1. Introduction

Opioids are often used in adult patients who are receiving palliative care, particularly for treatment of pain and breathlessness. Like all medications there is a risk of undesirable effects when taking opioids. Certain conditions such as acute kidney injury may result in a physiological change which reduces the clearance of a drug. Other patients experience adverse effects following a dose increase in their opioids. The most severe adverse effect in these situations is respiratory depression which can be life-threatening. Management involves close monitoring of the patient and may require adjustment of their regular opioid dose. Some patients will benefit from administration of naloxone (an opioid antagonist) to temporarily reverse the effects of the opioids.

Inappropriate administration of naloxone can result in a rapid reversal of the analgesic effects of opioids and an increase in sympathetic nervous stimulation and cytokine release. This may precipitate an acute withdrawal syndrome leading to intense pain and distress. Additionally, hypertension, cardiac arrhythmias, pulmonary oedema and cardiac arrest may result from inappropriate doses of naloxone being used for these types of patients (NHSEngland, 2014).

Patients who are in their last days of life may show signs similar to those with opioid-induced respiratory depression. If the patient is expected to be dying it is unlikely to be appropriate to administer naloxone as this may result in a rapid reversal of analgesia. Instead, focus should be on managing symptoms and ensuring their comfort.

2. Scope

This guideline is for use by healthcare professionals caring for adult patients, aged 18 and above, at UHL where the focus of their care is on symptom control. This guideline excludes patients who are in the initial post-operative period or have toxicity secondary to opioid dependence (Please see Guidelines for the Management of Adult Patients with an Opioid Dependence). Administration of naloxone should be within the scope of practice of the healthcare professional.

3. Recommendations, Standards and Procedural Statements

See Appendix 1 for Decision Flow Chart (hyperlink)

3.1 Initial Assessment and Management

- 3.1.1 If suspicion of opioid toxicity based on clinical history
    - Attempt to stimulate patient using verbal stimuli (“hello, hello”) and physical stimuli such as trapezius squeeze (as per assessment in BLS/ILS/ALS)
    - Collect observations including respiratory rate (counting for 1 minute), O_2 saturations, ACVPU. Document on NerveCentre and in medical notes. Depending on clinical situation it may be appropriate to perform an ABG (particularly looking at pCO2 and pH)
    - Maintain airway and administer oxygen to maintain target O_2 saturations – 94-98% unless the patient is on a hypercapnic NEWS2 model (88-92%) or other individualised target range.
    - Obtain IV access and take bloods including FBC, U+Es, LFTs and Calcium.

- Discontinue regular opioid - stop syringe driver remove transdermal patch/ de-prescribe modified release opioids

- 3.1.2 If no improvement despite stimuli and initial assessment, follow decision flowchart (Figure 1)
  - Management of opioid toxicity can be broken down into 3 main categories as described in section 3.1.3. This is based on 2 step decisions:
    - 'Is this a life-threatening situation – unconscious patient with minimal/no respiratory effort?"
      1. YES then treat for immediately life threatening respiratory depression (section 3.1.3.1)
      2. NO then move to second question
    - "Is the patient unresponsive / responsive only to painful stimuli OR is there a change from their normal baseline consciousness level?"
      1. YES then treat for severe but not immediately life-threatening respiratory depression (section 3.1.3.2)
      2. NO then follow watchful waiting (section 3.1.3.3)

- 3.1.3 Management

  - **3.1.3.1 Immediately life-threatening respiratory depression**
    - ACTIONS:
      1. Give 400micrograms IV naloxone over 30 seconds (followed by a 0.9% sodium chloride 10mL flush)
      2. Assess after 1 minute
      3. Reassess respiratory rate and document this
      4. If no response, repeat steps 1-3 with increasing doses of naloxone:
         - Cycle 2: 800 micrograms
         - Cycle 3: 800 micrograms
         - Cycle 4: 2000 micrograms – 4000 micrograms
         - Additional Cycles: longer acting opioids (e.g. fentanyl patches and methadone) may require repeated cycles and often an IV infusion (Section 3.1.3.5).
      5. Stop when either:
         - > 8 breaths/min and easily rousable/returned to their normal conscious level
         - >= 10 breaths/min even if still drowsy
    - Intravenous administration of naloxone has a fast onset of action (2-3 minutes). If it is not possible to obtain IV access, naloxone can be given as an IM or SC injection although onset of action will be slower (2-5 minutes) and higher doses may be required.
    - If there is evidence of adverse consequences of naloxone administration the ongoing management should be discussed with the specialist palliative care team.
    - If requiring 3 or more naloxone administrations, an infusion may be required, see Section 3.1.3.5

