SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
ADULT HOSPITAL CHAPTER 20: EMERGENCIES AND INJURIES
NEMLC RECOMMEDATIONS FOR MEDICINE AMENDMENTS (2020-4 REVIEW CYCLE)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG) and supporting medicine reviews and costing analyses.

A: NEW STANDARD TREATMENT GUIDELINES

SECTION	CONDITION	MEDICINE MANAGEMENT	MEDICINE ADDED
20.11	Rapid sequence induction and intubation	No	n/a
20.11.1	Induction agents	Yes	Propofol, IV
			Etomidate, IV
			Ketamine, IV
20.11.2	Muscle relaxants	Yes	Suxamethonium, IV
			Rocuronium, IV
20.11.3	Post-intubation sedation -*Sedation*	Yes	Midazolam, IV
			Propofol, IV
			Lorazepam, IV
	-*Supplemental analgesia*	Yes	Morphine, IV
			Fentanyl, IV
			Ketamine, IV

20.11 RAPID SEQUENCE INDUCTION AND INTUBATION

The following STG was added, aligned with the Adult Hospital chapter 12: Anaesthesiology and intensive care.

Anaesthetic and sedative medication may only be administered by medical practitioners trained and experienced in their use. Sound theoretical and practical training followed by supervised experience in the administration of anaesthetic and sedative medication is essential. Even within the recommended dosage range, anaesthetic agents can cause death when inappropriately used.

Medicines and equipment for resuscitation should be functional and immediately available whenever general anaesthesia, regional anaesthesia or sedation is administered.

The doses of the medicines given are those recommended for healthy adults. Patients who are acutely or chronically sick, and or elderly, may require substantial reductions in the doses given otherwise life-threatening adverse effects may ensue.

Patients at risk of aspiration require a rapid sequence intubation. An IV induction agent is given through an IV line with fast running fluids, immediately followed by a rapidly acting muscle relaxant. The rapid onset of action enables the time to intubation to be short enough to avoid mask ventilation, as this can result in gastric insufflation and aspiration of gastric contents.

20.11.1 INDUCTION AGENTS

Propofol, IV: *added*
Etomidate, IV: *added*
Ketamine, IV: *added*
Thiopental, IV: *not added*

The following STG was added, aligned with the Adult Hospital chapter 12: Anaesthesiology and intensive care; section: 12.2.1 Intravenous induction (and/or maintenance) agents, noting that thiopental has been discontinued:

Respiratory depression occurs following induction of anaesthesia and ventilation should be supported as required.
Administer at appropriate doses, after consideration of patient factors and contraindications:

» Propofol is the most widely used IV induction agent but can produce hypotension.
» Etomidate or ketamine is preferred in haemodynamically unstable patients.

- Propofol, IV, 1.5–2.5 mg/kg.
- Etomidate, IV, 0.3 mg/kg (0.2–0.6 mg/kg)
- Ketamine, IV, 1–2 mg/kg.

20.11.2 MUSCLE RELAXANTS

Suxamethonium, IV: *added*
Rocuronium, IV: *added*

The following STG was added, aligned with the Adult Hospital chapter 12: Anaesthesiology and intensive care, section 12.3.1 Depolarising muscle relaxants:

- Suxamethonium, 1–1.5 mg/kg, IV. (See section 12.3.1: Depolarising muscle relaxants).
  - Preferred agent as, in the event of a failed intubation, it wears off quickly enabling spontaneous respiration to resume.
  - Contraindications to suxamethonium
    - Congenital and acquired medical conditions associated with severe, potentially lethal suxamethonium-induced hyperkalaemia.
    - Malignant hyperthermia.

If suxamethonium is contra-indicated, consider:

- Rocuronium, 0.9 mg/kg, IV.
  - Duration +/- 60 minutes.

Prolonged effect can be problematic in the event of a difficult or failed intubation and if the procedure is short.

20.11.3 POST-INTUBATION SEDATION

Sedation
Midazolam, IV: *added*
Propofol, IV: *added*
Lorazepam, IV: *added*
The following STG text was added, aligned with the Adult Hospital chapter 23: Sedation, with amendments

Sedation requirements fluctuate rapidly and warrant regular review. Individualised sedation objectives should be clearly defined, and level of sedation regularly recorded. Sedation protocols that recognise the need for dose minimisation, weaning and sedation interruptions probably improve outcomes.
Adequate pain control is often more efficacious than sedatives for reducing agitation. The doses listed apply to ventilated patients in whom short term respiratory depression is not a concern[1].

Sedation
Short term sedation (less than 24 hours)

- Midazolam, IV infusion, 0.05–0.2 mg/kg/hour.

OR

- Propofol, IV infusion, 0.5 mg/kg/hour.

Note: Propofol has cardiovascular effects; benzodiazepines are preferred.

Longer term sedation (expected 72 hours or more)

- Midazolam, IV, 0.2 mg/kg/hour.

OR

- Lorazepam, IV, 0.1 mg/kg/hour.

Note: Lorazepam (0.1 mg/kg/hour) is as effective (and as easy to wean) as midazolam 0.2 mg/kg/hour) but is more difficult to titrate. Due to high fat solubility, midazolam also becomes 'long acting' after infusions of more than 24 hours.

[1] Sedation protocols in intensive care: Jackson DL, Proudfoot CW, Cann KF, Walsh T. A systematic review of the impact of sedation practice in the ICU on resource use, costs and patient safety. Crit Care. 2010;14(2):R59. http://www.ncbi.nlm.nih.gov/pubmed/20380720
(Low certainty evidence, conditional recommendation)

Supplemental analgesia
Morphine, IV: *added*
Fentanyl, IV: *added*
Ketamine, IV: *added*

The following STG text was added, aligned with the Adult Hospital chapter 23: Sedation, with the addition of adjunctive ketamine in the haemodynamically unstable patient.

Supplemental analgesia:
ADD an analgesia to any of the above regimens:
- Morphine, IV infusion, 0.1–0.2 mg/kg/hour.

OR
- Fentanyl, IV infusion, 1 mcg/kg/hour (also becomes long acting after prolonged infusion due to fat solubility).

OR
- Ketamine, IV infusion, 0.5–1 mg/kg/hour.

Note: If haemodynamically unstable, use adjunctive ketamine for analgosedation.

Refer to the medicine review for ketamine as monotherapy and adjunctive therapy for analgosedation (review document included below) or the subsequent publication by Hendrikse et al. *Ketamine as adjunctive or monotherapy for post-intubation sedation in patients with trauma on mechanical ventilation: A rapid review*.[2]

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATIONS:

A: KETAMINE MONOTHERAPY

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		x			

Recommendation: The PHC/Adult Hospital Level Committee suggests not to use ketamine as monotherapy for postintubation sedation in intubated adults with trauma on mechanical ventilation (conditional recommendation, very low certainty of evidence).

Rationale: There is uncertainty for benefit and harms for ketamine as monotherapy.
Level of Evidence: Very low certainty
Review indicator: New better quality evidence

B: KETAMINE ADJUNCTIVE THERAPY

	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

Recommendation: The PHC/Adult Hospital Level Committee suggests the use of adjunctive ketamine for postintubation sedation in intubated adults with trauma on mechanical ventilation (conditional recommendation, low certainty of evidence.

Rationale: Ketamine may have benefit as adjunctive therapy but there is uncertainty for benefit and harms as monotherapy.
Level of Evidence: Low certainty of evidence
Review indicator: New high-quality evidence of a clinically relevant benefit or harm

NEMLC RECOMMENDATION – 20 OCTOBER 2022

NEMLC accepted the proposed recommendations, and the NEMLC review report was ratified for external comment (as amended).

Monitoring and evaluation considerations

Research priorities: High-quality RCTs for ketamine use is required for monotherapy, specifically in the prehospital setting for patient important outcomes.

[2] Hendrikse C, Ngah V, Kallon II, Leong TD, McCaul M. Ketamine as adjunctive or monotherapy for post-intubation sedation in patients with trauma on mechanical ventilation: A rapid review. Afr J Emerg Med. 2023 Dec;13(4):313-321. doi: 10.1016/j.afjem.2023.10.002. Epub 2023 Nov 10. PMID: 38033380; PMCID: PMC10682541.

B: PROPOSED AMENDMENTS

SECTION	MEDICINE/ MANAGEMENT	ADDED/DELETED/AMENDED/NOT ADDED/ RETAINED
• ***Cardiopulmonary resuscitation***		
CPR Algorithms	Cardiac arrest algorithm for suspected communicable diseases	Added
20.1 Cardiac arrest in adults	COVID-19 considerations guidance	Added
- Emergency treatment	Precordial thump	Deleted
- Initiate fluids, IV/IO access	Sodium chloride 0.9%, parenteral	Amended (directions for use added)
	Ringers lactate	Not added
- Additional guidance – termination of resuscitation (TOR)	Duration of asystole	Amended
20.2 Post cardiac arrest	Oxygen cut-off	Amended
	Temperature control	Amended
- Hypovolaemia	Sodium chloride 0.9%, parenteral	Amended (directions for use added)
-Pain	Paracetamol	Amended
• ***Medical emergencies***		
20.6 Angioedema	Hydrocortisone, IV	Amended (directions for use)
- If urticaria and/or itch present (no imminent airway compromise)	Promethazine, IV	Amended (directions for use)
	Cetirizine, oral	Deleted
20.7 Anaphylaxis/anaphylactic shock	Anaphylaxis associated with COVID-19 vaccination guidance	Added
20.8 Delirium	Haloperidol, IM	Retained
- Acute management: For agitated and acutely disturbed patient	Olanzapine, oro-dispersible	Added
	Olanzapine, IM	Added
- Acute management: For substance withdrawal, Parkinson's disease, or intolerability to olanzapine	Diazepam, IV	Amended (directions for use)
- If alcohol withdrawal/ Wernicke's encephalopathy suspected:	Thiamine, parenteral	Added
20.10 Pulmonary oedema, acute	Morphine, IV	Deleted & caution added to the STG
- If distressed consider adding morphine	GTN, IV	Amended
20.16 Burns	Figure to calculate body surface area % in children < 8 years	Deleted
	Paracetamol	Amended
	Pantoprazole, IV	Added
- Septic burns	Povidone iodine, topical	Added, aligned to PHC Chp 21
	Silver sulfadiazine, topical	Not added
	Mupirocin, topical	Not added
	Nano-crystalline dressings	Not added
	Melaleuca alternifolia, topical	Not added

CARDIOPULMONARY RESUSCITATION (CPR) ALGORITHMS

Cardiac arrest algorithm for suspected communicable diseases: *added*

Resuscitation Council of South Africa's "Advanced cardiac arrest algorithm - suspected respiratory communicable disease",[3] adapted with permission was included in the STG.

20.1 CARDIAC ARREST IN ADULTS

COVID-19 considerations

Similar to the NEMLC-approved PHC Emergencies and Injuries chapter[4], the STG text was updated. The following text was included in the STG, aligned with guidelines:[5]

[3] Resuscitation Council of South Africa. Advanced Cardiac Arrest Algorithm for Suspected Communicable Disease (Respiratory), 2021. https://resus.co.za/
Brown A, Schwarcz L, Counts CR, Barnard LM, Yang BY, Emert JM, et al. Risk for Acquiring Coronavirus Disease Illness among Emergency Medical Service Personnel Exposed to Aerosol-Generating Procedures. Emerg Infect Dis. 2021 Sep;27(9):2340-2348. https://pubmed.ncbi.nlm.nih.gov/34197282/

[4] Minutes of the NEMLC meeting of 23 June 2022.

[5] Atkins DL, Sasson C, Hsu A, Aziz K, Becker LB, Berg RA, et al.; Emergency Cardiovascular Care Committee and Get With the Guidelines-Resuscitation, Adult and Pediatric Task Forces of the American Heart Association in Collaboration With the American Academy of Pediatrics, American Association for Respiratory Care, American Society of Anesthesiologists, and the Society of Critical Care Anesthesiologists. 2022 Interim Guidance to Health Care Providers for Basic and Advanced

» The infection risk that CPR poses to providers due to aerosolization of coronavirus particles is not negligible.
» This potential risk should be weighed against the probability of achieving spontaneous return of circulation to inform the decision to initiate or stop CPR.
» For in hospital cardiac arrest in patients with suspected COVID-19, CPR has been shown to not be beneficial unless an immediate reversible cause is suspected, e.g., dislodgement of ET tube, etc. and is therefore not recommended.
» For out of hospital cardiac arrest in patients with suspected COVID-19, it is recommended to not start conventional CPR in unwitnessed cardiac arrest as it will likely not be beneficial.
» Appropriate PPE should be worn by all staff before initiating CPR: FFP3 mask, visor, gloves and gown.

Guidance regarding personal protective equipment (PPE) was based on a retrospective cohort study[6] that showed that overall, the incidence of rRT-PCR positive tests among Emergency Medical Services (EMS) personnel following PPE protocols (wearing a mask, eye protection, gloves, and a gown) was low: 0.57 per 10,000 person-days (30 positive tests in 525,154 person-days).

Level of Evidence: Low certainty evidence

Emergency treatment

Precordial thump: *deleted*

No available evidence could be sourced showing that precordial thumps are effective. The manoeuvre may lead to rhythm deterioration[7] and is not included in clinical guidelines.

Level of Evidence: Expert opinion

The following STG text was deleted:

» ~~Where a defibrillator is not immediately available, a single powerful precordial thump is recommended for witnessed cardiac arrest.~~

Initiate fluids, IV/IO access

Sodium chloride 0.9%, parenteral: *amended – directions for use added*

Aligned with the 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS)[8]. Considered a moderate to good quality guideline with an overall AGREE2 assessment of 75%.

Level of Evidence: Low certainty evidence

STG text was amended as follows:

- Sodium chloride 0.9%, IV.
  - Administer a bolus of 1 litre during CPR if an increase in preload may benefit the patient, e.g., hypovolaemic shock, distributive shock, haemorrhagic shock.
  - Administer fluid cautiously during CPR if an increase in the preload could be detrimental, e.g., massive pulmonary embolism or cardiac tamponade.

Ringers lactate: *not added*

Based on an evidence review updated in 2019[9], the NEMLC recommends that sodium chloride 0.9% be the primary resuscitation fluid (including for septic shock). Ringers lactate is included on the therapeutic interchange database for patients in whom balanced solutions may be more appropriate e.g. critically ill patients presenting with hyperchloraemia, patients previously receiving renal replacement therapy.

Additional guidance – termination of resuscitation (TOR)

Similar to the NEMLC-approved PHC Emergencies and Injuries chapter[10], the STG text was updated.

Duration of asystole: *amended*

Cardiac Life Support in Adults, Children, and Neonates With Suspected or Confirmed COVID-19: From the Emergency Cardiovascular Care Committee and Get With The Guidelines-Resuscitation Adult and Pediatric Task Forces of the American Heart Association in Collaboration With the American Academy of Pediatrics, American Association for Respiratory Care, the Society of Critical Care Anesthesiologists, and American Society of Anesthesiologists. Circ Cardiovasc Qual Outcomes. 2022 Apr;15(4):e008900. https://pubmed.ncbi.nlm.nih.gov/35072519/

[6] Brown A, Schwarcz L, Counts CR, Barnard LM, Yang BY, Emert JM, et al. Risk for Acquiring Coronavirus Disease Illness among Emergency Medical Service Personnel Exposed to Aerosol-Generating Procedures. Emerg Infect Dis. 2021 Sep;27(9):2340-2348. https://pubmed.ncbi.nlm.nih.gov/34197282/

[7] Smith J, Judge B. BET 1: Effectiveness of the precordial thump in restoring heart rhythm following out-of-hospital cardiac arrest. Emerg Med J. 2016 May;33(5):366-7. https://pubmed.ncbi.nlm.nih.gov/27099378/

[8] Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing, G, Harjola V, et al., The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). European Respiratory Journal Sep 2019, 54 (3) 1901647. https://pubmed.ncbi.nlm.nih.gov/31473594/

[9] NDoH Medicine Review. Ringer lactate for resuscitation in patients with hypovolaemia. Aug 2019. Microsoft Word - Ringer Lactate for resuscitation in Adults_Medicine review update_August2019 (health.gov.za)

[10] Minutes of the NEMLC meeting of 23 June 2022.

A more objective statement was considered for inclusion in the PHC STG, *"Asystole of >20 minutes is considered unsurvivable"*. However, there is a paucity of evidence that informs this decision and most recommendations are based on consensus.[11]

The 2020 AHA guidelines note that in a recent meta-analysis of seven published studies (n=33,795 patients), only 0.13% (95% CI 0.03 to 0.58%) of patients who fulfilled the Basic Life Support (BLS) termination criteria survived to hospital discharge[12]. The BLS TOR rule recommends terminating resuscitation if all the following three criteria are met: the cardiac arrest was not witnessed by EMS personnel, no return of spontaneous circulation (ROSC) before transport, and no shock delivered before transport.

The 2020 AHA guidelines also note in a meta-analysis of two published studies (n=10,178), only 0.01% (95% CI, 0.00-0.07%) of patients who fulfilled the Advanced Life Support (ALS) termination criteria survived to hospital discharge. The ALS TOR rule recommends terminating resuscitation if all the following four criteria are fulfilled: the cardiac arrest was not witnessed, there was no bystander CPR, there was an absence of ROSC before transport, and an absence of defibrillation before transport.

Both the BLS and ALS TOR (termination of resuscitation) rules have been shown to have good predictive value.[13]

Level of Evidence: Low certainty evidence

The STG text was aligned with the PHC STG text as follows:

ADDITIONAL GUIDANCE

Continue CPR until spontaneous breathing and/or heartbeat returns.

Assess continuously (every 2 minutes) until the patient shows signs of recovery.

Termination of resuscitation:

» The decision to stop CPR attempts depends on the specifics of the individual patient and should be based on clinical judgement.

» Consider stopping resuscitation attempts and pronouncing death if there is incurable underlying disease, or if asystole > 20 minutes.

Consider carrying on for longer especially with:

» hypothermia and drowning

» poisoning or medicine overdose

» neurotoxic envenomation (e.g., black and green mamba or Cape cobra snakebite) – see PHC STG Section 21.3.1.4: Snakebites

This decision should take into consideration the potential risk that CPR poses to the rescuer e.g., infectious diseases.

20.2 POST CARDIAC ARREST

Oxygen: *cut-off amended*

The cut-off for oxygen administration was made consistent with the NEMLC-approved draft PHC STG ratified on the 24 February 2022[14] and the extract from the respective NEMLC report below (refer to the Knowledge Hub for a copy of the full review):

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

Recommendation: Based on this review, the PHC/Adult Hospital Level Committee recommends that the current recommendation be retained for oxygen supplementation, only if saturation <94% with an additional caution not to administer oxygen if the patient is not hypoxic.

Rationale: Evidence suggests that acutely ill patients randomised to liberal oxygen therapy were more likely to die, without improving other patient outcomes. For pragmatic purposes the current recommendation of <94% be retained.

Level of Evidence: Moderate certainty evidence

[11] American Heart Association. 2020 American Heart Association Guidelines for CPR and ECC https://cpr.heart.org/en/resuscitation-science/cpr-and-ecc-guidelines

[12] Ebell MH, Vellinga A, Masterson S, Yun P. Meta-analysis of the accuracy of termination of resuscitation rules for out-of-hospital cardiac arrest. Emerg Med J. 2019 Aug;36(8):479-484. https://pubmed.ncbi.nlm.nih.gov/31142552/

[13] Lin YY, Lai YY, Chang HC, Lu CH, Chiu PW, Kuo YS, Huang SP, et al. Predictive performances of ALS and BLS termination of resuscitation rules in out-of-hospital cardiac arrest for different resuscitation protocols. BMC Emerg Med. 2022 Mar 27;22(1):53. https://pubmed.ncbi.nlm.nih.gov/35346055/

[14] Minutes of the NEMLC meeting of the 24 February 2022

Review indicator: New evidence that will change the recommendation
NEMLC RECOMMENDATION (24 FEBRUARY 2022): **DISCUSSION:** • *Altitude:* NEMLC discussed the effect of altitude on oxygen requirements. It was proposed that the PHC/Adult Hospital Level ERC review the evidence regarding this matter, but it would not affect the recommendation. **Recommendations:** • NEMLC accepted the PHC/Adult Hospital Level ERC's proposal and recommended that the evidence summary be circulated for external comment with the PHC Cardiovascular chapter. • The PHC/Adult Hospital Level ERC review the evidence of the impact of altitude on oxygen requirements, whilst the draft documents are circulated for external comment.
Monitoring and evaluation considerations
Research priorities

Temperature control

The STG text was amended as tabulated below, based on the open-label TTM1 RCT (n= 1900) with blinded outcome assessors that compared adults (with coma who had had an out-of-hospital cardiac arrest of presumed cardiac or unknown cause) undergoing hypothermia (33°C) or normothermia (≥37.8°C) found no difference in normothermia compared to hypothermia post cardiac arrest, with evidence of harm from hypothermia. [15]

Aim for normothermia by preventing fever in unconscious patients ~~Strictly avoid fever~~ ~~Aim to control temperature below 36ºC in unconscious patients~~ in the first 24 hours, using physical cooling methods e.g.: ice packs and fans, and antipyretics.

Level of Evidence: Low certainty evidence

Study results:

- At 6 months, there was no reduction in mortality - 50% (465/ 925) in the hypothermia group died vs 48% (446/ 925) in the normothermia group (RR 1.04; 95% CI 0.94 to 1.14; ARR).
- Functional assessment was similar between groups with a moderately severe disability scores of 55% in both the hypothermia and normothermia groups; RR 1.00; 95% CI, 0.92 to 1.09.
- Arrhythmia was more common in the hypothermia group vs normothermia group (24% vs. 17%, p<0.001).
- Adverse events did not differ significantly between the two groups.

A detailed evidence summary is included below.

Pain

Paracetamol dose: *Amended*

The dosing guidance for paracetamol for pain management has been aligned to guidance included in the PHC and AH Pain chapters. The chapter has been updated where relevant as tabulated below:

Amended from:
For pain:
• Paracetamol, oral, 1 g 4–6 hourly when required.
  ○ Maximum dose: 15 mg/kg/dose.
  ○ Maximum daily dose: 4 g in 24 hours.
 	
Amended to:
For pain:
Paracetamol, oral, 500mg -1 g 4–6 hourly when required (to a maximum of 4 g in 24 hours)
  ○ Maximum dose: 15 mg/kg/dose.

Hypovolaemia

Sodium chloride 0.9%, parenteral: *amended – directions for use added*

Aligned with section 20.1: Cardiac arrest in adults (see above)

[15] Dankiewicz J, Cronberg T, Lilja G, Jakobsen JC, Levin H, et al.; TTM2 Trial Investigators. Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest. N Engl J Med. 2021 Jun 17;384(24):2283-2294. https://pubmed.ncbi.nlm.nih.gov/34133859/

20.6 ANGIOEDEMA

Hydrocortisone, IV: *amended, directions for use*
Promethazine, IV: *amended, directions for use*
Cetirizine, oral: *deleted*

As glucocorticoids have no proven role in the treatment of acute angioedema, the STG was amended as follows, aligned with guidelines: Anaphylaxis - a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol. The guidelines were assessed to be of good quality with an AGREE 2 score of 83%.

If urticaria and/or itch present (no imminent airway compromise):

- ~~Hydrocortisone, IV, 100 mg as a single dose.~~

~~AND~~

- ~~Promethazine, IV, 25–50 mg as a single dose.~~

~~OR~~

- ~~Cetirizine, oral, 10 mg as a single dose.~~

- Promethazine, IM/IV, 25–50 mg as a single dose.

ADD

- Hydrocortisone, IV, 100 mg as a single dose.

Level of Evidence: Low certainty

Glucocorticosteroids have a slow onset of action binding to the glucocorticoid receptor on cell membranes, translocating the glucocorticoid/glucocorticoid receptor complex to the nucleus, and then inhibit gene expression and production of new inflammatory mediators. They are nonselective and ineffective in treating acute symptoms and are associated with multiple adverse effects related to high doses and prolonged use.

NEMLC RECOMMENDATION (20 OCTOBER 2022 MEETING):
The NEMLC recommended the deletion of oral cetirizine, as oral therapy was less likely to be administered for angioedema.

20.7 ANAPHYLAXIS/ ANAPHYLACTIC SHOCK

Aligned with the NEMLC-approved PHC emergencies and injuries chapter[16], as follows.

General measures

Guidance on anaphylaxis associated with vaccinations: *added*

Guidance was included in the STG on non-pharmacological management of anaphylaxis associated with vaccinations, aligned with WHO guidance[17], as follows:

Anaphylaxis associated with vaccinations:

- » Always keep a fully equipped emergency tray at the vaccination point.
- » It is advisable to observe clients for 15 minutes after a vaccination. If a client is known with severe allergies, an observation period of 30 minutes is advised.
- » Clients who develop symptoms should be assessed for possible vaccination associated anaphylaxis by considering the following:
  - If signs and symptoms are generalised – involving more than 2 body systems, manage as anaphylaxis.
  - If signs and symptoms are serious or life-threatening (including hypotension, respiratory distress, significant swelling of lips or tongue), even if only one body system is involved, treat as anaphylaxis.
  - If isolated rash in an otherwise well client, monitor for 30 minutes.
- » Clients who collapse following vaccination:
  - Call for help and put patient on his/her back and raise legs.
  - Check if responsive – if unresponsive, commence CPR (See section 21.1)
  - A vasovagal episode is usually associated with a transient loss of consciousness (< 1 minute), relieved by raising the legs when supine, transient low BP and low HR.
  - Collapsing after vaccination usually occurs 5-10 minutes post-vaccination, but can occur up to an hour afterwards.

[16] Minutes of the NEMLC meeting of 23 June 2022.

