Opioid Toxicity

Scottish Palliative Care Guidelines

Healthcare Improvement Scotland

Introduction

Opioid toxicity can occur with any opioid administered by any route, at any dose or time and for any indication. Opioids are prescribed in the palliative care setting for pain or breathlessness.

Whilst mild or moderate toxicity symptoms are not uncommon in the palliative setting, life-threatening respiratory depression is rare.

Initial assessment

Assess as part of an ABCDE approach

(ABCDE is an assessment and treatment method, and stands for Airway, Breathing, Circulation, Disability, and Exposure/Examination. The first steps are to ensure a clear airway and adequate breathing.)

- Measure respiratory rate (RR) and oxygen saturations over one minute as part of an ABCDE approach.
- Assess if the opioid toxicity is life threatening or non-life threatening. This determines management:

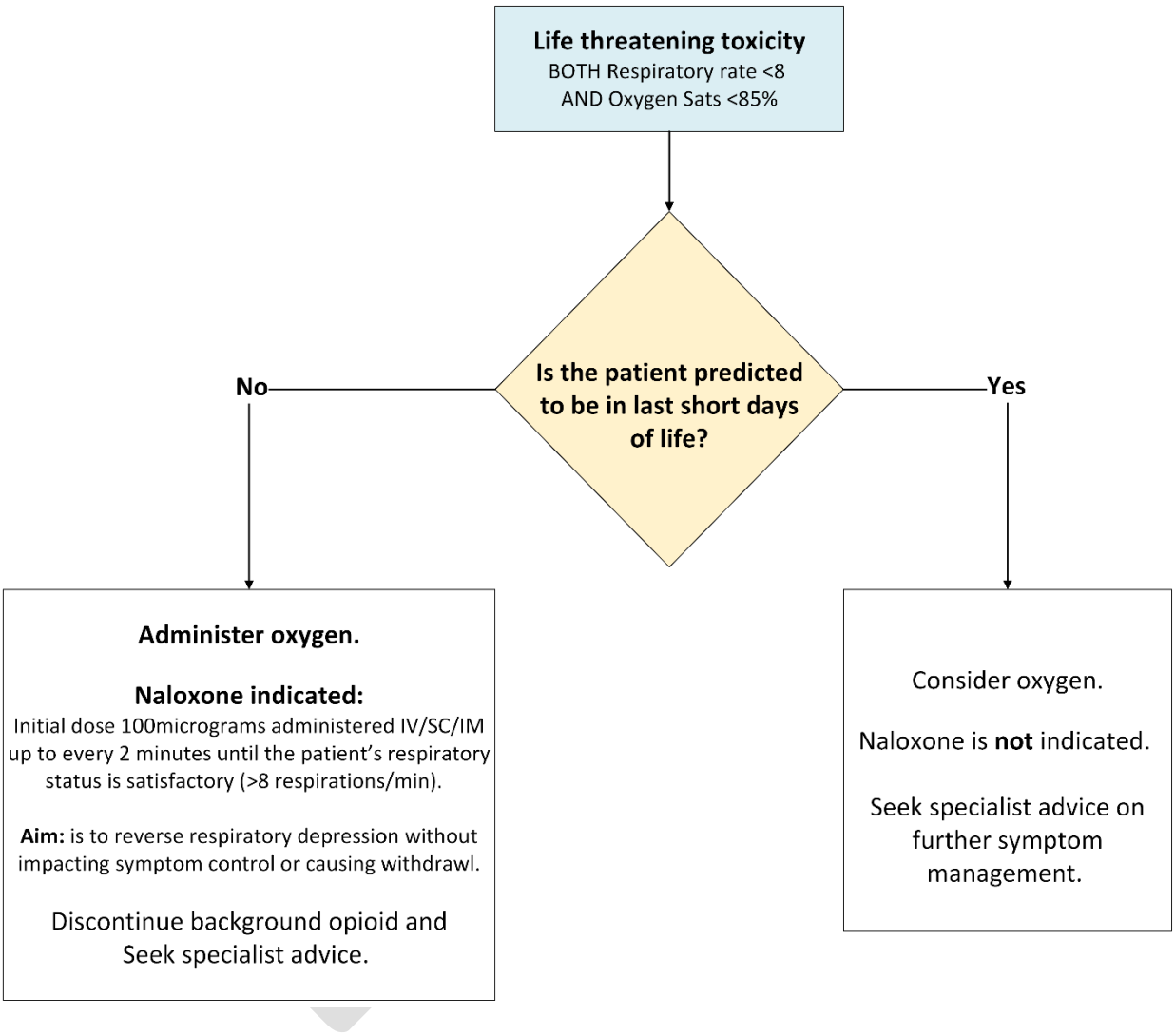
	Life-threatening	**Non-life-threatening**
Assessment	Respiratory rate: **Fewer than 8 breaths/minute** AND Oxygen sats**:** **Below 85%**	Respiratory rate: **8 or more breaths/minute** AND/OR Oxygen sats: **85% or above**
Assessment (continued)	Consider other possible causes for clinical deterioration including but not limited to: • dying • hypercalcaemia • infection, or • other medicines which may be contributing to clinical picture of CNS depression that may need withheld or stopped, for example, gabapentinoids or benzodiazepines	
	If **life-threatening,** see next section: Assessment and management of **life-threatening** opioid toxicity.	If **non**-life-threatening, see section on Assessment and management of non-life-threatening opioid toxicity.

