still no response (after a total of 2 mg), give a further 2 mg dose. Large doses (4mg) may be required in the seriously poisoned patient. Intravenous infusions of naloxone are often useful where repeated doses are required. An infusion of 60% of the initial dose required for resuscitation per hour is a useful starting point. For adults, a solution containing 10 mg (25 vials) is made up to the final volume of 50 mL with dextrose will produce a 200 microgram/mL solution for infusion using an IV pump (dose adjusted to clinical response).	Naloxone should be used with caution when the patient is at risk of acute withdrawal e.g. chronic opioid use or when there is a need for therapeutic effect e.g. pain relief. Small doses are also appropriate for post-respiratory depression.

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