[17] Immunization stress-related response. A manual for program managers and health professionals to prevent, identify and respond to stress related responses following immunization. Geneva: World Health Organization; 2019. https://apps.who.int/iris/handle/10665/330277

- Treat as anaphylaxis if loss of consciousness is not brief and not relieved by raising the legs, or when any of the warning signs for anaphylaxis occur.

	ANAPHYLAXIS	ACUTE STRESS RESPONSE	
		GENERAL	VASOVAGAL REACTION WITH SYNCOPE
Onset	Usually 5 min after immunization but may be delayed up to 60 min	Sudden, occurs before, during or shortly after (< 5 min) immunization	Sudden, occurs before, during or shortly after (< 5 min) immunization. May present after 5 min if the individual stands suddenly.
System			
Skin	Generalized urticaria (hives) or generalized erythema, angioedema, localized or generalized, generalized pruritus with or without skin rash, generalized prickle sensation, localized injection site urticaria, red and itchy eyes	Pale, sweaty, cold, clammy	Pale, sweaty, cold, clammy
Respiratory	Persistent cough, noisy breathing and airway constriction: wheeze, stridor. If very severe, respiratory arrest.	Hyperventilation (rapid, deep breathing)	Normal to deep breaths
Cardiovascular	↑ heart rate, ↓ blood pressure, circulatory arrest	↑heart rate, normal or ↑systolic blood pressure	↓ heart rate with or without transient ↓in blood pressure
Gastrointestinal	Nausea, vomiting, abdominal cramps	Nausea	Nausea, vomiting
Neurological and other symptoms	Uneasiness, restlessness, agitation, loss of consciousness, little response when supine or lying flat	Fearfulness, light-headedness dizziness, numbness, weakness, tingling around the lips, spasms in hands, feet	Transient loss of consciousness, good response once supine or lying flat, with or without tonic–clonic seizure

Table 20.1: Differences between anaphylaxis, general acute stress response and vasovagal reaction with syncope
Source: Immunization stress-related response. A manual for program managers and health professionals to prevent, identify and respond to stress related responses following immunization. Geneva: World Health Organization; 2019. https://apps.who.int/iris/handle/10665/330277

20.8 DELIRIUM

The subheading was simplified from "*Delirium with perceptual disturbances*" to "*Delirium*".

Acute management: For agitated and acutely disturbed patient
Haloperidol, IM: *retained*
Olanzapine, oro-dispersible: *added*
Olanzapine, IM: *added*

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

Recommendation: The PHC/ Adult Hospital Level Committee suggests using olanzapine (orodispersible and parenteral formulations) as an option to manage delirium where non-pharmacological management is not sufficient and if haloperidol, intramuscular formulation is unavailable
Rationale: Available low-quality evidence shows that olanzapine is comparable to haloperidol.
Level of Evidence: Low to very low certainty evidence
Review indicator: Evidence of harm, efficacy

NEMLC RECOMMENDATION (20 OCTOBER 2022 MEETING):
NEMLC recommended the use of olanzapine oro-dispersible tablet or IM injection for delirium with agitated and acutely disturbed behaviour. Once the patient is able to swallow, to continue with oral haloperidol or olanzapine, until behaviour is contained.

Monitoring and evaluation considerations
Research priorities

Refer to the medicine review below for more detail.

Oro-dispersible olanzapine dissolves on the tongue and is absorbed via the oral mucosa and therefore may be administered in those who cannot/will not swallow which may be beneficial in agitated patients.

Acute management: For substance withdrawal, Parkinson's disease, or intolerability to olanzapine

Diazepam, IV: *amended – directions for use*

Guidance pertaining to dosing in the elderly, "*In elderly, a starting dose of 2mg is recommended*", was added aligned to SAMF 2022 and Maudsley Prescribing Guidelines, 13th edition.

Level of Evidence: Guidelines

The STG has been amended as tabulated below:

Amended from:

Acute management

For management for severe aggression and disruptive behaviour: see section 15.1: Aggressive disruptive behaviour in adults.

For agitated and acutely disturbed patient:

- Haloperidol, IM, 0.5–1 mg
  - This can be repeated in 30–60 minutes, if required and then 4 hourly to a maximum dose of 10 mg within 24 hours.
  - Monitor vital signs and beware of acute dystonia and neuroleptic malignant syndrome.
  - Dosing may vary according to clinical circumstances, e.g. lower doses in the elderly or where HIV infection or HIV-related dementia is known or suspected.

AND/OR

- Benzodiazepine, repeat as necessary, to achieve containment, e.g.:
- Lorazepam, IM, 1–4 mg.

OR

Clonazepam, IM, 0.5–2 mg.

OR

Diazepam, IV, 10 mg.

- Switch to oral route once containment is achieved.

Amended to:

Acute management

For management of severe aggression and disruptive behaviour: see section 15.1: Aggressive disruptive behaviour in adults.

For agitated and acutely disturbed patient:

- Haloperidol, oral, 0.75–1.5 mg twice daily
  - May be repeated 4 hourly if needed to a maximum dose of 10mg in 24 hours.
  - May be continued short-term (usually 7 days or less) at lowest dose at which behaviour is contained.

OR

If unable to swallow or oral medication declined:

- Haloperidol, IM, 0.5–1mg
  - May be repeated after 30–60 minutes if needed and then 4 hourly, to a maximum dose of 10mg in 24 hours.
  - Monitor vital signs and beware of acute dystonia, other extra-pyramidal side effects, and neuroleptic malignant syndrome.

OR

If haloperidol, IM is not available:

- Olanzapine, oral dispersible tablet or IM, 2.5–5 mg.
  - This can be repeated in 30–60 minutes, if required and then 6 hourly, to a maximum dose of 20 mg within 24 hours.
  - Monitor vital signs and beware of over-sedation, neuroleptic malignant syndrome, and acute dystonia.

OR

For substance withdrawal, Parkinson's disease, or intolerability to haloperidol or olanzapine:

- Benzodiazepine, repeat as necessary, to achieve containment, e.g.:
- Lorazepam, IM, 0.25–1 mg, 2 to 4 hourly, maximum dose 3 mg in 24 hours

OR

- Clonazepam, IM, 0.5–2 mg.

OR

- Diazepam, IV, 5–10 mg.
  - Switch to oral route once containment is achieved.
  - In the elderly, a starting dose of 2 mg is recommended

If alcohol withdrawal/ Wernicke's encephalopathy suspected

Aligned with NEMLC-approved PHC emergencies and injuries chapter[18]– see below:

Thiamine, parenteral - *added*

NEMLC report for the PHC emergencies chapter & respective NEMLC recommendation (Meeting of 23 June 2022)

- *Thiamine dose: There is limited evidence - a Cochrane review[19] reviewed one RCT (n=169)[20], showing that 200mg IM (once a day for 2 days) differed significantly from 500mg dose on cognitive testing post-treatment (mean difference: -17.90, 95% confidence interval -35.4 to -0.40, P = 0.04) for the prevention of . Whilst case series reports suggests a 500mg IV dose. Guideline recommendations vary, but generally use the higher dose for treatment of Wernicke's encephalopathy.*
- *Route of administration: It was noted that the SAMF[21], 2016 as well as the British National Formulary[22] cautions about anaphylaxis reactions associated with IV administration of thiamine; the latter citing MHRA/CHM advice, 2007:*

  IMPORTANT SAFETY INFORMATION MHRA/CHM ADVICE (SEPTEMBER 2007):
  Although potentially serious allergic adverse reactions may rarely occur during, or shortly after, parenteral administration, the CHM has recommended that:
  - *This should not preclude the use of parenteral thiamine in patients where this route of administration is required, particularly in patients at risk of Wernicke-Korsakoff syndrome where treatment with thiamine is essential;*
  - *Intravenous administration should be by infusion over 30 minutes;*
  - *Facilities for treating anaphylaxis (including resuscitation facilities) should be available when parenteral thiamine is administered.*
- *Pragmatic implications: Thiamine is only available as 100mg/ml vials and large volume 5ml IM injection may be poorly tolerated by patients and possibly considered to be impractical.*

Recommendations:

- *Dose to be amended to a maximum of 200 mg IM in both the Adult Hospital and PHC STGs and EML for prevention of Wernicke's encephalopathy.*

NEMLC MEETING OF 23 JUNE 2022:

NEMLC accepted the proposal to amend the dose of thiamine from "100mg" to "200mg", aligned with available RCT evidence, for the prevention of Wernicke's encephalopathy. NEMLC also deliberated on the route of administration and recommended that for the prevention of Wernicke's encephalopathy, that thiamine should be administered intramuscularly and not by the intravenous route.

Refer to the Knowledge Hub for the detailed evidence summary.

The following guidance has been added to the STG:

If alcohol withdrawal/ Wernicke's encephalopathy suspected:

- Thiamine, IM, 200 mg immediately.

20.10 PULMONARY OEDEMA, ACUTE

If distressed, consider adding morphine

Morphine, IV: *deleted & caution added*

Aligned with NEMLC-approved PHC emergencies and injuries chapter[23]– for a copy of the full evidence summary see below, or alternatively the publication by Hendrikse et al. *Signal of harm in morphine use in adults with acute pulmonary oedema: A rapid systematic review*.[24]

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:

[18] Minutes of the NEMLC meeting of 23 June 2022.

[19] Day E, Bentham PW, Callaghan R, Kuruvilla T, George S. Thiamine for prevention and treatment of Wernicke-Korsakoff Syndrome in people who abuse alcohol. Cochrane Database Syst Rev. 2013 Jul 1;2013(7):CD004033. https://pubmed.ncbi.nlm.nih.gov/23818100/

[20] Ambrose ML, Bowden SC, Whelan G. Thiamin treatment and working memory function of alcohol-dependent people: preliminary findings. Alcohol Clin Exp Res. 2001 Jan;25(1):112-6. https://pubmed.ncbi.nlm.nih.gov/11198705/

[21] SAMF, 2022

[22] British National Formulary, 2020

[23] Minutes of the NEMLC meeting of 23 June 2022.

[24] Hendrikse C, Ngah V, Kallon II, Thom G, Leong TD, Cohen K, McCaul M. Signal of harm in morphine use in adults with acute pulmonary oedema: A rapid systematic review. S Afr Med J. 2023 Aug 3;113(8):39-43. doi: 10.7196/SAMJ.2023.v113i8.348. PMID: 37882120.

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		x			

Recommendation: The PHC/Adult Hospital Level Committee suggests not to use morphine for the treatment of acute pulmonary distress.

Rationale: Available evidence shows that morphine may increase in-hospital and all-cause mortality and may result in a large increase in invasive mechanical ventilation compared to not using morphine. No available data could be found on whether morphine increases non-fatal adverse events, ICU or hospital length of stay.

Level of Evidence: Low certainty of evidence

Review indicator: New high-quality evidence of a clinically relevant benefit

NEMLC RECCOMENDATION – 23 JUNE 2022:

NEMLC MEETING OF 23 JUNE 2022:

NEMLC accepted the proposal to amend the remove morphine the treatment of acute pulmonary distress. However, recommended that a caution be included in the STG, accordingly:

CAUTION

Do not use morphine for pulmonary oedema, as there is observational data providing a signal of harm.

Furthermore, once the respective chapter is finalised, it was recommended that a circular be drafted and disseminated regarding the harms associated with use of morphine for distress in pulmonary oedema.

Monitoring and evaluation considerations

Research priorities

GTN IV – guidance on administration: *Amended*

Guidance on the administration of glyceryl trinitrate (GTN) IV has been updated to accommodate for the formulation that is currently procured by State facilities i.e. a 1mg/mL solution. Editorial amendments have also been made to improve clarity and understanding:

Amended from:

- Glyceryl trinitrate, IV, 5–200 mcg/minute, titrated to response.
  - Start with 5 mcg/minute and increase by 5 mcg/minute every 5 minutes until response or until the rate is 20 mcg/minute.
  - If no response after 20 mcg/minute increase by 20 mcg/minute until response.
  - Flush the PVC tube before administering to patient.
  - Monitor blood pressure carefully.

Volume of diluent	Glyceryl trinitrate 5 mg/mL	Concentration of dilution
250 mL	5 mL (25 mg)	100 mcg/mL
	10 mL (50 mg)	200 mcg/mL
	20 mL (100 mg)	400 mcg/mL
500 mL	10 mL (50 mg)	100 mcg/mL
	20 mL (100 mg)	200 mcg/mL
	40 mL (200 mg)	400 mcg/mL

Solution concentration (mcg/mL)	100 mcg/mL solution	200 mcg/mL solution	400 mcg/mL solution
Dose (mcg/min)	Flow rate (microdrops/min = mL/hr)		
5	3	–	–
10	6	3	–
15	9	–	–
20	12	6	3
30	18	9	–
40	24	12	6
60	36	18	9
80	48	24	12
100	60	30	15
120	72	36	18
160	96	48	24
200	–	60	30

Amended to:

- Glyceryl trinitrate, IV, 5–200 mcg/minute, titrated to response.
  Guidance on preparation and administration included below.

CAUTION
Glyceryl trinitrate IV formulation must be diluted before infusion

STEP 1: Select the concentration as required for the individual patient
- For patients who are fluid congested or require higher doses for a clinical response, consider using a more concentrated solution e.g. 200 or 400 mcg/mL.

STEP 2: Select the volume of the diluent
- Patients who are likely to require treatment for a longer duration e.g. unstable angina prepare a larger volume e.g. 500mL.
- Compatible diluents include sodium chloride 0.9% or dextrose 5%.

STEP 3: Confirm the formulation of glyceryl trinitrate available and mix with diluent
- Confirm the strength of the GTN solution i.e. whether a 1mg/mL or 5mg/mL formulation is available.
- Depending on the formulation available, select the number of ampoules to be used based on the concentration and volume of the diluent as decided in Step 1 and 2 above.
- Ensure that the equivalent volume of diluent is removed from the bag before adding the total GTN volume e.g. if 100mLs of GTN is to be added, first remove 100mL of diluent from the bag before adding the GTN.

STEP 4: Set the flow rate for infusion
- Flush the PVC tube before administering to patient.
- Start with the lowest flow rate possible based on the concentration of the solution prepared.
- Increase by 5 mcg/minute every 5 minutes until response achieved or until the rate is 20 mcg/minute.
- If no response after 20 mcg/minute increase by 20 mcg/minute until response.
- Monitor blood pressure carefully.

E.g. To prepare a 200mcg/mL solution for a patient likely to require several hours of the GTN infusion:
Use 10 ampoules (100mL) of the 1mg/mL GTN formulation mixed with 400mL of diluent (100mL to be removed from a 500mL bag). Initiate the infusion at a flow rate 3mL/hr and titrate the infusion rate based on the patient's response.

STEP 1	**STEP 2**	**STEP 3**			
Concentration of dilution	**Volume of diluent**	**Glyceryl trinitrate 1 mg/mL**		**Glyceryl trinitrate 5 mg/mL**	
		Volume (Dose)	Number of 10mL ampoules	Volume (Dose)	Number of 10mL ampoules
100 mcg/mL	250 mL	25 mL (25 mg)	2.5	5 mL (25 mg)	0.5
200 mcg/mL		50 mL (50 mg)	5	10 mL (50 mg)	1
400 mcg/mL		100 mL (100 mg)	10	20 mL (100 mg)	2
100 mcg/mL	500 mL	50 mL (50 mg)	5	10 mL (50 mg)	1
200 mcg/mL		100 mL (100 mg)	10	20 mL (100 mg)	2
400 mcg/mL		200 mL (200 mg)	20	40 mL (200 mg)	4

STEP 4	**Solution concentration (mcg/mL)**	**100 mcg/mL solution**	**200 mcg/mL solution**	**400 mcg/mL solution**
	Dose (mcg/min)	Flow rate (microdrops/min = mL/hr)		
	5	3	–	–
	10	6	3	–
	15	9	–	–
	20	12	6	3
	30	18	9	–
	40	24	12	6
	60	36	18	9
	80	48	24	12
	100	60	30	15
	120	72	36	18
	160	96	48	24
	200	–	60	30

20.16 BURNS

Figure to calculate body surface area % in children < 8 years: *deleted*
As not relevant to the Adult Hospital Level STGs and EML.

Paracetamol dose: *Amended*

The dosing guidance for paracetamol for pain management has been aligned to guidance included in the PHC and AH Pain chapters. The chapter has been updated where relevant as tabulated below:

Amended from:

For pain:

- Paracetamol, oral, 1 g 4–6 hourly when required.
  - Maximum dose: 15 mg/kg/dose.
  - Maximum daily dose: 4 g in 24 hours.

Amended to:

For pain:

Paracetamol, oral, 500mg -1 g 4–6 hourly when required (to a maximum of 4 g in 24 hours)

- Maximum dose: 15 mg/kg/dose.

Pantoprazole, IV**:** *Added*

Pantoprazole IV has been added for the management of stress ulcer prophylaxis for patients who are not tolerating feeds in alignment with the AH Critical Care chapter Section 23.7.2 Stress Ulcer Prophylaxis. Amendments to the chapter as tabulated below:

Stress ulcer prophylaxis

» Feeding patients provides protection against gastric ulcers developing and prophylaxis is not necessary in patients who are tolerating feeds.

» Stress ulceration, a complication of critical illness, needs to be prevented.

» Oral or enteral feeding should be initiated as soon as possible.

- Pantoprazole, 40mg, IV daily.
  - Stop stress ulcer prophylaxis once the patient is tolerating enteral feeds.

Septic burns

Aligned with the NEMLC-approved PHC Emergencies and Injuries chapter[25] (PHC Chp 21 Section 21.3.2), as follows:

Povidone iodine, topical: *added*

Silver sulfadiazine, topical: *not added*

Mupirocin, topical: *not added*

Nano-crystalline dressings: *not added*

Melaleuca alternifolia, topical: *not added*

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

Recommendation: Current standard of care in the STG to be retained – topical povidone iodine for infected burns.
Rationale: No new evidence could be identified for alternative treatment options for septic burns.
Level of Evidence: Low to very low certainty
Review indicator: New evidence sufficient to change the recommendation

NEMLC RECOMMENDATION (MEETING OF 23 JUNE 2022):

NEMLC accepted the review and proposed recommendation, but recommended that the PHC/Adult Hospital Level Committee consider reviewing other dressings for wounds, noting that this topic would be prioritised in the topic prioritisation project plan and may be reviewed in the next review cycle. Furthermore, it was noted that wound dressings are not funded from the Provincial Pharmaceutical budgets.

Monitoring and evaluation considerations

Research priorities

[25] Minutes of the NEMLC meeting of 23 June 2022.

South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Emergencies and injuries

MEDICINE REVIEW

Executive Summary

Date: 29 September 2022
Medicine (INN): Ketamine / dissociative analgesic and anaesthetic
Medicine (ATC): N01AX03
Indication (ICD10 code): Dependence on a respirator: Z99.1; Unspecified multiple injuries: T07
Patient population: Intubated adults with trauma on mechanical ventilation in ICU, EC, prehospital
Level of Care: PHC, Adult Hospital Level
Prescriber Level: Clinician (Doctor) and for Emergency Care Practitioners (ECP) and Critical Care Assistants (CCA) (Advanced Life Support Paramedics)
Current standard of Care:
Ketamine as monotherapy: IV/IO Morphine; IV/IO Fentanyl; IV/IO Midazolam + Morphine combined; IV/IO Propofol + Fentanyl; IV/IO Propofol + Morphine
Ketamine as adjunctive therapy: Standard of care: IV/IO Morphine; IV/IO Fentanyl; IV/IO Midazolam + Morphine combined; IV/IO Propofol + Fentanyl; IV/IO Propofol + Morphine
Efficacy estimates: (preferably NNT): 34 NNT Adjunctive Therapy (Mortality), Unknown NNT Monotherapy
Motivator/reviewer name(s): Michael McCaul, Clint Hendrikse, Idriss Kallon, Veranyuy D Ngah
PTC affiliation: CH is member of PTC of Mitchells Plain/Klipfontein Substructure

Key findings

- We conducted a rapid review of clinical evidence on adjunctive or monotherapy ketamine should be used in the treatment for intubated adults with trauma on mechanical ventilation.
- We identified seven systematic reviews addressing adjunctive therapy and one systematic review addressing monotherapy. The most relevant, up-to-date, and highest quality review was used to inform recommendations for critical outcomes.

Adjunctive Therapy:

- Adjunctive ketamine showed a morphine sparing effect (MD= -13.19 µg kg^{-1} h^{-1}, 95% CI -22.10 to -4.28, p<0.001), but no to little effect on midazolam (MD = 0.75 µg kg^{-1} h^{-1}, 95% CI −1.11 to 2.61) or duration of mechanical ventilation in days (MD −0.17 days, 95% CI −3.03 to 2.69, P = 0.91).
- We are uncertain whether adjunctive ketamine therapy reduces mortality (OR 0.88, 95% CI 0.54-1.43, P = 0.60, low certainty of evidence, 5 RCTs, n= 3076 patients) and may result in 30 fewer deaths per 1000, ranging from 132 fewer to 87 more. Ketamine adjunctive therapy results in little to no difference in length of ICU stay (MD 0.04 days, 95% CI −0.12 to 0.20, P = 0.60, high certainty of evidence, 5 RCTs n=390 patients) or length of hospital stay (MD −0.53 days, 95% CI −1.36 to 0.30, P = 0.21, high certainty of evidence, 5 RCTs, n=277 patients).

Monotherapy:

- No evidence found for this review's prespecified outcomes such as sedation and analgesia, ventilator asynchrony, provider satisfaction, RASS scale mortality and hospital length of stay.
- Monotherapy may improve respiratory outcomes (respiratory depression, chest wall compliance, PO_2, PCO_2) and haemodynamic outcomes (systolic blood pressure, mean arterial pressure, vasopressor use, shock), however, certainty of evidence is very low.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATIONS:

A: KETAMINE MONOTHERAPY

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		x			

Recommendation: The PHC/Adult Hospital Level Committee suggests not to use ketamine as monotherapy for postintubation sedation in intubated adults with trauma on mechanical ventilation (conditional recommendation, very low certainty of evidence).

Rationale: There is uncertainty for benefit and harms for ketamine as monotherapy.
Level of Evidence: Very low certainty
Review indicator: New better quality evidence

B: KETAMINE ADJUNCTIVE THERAPY

	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

Recommendation: The PHC/Adult Hospital Level Committee suggests the use of adjunctive ketamine for postintubation sedation in intubated adults with trauma on mechanical ventilation (conditional recommendation, low certainty of evidence.

Rationale: Ketamine may have benefit as adjunctive therapy but there is uncertainty for benefit and harms as monotherapy.
Level of Evidence: Low certainty of evidence
Review indicator: New high-quality evidence of a clinically relevant benefit or harm

NEMLC RECCOMENDATION – 20 OCTOBER 2022

NEMLC accepted the proposed recommendations, and the NEMLC review report was ratified for external comment (as amended).

Monitoring and evaluation considerations

Research priorities: High-quality RCTs for ketamine use is required for monotherapy, specifically in the prehospital setting for patient important outcomes.

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Costing analysis: Trudy Leong[4]
[4] Right to Care consultant supporting NDoH Secreteriat

Declarations of interest: IK, VN, MM, TL have no interests pertaining to Ketamine.

Background

Post-intubation sedation for long periods with Midazolam and Propofol have side effects, especially when patients are already haemodynamically compromised, e.g., a polytrauma patients who are being ventilated. Ketamine is a viable alternative: relatively inexpensive, widely available and fewer haemodynamic side effects. It is currently widely being used, despite it not being in STG/EML for this indication. Its efficacy as standalone or in combination with other agents need to be investigated. As adjunctive therapy, it is currently used as an opioid sparing alternative and as monotherapy it is often used for analgosedation.

Guidance Questions

- Should ketamine be used as an adjunctive therapy in intubated adults with trauma on mechanical ventilation?
- Should ketamine be used as a monotherapy in intubated adults with trauma on mechanical ventilation?

Methods

We conducted a rapid review of evidence for the use of ketamine as 1) adjunctive or 2) monotherapy in intubated adults with trauma on mechanical ventilation. We systematically searched Ovid MEDLINE, Embase and Cochrane on 1 June 2022 for Systematic Reviews (SRs) of Randomized Controlled Trials (RCTs) and RCTs. One search was conducted for both adjunctive and monotherapy questions (Appendix 1), results reported separately. Additionally, we searched the Pan African Clinical Trial registry for any ongoing studies from 2021. Screening of title and abstracts and full text screening, selection of studies and data extraction was conducted independently and in duplicate by two reviewers (IK and CH). Title and abstract, including full text screening was done using Covidence.

AMTSTAR II was used to appraise all the systematic reviews included in the study by a single reviewer (VN), checked by a second reviewer (IK), disagreements resolved by a senior methodologist (MM). GRADE was applied to determine the certainty of evidence and the GRADEpro software was used to generate evidence profiles. Relevant study data were extracted into a narrative table of results. MM, IK, VN and CH reviewed the overall report.

We extracted, where available, effect estimates from included RCTs if not reported by the included SRs to provide clearer benefit and harm EtD judgements. Where possible, we calculated effect estimates (i.e., RR or MD) with confidence intervals in STATA 16 using reported aggregate data from trials. Otherwise, results were reported narratively.