Assessment and management of life-threatening opioid toxicity

When both RR <8 breaths/minute AND oxygen saturations <85%:

- commence oxygen therapy, and
- consider naloxone administration.

Naloxone should only be administered where there is a concern of life-threatening respiratory depression.



Use of naloxone for the management of life-threatening opioid toxicity

Naloxone is an opioid antagonist.

The aim of naloxone use is to reverse life-threatening, opioid-induced respiratory depression without impacting symptom control or causing withdrawal.

Cautions

- Naloxone is not indicated for:
    - opioid-induced drowsiness and/or delirium that are not life-threatening.
    - people on opioids who are in the last short days of life, in which case seek specialist advice about further symptom management.
- Individuals on regular opioids for pain and symptom control are physically dependent; naloxone given in too large a dose or too quickly can cause an acute withdrawal reaction and an abrupt return of pain that is difficult to control.
- People with pre-existing cardiovascular disease are at more risk of side effects.
- **Do not use 'take home naloxone' for people receiving palliative care.** These preparations are intended for use in substance use disorder and the doses are usually too high for the palliative setting.

Side effects

In those on regular opioids, total antagonism will result in severe pain with hyperalgesia and, if physically dependent, severe physical withdrawal symptoms, including:

- anxiety
- irritability
- marked agitation
- muscle aches
- nausea and vomiting
- diarrhoea
- dizziness
- headache
- tremor
- seizures
- hyperventilation, and
- hypertension.

Important: Life-threatening tachycardia/cardiac arrhythmias, pulmonary oedema and cardiac arrest have also been reported as side effects.

Dose and administration

- Discontinue the background opioid.
- Use the 400 micrograms/ml injection (1 ml ampoule) for those receiving palliative care.
- Naloxone injection is licensed for intravenous (IV) administration.
    - Small doses of naloxone by slow IV injection improve respiratory status without completely blocking the opioid analgesia.
    - Onset of action of IV naloxone is one to two minutes.
- If IV access is not readily available, it may also be administered subcutaneously (SC) or intramuscularly (IM) with no dose adjustment. However, an IV line should be sited as soon as possible.

