SPAGG

Coversheet for Specialist Palliative Audit and Guideline Group Agreed Documentation

This sheet is to accompany all documentation agreed by SPAGG. This will assist maintenance of the guidelines as well as demonstrating the governance process undertaken prior to members seeking local approval in their areas of work.

Document Title	**Guidelines for the use of naloxone in palliative care in adult patients**
Document Date	March 2025
Document Purpose and **Intended Audience**	This guideline provides information about the use of naloxone, an opioid antagonist in the palliative patient who is receiving prescribed opioid medication in the clinical setting.
Authors	Previous version reviewed and updated by Michelle Aslett, Specialist Palliative Care Pharmacist.
References	At end of document
Consultation Process	Discussed and ratified at SPAGG
Monitoring	Review by SPAGG
Review Date	March 2028
Approval Signatures: SPAGG chair SPAGG deputy chair SPAGG secretary	 Dr Jon Tomas Dr Hannah Fox

Date Approved by SPAGG: 12th March 2025

Date submitted to Area Prescribing Committee:

1. Scope of the guideline

1.1. This guideline provides information about the use of naloxone, an opioid antagonist in the palliative patient who is receiving prescribed opioid medication in the clinical setting.
The use of naloxone in this clinical situation is with the intent of reversing opioid-induced respiratory depression which is immediately life-threatening (i.e. requires intervention to prevent death from opioids rather than disease)

1.2. It is **not** intended to cover the management of acute opioid overdose

1.3. It is **not** intended to cover alternative use/indications of naloxone in the palliative care setting

1.4. It does **not** cover administration in the patient's home environment

2. Guideline background

2.1. This guideline was initially produced in response to the National Patient Safety Agency recommendation (May 2006) that naloxone is available in all clinical locations where morphine and diamorphine injections are administered or stored.[1] Subsequent patient safety alerts NHS/PSA/W/2014/016 [2] and NHS/PSA/Re/ 2015/009 [3] recommended that 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. It acknowledges that the BNF doses recommended for 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.

2.2. This guidance on the use of naloxone for overdose of prescribed opioids in palliative care patients has been developed to address this. They are based on information in PCF 8 – Palliative Care Formulary accessed February 2024 via www.medicinescomplete.com

Guideline statements

3. General principles

3.1. Naloxone should only be used in palliative care in those circumstances where a clinician suspects opioid-induced toxicity.

3.2. Naloxone is not indicated for:

- patients on opioids who are dying as a natural result of their disease progression
- symptoms solely induced by non- opioids e.g. barbiturates, benzodiazepines opioid induced drowsiness and/or delirium which is not life threatening

3.3. It is important, in the management of patients in pain, that the signs of advanced progressive disease are not confused with those of opioid overdosage, leading to inappropriate use of naloxone.

3.4. Patients 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.

3.5. Total antagonism of opioids can result in severe pain with hyperalgesia. Physical withdrawal symptoms and marked agitation can also occur. Opioid withdrawal syndrome is characterised by anxiety, irritability, muscle aches, nausea and vomiting. In severe cases, this can include life-threatening tachycardia and hypertension. Cardiac arrhythmias, pulmonary oedema and cardiac arrest have been described.

3.6. Patients who are taking opioids and have recently received another intervention e.g. Radiotherapy or nerve block are at risk of opioid toxicity. Concomitant administration of gabapentinoids can increase the risk of respiratory depression.
Gabapentin (Neurontin): risk of severe respiratory depression - GOV.UK (www.gov.uk) Pregabalin (Lyrica): reports of severe respiratory depression - GOV.UK (www.gov.uk)

3.7. Naloxone's antagonism of buprenorphine is less complete because of the latter's high receptor affinity and prolonged receptor binding -see section 5 for reversal of buprenorphine induced respiratory depression. Naloxone has been reported to be only partially effective in reversing the effects of tramadol.

4. Diagnosis and treatment of opioid induced respiratory depression

4.1. If respiratory rate > 8 breaths/min with normal oxygen saturations, and the patient is easily rousable and not cyanosed, adopt a policy of 'wait and see'; consider reducing or omitting the next regular dose of opioid or reducing rate of/discontinuing continuous parenteral administration.