- **3.1.3.2 Severe but not immediately life-threatening respiratory depression**
  - ACTIONS
    1. Give naloxone 100micrograms IV over 30 seconds
       a. Draw up a 1mL ampoule (400 micrograms) of naloxone into a 5mL syringe, then make up to a total of 4mL with sodium chloride 0.9%.
       b. Administer 1mL (100micrograms) by slow IV over 30 seconds
       c. Follow with a 0.9% sodium chloride 10mL flush
    2. Wait 2 minutes
    3. Reassess respiratory rate and conscious level and document
    4. If no response, repeat steps 1-3
    5. Stop when either:
       - > 8 breaths/min and easily rousable/returned to their normal conscious level
       - >= 10 breaths/min even if still drowsy

- **3.1.3.3 Watchful Waiting**
  - Please note that if an ABG has been performed and the patient's pCO2 is > 6.5KpA a Watchful Waiting approach is not appropriate.
  - ACTIONS
    1. NOT for naloxone at this time
    2. Continue monitoring (Section 3.1.3.4)
    3. Review other factors
       - Excessive dosing
       - Drug-drug interaction
       - Drug accumulation because of an opioid with a long half-life
       - Reduced elimination because of renal impairment

- 3.1.4 Ongoing Management
  - Repeat observations depending on what type of opioid has caused toxicity:
    1. If IR opioid - every 15 minutes for 2 hours, then every hour for 4 hours, then every 30 minutes for 2 hours.
    2. If MR opioid - every 15 minutes for 2 hours, then every hour for 10 hours, then every 30 minutes for 2 hours.
    3. If methadone - every 15 minutes for 2 hours, then every hour for 24 hours, then every 30 minutes for 2 hours.
  - A maximum of 100-200micrograms (approximately 1.5-3micrograms per kg) is usually sufficient to produce an optimum respiratory response while maintaining adequate analgesia.
  - Duration of action of naloxone is 15-90 minutes; therefore if the clinical situation changes and the patient's respiratory rate or consciousness level worsens, repeated doses of naloxone may be required. Reassess and treat as per guidelines above.
  - See section 3.3 regarding adjustments to analgesia.

- Check bloods including FBC, U+Es, LFTs and Calcium – to allow identification of possible clinical changes that led to opioid toxicity (e.g. new onset renal failure, liver failure or hypercalcaemia). They may also highlight alternative diagnoses.
- Documentation:
    1. Ensure clear documentation in the medical notes and on NerveCentre regarding the clinical situation that led to the need for consideration of naloxone.
    2. If naloxone was used, the doses used and the response to each dose must be documented as well as the plan to manage ongoing analgesia. To support documentation see Appendix 2 for a proforma that can be put into the medical notes.
    3. Complete a DATIX to allow for review of clinical situation

- 3.1.5 Prolonged or Recurrent Respiratory Depression Requiring Repeated Naloxone Doses (Naloxone Infusion)
    - Naloxone has a shorter half-life then morphine and other opioids; it may therefore be necessary to administer further bolus doses. If more than three 'episodes' of naloxone are required then an IV naloxone infusion should be considered.
    - Ideally naloxone IV Infusions should be administered in a high dependency level setting due to the increased monitoring that is required to ensure safe and effective titration.
    - To setup an IV infusion
        - Draw up 25 x naloxone (400micrograms in 1mL) ampoules into a 50mL syringe. Make up to a total of 50mL with 25mL of 5% glucose. This will give a 200microgram/mL naloxone solution.
        - Administer via large peripheral vein or central venous catheter using a 50ml IV Syringe Pump (**not a T34 syringe driver**).
        - The initial hourly dose should be set at 60% of the dose of naloxone which had previously maintained a respiratory rate of >= 10 breaths/min and a patient who was easily rousable for more than 15 minutes.
            - e.g. if patient had required three 'episodes', each requiring 3x 100microgram naloxone doses each time achieving stable respiratory rate and conscious level,

Episode	Dose 1	Dose 2	Dose 3	Total
1) 14:00	100micrograms	100micrograms	100micrograms	300micrograms
2) 14:30	100micrograms	100micrograms	100micrograms	300micrograms
3) 15:00	100micrograms	100micrograms	100micrograms	300micrograms

                - Note, each episode was over 15 minutes apart; therefore the infusion only needs to be based on the last episode.
                - The hourly rate for infusion would be: 300micrograms x 0.6 = 180micrograms naloxone/ hr (0.9mLs/hr)
            - e.g if patient had required 400mcg naloxone, 1200mcg naloxone and 1200mcg naloxone in three separate 'episodes' – each time achieving stable respiratory rate and conscious level