Eligibility criteria for review (Monotherapy)

Population:	Adult 18 years and older trauma patients intubated on mechanical ventilation in ICU, EC or prehospital
Intervention:	Ketamine as monotherapy: IV/IO Ketamine infusion; IV/IO Ketamine bolus and infusion or; IV/IO Ketamine bolus only
Comparator:	V/IO Morphine; IV/IO Fentanyl; IV/IO Midazolam + Morphine combined; IV/IO Propofol + Fentanyl; IV/IO Propofol + Morphine
Outcomes:	Sedation and analgesia, Ventilator asynchrony, provider satisfaction, RASS scale, physiological parameters, Mortality, Hospital length of stay
Studies:	RCTs and SRs

Eligibility criteria for review (Adjunctive)

Population:	Adult 18 years and older trauma patients intubated on mechanical ventilation in ICU, EC or prehospital
Intervention:	Ketamine as adjunctive therapy: IV/IO Ketamine + Morphine infusion combined; IV/IO Ketamine + Propofol infusion combined; IV/IO Ketamine + Fentanyl infusion combined
Comparator:	Standard of care: IV/IO Morphine; IV/IO Fentanyl; IV/IO Midazolam + Morphine combined; IV/IO Propofol + Fentanyl; IV/IO Propofol + Morphine
Outcomes:	Reduction in opioid requirements, Mortality, Hospital length of stay, SAEs and AEs
Studies:	RCTs and SRs

Results

The search yielded 841 records, 9 duplicates were removed, 791 were irrelevant, 41 studies were screened at full text. After exclusion of 28 studies, only 8 Systematic Reviews were included in the final review (Appendix 2). AMSTAR II assessment of all eight reviews ranged from low quality to critically low quality (Appendix 3). Chan et al. (2022) was considered the most relevant, trustworthy and up-to-date review and included GRADE certainty of evidence judgements. Outcomes of interest not reported in Chan et al. (2022) were reported from Manasco et al. (2020) and Wang et al. (2019). All relevant RCTs addressing the research question were found in the systematic reviews included in the study, hence they were excluded from the analysis to avoid double counting. No additional trials were found outside those included in the SRs. Where required, we extracted effect estimates from included RCTs in the SRs

Description of included studies

Table 1 has detailed description of the included studies stratified by monotherapy and adjunctive therapy.

Adjunctive therapy studies

Chan et al. (2022) aimed to assess the impact of continuous ketamine infusion on opioid and sedative consumption in critically ill patients on mechanical ventilation as primary outcome. The review included trials with ketamine as adjunctive therapy (with sedatives or opioids) compared to various standard treatment control combinations. Their secondary outcome was to assess the effect of ketamine on all-cause mortality, the duration of mechanical ventilation, duration of ICU and hospital stay and intracranial pressure elevation. They included 13 RCTs and 6 observational studies with a total of 2258 participants. Risk of Bias (ROB) was well assessed in all included studies using the Cochrane ROB 1.0 tool or ROBINS-I for cohort studies. GRADE was reassessed for critical outcomes namely mortality and length of ICU and hospital stay. GRADE certainty of evidence overall ranged from high to very low certainty across outcomes.

Manasco et al. (2020) assessed Ketamine use in mechanically ventilated patients to determine its effect on sedative use and patient-oriented outcomes. Three RCTs and 12 cohort studies with a total of 892 patients were included in the review.

Wheeler at al., 2020 assessed the efficacy and safety of non-opioid adjunctive analgesia for patience in the intensive care unit. They included 34 RCTs examining various analgesia with only 4 studies evaluating the effect of ketamine as an adjunctive therapy. This study does not mention the number of study participants included in the study.

Wang et al. (2019) conducted a network meta-analysis that determined the effect of sedative drugs on all-cause mortality, duration of mechanical ventilation, and ICU stay, risk of delirium and hypotension in in mechanically ventilated ICU patients. Only one study (and comparison) directly considered Ketamine (with benzodiazepines) with a total of 25 patients.

Patanwala et al. (2017) compared the ketamine and non-ketamine analgesic and sedative effects in mechanically ventilated ICU patients. They included 6 RCTs, 1 cohort study and 6 case reports with a total of 256 patients in their review.

Cohen, et al. (2015) determined the effect of ketamine on intracranial and cerebral perfusion pressure and health outcomes in mechanically ventilated ICU patients. They included 5 RCTs and 5 non-RCTs with a total of 953 patients in the review.

Zeiler et al. (2014) investigated the effect of Ketamine on intracranial pressure in ventilated patients with traumatic brain injury. They included 4 RCTs, 2 cohort studies and 1 case-report with a total of 166 patients.

Monotherapy studies

Miller et al. (2011) assessed the pulmonary and haemodynamic effects of continuous ketamine infusion for sedation maintenance in patients on mechanical ventilation. They included four small RCTs in which the comparator sedative agents were Fentanyl and Midazolam, 11 case series and 5 case reports with a total of 281 patients. Miller provided a narrative report for Ketamine monotherapy with no meaningful effect estimates. We extracted, where reported, meaningful effect

estimates from three accessible and included RCTs (Nayar 2008, Allen 2005, Howton 1996) from Miller et al. Effect estimates was only available for blood pressure and other non-prioritised outcomes such as treatment assessment scores.

Internal validity of the systematic reviews and GRADE SoFs

AMSTAR II was used to evaluate the internal validity of the systematic reviews included in the study. In order to reduce the duplication of synthesis, we used the SR that was most recent, was of highest quality and most relevant to our PICO. Chan et al. (2022) and Mancosa et al. (2020) included RCTs relevant to the PICO and any found in the review searches were excluded to avoid double counting. Of all the studies included, Chan et al, (2022) and Mancosa et al. (2020) had the highest AMSTAR II overall score (Low quality review), however Chan was considered in the analysis as this review was the most recent, included the most recent trials, considered the most relevant and used GRADE in reporting its findings. The author team reGRADED the Chan et al outcomes prioritised by PHC EDL committee.

Risk of bias of included trials in SRs

Chan *et al* (2022) reported high risk of bias across five of the 13 RCTs and high risk of bias across all 6 observational (cohort) included studies. Overall, the ROB was considered to be low to unclear across included trials in Chan 2022.

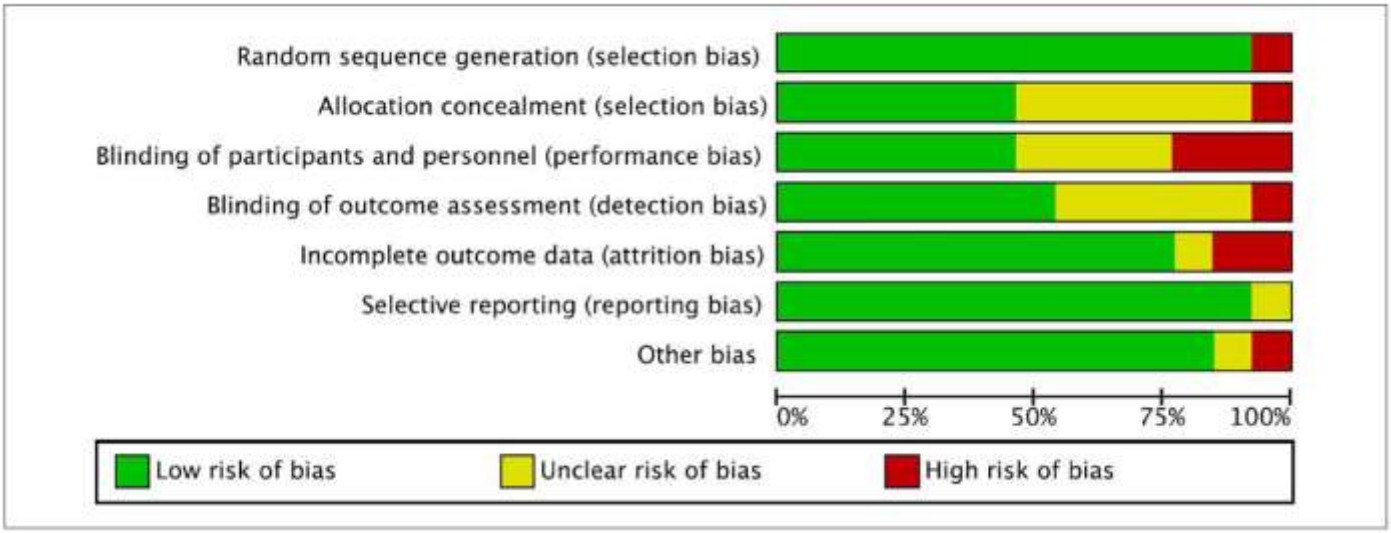


Figure 1: Breakdown of bias of included RCTs using the Cochrane RoB 1 tool (n = 13), Chan et al (2022). *Abbreviations: RCT, randomized controlled trials; RoB 1, risk of bias 1.*

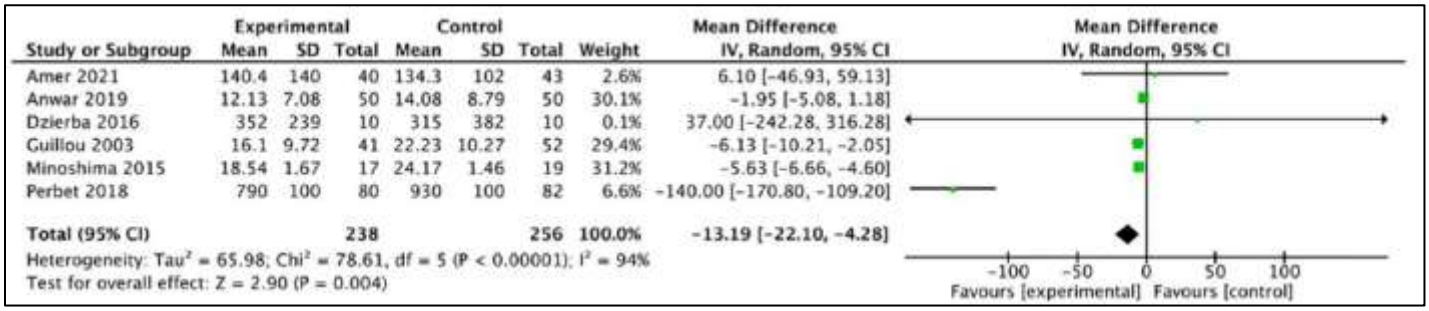
A: Effect of interventions (Ketamine adjunctive)

Sedation and analgesia

- ***Morphine consumption***

Ketamine as adjunctive therapy reduces the consumption of morphine compared to non-ketamine analgesia therapy (Fentanyl, Midazolam, Sufentanil, Pregabalin) in mechanically ventilated patients (MD= -13.19 µg kg^{-1} h^{-1}, 95%CI -22.10 to -4.28, very low certainty of evidence, 6 RCTS, n=494 participants), which equates to ~1mg/hr less Morphine consumption for an average 70kg adult, ranging from 1.5mg/hr less to 0.3mg/hr less (Chan et al. 2022).

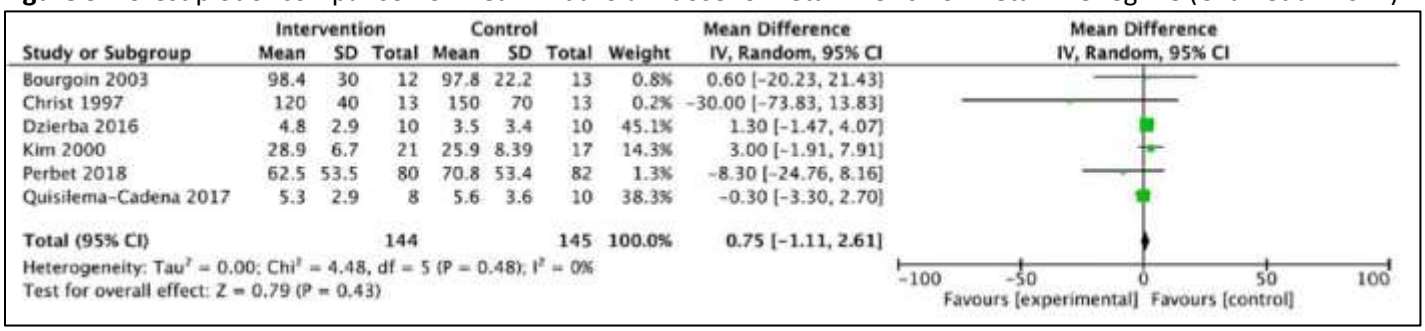
Figure 2: Forest plot of comparison of mean morphine dose for Ketamine vs non-ketamine regime (Chan et al. 2022)



Mean morphine equivalent dose (ME) (µg kg–1 h–1)

- ***Midazolam consumption***: Ketamine has a trivial effect on the consumption of Midazolam compared to non-ketamine analgesia (Fentanyl, Midazolam, Sufentanil, Pregabalin) in mechanically ventilated patients (MD 0.75 µg kg^{-1} h^{-1}, 95% CI −1.11 to 2.61, P = 0.43, very low certainty of evidence, 6RCTs, n=289 patients), which equates to 0.05 mg/hr more Midazolam consumption for an average 70kg adult, ranging from 0.078 less to 0.18 more (Chan et al. 2022). Mancosa *et al.* 2020 similarly reported no significant effect of Ketamine on the consumption of Midazolam (MD −0.3 mg/h, 95% CI −0.95 to 0.35, p = 0.37, 5 RCTs, n=234 patients)

Figure 3: Forest plot of comparison of mean midazolam dose for ketamine vs non-ketamine regime (Chan et al. 2022)

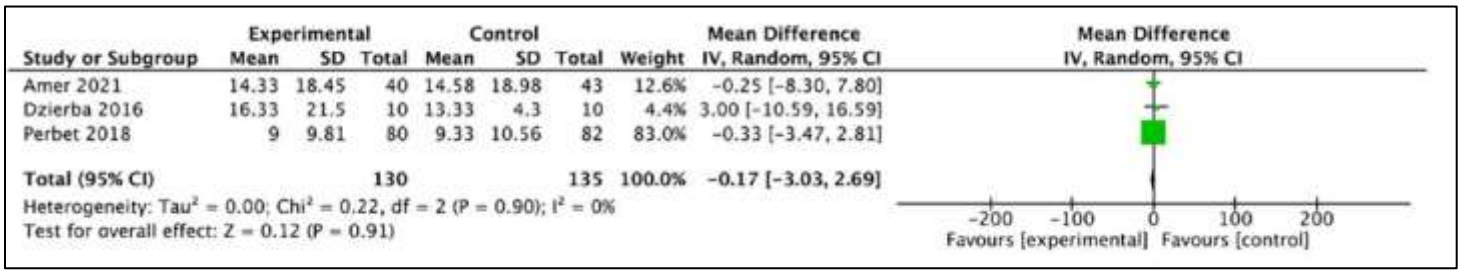


Mean midazolam dose (µg kg–1 h–1)

Mechanical ventilation

There was no significant difference in the duration of mechanical ventilation between Ketamine group and control group (MD −0.17 days, 95% CI −3.03 to 2.69, P = 0.91, very low certainty of evidence, 3 RCTs, n=265 patients) (Chan et al. 2022). No significant difference in duration of mechanical ventilation was also reported by Mancosa et al. (2020), (MD 0.4 days, 95% CI −0.6 to 1.4, p = 0.47, 3 non-randomized studies, n=287).

Figure 4: Forest plot of comparison of mean duration of mechanical ventilation for ketamine vs non-ketamine analgesia (Chan et al. 2022)

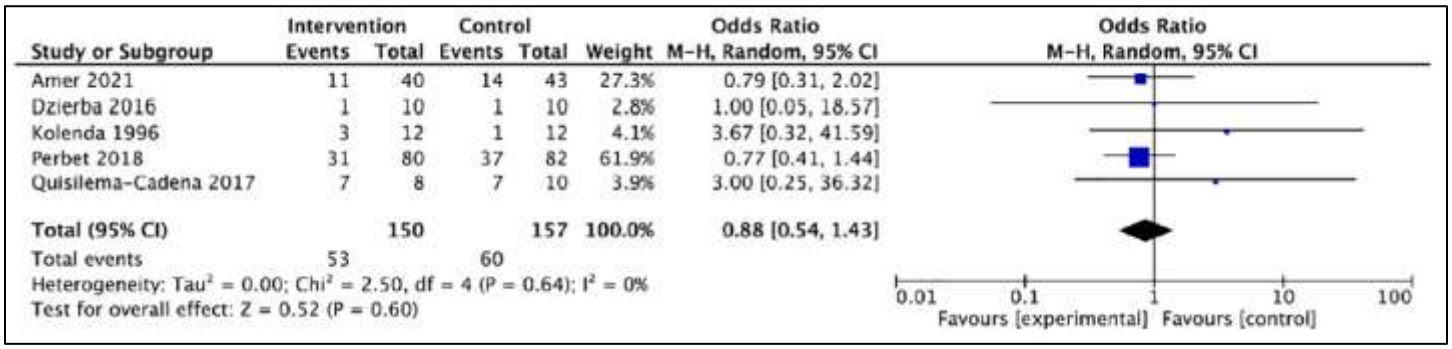


Mortality

Chan et al. (2022) found ketamine adjunctive therapy may reduce mortality (OR 0.88, 95% CI 0.54-1.43, P = 0.60, low certainty of evidence, 5RCTs, n= 3076 patients) resulting in 30 fewer deaths per 1000, ranging from 132 fewer to 87

more. Similar findings were also reported by Mancosa et al. (2020) (OR 1.13, 95% CI 0.70 to 1.81, p = 0.61, 1 RCT, 5 non-randomized studies n= 385 patients).

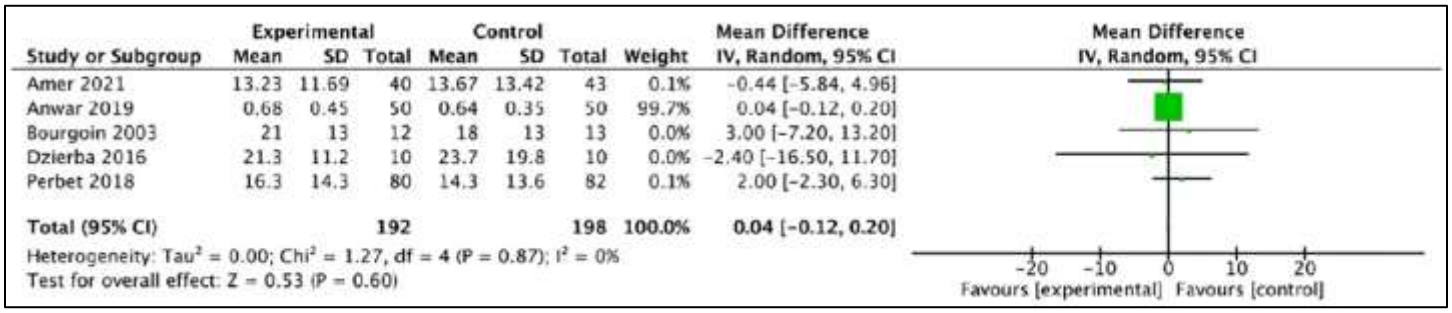
Figure 5: Forest plot of Ketamine effect on mortality (Chan et al. 2022)



Length of ICU stay (days)

Although Chan et al. (2022) ketamine adjunctive therapy results in little to no difference in length of ICU stay (days) (MD 0.04 days, 95% CI −0.12 to 0.20, P = 0.60, high certainty of evidence, 5 RCTs n=390 patients). Mancosa *et al* (2020) reported longer stay in ICU with the use of Ketamine, (MD 2.4 days, 95% CI, 1.3–3.5, p<0.001, 2 RCTs, 2 non-RCTs, n= 312 patients). Likely inflated by inclusion of observational data.

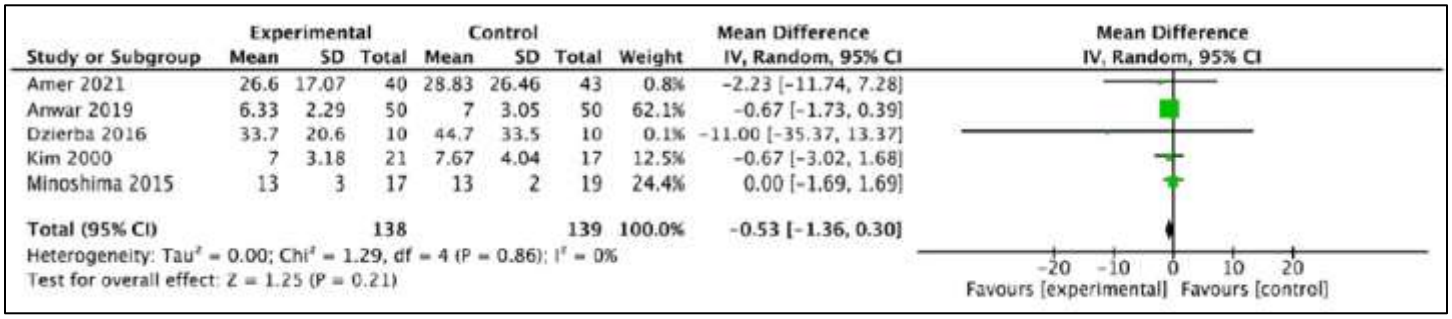
Figure 6: Forest plot of Ketamine effect on ICU length of stay (Chan et al. 2022)



Length of hospital stay (days)

Both Chan et al. (2022) (MD −0.53 days, 95% CI −1.36 to 0.30, P = 0.21, high certainty of evidence, 5 RCTs, n= 277 patients) and Mancosa et al. (2020) (MD 0.5 days, 95%CI -6.0–7.0, p = 0.88, 3 non-randomized studies, n= 173 patients) reported no change in length of hospital stay with the use of Ketamine or that Ketamine adjunctive therapy results in little to no difference in length of hospital stay (days).

Figure 7: Forest plot of Ketamine effect on Hospital length of stay (Chan *et al*. 2022)



Ventilator asynchrony

Not reported across any systematic review or trials

Provider satisfaction
Not reported across any systematic review or trials

RASS scale
In Mancosa *et al*. (2020) qualitative analysis was done by one non-randomized study reporting no difference in proportion of time at RASS goal, while another non-randomized study reported greater time within target RASS

Physiological parameters
Not reported across any systematic review or trial

B: Effect of interventions (Ketamine monotherapy)

Overall, the evidence indicated very low certainty (downgraded for ROB, indirectness and inconsistency) that Ketamine monotherapy provides an overall positive effect on respiratory and haemodynamic outcomes. No outcomes were reported for sedation and analgesia, ventilator asynchrony, provider satisfaction, RASS scale, mortality or hospital length of stay. Trials included for monotherapy from the Miller monotherapy SR were very poorly reported with little or no effect estimates.

Respiratory parameters (Miller *et al*, narrative review)
Respiratory rate changes

3 RCTs reports changes in respiratory rate. 1 RCT (n=60) reported significant higher systolic (F=7.13; df=2.57; P=0.002), and diastolic blood pressure (F=3.6; df=2.57, P=0.034) post induction in ketamine group compared to control (Nayar et al. 2008). 1 RCT (n=44) reported insignificant decrease in systolic (MD 8.1, 95%CI -2.4 to 18) and diastolic blood pressure (MD 2.4, 95% CI -5 to 9.8) (Howtorn et al., 1996). The 3rd RCT reported no significant difference in pulmonary index score between ketamine and control group (MD 0.4 95%CI -0.4 to 1.3) (Allen et al., 2005).

Haemodynamic parameters (Miller *et al*, narrative review)
Mean arterial blood pressure
2 RCTs (n=29) found an increase in mean arterial blood pressure with continuous ketamine use compared to the control group (Elamin et al., 2007; Kolenda et al., 1996)[1].

Use of Vasopressors

1 RCT (n=24) reported decrease in vasopressor in ketamine group compared to control (Kolenda et al., 1996[1]) and another RCT (5 patients) reported decrease in shock with continuous Ketamine use (Elamin et al., 2007[1]).

Cerebral perfusion pressure (CPP)

1 RCT found increase in CCP (8 mmHg) with the use of Ketamine compared to control on the first day (Kolenda et al., 1996[1]).

Conclusion
The evidence of use of adjunctive Ketamine for post-intubation sedation in intubated adults with trauma on mechanical ventilation shows clinically meaningful morphine sparing effects and may reduce mortality. Ketamine compared to other agents shows little to no difference in ICU or hospital length of stay. Overall, the introduction of adjunctive Ketamine for post-sedation intubation results in a moderate meaningful net benefit.

Monotherapy showed an overall positive effect on respiratory and haemodynamic outcomes, however with very low certainty of evidence. Additionally, we are very uncertain about benefit vs harm profile of monotherapy on critical patient outcomes due to poor trial reporting and lack of meaningful effect estimates.

[1] Note that full-text RCTs could not be sourced.

Evidence to Decision Framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**A: ADJUNCTIVE THERAPY** **What is the certainty of evidence?** High [ ] Moderate [ ] Low [x] Very low [ ]	Across critical outcomes (mortality and length of stay) certainty of evidence ranged from low to high. Overall certainty is thus rated as low considering the overall gestalt of the evidence. See GRADE Evidence Profile.
	B: MONOTHERAPY **What is the certainty of evidence?** High [ ] Moderate [ ] Low [ ] Very low [x]	Evidence not GRADED in SR. AMSTAR score however was *critically low quality* and overall certainty of evidence likely to be similar. The evidence indicated very low certainty (downgraded for ROB, indirectness and inconsistency)
EVIDENCE OF BENEFIT	**A: ADJUNCTIVE THERAPY** **What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [x] Small [ ] None [ ]	See GRADE Evidence Profile. Ketamine compared to either Fentanyl, Midazolam, Sufentanil, Pregabalin. Mortality: 30 fewer per 1000 (132 fewer to 87 more) Length of hospital stay: MD 0.53 days lower (1.36 lower to 0.3 higher) Clinically meaningful morphine sparing effect (MD= -13.19 µg kg^{-1} h^{-1}, 95% CI=-22.10 to -4.28) Duration of mechanical ventilation: MD −0.17 days, 95% CI −3.03 to 2.69, P = 0.91
	B: MONOTHERAPY **What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [ ] Small [ ] None/trivial [ ] Uncertain [X]	Overall positive effect on respiratory (respiratory depression, chest wall compliance, PO_2, PCO_2) and haemodynamic (systolic blood pressure, mean arterial pressure, vasopressor use, shock) outcomes. Measures of effect not reported in review *or in included RCTs*, however there may be benefit (above) and congruent with judgements from adjunctive therapy. Calculated effect estimates from 1 RCT, N= 44) in Asthma patients. SBP: MD 8.1 (95%CI -2.4 to 18) DBP: MD 2.4 (95% CI -5 to 9.8) It is however unclear what the magnitude of beneficial effects are of monotherapy.
EVIDENCE OF HARMS	**A: ADJUNCTIVE THERAPY** **What is the size of the effect for harmful outcomes?** Large [ ] Moderate [ ] Small [x] None/trivial [ ]	See GRADE Evidence Profile Ketamine compared to either Fentanyl, Midazolam, Sufentanil, Pregabalin. Length of ICU stay: MD 0.04 higher (0.12 lower to 0.2 higher) Length of hospital stay: MD 0.53 days lower (1.36 lower to 0.3 higher) Small increase in midazolam use: (MD = 0.75 µg $kg^{-1}h\text{-}^{1}$, 95% CI −1.11 to 2.61)

<table>
<tr><td></td><td>B: MONOTHERAPY
What is the size of the effect for harmful outcomes?