Pupil size is an unreliable indicator of opioid overdose in patients taking regular opioids.

Consider "is the patient more drowsy than usual" as this will also help evaluate the clinical situation and assess if naloxone is indicated.

4.2. Administer high flow oxygen via face mask if the patient is hypoxic. Administer oxygen to maintain SpO_2 >95% (88–92% if pre-existing hypercapnic respiratory failure)

4.3. Naloxone is best given IV but, if not practical, may be given IM or SC.

4.4. If respiratory rate < 8 breaths/min, and the patient is comatose/unconscious and/or cyanosed:[4,5]

- Stop opioid administration
- Follow the authorisation chart to prepare the naloxone injection concentration and administration of stepwise doses according to patient response.
- The aim is for slow, paced administration of the drug to avoid a surge of pain from complete antagonism of opioid
- After the last dose of naloxone, monitor consciousness and respiratory rate every 15 mins for 2 hours then hourly for 6 hours after immediate release opioid, 12 hours after sustained release opioid, and 24 hours after methadone or transdermal opioid.
- Wait until there has been a sustained improvement in consciousness before restarting a lower dose of opioid, it may be preferable to switch the type of opioid
- If there is little or no response, consider other causes (e.g. other sedatives)

4.5 If repeated naloxone doses (more than 3 repeat bolus doses) are required, consider starting a continuous intravenous infusion of naloxone [4]

An infusion of naloxone is a specialist intervention – clinicians need to consider the intensive monitoring requirements which is suggested to be every 15 minutes including blood pressure, pulse, respiratory rate, oxygen saturation and level of consciousness. Patients should be observed for a minimum of six hours after the last dose of naloxone.

In this circumstance, transfer to the acute hospital setting should be considered and discussed with the patient or their advocate, and the consultant in charge of the patient's care or the on-call consultant.

Nursing and medical staff should be competent at IV administration and monitoring of opioid toxicity and withdrawal prior to a decision to utilise a continuous intravenous infusion in the hospice setting.

Dilute Naloxone 400micrograms/1ml in 100 ml 0.5% glucose or 0.9% sodium chloride to produce a 4microgram/ml solution. If 100ml bags are not available, this can be multiplied accordingly to achieve the same concentration i.e. 1mg Naloxone in 250ml, or 2mg Naloxone in 500ml)

- Administer via a large peripheral vein (or central venous catheter) Use an IVI device e.g. volumetric infusion pump to deliver dose
- Use 60% of the stat dose which had previously maintained satisfactory ventilation for more than 15mins, every hour. If 60% equates to a difficult dose, it is possible to round up or down to the nearest whole number. For example, if 60mcg has been the last dose to previously maintain respiratory rate, start infusion of 36mcg/hr or 9ml/hr of 4mcg/ml solution.

Adjustment of infusion rate may be required according to patient respiratory rate (aim to keep above 8/min)

- continue to monitor the patient closely with minimum of respiratory rate, oxygen saturations and alertness (AVPU) measured every 30 minutes
- continue the infusion until the patient's condition has stabilised, and respiratory rate is greater than 10/min with oxygen saturations greater than 92% on air
- When the decision is taken to cease the infusion, close observation should again take place in case of ongoing toxicity being masked by the naloxone infusion
- Nursing and medical staff should take care to review for signs of opioid withdrawal and adjust the naloxone infusion rate as required.
- additional IV boluses may need to be given using naloxone diluted in sodium chloride 0.9% as above

There is no current evidence for use of naloxone via continuous subcutaneous syringe driver. However, the authors are aware of cases where this has been done where hospital transfer was not appropriate – refer to Syringe Driver Database.