Episode	Dose 1	Dose 2	Dose 3	Total
1) 14:00	400micrograms			400micrograms
2) 14:30	400micrograms	800micrograms		1200micrograms
3) 15:00	400micrograms	800micrograms		1200micrograms

        - the hourly rate for infusion would be based on the most recent episode: 1200 x 0.6 = 720micrograms naloxone/ hr (3.6mLs/hr)
    - If you don't yet have a dose that can maintain ventilation for this period of time it will be necessary to continue to up titrate the bolus doses before setting up an infusion
    - The hourly rate should be titrated to response based on the same criteria as the initial setting up dose (a respiratory rate of >= 10 breaths/min and a patient who was easily rousable).

3.2 Reversal of buprenorphine-induced respiratory depression

- Buprenorphine has both a high receptor affinity and prolonged receptor binding therefore naloxone in standard doses does not reverse the effects of buprenorphine; it will be necessary to use higher doses. Buprenorphine comes in the form of transdermal patches and oral/buccal lozenges. This additional guidance does not apply to other transdermal patches such as fentanyl patches.
- Discontinue buprenorphine – remove patches and de-prescribe oral tablets
- Give oxygen by mask to maintain target oxygen saturations as per NEWS2 model
- Give IV naloxone **2mg** stat over 90 seconds (5x 400microgramsnaloxone in 1mL ampoules)
- Commence naloxone 4mg/hr IV infusion (20mL/hr based on a naloxone 200micrograms/mL infusion)
- Continue naloxone infusion until the patient condition is satisfactory (probably < 90 minutes)
- Contact the On call Palliative Care Consultant for ongoing advice/support.
- Monitor the patient for the next 24hrs and restart infusion if respiratory depression recurs. Observations every 15 minutes for 2 hours, then every hour for 24 hours.
- If the patient's condition remains satisfactory (>= 10 breaths/min and the patient is easily rousable or returned to their usual baseline conscious level) restart buprenorphine patches at a reduced dose (e.g. 50% dose reduction) and consider reducing the minimum interval and/or doses for oral/buccal doses.

3.3 Pain Management following administration of naloxone

- Adjusting Background Opioids after naloxone administration:
    - Modified Release (MR) – omit next dose and reduce subsequent dose (e.g. 50% reduction)
    - Subcutaneous Syringe Driver – discontinue current driver and once there is sustained respiratory improvement (>= 10 breaths/ min) restart at lower dose (e.g. 50% reduction)
    - Transdermal Patch – remove, recommended that a patch is removed for at least 24 hours and once sustained respiratory improvement, restart at lower dose (e.g. 50% reduction) An alternative option would be to switch to a shorter acting opioid and re-titrate, for further advice discuss with the Palliative Care Team.
- Adjusting PRN medication
    - Reduce current dose by 50% and consider increasing the minimal interval
    - Consider switching to alternative opioid analgesia as the opioid that was being administered that led to toxicity may now not be appropriate.
- Managing pain can be complicated following naloxone administration and pain control can be unstable for a prolonged period of time. For further advice in managing unstable pain please contact the Palliative Care Team.

4. Education and Training

- Relevant training will be incorporated into ongoing training programs including ward based palliative care link nurses.

5. Monitoring and Audit Criteria

All guidelines should include key performance indicators or audit criteria for auditing compliance,

if this template is being used for associated documents (such as procedures or processes) that support a Policy then this section is not required as all audit and monitoring arrangements will be documented in section 8 of the Policy.

Key Performance Indicator	Method of Assessment	Frequency	Lead
Correct identification of clinical indicators for administration of Naloxone	Sample of cases involving Naloxone administration	Annually	Dr James Coxon
Outcomes from Naloxone administration	Sample of cases involving Naloxone administration	Annually	Dr James Coxon

6. Supporting Documents and Key References

- gov.uk, 2019. *Widening the availability of naloxone.* [Online]
  Available at: https://www.gov.uk/government/publications/widening-the-availability-of-naloxone/widening-the-availability-of-naloxone
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- LOROS, 2020. *NALOXONE: Use in Management of Opioid Induced Respiratory Depression,* s.l.: s.n.
- NHSEngland, 2014. *Risk of distress and death from inappropriate doses of naloxone in patients on long-term opioid/opiate treatment,* s.l.: s.n.
- Robert Twycross, A. W. P. H., n.d. Quick Clinical Guide: Reversal of opioid-induced respiratory depression. In: *Palliative Care Formulary Seventh Edition.* s.l.:Pharmaceutical Press, p. 488.
- ToxBase – *Naloxone – Patients at risk of acute withdrawal* (Updated 3/2021 accessed 12/04/2023)

7. EQUALITY IMPACT ASSESSMENT

The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.