Large [ ] Moderate [ ] Small [ ] None/trivial [ ] Uncertain [x]</td><td>1 case report found a decrease in systolic blood pressure with continuous ketamine infusion

Size of effect not reported in review or included RCTs</td></tr>
<tr><td rowspan="2">BENEFITS & HARMS</td><td>A: ADJUNCTIVE THERAPY
Do the desirable effects outweigh the undesirable harms?
Favours intervention [x] Favours control [ ] Intervention = Control or Uncertain [ ]</td><td>Benefit: Moderate

Harms: Small</td></tr>
<tr><td>B: MONOTHERAPY
Do the desirable effects outweigh the undesirable harms?
Favours intervention [ ] Favours control [ ] Intervention = Control or Uncertain [x]</td><td>Benefit: Uncertain

Harms: Uncertain</td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:
Yes [ ] No [x]</td><td></td></tr>
<tr><td>FEASABILITY</td><td>Is implementation of this recommendation feasible?
Yes [x] No [ ] Uncertain [ ]</td><td>SAHPRA registered.
Training would be required for recommended use of ketamine as adjunctive therapy in this clinical setting.</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive [ ] Less intensive [ ] Uncertain [x]</td><td>Price of medicines:
<table>
<tr><th>Medicine</th><th>Tender price (ZAR)*</th><th>100% OF SEP (ZAR)**</th><th>60% OF SEP (ZAR)</th></tr>
<tr><td>Ketamine 500mg/10ml injection, 10 ml</td><td>49.20</td><td>n/a</td><td>n/a</td></tr>
<tr><td>Morphine 15mg/ml injection, 1 ml</td><td>4.23</td><td>n/a</td><td>n/a</td></tr>
<tr><td>Fentanyl 500mcg/10ml injection, 10ml</td><td>10.20</td><td>n/a</td><td>n/a</td></tr>
</table>
* Contract circular HP09-2021SD, August 2022 (weighted average prices used where relevant)

Model assumptions:
1. Modelled on a 70 kg adult patient.
2. Duration of therapy estimated as 3 days for analgosedation in emergency care.
3. Drug vehichle and administration set considered to be similar across interventions so not included in the price comparison
4. Wastage considered to be neglible and not factored in the costing model

Comparative cost analysis across treatments (using direct medicine prices only):
• Ketamine 0.5-1 mg/kg/hour = 70mg/hour = 1680 mg/day (using 4 x 500mg/10 ml inj): 3-day course = R590.40

• Morphine, IV infusion, 0.1-0.2 mg/kg/hour = 14mg/hour = 336mg/day (using 67 x 15mg/ml inj): 3-day course = R849.23</td></tr>
</table>

		• **Fentanyl, IV infusion, 1 mcg/kg/hour** = 70mcg/hour = 1680mcg/day (using 4 x 500mcg/10ml inj): 3-day course = **R122.40**
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [x] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [x] No [ ] Uncertain [ ]	There is no local survey data, however ketamine is currently in use by clinicians and paramedics across the country.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [x] Uncertain [ ]	

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	29 September 2022	ID, VN, CH, GT, MM	***Montherapy:*** Suggest not to be used as postintubation sedation in ventilated trauma patients. ***Adjunctive therapy:*** Suggest to use as postintubation sedation in ventilated trauma patients. *Rationale:* Ketamine may have benefit as adjunctive therapy but there is uncertainty for benefit and harms as monotherapy.

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Appendix 1: Search Strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions

1exp Respiration, Artificial/85998
2(mechanical* adj2 (ventilation or ventilated or ventilator)).tw. 61013
3Intubation, Intratracheal/ or (Rapid Sequence Induction and Intubation).mp.38932
4(intubated or intubation).tw.61593
51 or 2 or 3 or 4183883
6ketamine.mp. or Ketamine/22462
75 and 61354
8(random* or factorial* or placebo* or assign* or allocat* or crossover*).tw.1729191
9((blind* or mask*) and (single or double or triple or treble)).tw.212359
10randomized controlled trial.mp. or Randomized Controlled Trial/ 606340
11Controlled Clinical Trial/94882
128 or 9 or 10 or 111924799
13exp animals/ not humans/5010745
1412 not 131727082
157 and 14232
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17(meta-analysis or metaanalysis).mp.245008
1816 or 17394149
197 and 1834
2015 or 19240

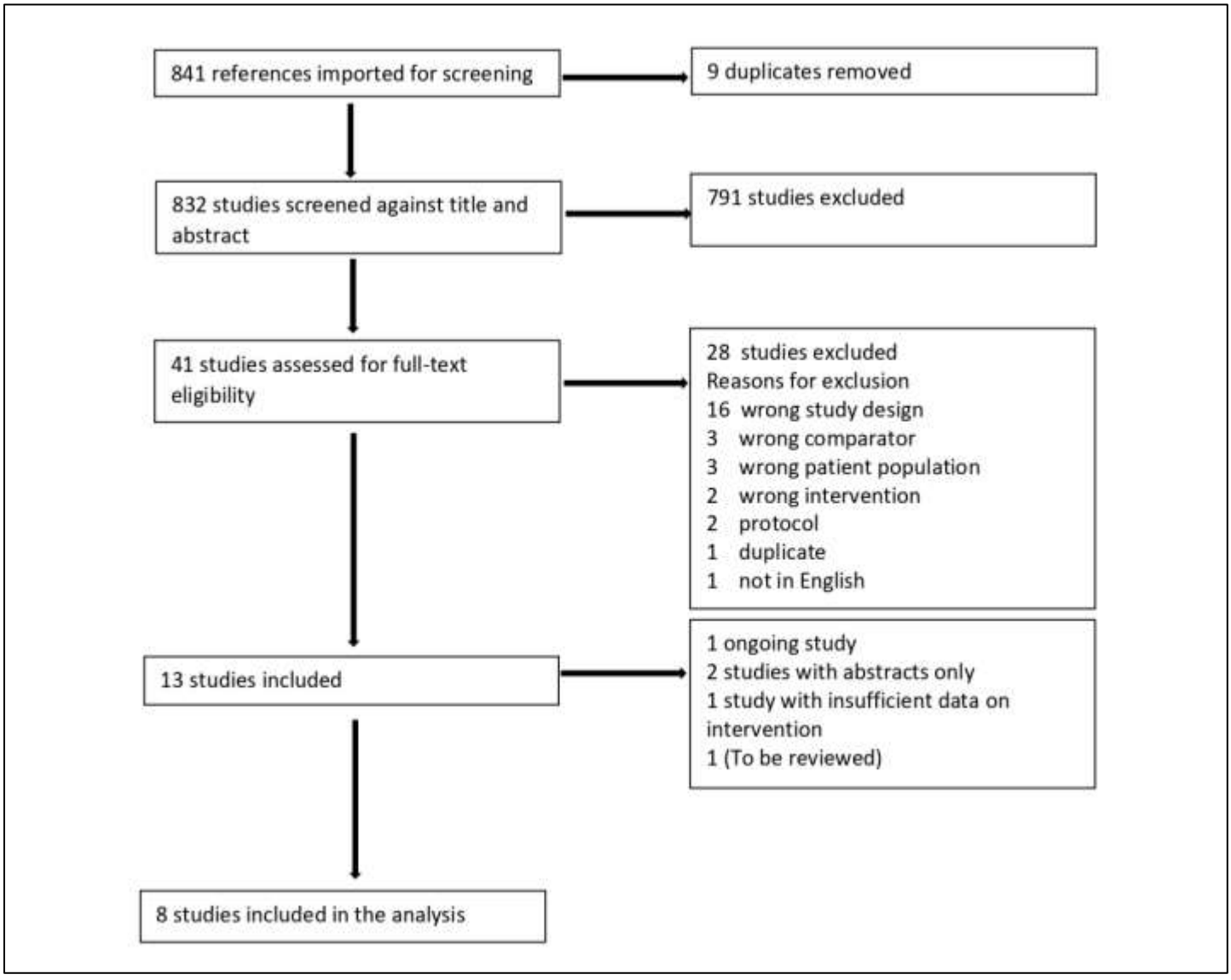
Embase

1(exp artificial ventilation/222541
2 (mechanical* adj2 (ventilation or ventilated or ventilator)).tw. 98025
3(Rapid Sequence Induction and Intubation).mp. or endotracheal intubation/ or awake tracheal intubation/ or fiberoptic tracheal intubation/ or nasotracheal intubation/ or respiratory tract intubation/66451
4(intubated or intubation).tw.103611
51 or 2 or 3 or 4340152
6ketamine.mp. or Ketamine/54298
75 and 65079
8(random* or factorial* or placebo* or assign* or allocat* or crossover*).tw.2329913
9((blind* or mask*) and (single or double or triple or treble)).tw.305905
10Randomized Controlled Trial/ or controlled clinical trial/ 902622
11crossover procedure/ or double-blind procedure/ or single blind procedure/ or randomization/ or placebo/654587
128 or 9 or 10 or 112782740
13systematic review*.mp.450614
14(meta-analysis or metaanalysis).mp.361515
15exp ANIMAL/ or exp NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp ANIMAL MODEL/32727738
16exp human/25006653
1715 not 167721085
1812 or 13 or 143169702
1918 not 172819922
207 and 19733
21(child* or infant* or pediatric).m_titl.1481499
2220 not 21593

Cochrane Database of Systematic Reviews

#1MeSH descriptor: [Respiration, Artificial] explode all trees6880
#2MeSH descriptor: [Intubation, Intratracheal] explode all trees4695
#3(intubated or intubation):ti,ab,kw20699
#4mechanical* and (ventilation or ventilated or ventilator)14361
#5#1 or #2 or #3 or #435762
#6ketamine5978
#7#5 and #6575

Appendix 2: PRISMA



Appendix 3

Table 1: Characteristics of included studies

Citation	Study design	Population	Treatment	Main Findings	Comments
Adjunctive Therapy					
Chan et al. "Impact of Ketamine on Analgosedative Consumption in Critically Ill Patients: A Systematic Review and Meta-Analysis" Annals of Pharmacotherapy DOI: 1 1-20 (2022) 0.1177/10600280211069617	Systematic review	19 studies 13 RCTs: n=731 6 cohort studies: n=1527 Total n=2258	**Interventions** Ketamine + other sedatives including Morphine, Midazolam, Pregabalin, Propofol, Fentanyl and Remifentanil (various doses) **Control** Fentanyl, Sufentanil, Morphine, Midazolam, Remifentanil, Pregabalin, Propofol and placebo (various doses)	**Primary outcomes** **Sedative consumption:** Morphine equivalent dose 6 RCTS, n=494 Ketamine group, n=238 Non-ketamine group, n=256 Significant difference between treatment and placebo group MD= -13.19 mg kg–1 h–1, 95%CI=-22.10 to -4.28, p<0.000 (very low certainty of evidence) Midazolam 6RCTs, n=289 Ketamine group, n=144 Non-morphine group, n=145 No difference between groups treated with and without ketamine MD = 0.75 mg kg–1 h–1, 95% CI −1.11 to 2.61, P = 0.43, (very low certainty of evidence) **Mortality:** 5RCTS, n=307 patients No difference between intervention and comparator Odds Ratio 0.88, 95% CI 0.54-1.43, P = 0.60, (low certainty of evidence) **Length of ICU stay:** 5RCTs, n=390 patients No difference between the ketamine and non-ketamine groups MD 0.04 days, 95% CI −0.12 to 0.20, P = 0.60, (low certainty of evidence) There was significant difference in several observational studies, but data not pooled due to bias **Length of hospital stay:**	5 of the 13 RCTs had high risk of bias. 5 RCTs had some concerns of bias and 3 RCTs were judged to have low risk of bias. Assessment of ROB was done using Cochrane RoB 1 tool All 6 cohort studies were judged to have high risk of bias according to the ROBBINS-1 tool GRADE assessment for all outcomes reported showed low to very low certainty of evidence

				5RCTs, n=277 patients MD −0.53 days, 95% CI −1.36 to 0.30, P = 0.21, (low certainty of evidence) There was significant difference in several observational studies, but data not pooled due to bias **Intracranial pressure:** 3 RCTs, n=79 no significant difference with ketamine administration MD 0.72 mmHg, 95% CI −1.92 to 3.36, P = 0.59, (low certainty of evidence) **Duration of mechanical ventilation:** 3 RCTs, n=265 patients Ketamine group, n=130 Non-ketamine group, n=135 No difference between intervention and control MD −0.17 days, 95% CI −3.03 to 2.69, P = 0.91, (very low certainty of evidence) MV duration was significantly shorter in one cohort study median 17.0 vs 7.5 days (no p value reported here) N= 64 in ketamine group N=120 in fentanyl group	
Manasco et al., "Ketamine sedation in mechanically ventilated patients: A systematic review and meta-analysis". Journal of Critical Care 56 (2020) 80–88. https://doi.org/10.1016/j.jcrc.2019.12.004	Systematic review	15 studies 3 RCTS, n=247 12 cohort studies, n= 645 Total n= 892	**Intervention** Ketamine + other sedatives including dexmedetomidine, Midazolam (various doses of ketamine) **Control** Sufentanil, Midazolam, dexmedetomidine and Placebo (various doses)	**Primary outcomes** **Sedative consumptions:** Ketamine was associated with a significant reduction in Propofol dose 6 studies, n= 325 patients Ketamine group, n=253 Non-ketamine group, n=272	1 RCT had low risk of bias and 2 were graded with uncertainty risk of bias according to the Cochrane ROB tool 6 of the cohort studies were graded as high-quality studies and 6 were graded as poor quality according to the

				MD−699 µg/min, 95% CI -1168 to −230, p = 0.003 Ketamine was not associated with a reduction in fentanyl dose 6 studies, n=628 patients Ketamine group, n=308 Non-ketamine group, n=320 MD=−21.5 µg/h, 95% CI −48.2–5.1, p = 0.11 Ketamine was not associated with a reduction in midazolam dose 5 studies, n= 234 patients Ketamine group, n=167 Non-ketamine group, n=167 MD= −0.3 mg/h, 95% CI −0.95–0.35, p = 0.37. **Mortality:** 6 studies, total n= 385 Ketamine =60/197 Non-ketamine = 61/198 No significant difference between Ketamine group and control group OR= 1.13, 95% CI 0.70 to 1.81, p = 0.61 **Length of ICU stay:** 4 studies, n=312 Ketamine group, n= 148 Non-Ketamine group, n=164 Ketamine sedation was associated with significantly longer ICU length of stay MD= 2.4 days, 95% CI, 1.3–3.5, p<0.001 **Hospital length of stay:** 3 studies, n= 173 Ketamine group, n=64 Non-ketamine group, n=109 No difference in hospital length of stay	Newcastle Ottawa Scale assessment tool.

				MD= 0.5 days, 95%CI -6.0–7.0, p = 0.88 **Mechanical Ventilation:** 3 studies, n=287 patients Ketamine group, n=136 Non-ketamine group, n=151 No difference between groups. MD=0.4 days, 95% CI= −0.6–1.4, p = 0.47 **RASS SCORE:** Qualitative analysis 1 study reported no difference in proportion of time at RASS goal 1 study reported greater time within target RASS **Delirium:** 2 studies, Total n= 241 Ketamine = 46/119 Non-ketamine= 64/122 OR= 0.48, 95% CI 0.26 to 0.87, p = 0.02	
Wheeler, Kathleen E., et al. "Adjuvant analgesic use in the critically ill: a systematic review and meta-analysis." Critical care explorations 2.7 (2020). https://doi.org/10.1097/cce.0000000000000157.	Systematic review	34 RCTs, Number of patients not mentioned Only 4 studies looked at the intervention of interest, n=unknown	**Intervention** Ketamine+ Morphine, Ketobemidone and Remifentanil, **Control** Not stated	**Primary outcome** **Sedative consumption** 2RCTs, n=unknown Significant difference between Ketamine and control group MD = -36.8, 95%CI -46.3, -27.3, p,0.000 (low certainty of evidence) **Pain score** 2RCTs, n= unknown No significant difference between ketamine and control group MD= 0.13, 95% CI -0.46, 0.71, p=0.2 (low certainty of evidence)	Cochrane ROB 1 tool used to assess bias in all included RCTs. 3 of the 4 RCTs with intervention of interest rated as low ROB and 1 as high ROB
Wang et al. “Sedative drugs used for mechanically ventilated patients in intensive care units: a systematic review and network	Systematic review	31 RCTs, N=4491	**Intervention** Ketamine + benzodiazepines	**Primary outcomes** **Mortality**	The Jade score was used to evaluate the one RCT on

meta-analysis" Current Medical Research and Opinion. 35:3, (2019) 435-446, DOI: 10.1080/03007995.2018.1509573		Only 1 study looked at intervention of interest, n= 25 patients with head injury	**Control** Benzodiazepines, placebo, Propofol	N=12 patients included 4 deaths ketamine vs 3 in placebo HR=1.46, 95%CI 0.28-8.3 **Length of ICU stay** Pooled (network) MD=2.91 days, 95% CI -9,28-15.2	intervention of interest and given a score of 4no
Cohen, et al. "The effect of ketamine on intracranial and cerebral perfusion pressure and health outcomes: a systematic review." Annals of emergency medicine 65.1 (2015): 43-51. DOI:https://doi.org/10.1016/j.annemergmed.2014.06.018	Systematic review	10 studies 5 RCTs: n=854 5 non-RCTs: n=99 Total N=953	**Intervention:** Ketamine + other interventions including Midazolam, Fentanyl, Sufentanil, Propofol, Methohexitone, Meperidine, Thiopental and Isoflurane **Comparator** Remifentanil, Fentanyl, Etomidate, Sufentanil, and patient's baseline care.	**Primary outcome:** **Mortality (28 day)** 2 RCTs, n=680 patients Data not pooled-both studies found no significant difference between Ketamine group and comparison group. **ICU length of stay:** 2 RCTs, n=145 patients Data not pooled-both studies found no significant difference in length of stay between ketamine and control group **Intracranial pressure and cerebral perfusion pressure:** 3 RCTs and 5non-RCTs N=168 patients Narrative review 4 studies including 2RCTs found no significant difference in intracranial pressure and cerebral perfusion between Ketamine group and control group One study reported a minimal significant decrease in intracranial pressure but no difference in cerebral perfusion. 3 studies reported significant increase in intracranial pressure in the ketamine group	Methods of assessing ROB in included studies described Adequate description of risk of bias in included RCTs and non-RCTS 7 of the 10 studies described to have a high risk of selection bias

Patanwala AE, et al. Ketamine for Analgosedation in the Intensive Care Unit: A Systematic Review. Journal of Intensive Care Medicine. 2017;32(6):387-395. doi:10.1177/0885066615620592	Systematic review	12 studies 6 RCTs, n=221 1 cohort, n=30 5 case report Total n=256	**Intervention**: Ketamine + Midazolam, Morphine **Control:** Sufentanil, Midazolam, Fentanyl and Placebo	**Primary outcome** **Sedative consumption** 1 RCT, n=93 patients Decrease in morphine consumption in intervention group compared to control MD=22, no 95%CI, p<0.05 **Cerebral Haemodynamics (ICP&CPP**) 4 RCTs, n=103 3 RCTs reported no difference in ICP and CCP in ketamine group compared to control 1 RCT reported significant increase in ICP by about 2mm/Hg and CPP by about 8mm/Hg in ketamine group	Risk of Bias assessed in all RCTs using Cochrane ROB 1 tool 4 RCTs assessed to have high ROB 1 RCT assessed to have low ROB
Zeiler, F.A. et al. The Ketamine Effect on ICP in Traumatic Brain Injury. Neurocrit Care 21, 163–173 (2014). https://doi.org/10.1007/s12028-013-9950-y	Systematic review	7 studies 4RCTs, n= 103 2 cohort, n=38 1 case-control, n=25 Total n=166	**Treatment** Ketamine + other interventions including methohexitone, Midazolam **Control** Fentanyl, methohexitone, sufentanil, Midazolam	Narrative review of outcomes **Cerebral Haemodynamics (ICP CPP)** Continuous infusion of Ketamine 4 RCTs, n=103 No significant difference in ICP and CPP between ketamine group and control groups. 2RCTs, n=48 showed increase in CPP Bolus Ketamine 3 studies, n=63 Trends toward a decrease in ICP. There was no difference in CPP between ketamine group and control group	Risk of Bias assessment not done for RCTs, GRADE reported for all outcomes

Citation	Study design	Population	Treatment	Main Findings	Comments
Monotherapy					
Miller et al. “Continuous intravenous infusion of Ketamine for maintenance sedation”. Minerva Anestesiol 2011;77:812-820	Systematic review	20 studies 4 RCTs, n=150 patients	**Intervention** Ketamine maintenance does for >2hours of various doses	**Respiratory parameters** **Changes in respiratory rate** 6 studies, n=73	

		11 case series, n=126 patients 5 case reports Total n=281	**Control** Fentanyl + Midazolam	No respiratory depression in ketamine group compared to control group **Chest wall dynamic compliance** 5 studies, n=41 patients There was an increase in chest wall dynamic compliance in ketamine group compared to control **Wheezing** 6 case reports, n=7 patients Decrease in wheezing in Ketamine group compared to control **Bronchodilator use** 1 case series, n=5 patients Decrease in bronchodilator use in Ketamine group **Clinical dyspnoea** 1 study=53 patients Decrease in clinical dyspnoea in Ketamine group compared to control **Peak inspirational pressure** 5 studies, n=32 patients Decrease in peak inspirational pressure in Ketamine group **Tidal volume** 1 study, n=14 patients No difference in tidal volume between Ketamine group and control group **Partial oxygenation** 10 studies, n=64 patients	

				Increase in partial oxygenation in Ketamine group compared to control **Partial carbon dioxide** 7 studies, n=46 patients Decrease in partial carbon dioxide in Ketamine group compared to control **Haemodynamic parameters** 9 studies, n=102 patients **Blood pressure** 2 studies, n=20 patients reported no changes in systolic blood pressure in ketamine group compared to control. 1 case report found a decrease in systolic blood pressure 1 study, n=12 patients found no change in diastolic blood pressure **Mean arterial pressure** 3 studies, n=21 patients found no difference in mean arterial pressure. 2 studies, n=29 found increase in mean arterial pressure **Vasopressor** 1 study, n=24 patients reported decrease in vasopressor in ketamine group compared to control.	