5. Buprenorphine

5.1 Due to very strong receptor affinity (reflected in its high relative potency with morphine), naloxone in standard doses does not reverse the effects of buprenorphine and higher doses must be used, see table below

Reversal of buprenorphine induced respiratory depression
1. Discontinue buprenorphine (remove transdermal patch) 2. Give Oxygen by mask 3. Give IV naloxone 2mg stat over 90 seconds 4. Commence naloxone 4mg/hour by CIVI 5. Continue CIVI until the patient's condition is satisfactory (probably <90min) 6. Monitor the patient frequently for the next 24h, and restart CIVI if respiratory depression recurs 7. If the patient's condition remains satisfactory, restart buprenorphine at a reduced dose, e.g. half of the previous dose

6. Other management issues

6.1. Intra-venous is the preferred route of administration for naloxone, but can be given intra-muscularly or subcutaneously if venous cannulation is not possible
If using IM/SC route, be aware that onset of action will be slower, approx 2-5 minutes compared to IV onset of action 1-2mins, though duration of action may be more prolonged.

Nasal naloxone is also available (Nyxoid 1.8mg naloxone dose per spray or Naloxone 1.26mg dose per spray

6.2. Administer high flow oxygen via face mask, if the patient is hypoxic.

6.3 Delayed-onset pulmonary oedema (48h after overdose treated with naloxone) due to acute cardiomyopathy has also been reported, possibly the result of cardiac muscle damage caused by hypoxaemia.

6.4 Complete an incident form for your organisation that naloxone has been administered.

7. Monitoring of the patient after first Naloxone administration

7.1. Naloxone has a much shorter half-life than morphine. There is a risk that opioid toxicity will recur as the naloxone wears off and the opioid is still active. Respiratory rate and oxygen saturation should be monitored closely until stable. The length of this period of monitoring will be dependent on the half-life of the opioid causing toxicity. The half-life of morphine and some other opioids is prolonged in renal failure and other metabolic disturbance.

After the last dose of naloxone, monitor level of consciousness and respiratory rate every 15min for 2h, then hourly for 6h after immediate-release opioid; monitor for longer after a modified-release opioid or an opioid with a long half-life, e.g. 12h after a 12-hourly modified-release opioid, 24h after methadone

7.2. It may be appropriate to transfer the patient to a facility where naloxone infusion and monitoring can be initiated. This course of action should be considered if respiratory depression continues to recur despite repeated administration of naloxone (as above).

8. Patient information and counselling

As per the NICE Guidance for use of opioids in palliative care, all patients, should be offered access to appropriate written information during their investigation and treatment, including information about opioid side effects and signs of toxicity

9. Monitoring of the guideline

Adherence to the Network guidelines may from time to time be formally monitored.

Any use of naloxone should be reported as an incident within your organisation and to the CDAO who will need to add to their CDLIN quarterly report. The aim of incident reporting is to review and reflect on the time preceding the intervention and identify any changes in practice as a result

References

1. National Patient Safety Agency. Ensuring safer practice with high dose ampoules of diamorphine and morphine. Issued- 25th May 06. Available at: www.npsa.nhs.uk/nrls/alerts-and-directives/notices/morphine-diamorphine/ Accessed November 2008
2. Patient Safety Alert. Stage One: Warning. Risk of distress and death from inappropriate doses of naloxone in patients on long-term opioid/opiate treatment. NHS/PSA/W/2014/016, 20/11/2014. Available via https://www.england.nhs.uk/wp-content/uploads/2014/11/psa-inappropriate-doses-naloxone.pdf
3. Patient Safety Alert. Stage Two: Resources. Support to minimise the risk of distress and death from inappropriate doses of naloxone. NHS/PSA/Re/2015/009, 26/10/2015. Available via https://www.england.nhs.uk/patientsafety/wp-content/uploads/sites/32/2015/10/psa-naloxone-stage2.pdf
4. Twycross R. Wilcock A. et al. Palliative Care Formulary 6. Available via: www.palliativedrugs.com . Accessed November 2019.
5. UKMI Medicines Q&A. What naloxone doses should be used in adults to reverse urgently the effects of opioids or opiates? July 2017. Available via https://www.sps.nhs.uk/wp-content/uploads/2015/11/UKMi_QA-_Naloxone-dosing_Aug-17_FINAL.pdf
6. Scottish Palliative Care Guidelines – Naloxone monograph. 04/05/2014. Review date 04/05/2017. Available via http://www.palliativecareguidelines.scot.nhs.uk/media/1216/scottish-palliative-care-guideline-naloxone.pdf

STOP AND THINK

Is this Patient in the Last Days of Life?