	How to prepare	Dose to give	Notes
IV administration (where IV access is immediately available) Onset of action 1–2 mins (plasma half-life ~1 hour)	Dilute 400 micrograms naloxone (1 ampoule) to 10 ml with sodium chloride 0.9% injection in a 10 ml syringe.	**100 micrograms** (2.5 ml of diluted solution) as a slow IV bolus every 2 minutes until the patient's respiratory status is satisfactory (>8 respirations/minute).	Flush the cannula with 1–2 ml sodium chloride 0.9% between the naloxone doses.
IM/SC administration (where IV access is not immediately available) Onset of action 2–5 mins (plasma half-life ~1 hour)	Give undiluted.	**100 micrograms** (0.25 ml) of naloxone IM/SC, repeated after five minutes if there is no improvement.	An IV line should be sited as soon as possible

Patient response and initial management

- Individuals usually respond after 100 to 200 micrograms naloxone with deeper breathing and an improved conscious level. Note that IM or SC administration may have slower onset of action than intravenous.
- Naloxone should be titrated to respiratory rate, not conscious level.
- If there is little or no response, consider other causes (for example, other sedatives, an intracranial event, acute sepsis or acute renal failure causing opioid accumulation).
- In exceptional circumstances individuals may need 1 mg to 2 mg of naloxone (requiring 3 to 5 ampoules).
- **Obtain specialist palliative care advice before restarting background opioid** – see section Management of background opioid.

Monitoring

- Closely monitor respiratory rate and oxygen saturation for a minimum of 4 hours after respiratory rate reaches >8/min.
- For opioid-associated delirium or hallucinations, consider low-dose haloperidol until symptoms resolve, such as 500 micrograms 8-hourly when required.
- Consider IV or SC fluids to promote renal excretion of opioid metabolites.
- Consider appropriateness of checking bloods for U&Es, calcium, LFTs, CRP and FBC.
- Review other Risk factors, addressing reversible causes, where appropriate.
- Review other medicines which may be contributing to clinical picture of CNS depression that may need withheld or stopped, including for example, gabapentinoids or benzodiazepines.

Important: further doses or IV infusion may be needed as the duration of action of naloxone (15 to 90 minutes) is much shorter than most opioids, and impaired liver or renal function will slow clearance of the opioid**.**

Prolonged, or recurrent, opioid-induced respiratory depression

If giving via the SC/IM route, site an IV line as soon as possible.