As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

8. Key Words

Naloxone, Opioid, Opiate, Palliative Care, Palliative Medicine, Overdose, Pain, Analgesia, Morphine, Oxycodone, Alfentanil, Hydromorphone, Methadone, Fentanyl, Buprenorphine, Toxicity, Dignity

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This table is used to track the development and approval and dissemination of the document and any changes made on revised / reviewed versions

DEVELOPMENT AND APPROVAL RECORD FOR THIS DOCUMENT		
Author / Lead Officer:	James Coxon	**Job Title:** Consultant in Palliative Medicine
Reviewed by:		
Approved by:	**Policy and Guideline Committee**	**Date Approved: 19.4.24**

REVIEW RECORD			
Date	**Issue Number**	**Reviewed By**	**Description Of Changes (If Any)**

DISTRIBUTION RECORD:			
Date	**Name**	**Dept**	**Received**

Appendix 1 – Decision Flow Chart

Clinical Suspicion of Opioid Toxicity

Consider alternative causes, if patient is recognised to be dying and supported by a personalised care plan naloxone is unlikely to be appropriate – discuss with senior doctor or SPC team.

Measure Respiratory Rate over 1 minute

≥8 breaths/min

UNLIKELY TO BE OPIOID TOXICITY

Consider alternative diagnosis

NOT FOR NALOXONE

< 8 breaths/min

1. **Administer oxygen to maintain target sats**
2. **Obtain IV access**
3. **Discontinue regular opioid - stop syringe driver/ remove patch/ stop MR opioid**

Is this a life threatening situation – unconscious patient with minimal/no respiratory effort?

No

Patient unresponsive / responsive only to painful stimuli OR change from their normal baseline consciousness level

No

WATCHFUL WAITING

If patient is alert/ opens eyes to verbal commands, adopt a policy of watchful waiting

1. **NOT for naloxone at this time**
2. **Monitor as below**
3. **Review for other factors**

- excessive dosing e.g. rapid dose escalation, multiple PRN doses, prescribing/ administration error

- drug accumulation

- reduced elimination e.g. renal impairment

- drug interactions

Yes

SEVERE BUT NOT IMMEDIATELY LIFE-THREATENING RESPIRATORY DEPRESSION

1. **Give naloxone 100micrograms IV over 30 seconds**

Lower doses of naloxone are used to avoid a severe acute reversal of analgesia

(Draw up a 1mL ampule of 400micrograms naloxone into a 5mL syringe. Make up to a total of 4mL with 0.9% sodium chloride. Administer 1mL)

2. **Wait 2 minutes**
3. **Reassess respiratory rate and conscious level**

If no response, repeat steps 1-3

If no response despite giving a total of 400micrograms switch to Immediately Life-Threatening Respiratory Depression (Red Box)

Stop when either:

- **>8 breaths/min and easily rousable/ returned to their normal conscious level**
  OR
- **≥10 breaths/min even if still drowsy**

Yes

IMMEDIATELY LIFE-THREATENING RESPIRATORY DEPRESSION

1. **Give naloxone 400micrograms IV over 30 seconds**
2. **Wait 1 minute**
3. **Reassess respiratory rate**

If no response, repeat steps 1-3 with increasing doses of naloxone:
Cycle 2 – 800micrograms IV
Cycle 3 – 800micrograms IV
Cycle 4 – 2000micrograms IV

Stop when either:

- **>8 breaths/min and easily rousable/ returned to their normal conscious level**
  OR
- **≥10 breaths/min even if still drowsy**

ONGOING MANAGEMENT

Check obs (even if on an 'end of life' obs chart) and document in medical notes

- every 15 mins for 2 hours
- then every hour for: 6 hours (due to IR opioid) / 12 hours (due to MR opioid) / 24 hours (due to methadone)

If clinical situation deteriorates, further naloxone may be required. Reassess and treat as per guidelines above
If more than three 'episodes' requiring naloxone occur, consider IV infusion of naloxone. Discuss with senior doctor.