Flow Chart for Naloxone Administration

Is this situation life-threatening i.e. respiratory arrest secondary to opioid use?

YES

Maintain airway
Administer oxygen
Secure IV access
Stop opioid

Give Naloxone 400micrograms IV

If no response after 1 min

Give Naloxone 800micrograms IV

If no response after 1 min

Give Naloxone 800micrograms IV

If no response after 1 min

Give Naloxone 2-4mg IV

If no response consider alternative cause.

NO

Is resp rate <8

YES

Administer oxygen
Stop opioid

Dilute 1ml of naloxone 400micrograms/ml ampoule to 8ml in sodium chloride 0.9%.

This gives 100micrograms/2ml

Give

Naloxone 100micrograms/ 2ml

- IV every 2 minutes

or

- SC/IM every 5 minutes

Continue until respiratory rate improves

If more than 3 doses have been needed, consider if a naloxone infusion is needed.

NO

If **normal** oxygen sats, no cyanosis and easily rousable then "watch and wait"

Consider reducing or omitting next due dose of opioids.

Monitoring post-Naloxone administration

Patient name: NHS no: DOB:

When to check	Date	Time	Resp Rate	Consciousness level	Length of monitoring dependent on drugs/ formulations		
					Immediate release	Modified Release	Patches Methadone Buprenorphine
Baseline							
+15 mins							
+30 mins							
+45 mins							
+1 hour							
+ 1 hour 15mins							
+ 1 hour 30 mins							
+ 1 hour 45 mins							
+ 2 hours							
+ 3 hours							
+ 4 hours							
+ 5 hours							
+ 6 hours							
+ 7 hours							
+ 8 hours							
+ 9 hours							
+ 10 hours							
+ 11 hours							
+ 12 hours							
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+ 14 hours							
+ 15 hours							
+ 16 hours							
+ 17 hours							
+ 18 hours							

+ 19 hours							
+ 20 hours							
+ 21 hours							
+ 22 hours							
+ 23 hours							
+ 24 hours							

Naloxone for emergency use – Authorisation to Administer

Reason for naloxone:

Naloxone protocol initiated by _____

Date and time initiated_____

Prescriber signature_____

Opioid infusion/patch stopped at time_____
NB if Buprenorphine then use administration guide below

Oxygen commenced at time _____ Resp Rate =

By (staff signatures)_____

Dilute naloxone 400 micrograms (1ml ampoule) to 8ml with 0.9% sodium chloride for injection in a 10ml syringe.

This is now Naloxone 50 micrograms/ml strength injection.

Time 0 min	**Naloxone**	**100 micrograms (2ml of solution made above)**	**IV slow bolus (30-60s)** or **SC** or **IM**	**Given by**
	Flush cannula with 0.9% sodium chloride Given by:			
+2 mins	Resps are:- Staff signature			
If resps <8 breaths/min give:-				
	Naloxone	**100 micrograms (2ml of solution made above)**	**IV slow bolus (30-60s)** or **SC** or **IM**	**Given by**
	Flush cannula with 0.9% sodium chloride Given by:			
+4 mins	Resps are:- Staff signature			
If resps <8 breaths/min give:-				
	Naloxone	**100 micrograms (2ml of solution made above)**	**IV slow bolus (30-60s)** or **SC** or **IM**	**Given by**
	Flush cannula with 0.9% sodium chloride Given by:			
+6 mins	Resps are:- Staff signature			
If resps <8 breaths/min consider NALOXONE INFUSION				

ADMINISTRATION FOR BUPRENORPHINE OVERDOSE ONLY

Time 0 min	**Naloxone**	**2mg/5ml**	**IV slow bolus (90 seconds)**	**Given by**
START NALOXONE INFUSION at 4mg/hour until the patient's condition is satisfactory (full reversal takes 40–60min).				