				Shock 1 study, n=5 patients reported a decrease in shock in patients treated with continuous Ketamine infusion	
Nayar, R. and Sahajanand, H., 2008. Does anesthetic induction for Cesarean section with a combination of ketamine and thiopentone confer any benefits over thiopentone or ketamine alone? A prospective randomized study. Minerva anestesiologica, 75(4), pp.185-190.	RCT (included in Miller)	Pregnant women for elective caesarean section Total N=60 Number of patients in intervention and control groups not specified. **Exclusion criteria** Patients with known allergies to induction medication Pregnancy induced hypertension Pre-eclampsia Diabetes	**Intervention** 1mh/kg of intravenous bolus ketamine during anaesthetic induction **Control** 5mg/kg of intravenous bolus thiopentone during anaesthetic induction Combined 0.5mg/kg ketamine and 2.5mg/kg thiopentone bolus on induction	**Analgesic effect** No significant difference in VAS pain score post-surgery **Blood pressure** Significant higher systolic blood pressure in ketamine group compared to control groups for 25 minutes post induction (F=7.13; df=2.57; P=0.002). Significant higher diastolic blood pressure in ketamine group compared to control groups for 30 minutes post induction (F=3.6; df=2.57, P=0.034). **Heart rate** Significantly lower heart rate in ketamine group compared to control groups during intubation. Relevant measures of effect not reported.	High ROB as there is no information on the randomization process and blinding.
Allen, J.Y. and Macias, C.G., 2005. The efficacy of ketamine in pediatric emergency department patients who present with acute severe asthma. Annals of emergency medicine, 46(1), pp.43-50.	Double-blind RCT (Included in Miller)	Children aged 2-18 years with clinical diagnosis of acute Asthma	**Intervention** 0.2 mg/kg bolus of intravenous ketamine during 1 to 2 minutes, followed by a 0.5 mg/kg per hour	**Blood pressure** **Pulmonary Index Score** No significant difference between Ketamine group and placebo group of pulmonary	Some concerns of ROB as allocation concealment in not mentioned and it is unclear

		Total N=68 patients Males=41 patients Females=27 Mean age 6.5 years (SD3.8) **Inclusion criteria** Presenting to the emergency department with acute episodes of wheezing **Exclusion criteria** Temperature >39C^{o} Focal infiltrate on chest radiograph Oral, parenteral, or inhaled glucocorticoids within the previous 72 hours History of prematurity, bronchopulmonary dysplasia, coexisting primary parenchymal pulmonary disease	continuous infusion of ketamine for 2 hours Total N=35patients Males=20 patients Females =15patients Control Normal saline placebo Total N=33 patients Males=21 patients Females =12patients	index score by 2 points 120 minutes Ketamine group 3.2(SD 2) points Placebo group 3.6 (SD 1.3) point **MD 0.4 95%CI -0.4 to 1.3**	
Howton, Joseph C., et al. 1996 "Randomized, double-blind, placebo-controlled trial of intravenous ketamine in	Double-blind RCT	Adults aged 18-65 years with clinical diagnosis	**Intervention** Intravenous bolus dose of ketamine hydrochloride at	**Blood pressure** Decrease in **systolic blood pressure** in both groups but no	High ROB as there is no mention of allocation concealment and no

acute asthma." Annals of emergency medicine 27.2: 170-175.	(Included in Miller)	exacerbation of asthma Total N=44 patients **Inclusion criteria** Peak expiratory flow of 40% after nebulizer treatment **Exclusion criteria** Chronic obstructive pulmonary disease Hypertension	0.2mg/kg over 5-minute period followed by a 0.5mg/kg for an hour Total N=23patients Male n=14 Female n=9 **Control** Normal saline placebo Total N=21 Male n=17 Female n=7	significant difference between Ketamine and control group for systolic blood pressure Ketamine mean 140.1(SD24.1) Placebo mean 131.9 (SD3.6) (no report of mean difference) Calculated MD (STATA): **MD 8.1 (95%CI -2.4 to 18)** Decrease in **diastolic blood pressure** in both groups but no significant difference between ketamine and placebo group for diastolic blood pressure Ketamine mean 81.9 (SD11.4) Placebo mean 78.6 (SD13.0) (No report of mean difference) Calculated MD (STATA): **MD 2.4 (95% CI -5 to 9.8)** **Treatment assessment score by patient** Patient in ketamine group rated their treatment to be more favourable compared to those in placebo group (4.3, Sd 6 Vs 3.7, sd1.2, respectively; P=.0285). No significant difference in treatment success score by physician between ketamine and placebo group 3.7, sd 0.6 Vs 3.4 Sd 0.7	mention of who was blinded

Appendix 4

Table 2: Characteristics of excluded studies

Citation	Type or record	Reason for exclusion
Abdennor L, Puybasset L. Sedation and analgesia for brain injured patient. Annales Franc¸aises d'Anesthe´sie et de Re´animation. 2008;27:596–603. doi:10.1016/j.annfar.2008.04.012.	Journal article	Wrong study design
Amer, M. et al. Adjunctive ketamine for sedation in critically ill mechanically ventilated patients: an active-controlled, pilot, feasibility clinical trial. Journal of Intensive Care 2021;9(54):1-2. https://doi.org/10.1186/s40560-021-00569-1.	Journal article	Duplicate
Aminiahidashti et al. Propofol–fentanyl versus propofol–ketamine for procedural sedation and analgesia in patients with trauma. American Journal of Emergency Medicine 36 (2018) 1766–1770. https://doi.org/10.1016/j.ajem.2018.01.080.	Journal article	Wrong population
Bawazeer M, Amer M, et al. Adjunct low-dose ketamine infusion vs standard of care in mechanically ventilated critically ill patients at a Tertiary Saudi Hospital (ATTAINMENT Trial: study protocol for a randomized, prospective, pilot, feasibility trial. Trials 2020; 21(288): 1-13. https://doi/10.1186/s13063-020-4216-4.	Protocol	Protocol
Bourenne J, et al. Sedation and neuromuscular blocking agents in acute respiratory distress syndrome. Ann Transl Med 2017;5(14):291. http://dx.doi.org/10.21037/atm.2017.07.19.	Journal article	Wrong study design
Bourgoin A, et al. Safety of sedation with ketamine in severe head injury patients: Comparison with sufentanil. Crit Care Med 2003;31(3):1-7. DOI: 10.1097/01.CCM.0000044505.24727.16.	Journal article	Wrong comparator
Chang LC, et al. The Emerging Use of Ketamine for Anesthesia and Sedation in Traumatic Brain Injuries. CNS Neuroscience & Therapeutics. 2013; 19:390–395. DOI: 10.1111/cns.12077.	Journal article	Wrong study design
Furyk J, Banks C. From other journals: June 2019. Emergency Medicine Australasia. 2019; 31(3): 497-500. From other journals: June 2019 - Furyk - 2019 - Emergency Medicine Australasia - Wiley Online Library.	Journal article	Wrong intervention
Gamberini L, et al. Prehospital Airway Management in Severe Traumatic Brain Injury. Air Medical Journal. 2019; 38:366−373. https://doi.org/10.1016/j.amj.2019.06.001.	Journal article	Wrong study design
Garber PM, et al. Continuous Infusion Ketamine for Adjunctive Analgosedation in Mechanically Ventilated, Critically Ill Patients. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2019; 39(3): 288-296. https://doi-org.ezproxy.uct.ac.za/10.1002/phar.2223.	Journal article	Wrong study design
Grawe ES, Bennett S. Sedation of Critically Ill Patients Undergoing Mechanical Ventilation. 2013; 51(2): 62-80.	Journal article	Wrong study design
Green SM, et al. Ketamine and Intracranial Pressure: No Contraindication Except Hydrocephalus. 2014; 65(1): 52-54. http://dx.doi.org/10.1016/j.annemergmed.2014.08.025.	Journal article	Wrong study design
Gupta B K, et al. A comparative study of sedo-analgesic effect of dexmedetomidine and dexmedetomidine with ketamine in postoperative mechanically ventilated patients. Journal of Anaesthesiology Clinical Pharmacology. 2022; 38(1): 69-72.	Journal article	Wrong population
Kim T, et al. 2000. Comparison of the Efficacy between Ketamine and Morphine on Sedation and Analgesia in Patients with Mechanical Ventilation.	Journal article	Not in English
Kurdistan university of medical sciences. Comparison of the effects of etomidate versus ketamine on outcome of adult patients with multiple trauma requiring rapid sequence intubation. 2022. https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2020/01/022959.	Trial registry	Wrong study design
Leone M, et al. What sedation for prevention and treatment secondary brain insult? Annales Françaises d'Anesthésie et de Réanimation. 2006; (25): 852–857. DOI:10.1016/j.annfar.2006.03.012.	Trial registry	Wrong study design
Madsen FA, et al. Ketamin for critically ill patients with severe acute brain injury: Protocol for a systematic review with meta-analysis and Trial Sequential Analysis of randomised clinical trials. PLoS ONE 2021; 16(11): 1-14. https://doi.org/10.1371/journal.pone.0259899.	Journal article	Protocol

Mamoud HF. Dexmedetomidine Versus Ketamine to Facilitate Non-invasive Ventilation After Blunt Chest Trauma. 2022. Cinical trials.gov. Sedation for Non-invasive Ventilation in Blunt Chest Trauma - Full Text View - ClinicalTrials.gov.	Journal article	Wrong intervention
Matthes G, et al. Emergency anesthesia, airway management and ventilation in major trauma · Background and key messages of the interdisciplinary S3 guidelines for major trauma patients. Unfallchirurg 2012; 115:251-266. DOI 10.1007/s00113-011-2138-z.	Journal article	Wrong study design
Neme D, et al. Evidence-Based Guideline for Adult Sedation, Pain Assessment, and Analgesia in a Low Resource Setting Intensive Care Unit: Review Article. International Journal of General Medicine. 2020; 13:1445-1452.	Journal article	Wrong study design
Perbet S, et al. Low doses of ketamine reduce delirium but not opiate consumption in mechanically ventilated and sedated ICU patients: A randomised double-blind control trial. Anaesth Crit Care Pain Med. 2018; 37: 589–595. https://doi.org/10.1016/j.accpm.2018.09.006.	Thesis	Wrong population
Ramchard, MV. Comparison of intravenous Dexmedetomidine alone versus Dexmedetomidine plus Ketamine combination on sedation, intubation response, safety profile and patient satisfaction during awake fiberoptic nasotracheal intubation. CTRI/2020/01/022959. CTRI Website URL - http://ctri.nic.in.	Trial registry	Wrong comparator
Roberts DJ, et al. Sedation for Critically Ill or Injured Adults in the Intensive Care Unit A Shifting Paradigm. 2012; 72 (14): 1881-1916.	Journal article	Wrong study design
Sabertanha A, et al. Comparison of Infusion of Propofol and Ketamine-Propofol Mixture (Ketofol) as Anesthetic Maintenance Agents on Blood Pressure of Patients Undergoing Orthopedic Leg Surgeries. Anesth Pain Med. 2019; 9(6):1-6. DOI: 10.5812/aapm.96998.	Journal article	Wrong comparator
Sih K, et al. Ketamine in Adult Emergency Medicine: Controversies and Recent Advances. The Annals of Pharmacotherapy. 2011; 45:1525-1534.	Journal article	Wrong population
Synnot A, et al. 2018. The currency, completeness and quality of systematic reviews of acute management of moderate to severe traumatic brain injury: A comprehensive evidence map. PLoS ONE. 2018; 13(6): 1-25. https://doi.org/10.1371/journal.pone.0198676.	Journal article	Wrong study design
Tobin CDR JM, et al. Anesthesia for Trauma Patients. MILITARY MEDICINE. 2018;183 (9/10):32-34.	Journal article	Wrong study design
Wang WF, et al. A study of the protective effect and mechanism of ketamine on acute lung injury induced by mechanical ventilation. European Review for Medical and Pharmacological Sciences. 2017; 21: 1362-1367.	Journal article	Wrong study design
Wolf SE, Arnoldo BD. The year in burns 2011. Burns. 2012; 1096-1108. http://dx.doi.org/10.1016/j.burns.2012.10.002.	Journal article	Wrong study design
Kolenda H, Gremmelt A, Rading S, Braun U, Markakis E. Ketamine for analgosedative therapy in intensive care treatment of head-injured patients. Acta neurochirurgica. 1996 Oct;138(10):1193-9.	Journal article	Wrong study design
Elamin, E.M., Huges, L.F. and Drew, D., 2007. Is ketamine the right sedative for mechanically ventilated patients? Chest, 132(4), p.574A.	Poster presentation	Poster presentation

Appendix 5: Certainty assessment

Author(s): M. McCaul. Modified from Chan *et al* 2022
Question: Ketamine **adjunctive** therapy compared to standard of care for trauma patients intubated on mechanical ventilation in ICU, EC or prehospital

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ketamine adjunctive therapy	standard of care	Relative (95% CI)	Absolute (95% CI)	
Mortality											
5	randomised trials	not serious[a]	not serious	not serious	very serious[b]	none	53/150 (35.3%)	60/157 (38.2%)	**OR 0.88** (0.54 to 1.43)	**30 fewer per 1,000** (from 132 fewer to 87 more)	⊕⊕◯◯ Low
Length of ICU stay (days)											
5	randomised trials	not serious[c]	not serious	not serious	not serious	none	192	198	-	MD **0.04 days higher** (0.12 lower to 0.2 higher)	⊕⊕⊕⊕ High
Length of hospital stay (days)											
5	randomised trials	not serious	not serious	not serious	not serious	none	138	139	-	MD **0.53 days lower** (1.36 lower to 0.3 higher)	⊕⊕⊕⊕ High
Ventilator asynchrony - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Provider satisfaction - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Explanations

a. Although 3/5 trial had at least one domain with high ROB, Perbet (2018) had overall low ROB and contributed to the majority of the pooled effect.
b. Very serious imprecision: 95% CI of the absolute effect ranges from large benefits to moderate to large harms. Additionally, clinically meaningful inconsistency across included trials (varied direction of effects), undetected statistically (I^2 = 0%), however likely due to small study effects contributing to imprecise trial effect estimates. Not downgraded for inconsistency as linked to imprecision.
c. Anwar contributed 99% of the pooled estimate with overall low ROB

Appendix 6: Overall AMSTAR score for each of the included studies

STUDY	AMSTAR RESULTS
Chan et al. “Impact of Ketamine on Analgosedative Consumption in Critically Ill Patients: A Systematic Review and Meta-Analysis” Annals of Pharmacotherapy DOI: 1 1-20 (2022) 0.1177/10600280211069617	Low quality review
Manasco et al., “Ketamine sedation in mechanically ventilated patients: A systematic review and meta-analysis”. Journal of Critical Care 56 (2020) 80–88. https://doi.org/10.1016/j.jcrc.2019.12.004	Low quality review
Wheeler, Kathleen E., et al. "Adjuvant analgesic use in the critically ill: a systematic review and meta-analysis." Critical care explorations 2.7 (2020). https://doi.org/10.1097/cce.0000000000000157.	Critically low-quality review
Wang et al. “Sedative drugs used for mechanically ventilated patients in intensive care units: a systematic review and network meta-analysis” Current Medical Research and Opinion. 35:3, (2019) 435-446, DOI: 10.1080/03007995.2018.1509573	Critically low-quality review
Cohen, et al. "The effect of ketamine on intracranial and cerebral perfusion pressure and health outcomes: a systematic review." Annals of emergency medicine 65.1 (2015): 43-51. DOI:https://doi.org/10.1016/j.annemergmed.2014.06.018	Critically low quality
Patanwala AE, et al. Ketamine for Analgosedation in the Intensive Care Unit: A Systematic Review. Journal of Intensive Care Medicine. 2017;32(6):387-395. doi:10.1177/0885066615620592	Critically low quality
Zeiler, F.A. et al. The Ketamine Effect on ICP in Traumatic Brain Injury. Neurocrit Care 21, 163–173 (2014). https://doi.org/10.1007/s12028-013-9950-y	Critically low quality
Miller et al. “Continuous intravenous infusion of Ketamine for maintenance sedation”. Minerva Anestesiol 2011;77:812-820	Critically low quality

Ongoing studies

Madsen et al. “Ketamine for critically ill patients with severe acute brain injury: Protocol for a systematic review with meta-analysis and Trial Sequential Analysis of randomised clinical trials”

Brief summary: This study is a systematic review of randomised clinical trials assessing the beneficial and harmful effects of ketamine for patients with severe acute brain injury.

Study type: Systematic review

South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Emergencies and injuries

EVIDENCE SUMMARY

TITLE: TEMPERATURE CONTROL IN POST-CARDIAC ARREST

Preventing fever post CPR vs therapeutic hypothermia

A systematic review was published in 2022 for the European Resuscitation Council (ERC) and ILCOR (international liaison committee on resuscitation).(1) They followed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess the certainty of evidence and grade recommendations. They found the following:

Table 2 ERC-ESICM Recommendations for temperature control after cardiac arrest in adults



For the STG/EML:

1) Proposed wording: from “cooling” to “prevent fever”.

2) This is based on the best evidence that exists on this topic and may save resources.

Details of main trial including TTM2 trial:

The evidence for therapeutic hypothermia post CPR was based on two trials – both with significant limitations and biases:

1) The Bernard trial was a small quasi randomised trial with substantial methodological limitations.
2) The HACA trial was a larger RCT and found a 14% mortality reduction with therapeutic hypothermia (absolute benefit). Significant bias: this trial was unblinded; withdrawal of care was not standardized – pts on the treatment arm had longer times to neuroprognostication; care was not standardized between the two arms.
3) A few trials showed net harm or no benefit, including the TTM1 trial.

The TTM2 trial was a large trial – well conducted – nearly 2000 patients and compared hypothermia (33 degrees vs normothermia (fever control).(2) In the control group, they initiated cooling when the temperature rised above 37.8 degrees only and only cooled to 37.5 (normothermia).
This trial had a very low risk of bias as the treatment and neuroprognostication procedures were standardized. It was a multicentered randomised superiority trial. Outcomes were assessed at 30 days and 180 days. Research question: Does targeted hypothermia lead to improved outcomes in comparison to targeted normothermia (and avoidance of fever) in patients with ROSC after OHCA? (return of spontaneous circulation and out of hospital cardiac arrest)

Main findings:

1) Hypothermia had no effect on mortality or neurological endpoints.
    a. Death from any cause: 50% in hypothermia vs 48% in normothermia, RR 1.04 95% CI 0.94 to 1.14 p=0.37
2) Numerous signs of iatrogenic harm in hypothermia group
    a. Patients in the hypothermia group had a higher risk of arrhythmia causing hemodynamic instability (24% vs. 17%, p<0.001).
    b. Patients in the hypothermia group required paralytics more often (66% vs. 45%, p<0.001).
    c. Patients in the hypothermia group had a longer median length of mechanical ventilation (3.8 days vs. 2.9 days).
    d. Patients in the hypothermia group experienced more than twice as many unexpected severe adverse events (3.7% vs. 1.4%, p=0.003).

Conclusions

1) Therapeutic hypothermia can cause substantial harm.
2) Therapeutic hypothermia is resource heavy: cooling vests, ice packs, invasive monitoring, and staff)
3) TTM2 trial is the highest level of evidence on this topic.

Low certainty evidence

References

1. Sandroni C, Nolan JP, Andersen LW, Böttiger BW, Cariou A, Cronberg T, et al. ICM RAPID PRACTICE GUIDELINE ERC-ESICM guidelines on temperature control after cardiac arrest in adults. Intensive Care Med [Internet]. 2022;48:261–9. Available from: https://doi.org/10.1007/s00134-022-06620-5
2. Dankiewicz J, Cronberg T, Lilja G, Jakobsen JC, Levin H, Ullén S, et al. Hypothermia versus Normothermia after Out-of-Hospital Cardiac Arrest. N Engl J Med. 2021;384(24):2283–94.

Author: Dr Clint Hendrikse
Date: 9 August 2022

South African National Essential Medicine List
Primary Healthcare/ Adult Hospital Level of Care Medication Review Process
Component: Emergencies and injuries

MEDICINE REVIEW

1. Executive Summary

Date: 18 August 2022
Medicine (INN): Olanzapine (IM, orodispersible)
Medicine (ATC): N05AH03
Indication (ICD10 code): Delirium F05.0/.1/.8/.9
Patient population: Adults with delirium who are agitated or considered a risk to themselves or others, and non-pharmacological measures are ineffective.
Prevalence of condition:
South African studies
- 12.3% of acute medical inpatients (Du Plooy, 2020)[1]
- 17.6% of acutely admitted people with HIV (Day, 2021)[2]

International studies
- Approximately 20% of general adult inpatients and 80% of mechanically ventilated patients in ICU (Nikooie, 2019)[3]

Level of Care: Primary Healthcare
Prescriber Level: Doctor prescribed
Motivator/reviewer name(s): Lesley Robertson, Shelley McGee, Tamara Kredo, Natasha Gloeck, Mashudu Mthethwa, Trudy Leong
PTC affiliation: Lesley Robertson affiliated to Sedibeng District PTC, Gauteng

Key findings

- We conducted a review of Clinical practice guidelines, health technology assessments, systematic reviews of randomised controlled trials (RCTs), RCTs and where necessary systematic reviews of non-randomised/ observational studies or observational studies. Ongoing trials were also sought.
- Two systematic reviews, three RCTS and three clinical guidelines were identified, including comparisons of interest.
- All three clinical guidelines were of relatively high quality assessed against AGREE II. Only one makes a weak recommendation for olanzapine for the treatment of delirium
- Comparison of olanzapine to placebo, was reported in one clinical trial, which rated poor in terms of quality, as part of a systematic review. The impact of olanzapine on duration of delirium (days) was uncertain (MD=-2.4, 95% CI 3.51,-1.29, n = 103, 1 trial. Change in delirium severity, appeared to favour olanzapine (reduction in the delirium rating scale (DRS) MD = -11.1, 95% CI 15.51 to -7.69, n=103, 1 trial.
- For comparison of olanzapine versus haloperidol, change in delirium severity results were reported in most studies however these were at different time points and using different measures. Overall, there was no difference in delirium severity between olanzapine and haloperidol (generally very low to low certainty of evidence). Duration of delirium (days) did not differ significantly between haloperidol and olanzapine, in 1 trial, included in a systematic review (mean Difference (MD) 0.62 days, 95% CI 0.06 to 1.18).
- No reviews nor trials were identified comparing olanzapine to benzodiazepines in the treatment of delirium.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:

	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
Type of recommendation				X	

Recommendation: The PHC/ Adult Hospital Level Committee suggests using olanzapine (orodispersible and parenteral formulations) as an option to manage delirium where non-pharmacological management is not sufficient and if haloperidol, intramuscular formulation is unavailable
Rationale: Available low-quality evidence shows that olanzapine is comparable to haloperidol.
Level of Evidence: Low to very low certainty evidence

Review indicator: Evidence of harm, efficacy
NEMLC RECOMMENDATION (20 OCTOBER 2022 MEETING): NEMLC recommended the use of olanzapine oro-dispersible tablet or IM injection for delirium with agitated and acutely disturbed behaviour. Once the patient is able to swallow, to continue with oral haloperidol or olanzapine, until behaviour is contained.
Monitoring and evaluation considerations
Research priorities

2. **Name of author(s)/motivator(s)**
   Lesley Robertson, Tamara Kredo, Mashudu Mthethwa, Natasha Gloeck, Shelley McGee, Trudy Leong

3. **Author affiliation and conflict of interest details**
   - Lesley Robertson, Department of Psychiatry, University of the Witwatersrand: no conflicts of interest related to olanzapine
   - Tamara Kredo, Cochrane South Africa, South African Medical Research Council; Division of Clinical Pharmacology, Department of Medicine, and Division of Epidemiology and Biostatistics, department of Global Health, Stellenbosch University: no conflicts of interest related to olanzapine
   - Mashudu Mthethwa, Cochrane South Africa, South African Medical Research Council: no conflicts of interest related to olanzapine
   - Natasha Gloeck, Cochrane South Africa, South African Medical Research Council: no conflicts of interest related to olanzapine
   - Shelley McGee, Ophthalmological Society of South Africa: no conflicts of interest related to olanzapine
   - Trudy Leong, Right-To-Care as Secretariat-support to PHC/ Adult Hospital Level Committee of the National Essential Medicines List, NDoH: no conflicts of interest related to olanzapine

4. **Introduction/ Background**
   The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5)[4] describes delirium as an acute disturbance in attention, awareness (reduced orientation to the environment), and cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception). It develops within hours to days and tends to fluctuate during the day, worsening in the evenings. Delirium may be 'hyperactive', with increased mood lability, agitation, and/or uncooperative behaviour, or 'hypoactive', with poor responsiveness and stupor.

   Delirium is a physiological consequence of another medical condition, substance intoxication or withdrawal, exposure to a toxin, or multiple aetiologies. Treatment of delirium necessitates treatment of the underlying cause. Non-pharmacological measures to reduce confusion include a calm, predictable care environment, effective communication, verbal reorientation, and maintenance of the circadian rhythm. Medicine management of agitation, distress, or uncooperative behaviour may be necessary to facilitate nursing and treatment of the underlying condition. Currently, haloperidol, IM is recommended if non-pharmacological measures are insufficient. Haloperidol IM 5mg/ml and 20mg/2ml were discontinued in South Africa by Pfizer and supply has been erratic.

5. **Purpose/Objective i.e., PICO question**:
   - **Population**
     People ≥18 years treated for delirium (formally diagnosed using a validated tool) or sub-syndromal delirium (presence of some delirium symptoms) in an acute care (e.g., primary health clinic/ community health clinic/ hospital emergency room, medical or surgical ward), intensive care, or palliative care setting. Exclude studies solely focusing on people with substance intoxication or withdrawal or people in psychiatric care settings.
   - **Intervention**
     Olanzapine IM and orodispersible tablets, any dose
   - **Comparators**
     Haloperidol IM +/- promethazine IM, any dose

Benzodiazepines: any dose, given orally or IM
Placebo

- **Outcomes**

  Efficacy
  - Duration of delirium (days)
  - Change in delirium severity, assessed by validated instruments.
  - Change in agitation score
  - Delirium resolution (defined as reduction of delirium rating scale below a target set by the authors or complete resolution of symptoms)
  - Use of physical restraint
  - Other – hospital/ intensive care unit (ICU) length of stay (days), hospital discharge disposition (e.g., rehabilitation, chronic care facility, home), health-related quality of life (as reported by study authors)

  Safety
  - Extrapyramidal side effects (EPS); use of anticholinergic medication
  - Adverse events as defined by the study authors (e.g., prolongation of the QTc interval, sudden cardiac death, cerebral vascular events, seizures, extrapyramidal effects, long-term cognitive impairment (e.g., change in Mini Mental Status Exam or as reported by study authors))
  - Mortality

- **Study types**

  Clinical practice guidelines, health technology assessments, systematic reviews of randomised controlled trials (RCTs), RCTs and, if the latter is unavailable, systematic reviews of non-randomised/ observational studies or observational studies. Ongoing trials were also sought.

Methods:

a. **Data sources**:
   Clinical Practice Guidelines sources searched were the Guidelines International Network (GIN) Library, the National Institute for Health and Care Excellence (NICE) and the British Association of Clinical Pharmacology, as well as relevant clinical practice guidelines from Australia, New Zealand and Canada on their government websites, searched via Google. Systematic reviews and randomised controlled trials were sought in PubMed, the Cochrane Library, and Epistemonikos.

b. **Search strategy –** A search strategy was developed for PubMed and adapted to other databases (Appendix 1). A search for systematic reviews and RCTs was conducted on PubMed, the Cochrane Library, and Epistemonikos on 4 March 2022 (Appendix 1). The search was inclusive of all populations (with acute agitation or delirium) as the two review topics were happening in parallel and this was most efficient approach for searching and screening.