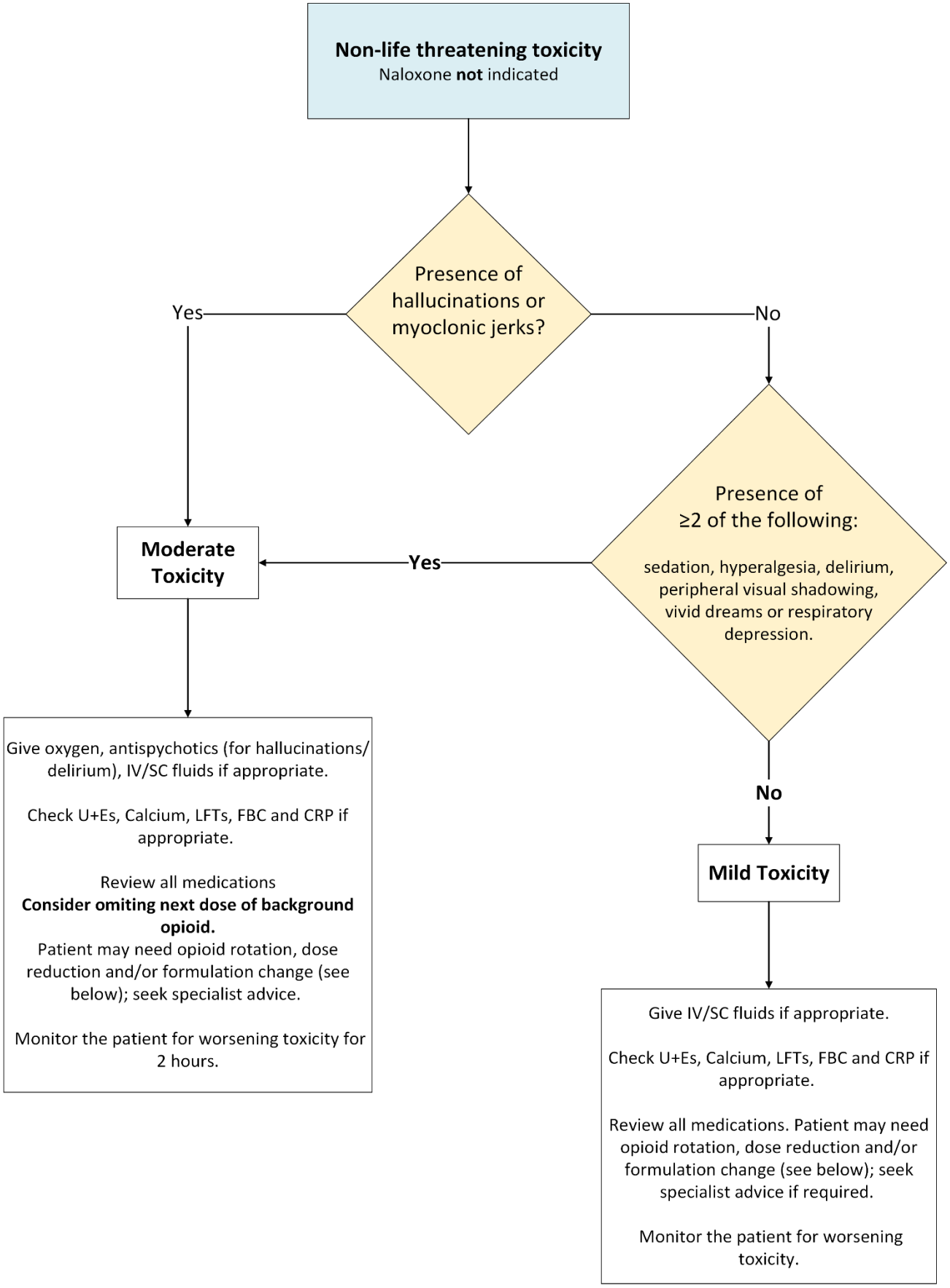
If repeated naloxone doses are required, start a continuous IV infusion of naloxone via an adjustable infusion pump:

- Add 1 mg of naloxone (= 2.5 ml of 400 micrograms/ml naloxone injection) to 100 ml of sodium chloride 0.9% to give a concentration of 10 micrograms/ml.
- Calculate the dose requirement per hour by totalling the naloxone bolus doses and dividing by the time period over which all the doses have been given.
- Start the IV infusion of naloxone at **60%** of this calculated hourly rate.
- Adjust the naloxone infusion rate to keep the respiratory rate above 8/min (do not titrate to the level of consciousness).
- Continue to monitor the individual closely.
- Continue the infusion until the individual's condition has stabilised.
- If needed give additional IV boluses using naloxone diluted in sodium chloride 0.9%. Refer to dose and administration section above.
- If appropriate, use other resuscitative measures such as administration of oxygen.
- Dependent on stage of disease trajectory, care setting, individual future care plans (such as a Treatment Escalation Plan or ReSPECT plan), the views of anyone with power of attorney (POA) or other relevant information, it may be appropriate to consider mechanical ventilation or artificial respiration, alongside naloxone, following discussion with the responsible consultant or palliative care specialist.

- Seek specialist advice before restarting or titrating opioid analgesia.
- Seek and treat the precipitating cause(s) of the opioid toxicity (see Risk factors section).
- Review the regular analgesic prescriptions.

Assessment and management of non-life-threatening opioid toxicity

When RR >8 breaths/minute and/or oxygen saturations >85%



Assessment

Signs and symptoms of moderate and mild toxicity

If either **hallucinations or myoclonic jerks** are present, manage as moderate toxicity.

If **neither** hallucinations nor myoclonic jerks are present, consider if any of the following are present:

- sedation
- peripheral visual shadowing
- cognitive impairment
- vivid dreams, or
- hyperalgesia.