- **Review prescribed opioids:**
  - Omit next dose of MR opioid & re-prescribe at 50% dose
  - Stop syringe driver & represcribe at 50% dose
  - Remove transdermal patch & after 24hrs replace at 50% dose
  - Reduce PRN dose by 50%
- **Documentation and reporting**
  - Complete proforma
  - Document events in medical notes in full
  - Complete DATIX re naloxone administration
  - Inform specialist palliative care team as soon as possible

Appendix 4 – Patient Safety Announcement

NHS England

Patient Safety Alert

Stage One: Warning

Risk of distress and death from inappropriate doses of naloxone in patients on long-term opioid/opiate treatment

20 November 2014

Alert reference number: NHS/PSA/W/2014/016

Alert stage: One - Warning

Naloxone is an opioid/opiate antagonist licensed for use in:

- complete or partial reversal of central nervous system depression and especially respiratory depression, caused by natural or synthetic opioids; and
- treatment of suspected acute opioid overdose or intoxication.

Naloxone must be given with great caution to patients who have received longer-term opioid/opiate treatment for pain control or who are physically dependent on opioids/opiates. Use of naloxone in patients where it is not indicated, or in larger than recommended doses, can cause a rapid reversal of the physiological effects for pain control, leading to intense pain and distress, and an increase in sympathetic nervous stimulation and cytokine release precipitating an acute withdrawal syndrome. Hypertension, cardiac arrhythmias, pulmonary oedema and cardiac arrest may result from inappropriate doses of naloxone being used for these types of patients.

The British National Formulary (BNF)[1] recommends a dose range to reverse acute opioid/opiate overdose in adults by intravenous injection of naloxone of 400 micrograms to 2mg. If there is no response, the dose is to be repeated at intervals of two to three minutes to a maximum of 10mg.

The BNF highlights that **doses used in acute opioid/opiate overdose may NOT be appropriate for the management of opioid/opiate-induced respiratory depression and sedation in those receiving palliative care and in chronic opioid/opiate use.** The recommended dose for adults in post-operative respiratory depression and for palliative care and chronic opioid/opiate use by intravenous injection is 100 to 200 micrograms (1.5 to 3 micrograms/kg). If the response is inadequate, give subsequent dose of 100 micrograms every two minutes. The naloxone doses in the BNF may differ from those in product literature. Even where doses are given as recommended, there is still a need for careful monitoring of vital observations and maintaining or restoring pain relief.

NHS England has received details of three patient safety incidents describing failure to follow the BNF guidance, including two incidents that resulted in death. Because this risk appears under-recognised, there may be significant under-reporting.

Additional safeguards that have been locally implemented include raising awareness of the risk of inappropriate doses of naloxone, the use of lower doses of naloxone in clinical protocols and resuscitation drug trays, teaching correct use of naloxone in annual cardiopulmonary resuscitation training sessions, and providing guidance on clinical monitoring and access to specialist pain relief advice after naloxone administration.

Actions

Who: All organisations providing NHS funded care where naloxone is prescribed, dispensed and/or administered.

When: As soon as possible but no later than 22 December 2014.

1. Establish if incidents involving inappropriate use of naloxone have occurred or have the potential to occur in your organisation.
2. Consider if immediate action needs to be taken locally and ensure that an action plan is underway, if required, to reduce the risk of further incidents occurring.
3. Disseminate this Alert to clinical staff who prescribe, dispense or administer naloxone injection.
4. Share any learning from local investigations or locally developed good practice resources by emailing: England.medication-safety@nhs.net

Patient Safety | Domain 5
www.england.nhs.uk/patientsafety

Contact us: patientsafety.enquiries@nhs.net

Publications Gateway Reference: 02531

Alert reference number:	NHS/PSA/W/2014/016
Alert stage:	One - Warning

Technical notes

NRLS search dates and terms
A search of NRLS medication incident involving naloxone for three years data (where incident date fell between 28.2.2011 to 28.2.2014 if reported by 21.05.2014) identified three incidents of wrong dose errors; two of these incidents resulted in fatal outcomes.

Stakeholder engagement
Advice was sought from the Medical Specialities Patient Safety Expert Group, which includes representatives of a range of professional and patient organisations.

Other
Reference [1] British National Formulary, September 2014 edition.

Acknowledgement
Mr Richard von Abendorff, for bringing to the attention to NHS England and the healthcare community the risks of harm from inappropriate dosing of naloxone, after a tragic incident involving the death of his mother, and for sharing with them a useful report by Dr Malcolm VandenBurg www.malcolmvandenburg.co.uk.

Patient Safety | Domain 5
www.england.nhs.uk/patientsafety

Contact us: patientsafety.enquiries@nhs.net

Publications Gateway Reference: 02531