Screening, data extraction and analysis, evidence synthesis: Records were uploaded into the reference management software, COVIDENCE. Titles and abstracts were screened independently and in duplicate (NG, MM, TK, LR). Thereafter, full text screening was done by two reviewers, including tagging the study design (RCT or SR) and the population (delirium or acute agitation) and checked by a third reviewer. Discrepancies were discussed with LR and TK to finalise selection. We took a step-wise approach, screening for systematic reviews first and then for RCTs. Data extraction for included reviews was done by one reviewer and checked by a second reviewer. Eligible clinical guidelines were appraised with the AGREE II tool by two reviewers (MM and NG). Eligible systematic reviews were appraised using the AMSTAR II Checklist, and eligible RCTs were assessed for Risk of Bias using the Cochrane's RoB 2.0 Tool. Data was extracted into Characteristics of Included studies tables (tables 2 and 3). For dichotomous outcomes, we reported risk ratios (RR) with 95% confidence intervals (CI). We reported results from the review or trial where possible. Despite the intervention in these studies being haloperidol, and olanzapine being the comparator, outcomes of results were not reanalysed in RevMan to align with the review

question as denominators for the systematic reviews were not available and we wanted to keep the results standardised. Where available, we reported on the GRADE (level of certainty) of the evidence.

c. Excluded studies: Reasons for excluding full-texts were agreed in duplicate with a third reviewer finalizing any disputes.

Results:

1. Search results

We searched PubMed, Epistemonikos and the Cochrane Library on 4 March 2022. We identified 778 records which were imported for screening, with 147 duplicates removed. Furthermore, three records were identified from experts in the field and three were identified through reference searching. We screened 636 abstracts, of which 541 were irrelevant. 95 full-text studies were assessed for eligibility; 86 studies were excluded. There were nine included studies: two systematic reviews, three RCTs and four ongoing studies.

The Prisma Flow Chart is available in Appendix 2.

2. Description of included clinical guidelines, systematic reviews and RCTs

Table 1 reports a summary of the guidelines, Table 2 reports the main characteristics and outcomes of the included systematic reviews, and Table 3 reports the main characteristics and outcomes of included randomised controlled trials. Appendix 2 describes the excluded studies and Appendix 3 provides a summary of ongoing trials.

2.1. Clinical guidelines:

We identified three guidelines

1. National Institute for Health and Care Excellence (NICE). Delirium: diagnosis, prevention and management[6]
2. Scottish Intercollegiate Guidelines Network (SIGN). Risk reduction and management of delirium[7]
3. Victorian Government Department of Human Services. Clinical practice guidelines for the management of delirium in older people[8]

Following appraisal with AGREE II, all three were assessed as moderate to good quality (see Table 1). The NICE guideline was first issued in July 2010, and updated in March 2019. This guideline offers guidance around modifiable risk factors to identify people at risk of developing acute delirium, diagnosis of delirium in long-term, critical and acute care settings, and pharmacological as well as non-pharmacological interventions for reducing delirium incidence and consequences, and reducing the severity, duration and consequences of delirium in adults (18 years and older) in a hospital or long-term residential care. This guideline had an overall AGREE II score of 83%. Of note is that olanzapine was removed from the updated NICE guideline (2019), as haloperidol now has UK marketing authorisation for delirium treatment (though, discontinued from the South African market).

The SIGN delirium guideline was first published in March 2019. This guideline provides guidance for reducing the risk of delirium, as well as the detection, assessment, treatment and follow up of adults with delirium in all settings (patient homes, long term care, hospitals, and hospices). This guideline had an overall AGREE II score of 67%.

The Victorian Government Department of Human Services' guideline for the management of delirium in older people was published in 2006 and provides recommendations in the assessment and management of older people (65 years and older, or 45 years and older in in Aboriginal and Torres Strait Islander people) in Australia in hospitals, and across healthcare settings, as well as the prevention of delirium in at-risk older people, identifying and defining appropriate health service provision and management options to ensure the best possible health outcomes. This guideline had an overall AGREE II score of 83%.

Recommendations related to this review (olanzapine vs haloperidol) are summarized in Table 1. Domain scores for the AGREE II Appraisals can be found in Appendix 3.

Table 1: Summary of Guidelines and AGREE II scores

Name	Recommendation	AGREE II
National Institute for Health and Care Excellence (NICE). **Delirium: diagnosis, prevention and management**	The NICE group recommends that if a person with delirium is distressed or considered a risk to themselves or others and verbal and non-verbal de-escalation techniques are ineffective or inappropriate, consider giving short-term (usually for 1 week or less) *haloperidol or olanzapine*, starting at the lowest clinically appropriate dose and titrating cautiously according to symptoms (conditional, very low certainty evidence) In the most recent review of this guidance (2019) olanzapine was removed as a treatment option in favour of haloperidol, which had achieved authorisation for the indication of delirium in the United Kingdom.	83%
Scottish Intercollegiate Guidelines Network (SIGN). **Risk reduction and management of delirium**.	The SIGN group states "Because the studies identified are underpowered, larger trials are needed before recommendations can be made on the use of antipsychotics for the treatment of patients in ICU with delirium." (1++ - High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias)	67%
Victorian Government Department of Human Services. **Clinical practice guidelines for the management of delirium in older people.**	The Victorian Government Department of Human services recommends that antipsychotic medication should only be used for the treatment of severe behavioural disturbances and or severe emotional disturbances when there is clear intent for its use (e.g. severe agitation interfering with sleep-wake cycle). When used, "Titrated antipsychotics need to be closely monitored by nursing and medical staff. The dosage and frequency should be titrated carefully against the level of agitation at each review. Titration must commence from a low dose typically commencing with the equivalence of 0.25-0.50mg of haloperidol; olanzapine 2.5 mg orally; or risperidone 0.25 mg orally." (III-2 – a comparative study with concurrent controls (non-randomised experimental trial, cohort study, case-control study, interrupted time-series with a control group))	83%

2.2 Systematic reviews

We identified two systematic reviews for inclusion

1. Finucane 2020. Drug therapy for delirium in terminally ill adults[9]
2. NICE Review within the NICE guideline[6]

Finucane 2020[9], a Cochrane Systematic Review, reviewed evidence of pharmacological therapy for delirium management in terminally ill adults (including terminal agitation, distress or restlessness). The setting was not specified. The NICE review[6] reviewed delirium management in hospitalized participants (age 18 years or older) regardless of whether in a surgical, medical, ICU and emergency ward, mental health settings, and long-term care settings. In both reviews, delirium was defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5 or earlier criteria).

Primary outcomes assessed in Finucane 2020 were 1) delirium symptoms within 24 to 48 hours, 2) agitation score within 24 to 48 hours and 3) the number of adverse events (including extrapyramidal side effects). Secondary outcomes included 1) the use of any rescue medication (such as midazolam), 2) cognitive status and 3) survival.

Primary outcome measures in the NICE review were 1) duration of delirium and 2) number recovered from delirium. The secondary outcomes included 1) severity of delirium, 2) length of stay, 3) incidence of cognitive impairment or dementia, 4) number of patients in hospital discharged to new long-term care placement, 5) mortality, 6) number of patients with persisting delirium, 7) quality of life (patient), 8) quality of life (carer), and

9) adverse effects associated with the intervention (including extrapyramidal side effects). Outcome results are summarised in Table 2.

There was only one included RCT (Lin 2008) in Finucane 2020 that compared haloperidol to olanzapine. The full text for the included RCT was not found despite extensive searching (searching online databases, contacting trial and review authors). Two outcomes of interest were reported in this RCT and are further detailed in Table 2.
Within the NICE review, olanzapine was considered in two comparisons: olanzapine versus no treatment (one RCT, Hu 2006 – 103 participants, full text not available for review) and haloperidol versus olanzapine (Hu 2006 and Skrobik 2004, Skrobik 2004 is summarized below under the RCTs, Table 3). Finucane 2020 had a moderate AMSTAR II rating. The quality was marked down as authors did not explain their selections of study designs included in the review. The NICE review had a high AMSTAR II rating of 4. GRADE evidence ratings are summarized in Table 2.

2.3 RCTs

We identified three randomised controlled trial for inclusion

1. Skrobik 2004. Olanzapine vs haloperidol: treating delirium in a critical care setting[10]
2. Jain 2017. Comparison of efficacy of haloperidol and olanzapine in the treatment of delirium[11]
3. Van der Vorst 2020. Olanzapine versus haloperidol for treatment of delirium in patients with advanced cancer: a phase III randomized clinical trial[12]

The trials were conducted in three countries (Canada (one site), India (one site) and The Netherlands (five sites)). Sample sizes varied from 73 to 100 participants and took place in a medical-surgical ICU (Skrobik 2004[10]), medical emergency wards (Jain 2017[11]) and a medical oncology ward or high-care hospice facility (van der Vorst 2020[12]). All three trials compared haloperidol to olanzapine. In Skrobik 2004, participants were randomised to haloperidol, initiated at 2.5 to 5mg 8 hourly (either orally or via an enteral tube) or olanzapine at 5mg daily. Older patients (60 years and above) received a lower starting dose (haloperidol 0.5 to 1mg, olanzapine 2.5mg). Titration thereafter was based on clinician judgment. In Jain 2017, the mean daily doses of olanzapine and haloperidol were 5.49mg (range 2.5mg) and 2.10mg (range 1 to 5mg) respectively. Doses were determined by the participants' Memorial Delirium Assessment Scale (MDAS) score. In van der Vorst 2020, dosing was age-adjusted and based on clinical practice guidelines. Patients under 75 years old were started on haloperidol 1mg or olanzapine 5mg. This was titrated every 40min for haloperidol and two hours for olanzapine, according to the delirium observation scale (DOS) to a maximum on day 1 of 20mg po or 10mg subcutaneously (sc) for haloperidol, and 20mg po or IM for olanzapine. The doses were halved for patients 75 years and older.

Jain 2017 reported on duration of delirium (days). Skrobik 2004, Jain 2017 and van der Vorst 2020 reported on change in delirium sensitivity – however, the three trials used different instruments of measuring this outcome and so we could not compare in meta-analysis (Skrobik 2004 used change in delirium index scores, Jain 2017 used mean MDAS scores at baseline and at the end of the study period, and van der Vorst used delirium response rate (DRR) as defined by Delirium Rating Scale-R-98 (DRS-R-98) assessment). Van der Vorst 2020 reported on delirium resolution (days). In terms of safety outcomes, Skrobik 2004 and van der Vorst 2020 reported on extrapyramidal side effects. Jain 2017 and van der Vorst 2020 reported on adverse events.

Two of the trials (Skrobik 2004 and Jain 2017) were rated as having a high risk of bias. Skrobik 2004 was rated high due to quasi-randomization of allocation sequence and baseline differences between allocation groups, no information around participant blinding and effects of assignment, no information around a prespecified plan or protocol. Jain 2017 was rated high due to this being a single-blind study, limited information on statistical methods, no information around data available for all participants and missingness, potential bias from researchers not being blinded, and no information around a pre-specified analysis plan. Van der Vorst 2020 was rated as having some concerns of bias due to no information around pre-specified plan or protocol.

3. Description of excluded studies

We excluded 86 full texts – 41 for wrong indication, 16 were awaiting classification, 10 for wrong study design, 7 for wrong intervention, 5 for wrong patient population, 3 for wrong outcomes, 3 for wrong language and 1 registered trial was stopped with recruitment issues. The excluded studies with reasons are listed in Appendix 2.

EFFECTIVENESS OF THE INTERVENTION

Comparison	Number of studies
1. Olanzapine vs Haloperidol	2 systematic reviews, 3 RCTs (one is quasi-randomised)
2. Olanzapine vs Benzodiazepines	0 studies identified
3. Olanzapine vs Placebo	1 systematic review

Comparison 1: Olanzapine vs Haloperidol

Efficacy

Critical outcomes: None of the 5 included studies reported on the following outcomes:

- change in agitation score,
- use of physical restraint,
- hospital/ICU length of stay,
- hospital discharge disposition and
- health related quality of life

Important outcomes

1. **Duration of delirium (days):**
   - *NICE review 2010 (updated in 2019):* The effect of haloperidol compared to olanzapine on duration of delirium is uncertain. Mean Difference (MD) 0.62 days, 95% CI 0.06 to 1.18, one RCT, n = 146, 1 trial, very low certainty evidence due to study quality, and imprecision
   - *Jain 2017:* The mean duration of treatment (days) was similar, 3.57 days (+- 0.92 days) in the olanzapine arm and 3.37 days (+- 0.71 days) in the haloperidol arm.

2. **Change in delirium severity:**

   Results were reported from three studies at different time points and using different measures. Overall, they found there was no difference in delirium severity between olanzapine and haloperidol.

   - *Finucane 2020:* Change in delirium severity: there may be little or no difference in change in delirium severity with olanzapine compared to haloperidol (Very low certainty evidence due to critical imprecision)
     1) within 24 hours: the mean difference (MD) between treatment arms was 2.36 (95% CI -0.75 to 5.47).
     2) between 24 and 48hrs: MD 1.90 (95% CI -1.50 to 5.30)
   - *NICE review:* There may be no difference in change in delirium severity score (delirium Rating Scale – DRS) comparing haloperidol and olanzapine. MD 0.7, 95% CI 0.45 to 1.85, n =146, 1 trial, moderate certainty evidence rated down due to poor study quality)
   - *Skrobik 2004:* There was a comparable reduction in the DI score in both groups over time (ANOVA time effect p 0.02, group effect p 0.83, interaction effect p 0.64)
   - *Jain 2017:* the mean MDAS score at baseline was 18.49 in the olanzapine group and 17.79 in the haloperidol group (the groups were comparable at baseline, p 0.791). The mean MDAS score at the end of the study period was 8.43 in the olanzapine group and 8.00 in the haloperidol group.
   - *Van der Vorst 2020:* The delirium response rate (DRR) was in the Olanzapine arm was 45% (95% CI 31 to 59) and 57% (95% CI 43 to 71) in the haloperidol arm (ΔDRR −12%; odds ratio [OR], 0.61; 95% CI, 0.2–1.4)

3. **Delirium resolution** (defined as reduction of delirium rating scale below a target set by the authors or complete resolution of symptoms): Results were reported from three studies. Overall, they found there was little or no difference in delirium resolution between olanzapine and haloperidol.
   - *NICE review:* There may be little to no difference comparing haloperidol and olanzapine. Risk Ratio (RR) 0.99, 95% CI 0.8 to 1.21, p=0.24, I^2=27%, n = 218, 2 trials (low certainty evidence due to poor study quality and indirectness from delirium assessment).
   - *Van der Vorst 2020:* The TRR (time from randomisation to resolution) was 4.5 days (95% CI 3.2 to 5.9) in the Olanzapine and 2.8 days (95% CI 1.9 to 3.7) in the haloperidol arm.

Safety

1. **Mortality**
   - Not reported.
2. **Extrapyramidal side effects (EPS):**
   - *NICE review:* We are uncertain about the difference in occurrence of EPS between haloperidol and olanzapine groups, RR 8.2, 95% CI 0.48 to 140.09, n = 73 , 1 quasi-RCT (very low certainty evidence due to study design limitations, and imprecision). Six participants rated low scores on extrapyramidal symptom testing (1 for the Ross Chouinard, 1–4 for the Simpson-Angus scale) in the haloperidol arm. There were no extrapyramidal manifestations in the olanzapine arm.
   - *Van der Vorst 2020:* six participants (12.2%) experienced EPS in the haloperidol group (three with tremors, two with muscle stiffness and one with QTc prolongation), compared to four (8.2%) in the olanzapine group (two with tremors, one with dizziness and one with muscle stiffness).

3. **Requiring anticholinergic medication:**
   - *Skrobik 2004:* no participants in either the haloperidol or olanzapine groups received prophylactic or therapeutic antiparkinsonian therapy.

4. **Adverse events:**
   - *Jain 2017:* There were two participants in the olanzapine group with adverse effects (one with excessive sedation, one with akathisia), and three in haloperidol group (drug-induced parkinsonism). All side effects were mild in severity. EPS were not defined separately but included under adverse events and as such have been reported here.
   - *Van der Vorst 2020:* 13 out of 46 patients (26.5%) in the olanzapine arm and 16 out of 49 patients (32.7%) in the haloperidol arm reported treatment-related adverse effects of any grade. Five patient (10.2%) in the olanzapine group and 10 patients (20.4%) in the haloperidol group reports Grade 3 or above TRAEs (OR 0.4, 95% CI 0.1 to 1.4, p=0.16). There were no treatment-related deaths.

Comparison 2: Olanzapine vs Benzodiazepines

None of the included studies compared olanzapine to benzodiazepines

Comparison 3: Olanzapine vs Placebo (NICE review)

Efficacy

Critical outcomes: The NICE review did not report on the following outcomes:

- change in agitation score
- use of physical restraint, hospital/ICU length of stay
- hospital discharge disposition and
- health related quality of life.

Less critical outcomes:

1. **Duration of delirium (days):** We are uncertain of the effect of olanzapine compared to placebo on duration of delirium MD=-2.4, 95% CI -3.51,-1.29, n = 103, 1 trial. (Low certainty evidence due to very poor study quality and imprecision)

2. Change in delirium severity: There is probably a reduction in the delirium rating scale (DRS) in favour of olanzapine compared to placebo MD = -11.1, 95% CI -15.51 to -7.69, n=103, 1 trial. (Moderate certainty evidence due to poor study quality and imprecision)

3. **Delirium resolution** (defined as reduction of delirium rating scale below a target set by the authors or complete resolution of symptoms): Outcome "Complete Response" reported that there is probably a more rapid resolution of delirium symptoms in favour of the olanzapine compared to placebo, RR=3.68, 95% CI 1.63 to 8.33, n=103, 1 trial. (Moderate certainty evidence due to poor study quality, indirectness and imprecision)

Safety

For this comparison, the NICE review did not report on extrapyramidal side-effects, if anticholinergic medication was required, drug-related adverse events or mortality.

Conclusion

We identified two reviews and three trials addressing the outcomes of interest, comparing olanzapine to haloperidol. In patients with delirium, there is probably little or no difference in olanzapine compared to haloperidol in the outcomes of interest. We are uncertain about the difference in occurrence of extrapyramidal side-effects and other adverse events in olanzapine compared to haloperidol.

We identified one review addressing the outcomes of interest, comparing olanzapine to placebo. In patients with delirium, we are uncertain of the effect of olanzapine compared to placebo in duration of delirium. There is probably a reduction in the delirium rating scale and a more rapid resolution of delirium symptoms in favour of olanzapine compared to placebo. There were no data on any safety outcomes.

Due to small study sizes and methodological limitations in the studies, the evidence was generally of low to very low certainty. This indicates a research gap. Larger rigorous RCTs are needed.

Table 2: Characteristics of Included Systematic Reviews: Delirium

CITATION	STUDY DESIGN	POPULATION (N)	INTERVENTION *vs* COMPARATOR	OUTCOMES & MAIN FINDINGS	COMMENTS
Comparison 1: Haloperidol compared to Olanzapine					
Finucane AM, Jones L, Leurent B, Samson EL, Stone P, Tookman A, et al. Drug therapy for delirium **in terminally ill adults**. Cochrane Database Sys. Rev. 2020;1. Doi: 10.1002/14651858.CD004770.pub3	Systematic review	Terminally ill adults (18 years or older) with delirium symptoms Included studies: RCTs	Haloperidol compared to Olanzapine	Delirium symptoms within 24 hours n= 28, one trial mean difference (MD) 2.36 (95% CI -0.75 to 5.47, p=0.14) Delirium symptoms between 24 and 48 hours n=24, one trial MD 1.9 (95% CI -1.5 to 5.3, p=0.27) **Very low certainty** (both outcomes), downgraded by 3 levels due to so few data that the results were highly susceptible to chance	AMSTAR – Moderate quality • Study design not explained • No meta-analysis
NICE Review (within CPG) National Institute for Health and Care Excellence (NICE). **Delirium: diagnosis, prevention and management** [Internet]. [London]: NICE; 2010 [updated July 2020]. (Clinical guideline 103 [CG103]). Available from: https://www.nice.org.uk/Guidance/CG103	Systematic review	Adult patients (18 years or older) in a hospital setting (surgical, medical, ICU, or emergency departments) or in long-term residential care with delirium. Included studies: RCTs and quasi randomized trials. Non-randomised studies (NRS) were included only if no other evidence, with preference to large cohort studies and comparative non-randomised designs. Exclusion criteria: Younger than 18 years Receiving end-of-life care Intoxication and or acute withdrawal from drugs or alcohol, with associated delirium	Haloperidol compared to olanzapine	Complete response (resolution) n=219, 2 trials RR=0.99 (95% CI 0.8 to 1.21, p=0.24, I^2=27%) **Low certainty** downgraded due to poor study quality (not blinded, inadequate sequence generation and allocation concealment, funding and outcome possibly inadequate) and imprecision. Duration of delirium n=146, 1 trial MD=0.62 (95% CI 0.06 to 1.18) **Very low certainty**, downgraded for very poor study quality, imprecision and reported as “time to take effect” in responders only, likely to be biased Severity of Delirium n=146, 1 trial MD=0.7 (95% CI 0.45 to 1.85) **Moderate certainty,** downgraded due to poor study quality (not blinded) and imprecision (number of patients < 400)	AMSTAR – High quality • Data extraction not in duplicate

				Adverse events n=73, 1 included trial RR=8.2 (95% CI 0.48 to 140.09) **Very low certainty**, downgraded due to very poor study quality (quasi-randomised, not blinded) and imprecision(wide confidence interval)	
Comparison 2: Olanzapine vs placebo					
NICE Review (within CPG) National Institute for Health and Care Excellence (NICE). **Delirium: diagnosis, prevention and management** [Internet]. [London]: NICE; 2010 [updated July 2020]. (Clinical guideline 103 [CG103]). Available from: https://www.nice.org.uk/Guidance/CG103	Systematic review	Adult patients (18 years or older) in a hospital setting (surgical, medical, ICU, or emergency departments) or in long-term residential care with delirium. Included studies: RCTs and quasi randomized trials. Non-randomised studies (NRS) were included only if no other evidence, with preference to large cohort studies and comparative non-randomised designs. Exclusion criteria: Younger than 18 years Receiving end-of-life care Intoxication and or acute withdrawal from drugs or alcohol, with associated delirium	Olanzapine compared to placebo	Complete response n=103, 1 included trial RR=3.68 (95% CI 1.63 to 8.33) **Moderate certainty** due to poor study quality (not blinded) indirectness (indirect outcome through delirium assessment method) and imprecision (number of events < 300). Duration of delirium n=103, 1 included trial MD=-2.4 (95% CI 3.51 to -1.29) **Very low certainty** due to poor study quality (evidence of confounding and not blinded) and imprecision (wide confidence interval). Severity of Delirium n=103, 1 included trial MD=-11.1 (95% CI 14.51 to -7.69) **Moderate certainty** due to poor study quality (not blinded) and imprecision (number of patients < 400).	AMSTAR – High quality • Data extraction not in duplicate

Table 3: Characteristics of Included Randomised Controlled Trials: Delirium

CITATION	STUDY DESIGN	POPULATION (N)	INTERVENTION *vs* COMPARATOR	OUTCOMES & MAIN FINDINGS	RISK OF BIAS
Comparison 1: Haloperidol versus Olanzapine					
Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a **critical care setting**. Intensive Care Med. 2004;30:444-9. Doi: 10.1007/s00134-003-2117-0	Design Prospective quasi-randomized trial. Single blinding (treating nurses and physician not blinded to assigned drug) Duration July 2000 to September 2001. Funding Peer-reviewed grant from the Zyprexa fund, Eli-Lilly, North America Ethics Protocol approved by the institutional scientific and ethics committee	Adults aged 18 to 75 years admitted to medical-surgical ICT in Montreal. All patients with delirium (as defined below) were considered eligible for the study. Sample size 73 included in final analysis (Haloperidol n=45, Olanzapine n=28) 103 considered eligible, 80 informed consent obtained, 3 withdrawn, 2 status changed to "no active treatment", 1 suspected drug interaction, 1 data lost Inclusion criteria Admitted for more than 24 hours, participants screened 3 times daily for delirium with the ICU Delirium Screening Checklist (ICU-DSC). In participants with a score >= 4 or with clinical manifestations of delirium, diagnosis confirmed by physician using DSM-IV criteria. Exclusion criteria Pregnant patients who received antipsychotic medication within 10 days prior to admission; Pregnant patients with contraindications to haloperidol or olanzapine; Gastrointestinal dysfunction that did not allow oral or enteral drug administration; Neurological status did not allow neuropsychiatric examination e.g. coma Other caveats Patients who developed agitation were allowed intravenous haloperidol ("rescue haloperidol")	Intervention Enteral olanzapine 5mg daily (>60yrs: 2.5mg daily) Comparator Enteral haloperidol 2.5 to 5mg every 8 hours (>60yrs: 0.5 to 1 mg 8 hourly) Subsequent titration based on clinical judgement. Benzodiazepine use noted as adjuvant therapy.	Outcomes 1. Change in mean daily delirium scores (delirium index (DI) scores) 2. Adjunct benzodiazepine use requirements over time 3. Use of rescue haloperidol, opiates, sedatives, Ramsay scores, vital signs and liver function tests in both groups. 4. Presence of extrapyramidal side effects (EPS) Results 1. Comparable reduction in DI score over time was noted in both groups, with no difference (ANOVA time effect p=0.02, group effect p=0.83 interaction effect p=0.64) 2. Benzodiazepines: Analysis of variance did not identify any difference between the two groups, at any of the 5 measurement times (interaction effect p=0.94 group effect p=0.9). 3. " The dose of rescue haloperidol, opiates, sedatives other than benzodiazepines, Ramsay scores, vital signs, and liver function tests were no different between groups." 4. Haloperidol: 6 rated low scores on extrapyramidal symptom testing (1 for the Ross Chouinard, 1–4 for the Simpson-Angus scale). Olanzapine: no extrapyramidal manifestations or adverse effects	**HIGH RISK OF BIAS** All outcomes: **High risk of bias** in domain 1 due to quasi-randomisation of allocation sequence and baseline differences between allocation groups, **some concerns** in domain 2 due to no information around participant blinding and effects of assignment, and **some concerns** in domain 5 due to no information around a prespecified plan or protocol. **Low risk of bias** in domains 3 and 4.