If **two or more** of these symptoms are present, manage as **moderate** toxicity (see section below).

If **only one** of these is present, manage as **mild** toxicity (see section below).

Note

- Pinpoint pupils in palliative patients are **not** necessarily a sign of opioid use or toxicity as this can occur due to other factors.
- In very rare cases respiratory depression can evolve from mild or moderate toxicity and can become life threatening. Regular nursing observations and review are necessary to ensure that this is identified early.

Risk factors

Understanding contributory factors can help both assessment and ongoing management.

Opioid toxicity can arise due to several factors including, but not limited to:

- high opioid dose and/or rapid increase in dose
- polypharmacy - especially coprescription of benzodiazepines/gabapentinoids/sedatives
- renal/liver impairment
- pharmacokinetics in cachexia can amplify toxicity risk
- non-medical opioid use/polysubstance or substance use disorder
- opioid dose not reduced when pain relieved by other interventions such as radiotherapy or nerve block.
- depressive or anxiety disorders
- frail elderly
- opioid naivety, and
- drug errors.

Moderate toxicity management

- **Consider omitting the next dose of modified release opioid.**
- For opioid-associated delirium or hallucinations, consider low-dose haloperidol until symptoms resolve, for example 500 micrograms 8-hourly when required.
- Consider appropriateness of checking bloods for U&Es, calcium, LFTs, CRP and FBC.
- Consider IV or SC fluids.
- Monitor the individual's **observations for a minimum of the next 2 hours**.
- Review other Risk factors, addressing reversible causes where appropriate.
- Review other medicines which may be contributing to clinical picture of CNS depression that may need withheld or stopped, such as gabapentinoids or benzodiazepines.

Mild toxicity management

- For opioid-associated delirium or hallucinations, consider low-dose haloperidol until symptoms resolve, such as 500 micrograms 8-hourly when required.
- Consider appropriateness of checking bloods for U&Es, calcium, LFTs, CRP and FBC.
- Consider IV or SC fluids.
- Review other Risk factors, addressing reversible causes where appropriate.
- Review other medicines which may be contributing to clinical picture of CNS depression that may need withheld or stopped, such as gabapentinoids or benzodiazepines.

Management of background opioid

The guidance below refers to ongoing management of opioid following treatment of mild/moderate **non**-life-threatening opioid toxicity. (See Initial assessment section for criteria).

In life-threatening opioid toxicity or where pain is poorly controlled, seek specialist advice.

Transdermal patch	Remove patch. After 24 hours, can replace at 50% dose if the patient is apyrexial. If remains at risk of pyrexia, consider changing opioid to an alternative route.
Syringe pump	Stop opioid in syringe pump. Review the need for any other medicines being given by this route. Reduce opioid dose by 50% and consider changing opioid. Time to restarting opioid will depend on the half-life of the opioid and factors such as renal or liver function, therefore seek specialist palliative care advice.
Modified-release opioid	Omit next dose. Reduce opioid dose by 50% and consider changing opioid. A regular immediate-release opioid may be indicated instead of modified release.

Immediate-release opioid As required opioid	Reduce opioid dose by 50% and consider changing opioid.

It may be clinically appropriate to deviate from these guidelines in people who are in the last days of life to avoid worsening of symptoms or opioid withdrawal.

Practice Points

- Naloxone should be available in all clinical areas where opioids are used (NHS England Enduring Standards).
- Prefilled syringes and nasal spray ("take home naloxone") are not appropriate for use in the palliative setting.
- Reversal of buprenorphine-induced respiratory depression may be incomplete. Larger naloxone doses may be needed.
- For opioid-associated delirium or hallucinations, consider low-dose haloperidol until symptoms resolve, such as 500 micrograms 8-hourly when required.
- Consider appropriateness of checking bloods for U&Es, calcium, LFTs, CRP and FBC.
- Consider IV or SC fluids.
- When reducing background opioid doses, remember to also reduce breakthrough opioid doses.

References

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