Naloxone Infusion – Authorisation to Administer

Date and time initiated_____ Prescriber signature_____		
There are two different options to make infusions depending on stocks available.		
1 x Naloxone 400 micrograms/ 1ml added to **100ml** Sodium Chloride 0.9% infusion bag	OR	**5** x Naloxone 400 micrograms/1ml (i.e. 2mg) added to **500ml** Sodium Chloride 0.9% infusion or Glucose 5% bag
Signature(s)		

This is now Naloxone 4 micrograms/ml strength infusion

Administer via a large peripheral vein or central venous catheter

(Once diluted, naloxone solutions should be used within 24 hours)

Time started	**Naloxone**	**Usual infusion rate is 25 - 100ml/hr (100- 400micrograms/hr)** Rate of infusion should be adjusted according to the response and can be increased up to 200ml/hr (800micrograms/hr).	**IV Infusion**	**Given by**
	Rate of infusion should be adjusted according to the response and can be increased up to 200ml/hr (800micrograms/hr).			

The initial hourly rate for infusion is set at **60% of the bolus** needed to obtain a response and may be adjusted according to clinical response:

Initial bolus dose giving response	**Initial hourly rate of infusion**	**Volume per hour (of 4 micrograms/mL solution)**
200 micrograms	120 micrograms/hour	30ml
400 micrograms	240 micrograms/hour	60ml
600 micrograms	360 micrograms/hour	90ml
800 micrograms	480 micrograms/hour	120ml
1000 micrograms (1mg)	600 micrograms/hour	150ml
1200 micrograms (1.2mg)	720 micrograms/hour	180ml
1400 micrograms (1.4mg)	*840 micrograms/hour*	
1600 micrograms (1.6mg)	*960 micrograms/hour*	
1800 micrograms (1.8mg)	*1080 micrograms/hour*	
2000 micrograms (2mg)	*1200 micrograms/hour*	

Naloxone for Immediately Life-Threatening Respiratory Depression – Authorisation to Administer

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.

Reason for naloxone:

Naloxone protocol initiated by _____

Date and time initiated_____

Prescriber signature_____

Opioid infusion/patch stopped at: **Oxygen commenced at:** **By (staff signature):**	A nasal spray product (Nyxoid®) is available for use in circumstances where IV access is not immediately available: • give 1.8mg (one spray) into one nostril and wait 2–3min • if there is no response (or if respiratory depression recurs), repeat the dose, alternating nostrils

Use Naloxone 400micrograms/ml ampoules

Time 0 min	**Naloxone**	**400 micrograms (1ml)**	**IV slow bolus (30s)**	**Given by**
	Flush cannula with 0.9% sodium chloride Given by:			
+1 mins	Resps are:- Staff signature			
If resps <8 breaths/min give:-				
	Naloxone	**800 micrograms (2ml)**	**IV slow bolus (30s)**	**Given by**
	Flush cannula with 0.9% sodium chloride Given by:			
+1 mins	Resps are:- Staff signature			
If resps <8 breaths/min give:-				
	Naloxone	**800 micrograms (2ml)**	**IV slow bolus (30s)**	**Given by**
	Flush cannula with 0.9% sodium chloride Given by:			
+1 mins	Resps are:- Staff signature			
	Naloxone	**2mg – 4mg**	**IV slow bolus (1-2 mins)**	**Given by**
	Flush cannula with 0.9% sodium chloride Given by:			
+1 mins	Resps are:- Staff signature			
If a total of 10mg has been administered and resp depression has not improved, consider alternate diagnosis, including the possibility of 'wooden chest' syndrome.				

MONITORING POST NALOXONE ADMINISTRATION

- A = Awake. The patient is Awake
- V = Verbal. The patient responds to a Verbal stimulus
- P = Pain. The patient responds to a Pain stimulus
- U = Unresponsive. The patient is Unresponsive to stimulus

Hourly monitoring for at least

- 6 hours for IR opioids
- 12 hours SR opioids
- 24 hours for transdermal/methadone/buprenorphine

Date	Interval	Actual Time	RR	Consciousness (AVPU)	Signature
	+15 mins				
	+15 mins				
	+15 mins				
	+15 mins				
	+15 mins				
	+15 mins				
	+15 mins				
	+15 mins				
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	+1 hour				
	+1 hour				

Date	Interval	Actual Time	RR	Consciousness (AVPU)	Signature
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	+1 hour				
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