Jain R, Arun P, Sidana A, Sachdev A. Comparison of efficacy of haloperidol and olanzapine in the treatment of delirium. Indian J Psychiatry. 2017;59(4):451-6. Doi: 10.4103/psychiatry.IndianJ Psychiatry_59_17	Design Open label, randomized controlled study. Randomisation through computer-generated random number table Duration December 2011 to December 2012. Patients assessed every 24 hours until delirium resolution. Trial registry Registered with the Clinical Trial Registry-India CTRI/2016/10/007331 Ethics Approved by local institutional ethics committee Funding None Other Assessment of delirium through Confusion Assessment Method (CAM), and diagnosis using DSM-IV criteria. Delirium severity assessed with Memorial Delirium Assessment Scale (MDAS). Simpson-Angus Scale (SAS) used to assess EPS	Delirious patients admitted to medicine emergency ward and referred to the Department of Psychiatry for consultation at the Government Medical College and Hospital, Chandigarh, India. Sample Size 100 132 enrolled; 32 dropped out after randomization and were not included in the final analysis; Olanzapine n=47 Haloperidol n=53 Inclusion criteria Delirious patient plus >18 years old; Verbally responsive; No dementia Exclusion criteria Mechanically ventilated; Mute; Currently on antipsychotics for any reason; Experiencing alcohol or benzodiazepine withdrawal delirium; Hypersensitivity to either olanzapine or haloperidol in the past.	Intervention Olanzapine, enteral only, 2.5 to 10mg daily orally or via nasogastric tube (NGT) Comparator Haloperidol, enteral only, 1 to 4mg orally or via NGT tube Doses based on MDAS scores of mild, moderate or severe delirium.	Outcomes 1. Efficacy of olanzapine and haloperidol in delirium 2. Tolerability of olanzapine and haloperidol in delirium 3. Phrenology of delirium and pattern of symptom improvement with treatment Results • Delirium severity – mean MDAS score (baseline) 18.49 olanzapine group, 17.79 haloperidol group (groups comparable at baseline, p=0.791). mean MDAS score (end study period) 8.43 olanzapine group, 8.00 haloperidol group; 54.7% reduction in mean MDAS scores (54.4% in olanzapine group and 55% in haloperidol group • Pattern of symptom improvement ○ Severity of attention on day 2 and severity of disorganized thinking on days 2 and 3 were less in the olanzapine group (p<0.05). ○ Severity of perceptual disturbances on day 4, and severity of psychomotor disturbances on days 3 and 4 were less in the haloperidol group (p<0.05). • Duration of treatment– mean duration of treatment (days) 3.57 olanzapine (+- 0.92 days), 3.37 haloperidol (+- 0.71 days), (p=0.233) • Drug-related adverse effects – 2 in olanzapine group (1 with excessive sedation, 1 with akathisia), 3 in haloperidol group (drug-induced parkinsonism). All side effects were mild in severity.	**HIGH RISK OF BIAS** All outcomes: **Some concerns** in domain 1 due to this being a single-blind study, **some concerns** in domain 2 due to single-blind study and limited information on statistical methods, **high risk of bias** in domain 3 due to no information around data available for all participants and missingness, **high risk of bias** in domain 4 due to potential bias from researchers not being blinded, and **some concerns** domain 5 due to no information around a pre-specified analysis plan.
Van der Vorst MJDL, Neefjes ECW, Boddaert MSA, Verdegaal BATT, Beeker A, Teunissen SCC, et al. Olanzapine versus haloperidol for treatment of delirium in patients with advanced cancer: a phase III randomized clinical trial. Oncologist.	Design Multicentre, randomized controlled, phase III trial. Conducted at five sites in the Netherlands. Study terminated early as unlikely to reach the predefined efficacy criteria. Trial registry	Patients ≥ 18 years old with advanced cancer, admitted to a medical oncology ward or high-care hospice facility Sample size 100 50 allocated to each group	Intervention Olanzapine, po or IMI Comparator Haloperidol, po or sc	Outcomes: *Primary endpoint:* Delirium Response Rate (DRR) on days 1 to 7 after randomization as defined by DRS-R-98 assessment *Secondary endpoints:* TRR (time from randomization to resolution of delirium in days) TRAEs (treatment related adverse events), according to the CTCAE version 4.03	**SOME CONCERNS** All outcomes: **Some concerns** in domain 5 due to no information around pre-specified plan or protocol. **Low risk of bias** in domains 1 to 4.

2020; 25:e570-7. Doi: https://doi.org/10.1634/theoncologist.2019-0470	NCT01539733 Duration January 2011 to July 2016 Funding Netherlands Organization for Health Research and Development (ZonMw) Palliative Care Program (No. 11510011). Ethics Written informed consent	Olanzapine – 9 discontinued treatment. Analysis – Intention-to-treat (ITT) n=49, per protocol n = 40 Haloperidol – 8 discontinued treatment. Analysis – ITT n = 49, per protocol n = 41 Inclusion criteria 18 years or older; Advanced cancer; Admitted to medical oncology ward or high-care hospice facility; Fluent in the Dutch language; Diagnosed with delirium. Exclusion criteria Diagnoses of glaucoma, Parkinson's disease, dementia or psychiatric disorders interfering with delirium assessment; history of neuroleptic malignant syndrome or convulsions; delirium due to substance withdrawal cardiac conduction abnormalities; Currently using other neuroleptic medication or lithium.		Delirium-related distress for patients and their caregivers assessed by DEQ Results DRR: Olanzapine 45% (95% CI 31 to 59) Haloperidol 57% (95% CI 43 to 71) (ΔDRR −12%, odds ratio [OR] 0.61, 95% CI 0.2–1.4 p = 0.23) (ITT) TRR: Olanzapine 4.5 days (95% CI 3.2 to 5.9) Haloperidol 2.8 days (95% CI 1.9 to 3.7) (p = 0.18) DRR for motor subtypes (ITT) Hyperactive OR 0.5, 95% CI 0.1 to 2.1, p=0.50 Hypoactive OR 0.2, 95% CI 0.04 to 1.5, p=0.12 Mixed OR 1.8, 95% CI 0.4 to 7.9, p=0.49 Safety TRAEs of any grade Olanzapine arm: 13 patients (26.5%) Haloperidol arm: 16 patients (32.7%) Grade ≥3 TRAEs Olanzapine arm: 5 patients (10.2%) Haloperidol arm: 10 patients (20.4%) (OR 0.4, 95% CI 0.1 to 1.4, p=0.16) No treatment related deaths Delirium-Related Distress Sixteen patients completed this DEQ in each treatment arm. Mean delirium-related distress level (0 – 4 numerical rating scale) Olanzapine 2.1 (SD 1.4) Haloperidol 2.3 (SD 1.4) Mean delirium-related distress level (spouse/caregiver) Olanzapine 3.0 (SD 1.2) Haloperidol 2.7 (SD 1.1) Mean delirium-related distress level (nurses) Olanzapine 1.1 (SD 1.1) Haloperidol 0.9 (SD 0.9)	

Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☒ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	For important outcomes there were limitations in the data: small study sizes, methodological limitations in the studies, the evidence was generally of low to very low certainty. No data on critical outcomes.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☒ None ☐	Olanzapine vs haloperidol: no difference (none) Olanzapine vs placebo: probably better efficacy (small and low levels of certainty) Olanzapine vs benzodiazepines: no data
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☒ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	For important outcomes there were limitations in the data: small study sizes, methodological limitations in the studies, the evidence was generally of low to very low certainty. No data on critical outcomes
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge ☐ Moderate ☐ Small ☒ None ☐	Olanzapine vs haloperidol: no difference (none) Olanzapine vs placebo: probably better efficacy (small) Olanzapine vs benzodiazepines: no data
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☐ Favours control ☐ Intervention = Control ~~*or* Uncertain~~ ☒	Olanzapine vs haloperidol: no difference (intervention = control) Olanzapine vs placebo: probably better efficacy (favours intervention) – but very low level of certainty of evidence Olanzapine vs benzodiazepines: no data
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: N/A	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☒ No ☐ Uncertain ☐	Olanzapine is not specifically registered for delirium; however, olanzapine oral is available in the public sector for other indications (bipolar disorder, schizophrenia). All formulations are available on the South African market. The loss of IM haloperidol is disruptive in the change of clinical practice.
RESOURCE USE	**How large are the resource requirements?** More intensive ☐ Less intensive ☐ Uncertain ☐	**Price of medicines:** **Medicine** | **Tender price (ZAR)*** | **100% OF SEP (ZAR)**** | **60% OF SEP (ZAR)** Haloperidol 5mg tablets, 500 | 23.23 | n/a | n/a

Haloperidol 5mg/5ml injection, single (discontinued)	n/a	45.68***	n/a
Olanzapine 10 mg injection	n/a	72.84	43.71
Olanzapine 5mg orodipersible (ODT, 30	n/a	267.41	160.45
Olanzapine 2.5mg tablet (SOT), 28	13.80	n/a	n/a

* Contract circular HP09-2021SD, August 2022
**SEP database, July 2022
***SEP database, February 2021 (Haloperidol injection discontinued)

Background:

- *Adult Hospital Level STG and EML, 2019 edition*

Recommends haloperidol IM injection, but this has been discontinued from the South African market.

- *NICE Guideline 2010 (updated in March 2019)*

Recommendations for olanzapine include:

- IM injection: 2.5–10 mg per day, depending on response; the effect was observed for one week; delirium had 3 occurred from 30 min to 17 days (Hu 2006)
- Orally or by enteral tube: given within 2 h of the diagnosis of delirium, initially 5 mg per day (patients over 60 years 2.5 mg) then titrated based on clinical judgement for up to 5 days (Skrobik 2004)
- Orally/ sublingually: initial dose 1.25–2.5 mg then adjusted, depending on response, to 1.25–20 mg per day; the effect was observed for one week; delirium had occurred from 30 min to 17 days (Hu 2006)

- *NEMLC report (Adult Hospital 2019 review of palliative care chapter)*

Haloperidol, oral: added
Haloperidol, SC/IV: added
Lorazepam, oral: added
Midazolam, SC/IV: added
Antipsychotic (haloperidol), oral/IV/SC: Low doses are generally recommended as 1strst line in guidelines, due to associated side-effects. However, a RCT (Agar,2017) showed that oral haloperidol and risperidone was less effective in reducing delirium symptoms than placebo and shortened overall survival. Limitations included the oral route of administration (possibly contributing to increased extrapyramidal side effects); increased administration of midazolam to the antipsychotic groups (possibly increasing paradoxical agitation and variable baseline demographics and precipitants of delirium were not reported in all groups. Cochrane review concluded that there is insufficient evidence to determine the role of medicine treatment for delirium in terminally ill patients; thus recommendations aligned with expert consensus.
***Recommendation:** Low dose haloperidol as 1st line treatment for delirium in palliative care at secondary level of care.*
Rationale: Aligned with guidelines.
Level of Evidence: III Guidelines

- *Pharmacokinetic study by Markowitz et al, 2006*

Both routes of ODT administration (above the tongue and sublingually) resulted in more measurable early concentrations relative to SOT. However, there were no statistically significant differences observed between any of the olanzapine exposures for observed pharmacokinetic parameters (C(max), T(max), AUC(0-8h)).

- *Medicines.org.uk: Olanzapine 5mg ODT tablets - Summary of Product Characteristics (SmPC)*

Olanzapine ODT should be placed in the mouth, where it will rapidly disperse in saliva, so it can be easily swallowed. Removal of the intact ODT from the mouth is difficult. Since the ODT is fragile, it should be taken immediately on opening the blister. Alternatively, it may be dispersed in a full glass of water or other suitable beverage (orange juice, apple juice or milk) immediately before administration. Olanzapine ODT is bioequivalent to olanzapine film-coated tablets, with a similar rate and extent of absorption. It has the same dosage and frequency of administration as olanzapine film-coated tablets. Olanzapine ODT may be used as an alternative to olanzapine film-coated tablets.

- *Pharmacokinetic parameters:*

On review of the pharmacokinetic properties of olanzapine ODT and SOT formulations, bioequivalence can be assumed.

	Tmax	T1/2	
Haloperidol, IM	10 minutes	13 to 35 hrs	*SAMF, 2022*
Olanzapine ODT	4 to 6 hrs	33 hrs	*Markowitz, 2006*
Olanzapine SOT	5 to 8 hrs	33 hrs	*Callaghan JT, 1999*
Olanzapine, IM	14 to 45 minutes	33 hrs	*FDA PI (drugs.com)*

Comparative cost analysis per treatment course *(comparing direct medicine prices):*

- **Haloperidol 0.5-1mg inj,** immediately 30 minutes later and 4-hourly to a max of 10mg per 24 hours *(Using the max dose of 2 x 5 mg inj per day for 3 days = 6 x 10 mg inj):* **R274.08** (Historic SEP price accessed through State S21)

- **Olanzapine 2.5-5mg inj**, immediately 30-60 minutes later and 4-hourly to a max of 20mg per 24 hours *(Using the max dose of 2 x 10 mg inj per day for 3 days = 6 x 10 mg inj):* **R437.06** (100% SEP) and **R262.24** (60% SEP).

- **Olanzapine 2.5-5mg SOT via NGT,** immediately 30-60 minutes later and 4-houlry to a max of 20mg per 24 hours *(Using the max dose of 8 x 2,5 mg tablets per day for 3 days = 24 x 2.5 mg tablets):* **R11.83** (Contract price)

- **Olanzapine 2.5-5mg ODT**, immediately 30-60 minutes later and 4-hourly to a max of 20mg per 24 hours *(Using the max dose of 4 x 5mg ODTs per day for 3 days = 12 x 5 mg ODT):* **R106.96** (100% SEP) and **R64.18** (60% of SEP)

NB: It is concerning to note that haloperidol injection had only been added to the NICE guidelines in 2019, as haloperidol was registered with the MHRA for delirium. Global vs local availability of medicines warrants investigation.

Other resources: n/a

VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [X]	There is no information available about the acceptability of olanzapine to stakeholders. However, given the absence of other options in the management of delirium, it could be a viable and acceptable alternative.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [X]	There is no available local survey data – based on expert opinion.

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	18 August 2022	LR, SM, TK, NG, MM, TL	Olanzapine (all formulations) suggested as an option to haloperidol to manage delirium where non-pharmacological management is not sufficient (conditional recommendation, low to very low certainty evidence).
V1.0	28 Mar 2024	LR	Updated to reflect erratic supplies of haloperidol IM

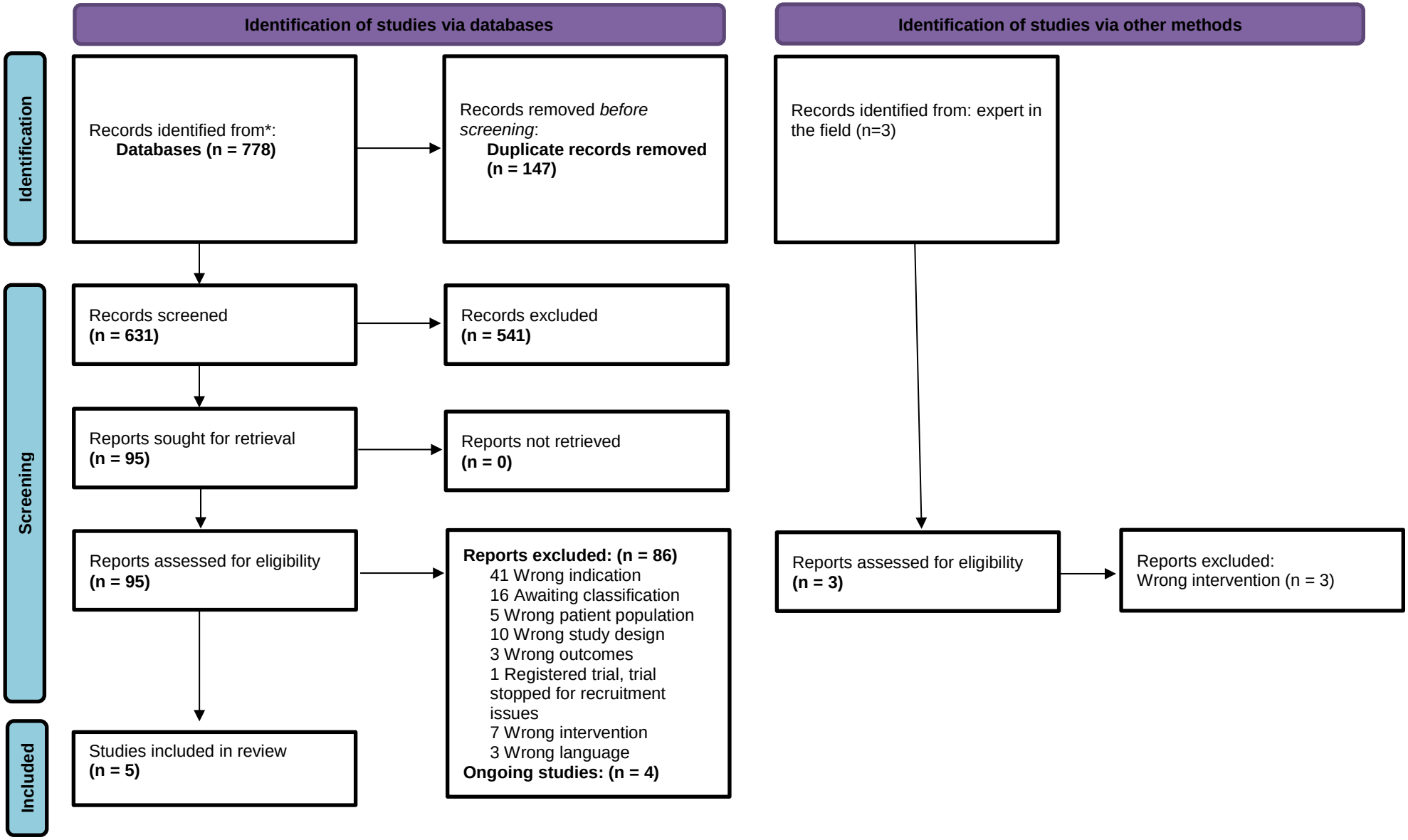
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Appendix 1: Search Strategy

#9	#1 AND #2 AND #8
#8	#3 OR #4 OR #5 OR #6 OR #7
#7	schizophrenia[mh] OR schizophreni*[tiab]
#6	dementia[mh] OR dementia*[tiab]
#5	confusion[mh] OR confus*[tiab] OR disorientat*[tiab] OR bewilderment[tiab] OR delirium*[tiab]
#4	paranoid disorders[mh] OR paranoi*[tiab]
#3	psychotic disorders[mh] OR psychosis[tiab] OR psychotic[tiab] OR psychoses[tiab] OR psychiatric disorder*[tiab] OR mental disorders[mh] OR mental illness*[tiab] OR mental disorder*[tiab] OR mood disorders [mh] OR mood disorder*[tiab] OR affective disorder*[tiab] OR bipolar disorder[mh] OR bipolar[tiab] OR mania*[tiab] OR manic[tiab]
#2	Search: aggression[mh] OR aggress*[tiab] OR disruptive behavior*[tiab] OR disruptive behaviour*[tiab] OR agitat*[tiab] OR violent behavior*[tiab] OR violent behaviour*[tiab]
#1	Search: olanzapine[mh] OR olanzapine*[tiab] OR zyprexa*[tiab] OR zolafren*[tiab] OR LY 170053[tiab] OR LY170053[tiab] OR LY 170052[tiab]

Appendix 2: PRISMA Flow Chart



Modified From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Appendix 3: AGREE II Appraisal Summary

Guideline	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	OA
NICE: DELIRIUM: diagnosis, prevention and management	94%	81%	88%	100%	67%	63%	83%
SIGN 157: Risk reduction and management of delirium	94%	97%	65%	81%	73%	58%	67%
Management of delirium in older people	100%	89%	72%	89%	50%	79%	83%

Domain 1: Scope and purpose
Domain 2: Stakeholder involvement
Domain 3: Rigour of development
Domain 4: Clarity of presentation
Domain 5: Applicability
Domain 6: Editorial independence
OA: overall assessment

Appendix 4: Table of excluded studies, with reasons

Author, date	Type of study	Reason for exclusion
1. Bak, 2019	SR*	Wrong indication
2. Belgamwar, 2005	SR	Wrong indication
3. Burry, 2018	SR	Wrong intervention
4. Burry, 2019	SR	Wrong intervention
5. Dundar, 2016	SR	Wrong indication
6. Fernández Sánchez, 2009	SR	Wrong indication
7. Huf, 2009	SR	Wrong language
8. Huf, 2016	SR	Wrong indication
9. Lacasse, 2016	SR	Wrong intervention
10. Maglione, 2011	SR	Wrong indication
11. Mühlbauer, 2021	SR	Wrong patient population
12. Nikooie, 2019	SR	Wrong intervention
13. Paris, 2021	SR	Wrong indication
14. Pelland, 2009	SR	Wrong language
15. Seida, 2012	SR	Wrong patient population
16. Shoptaw, 2009	SR	Wrong indication
17. Tulloch, 2004	SR	Wrong indication
18. Williamson, 2019	SR	Wrong indication
19. Yildiz, 2003	SR	Wrong language
20. Yildiz, Sachs 2003	SR	Wrong study design
21. Yunusa, 2019	SR	Wrong indication
22. Zaman, 2017	SR	Wrong indication
23. Baldaçara, 2011	RCT#	Wrong indication
24. Battaglia, 2003	RCT	Wrong indication
25. Battaglia, 2005	RCT	Wrong outcomes
26. Beasley, 1996	RCT	Wrong indication
27. Belgamwar, 2005	RCT	Wrong indication
28. Bozzatello, 2017	RCT	Wrong patient population
29. Breier, 2000	RCT	Awaiting classification
30. Breier, 2001	RCT	Awaiting classification
31. Breier, 2002	RCT	Wrong indication
32. Chan, 2014	RCT	Wrong indication
33. Clark, 2001	RCT	Wrong indication
34. David, 2001	RCT	Awaiting classification
35. Eli, 2005	RCT	Awaiting classification
36. Faay, 2020	RCT	Wrong indication
37. Fontaine, 2003	RCT	Wrong patient population
38. Gareri, 2004	RCT	Wrong indication
39. Hsu, 2010	RCT	Wrong indication
40. Huf, 2009	RCT	Wrong intervention
41. Huang, 2015	RCT	Wrong indication
42. Hwang, 2012	RCT	Awaiting classification
43. Jin, 2009	RCT	Awaiting classification
44. Katagiri, 2013	RCT	Wrong indication
45. Kinon, 2000	RCT	Wrong indication
46. Kinon, 2001	RCT	Wrong outcomes
47. Kinon, 2004	RCT	Wrong indication
48. Kittipeerachon, 2016	RCT	Wrong intervention
49. Kong, 2009	RCT	Awaiting classification
50. Krakowski, 2014	RCT	Wrong indication
51. Lindbord, 2003	RCT	Wrong outcomes
52. Meehan, 2001	RCT	Awaiting classification
53. Meehan, 2001 (1)	RCT	Awaiting classification
54. Meehan, 2001 (2)	RCT	Awaiting classification

55. Meehan, 2001 (3)	RCT	Wrong indication
56. Meehan, 2002	RCT	Wrong indication
57. Mintzer, 2002	RCT	Awaiting classification
58. Ono, 2008	RCT	Awaiting classification
59. Raveendran, 2007	RCT	Wrong indication
60. Schneider, 2006	RCT	Wrong indication
61. Smith, 2003	RCT	Awaiting classification
62. Street, 2000	RCT	Wrong patient population
63. Svestka, 2002	RCT	Awaiting classification
64. Verhey, 2006	RCT	Wrong indication
65. Villari, 2009	RCT	Wrong intervention
66. Wright, 2001	RCT	Awaiting classification
67. Wright, 2003	RCT	Wrong indication
68. Hirsch, 2019	Narrative review	Wrong study design
69. Houston, 2019	Narrative review	Wrong study design
70. Wagstaff, 2005	Narrative review	Wrong study design
71. Pascual, 2007	Observational study	Wrong study design
72. Walther, 2014	Observational study	Wrong study design
73. ACTRN12610000033044	Ongoing trial	Wrong indication
74. NCT00316238	Ongoing trial	Wrong indication
75. NCT00485810	Ongoing trial	Wrong indication
76. NCT00485901	Ongoing trial	Wrong indication
77. NCT011234082	Ongoing trial	Wrong indication
78. NCT00649510	Ongoing trial	Wrong indication
79. NCT00797277	Ongoing trial	Wrong indication
80. NCT00833300, 2009	Registered trial	Registered trial, trial stopped for recruitment issues
81. NCT00970281	Ongoing trial	Wrong indication
82. Elsayem, 2010	Pilot study	Wrong study design
83. Citrome, 2007	Quantitative review	Wrong study design
84. Srivastava, 2010	Summary of review	Wrong study design
85. deAlmeida, 2017	Review of reviews	Wrong study design
86. Jones, 2001	Summary of RCTs	Wrong study design

*SR = systematic review, #RCT = randomized controlled trial

Appendix 5: Table of Ongoing Trials

Citation	Study Design	Population (n)	Treatment
Arak University of Medical Sciences. IRCT20141209020258N114, first registered 3 July 2019, recruiting.	RCT with parallel assignment	50	Patients randomised to haloperidol 2.5mg (max 40mg) intramuscular injection (IMI) every 6 hours or olanzapine 2.5 to 10mg (max 20mg) orally
Arak University of Medical Sciences. IRCT20200927048852N1, first registered 13 October, recruiting.	Phase III RCT with parallel assignment	90	Patients randomised to haloperidol 2.5mg per day for up to 10 days or olanzapine 2.5mg to 10mg per day for up to 10 days or quetiapine 12.5 to 75mg per day
HCA Hospice Care. NCT04750395, first registered 11 February 2021, ongoing	RCT with parallel assignment	80	Patients randomised to transmucosal haloperidol, two doses of 2.5mg every 24 hours with up to two breakthrough doses or transmucosal olanzapine, two doses of 5mg with up to two breakthrough doses
Tan Tock Seng Hospital. NCT04833023, first registered 6 April 2021.	RCT with parallel assignment	72	Patients randomised to haloperidol oral solution 1mg (max 6mg in 24 hours), 2 hourly until max reached with midazolam 2mg as rescue dose (2mg q2h prn) or olanzapine orodispersible tablet 2.5mg (max 15mg in 24 hours), 2 hourly until max reached with midazolam 2mg as rescue dose (2mg q2h prn)

South African National Essential Medicine List
Adult Hospital Level and PHC Medication Review Process
Component: Emergencies and injuries

MEDICINE REVIEW

Executive Summary

Date: May 2022
Medicine (INN): Morphine
Medicine (ATC): N02AA01
Indication (ICD10 code): J81 (The relief of moderate to severe pain in patients with acute pulmonary oedema).
Patient population: Adult patients with acute pulmonary oedema with distress, anxiety, or restlessness
Prevalence of condition: According to the Global Health Data Exchange (GHDx) registry, a search with the keyword "heart failure", the current worldwide prevalence of HF is 64.34 million cases (8.52 per 1,000 inhabitants), or 0.8%. The overall prevalence of clinically identified heart failure is estimated to be 3–20 cases/1000 population, but rises to > 100 cases/1000 population in those aged ⩾65 years. The PICO population ONLY includes those patients with distress, anxiety or restlessness - there is limited prevalence data for this cohort but it is estimated as a small proportion of the total APE cohort.[28]
The average incidence of hospitalized ADHF was 11.6 per 1,000 persons, aged ≥55 years, per year.[29,30,31] Considering only the population with anxiety, restlessness and distress, no prevalence of these symptoms cold be found in literature. As approximately 15% of patients with acute decompensated heart failure has morphine prescribed - one can assume that anxiety could be present in around 15% of acute decompensated heart failure. So, 15% of 0.8% is approximately 0.12%.
Level of Care: PHC, Adult Hospital Level
Prescriber Level: Clinician (Doctor)
Current standard of Care: SL or IV Nitrates; IV or PO Furosemide, IV Morphine
Efficacy estimates: (preferably NNT): 67 NNH (mortality)
Motivator/reviewer name(s): Michael McCaul, Clint Hendrikse, Gustav Thom, Idriss Kallon, Veranyuy Ngah, Rephaim Mpofu Trudy Leong.
PTC affiliation: Gustav Thom – KZN PTC

Key findings

- We conducted a rapid review of clinical evidence on whether intravenous/intra-osseus morphine should be used in the treatment of acute pulmonary distress
- We identified four systematic reviews of observational studies. The two most relevant, up-to-date, and highest quality reviews were used to inform recommendations for critical outcomes.
- Morphine may increase in-hospital and all-cause mortality (OR 1.78; 95% CI 1.01 to 3.13; 15 more per 1000, from 0 fewer to 40 more; n=151 735 participants) and may result in a large increase in need for invasive mechanical ventilation (OR 2.72; 95% CI 1.09 to 6.80; 45 more per 1000, from 2 more to 136 more; n=167 847 participants) compared to not using morphine.
- No available data could be sourced on whether morphine increases non-fatal adverse events, ICU or hospital length of stay.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		x			

Recommendation: The PHC/Adult Hospital Level Committee suggests not to use morphine for the treatment of acute pulmonary distress.
Rationale: Available evidence shows that morphine may increase in-hospital and all-cause mortality and may result in a large increase in invasive mechanical ventilation compared to not using morphine. No available data could be found on whether morphine increases non-fatal adverse events, ICU or hospital length of stay.
Level of Evidence: Low certainty of evidence
Review indicator: New high-quality evidence of a clinically relevant benefit

NEMLC RECCOMENDATION – 23 JUNE 2022:

NEMLC MEETING OF 23 JUNE 2022:

NEMLC accepted the proposal to amend the remove morphine the treatment of acute pulmonary distress. However, recommended that a caution be included in the STG, accordingly:

CAUTION

Do not use morphine for pulmonary oedema, as there is observational data providing a signal of harm.

Furthermore, once the respetive chapter is finalised, it was recommended that a circular be drafted and disseminated regarding the harms associated with use of morphine for distress in pulmonary oedema.

Monitoring and evaluation considerations

Research priorities

Authors: Idriss Kallon[1], Veranyuy Ngah[1], Clint Hendrikse[2, 5], Gustav Thom[3, 5], Michael McCaul[1,4, 5], Rephaim Mpofu[5,6], Trudy Leong [7,8]

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[4]SA GRADE Network
[5] PHC/Adult Hospital Level Committee (2019-2023)
[6] Department of Medicine, Division of Clinical Pharmacology, Groote Schuur Hospital, University of Cape Town
[7]Essential Drugs Programme, National Department of Health
[8] Secretariat to the PHC/Adult Hospital Level Committee (2019-2023); Secretariat to the National Essential Medicines List Committee (2021-)

Declarations of interest: IK, VN, GT, MM and TL have no interests pertaining to morphine.

Acknowledgments: Rephaim Mpofu (affiliated to University of Cape Town, Groote Schuur Hospital, Adult Hospital Level Committee, National Department of Health, South Africa and PHC/Adult Hospital Level Committee, 2019-2023) assisted with the costing analysis.

Background

Morphine has been prescribed for patients with acute decompensated heart failure, but there is little evidence for safety and efficacy when used for this indication. The suggested mechanism is that morphine may assist with anxiolysis and reduce preload (Ellingsrun, 2016). However, a mortality benefit has not been demonstrated, and recent evidence suggests increase in adverse events and 30-day mortality. Morphine is included in both the Adult and PHC EML/STG for the management of pulmonary oedema/acute decompensated heart failure, specifically for patients who are experiencing anxiety. In the Adult Hospital EML/STG it is recommended under Acute Pulmonary Oedema "if distressed. Consider adding Morphine". In the PHC EML/STG, it is recommended "if patient is very anxious or restless". The evidence to support this is unclear/lacking (expert opinion) and recent evidence of harm has emerged (Gao *et al*, 2021 and Lin *et al*, 2021).

Research Question

Should intravenous morphine be used in the treatment of acute pulmonary distress?

Methods

We conducted a rapid review of evidence for the use of intravenous morphine in patients with acute pulmonary oedema. We systematically searched Ovid MEDLINE, Embase and the Cochrane Database of Systematic Reviews on February 12, 2022 for Randomised Controlled Trials (RCTs) and Systematic Reviews (SRs) of RCtTs or observational studies. Additionally, we searched the Pan African Clinical Trial registry for any ongoing studies from 2021. The search strategy can be seen in Appendix 1. Screening of title and abstracts and full text screening, selection of studies and data extraction was conducted

independently and in duplicate by two reviewers (IK and VN). Title and abstract, including full text screening was done using the Covidence systematic review software. AMSTAR II was used to appraise all the systematic reviews included in the study by a single reviewer (VN), checked by a second reviewer (IK). GRADE was applied to determine the certainty of evidence and the GRADEPro software was used to generate evidence profiles. Relevant study data were extracted into a narrative table of results. MM, IK, VN and CH reviewed the overall report. Where multiple eligible SRs were included, we reported evidence from the most relevant, recent and high-quality review or reviews in order to provide evidence across all *a priori* outcomes.

Eligibility criteria for review

Population:	Adult 18 years and older patients with acute pulmonary oedema with distress, anxiety, or restlessness in-hospital or prehospital. **Exclusion**: post-op complications, non-cardiogenic, congested cardiac failure*
Intervention:	Standard of care without Morphine: Standard of care includes IV and Sublingual nitrates and IV and PO Furosemide)
Comparator:	Standard of care with intravenous/intra-osseus Morphine: Standard of care includes IV and Sublingual nitrates and IV and PO Furosemide
Outcomes:	Mortality, AEs, SAEs, ICU length of stay, Hospital length of stay
Studies:	RCTs and SRs

**This question is restricted to acute pulmonary oedema*

Results

The search produced 709 records where 683 reports were irrelevant. We included 25 reports for full text review, excluded 21, and included four systematic review reports for data extraction and synthesis. See the PRISMA (Appendix 2) for further details, which include reasons for exclusions. Also, refer to table of excluded studies with reasons (Table 2). Gao *et al*., (2021) and Zhang *et al* (2021) were assessed to be of moderate quality (according to AGREE II) of the four included systematic reviews and were considered most relevant and up-to-date. AMSTAR II assessment results in Appendix 4. Relevant pooled outcomes from Gao and Zhang were re-GRADED (see Appendix 5)

Description of included studies

We found no RCTs addressing this question. The four included studies were systematic reviews of observational studies, with three using meta-analyses to aggregate results. The effect estimates in the meta-analysis were adjusted. Standard of care was not stated in the reviews.

Gao *et al* (2021) investigated the risk of mortality associated with opioid use in acute heart failure. They included 6 observational retrospective studies, with 15 1735 participants in total. Treatment given to the control groups was not described. The authors report extracting adjusted measures of effect from primary studies for meta-analysis where reported, however do not report on which factors were adjusted for. Gil *et al* (2019) assessed morphine use in the treatment of acute cardiogenic pulmonary edema. They included seven studies (one randomized controlled trial, one non-randomized control trial and five observational studies), and 150639 participants. Lin *et al* (2021) studied intravenous morphine in heart failure and Zhang *et al* (2021) investigated the safety of morphine in patients with acute heart failure. Lin *et al* (2021) included five studies (three propensity-matched cohorts and two retrospective analysis (one unpublished) with 14 9967 participants. Zhang *et al* (2021) included seven retrospective case-control studies and 172 226 participants, including adjusted measures of effect similar to Gao (2011). The treatment given to control groups in included studies was not stated.

See Table 1 for detailed information on included studies.

Internal validity of the systematic reviews, GRADE and absolute effects

AMSTAR II was used to determine the internal validity of included SRs (Appendix 5). In an effort to reduce duplication of effort in synthesis, we used the most relevant (to the PICO), up-to-date and highest quality SRs, among those, we prioritized reviews using GRADE. If a selected review did not report on all relevant outcomes, the next best review with relevant outcomes reported was used. Where needed outcomes were re-GRADED accounting for differencing in contextual/clinical interpretation such as indirectness and imprecision. Gao et al., (2021) included one secondary analysis of a previously conducted RCT which was excluded from our list of included studies to avoid double counting.

Gao and Zang had the highest AMSTAR II scores overall (moderate quality review), however Goa was considered overall to be the most relevant, up-to-date and internally valid as they also used GRADE. Gao did not report their reasons for the selection of type of studies included in the review neither did they report on the funding sources of each study included in the review hence scored as moderate quality. The Lin and Gil reviews were of critically low quality.

Absolute effects were calculated from pooled effect data where possible. In the absence of baseline event data (control event rates for pooled effects), absolute effects were calculated using reported baseline events either (where available) from pooled baseline event data from included reviews across the same outcome or large risk observational studies for that outcome to determine baseline prevalence. This was done for mortality and SAEs.

Effect of interventions

Mortality (in-hospital mortality and 30-day mortality)

Morphine may increase in-hospital mortality (OR 1.78; 95% CI 1.01 to 3.13, low certainty of evidence, six observational studies, n=151 735 participants) resulting in 15 more per 1000, from 0 fewer to 40 more in hospital deaths (Evidence Profile in Appendix 5 and Figure 1). (Gao, 2021) Gao *et al* (2021) did not report any baseline event rates for standard of care or for the intervention arms, thus to calculate absolute effects we assumed a baseline control event rate of 2% for overall mortality based on Lin (2019).

Zhang *et al* (2021) found no association between morphine and in-hospital mortality (OR: 1.94; 95% CI 0.93 to 4.03; p = 0.08, Figure 2) however the direction of effect is still in line with Gao *et al* (2021).

Figure 1: Forest plot of the pooled analysis evaluating in-hospital and 30-day mortality according to opioid use. IV, inverse variance (Gao, 2021)

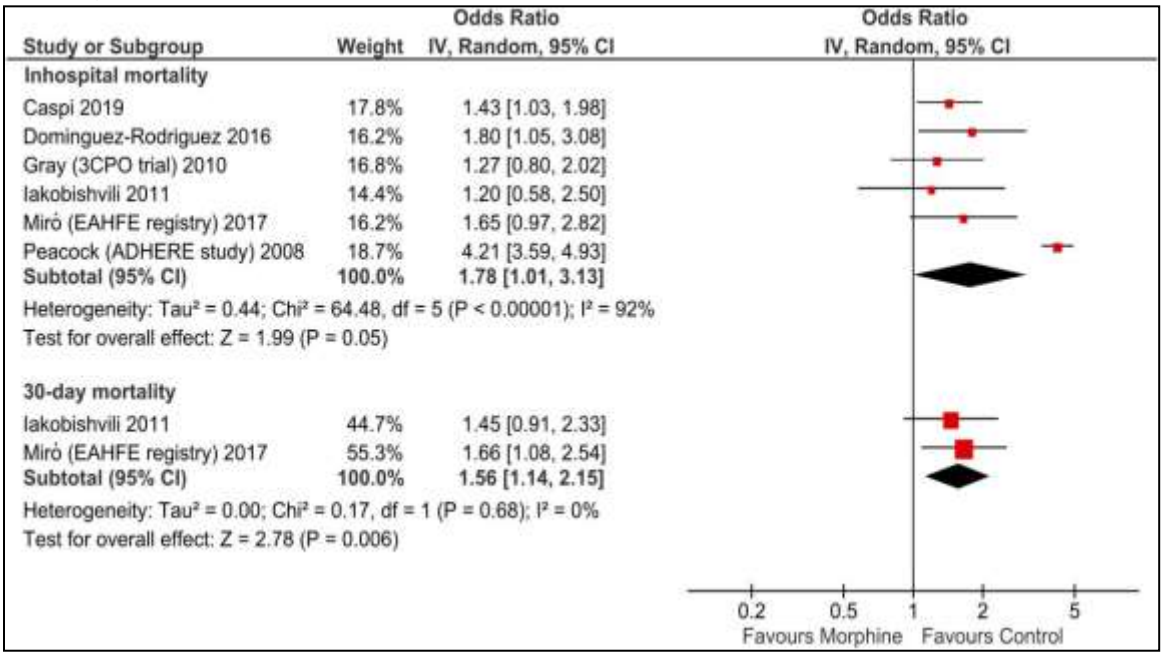


Figure 2: Forest plot of in-hospital mortality (Gao, 2021)

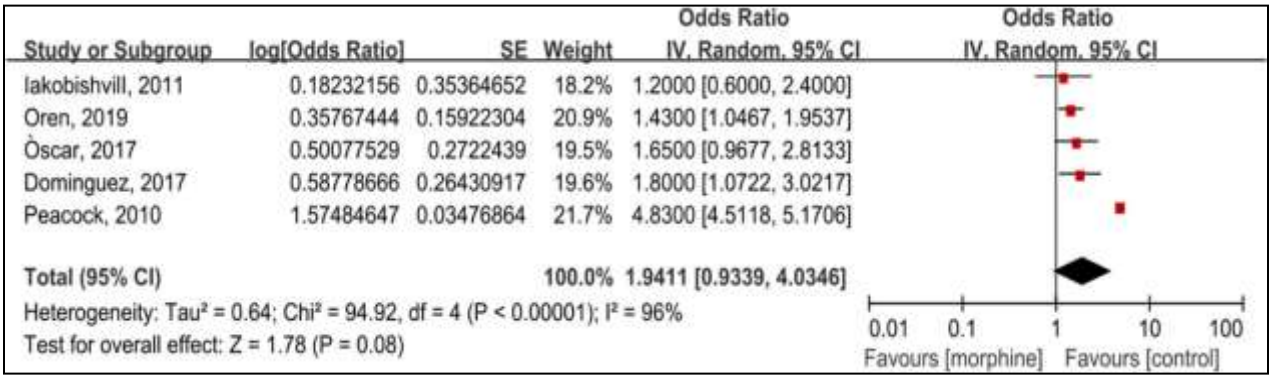
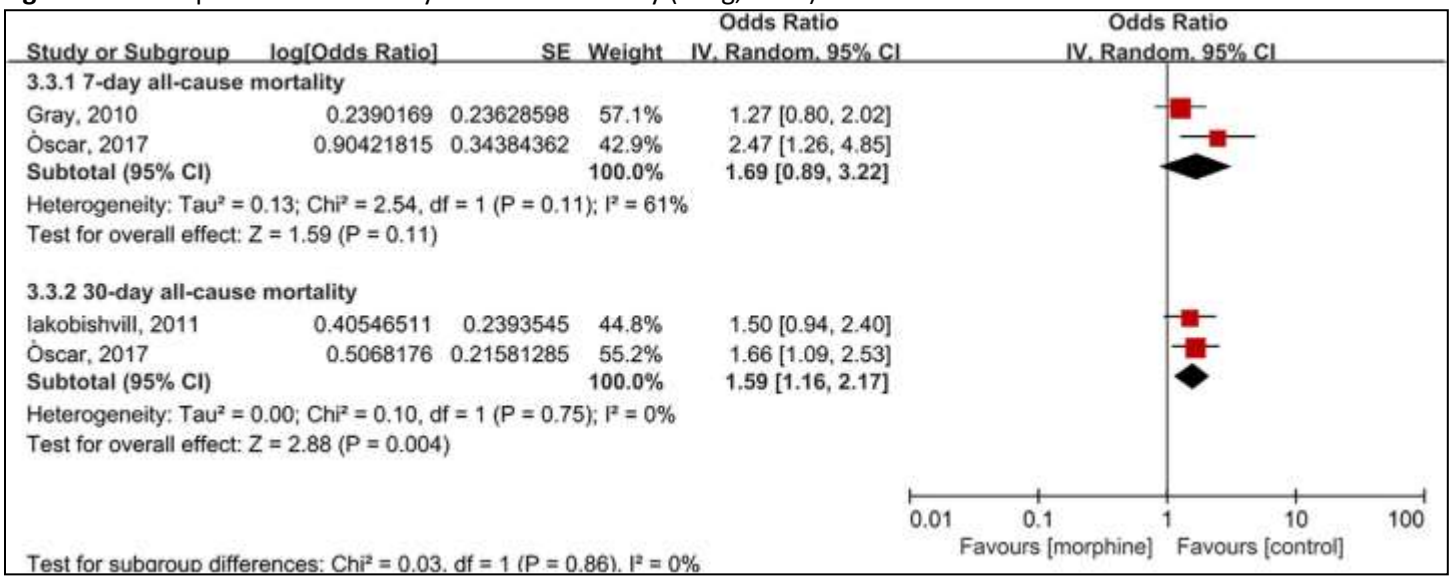


Figure 3: Forest plot of 7 and 30-day all-cause mortality (Zang, 2021)

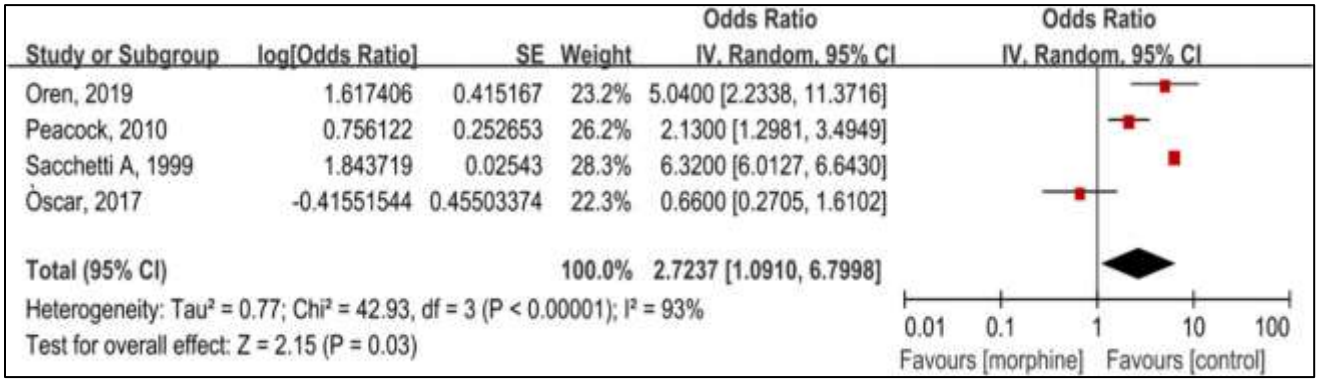


Zhang et al (2021) found that morphine treatment was associated with an increased significant 30-day all-cause mortality (OR 1.59; 95% CI 1.16 - 2.17) from three studies (n=9 904). Gao et al (2021) reported a similar association between morphine use and 30-day mortality (OR 1.56; CI 1.14 -2.15) from two studies (n=986) (Figure 3).

SAE (need for invasive mechanical ventilation)

Morphine may result in a large increase in invasive mechanical ventilation (OR 2.72; 95% CI 1.09-6.80, low certainty of evidence, four observational studies, n=167 847 participants) (Figure 4) (Zang, 2021). Baseline event rate not reported in review thus calculated from estimates of mechanical ventilation baseline event rate based on Gray (2008, NEJM).[27]

Figure 4: Forest plot of invasive mechanical ventilation



Adverse events
Not measured.

ICU or hospital length of stay
Not measured.

Conclusion

This evidence review of use of intravenous morphine in the treatment of acute pulmonary distress included four systematic reviews of observational studies. This review focuses on adjusted pooled evidence from two high-quality, relevant and up-to-date reviews pooling more than 150 000 participants, with direction and magnitude of effects consistent across other included systematic reviews. Based on the most recent, relevant, and highest quality reviews, morphine may increase in-hospital and all-cause mortality and may result in a large increase in invasive mechanical ventilation compared to not using morphine. We have no data on whether morphine increases non-fatal adverse events, ICU or hospital length of stay.

Evidence to Decision Framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty of evidence?** High [ ] Moderate [ ] Low [X] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Observational evidence (using ROBINS-1) downgraded by one level for risk of bias and by one level for inconsistency. Goa (2021) judged indirectness as serious (for unclear reasons), thus scoring very low certainty. The committee did not consider this evidence as indirect as evidence has clear alignment to PICO and is across various settings, including HIC and LIMCs.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [ ] Small [ ] None [x]	The review identified no beneficial anticipated effects.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large [ ] Moderate [x] Small [ ] None [ ]	• Morphine may increase in-hospital mortality (OR 1.78; 95% CI 1.01 to 3.13, low certainty of evidence, six observational studies, n=151 735 participants) resulting in 15 more per 1000, from 0 fewer to 40 more in hospital deaths (NNH 67) • Morphine may result in a large increase in invasive mechanical ventilation (OR 2.72; 95% CI 1.09-6.80, low certainty of evidence, four observational studies, n=167 847 participants) 45 more per 1,000 (from 2 more to 136 more) baseline event rate based on Gray (2008, NEJM)[27] • Absolute effects for mortality based on baseline event rates provided by Lin (assuming 2% mortality rate)
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention (No Morphine) [x] Favours control (Morphine) [ ] Intervention = Control *or* Uncertain [ ]	**Desirable effects** (of morphine): None **Undesirable effects** (of morphine): moderate
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: n/a Yes [ ] No [ ]	n/a
FEASABILITY	**Is implementation of this recommendation feasible?** Yes [x] No [ ] Uncertain [ ]	No evidence of feasibility was reviewed/sought. The Committee was of the opinion that not giving morphine is standard practice in most settings and clinicians would accept such a recommendation.

RESOURCE USE

How large are the resource requirements?

More intensive	Less intensive	Uncertain
	x	

The Committee was of the opinion that removing a medicine would result in cost savings, with less mechanical ventilation.

Price/treatment course of morphine, IV per patient *(direct medicine prices only)*

Medicine	Tender price (ZAR)*
Morphine 10mg/mL ampoule	4.03**
Sodium chloride 0.9% 10 ml	1.56**
Total	**5.59**

**Weighted average tender prices*

*** Contract circular HP06-2021SVP, June 2022*

Prevalence assumptions:

- According to the Global Health Data Exchange (GHDx) registry, the current worldwide prevalence of HF is approximately 0.8%.
- Meta-analysis by Platz et al (2015) showed that the prevalence of pulmonary oedema in heart failure and reduced ejection fraction (HF-REF) trials ranged from 75% to 83% (though the criteria defining HF varied across trials).
- Experts suggest that approximately 15% of HF-REF patients are administered morphine (as per the 2019 Adult Hospital and 2020 PHC STGs and EML recommendations).

Other assumptions:

- Adult population estimated to be >19 years of age (38189762); based on StatsSA mid-year population estimates of 2021.
- 85.04% of the population is uninsured (>19 years = 32476574)
- Most patients would use a maximum dose of morphine, IV (10 mg).
- Patients would only have one episode per year.

Estimated annual budget impact (medicine costs only):

1: Lower prevalence of HF-REF 75%:
Administered morphine: 0.09 % of 32 476 574 = 28 449
Estimated medicine cost per annum: R159 033

2. Upper prevalence of HF-REF of 83%:
Administered morphine: 0.1 % of 32 476 574 = 32 347
Estimated medicine cost per annum: R180 818

Therefore, disinvesting morphine IV for the treatment of anxiety in adult patients with pulmonary oedema would result in a saving of R159 000 to R180 000 per year.

References:

- Council for Medical Schemes Annual report, 2018/9. Available at: https://www.medicalschemes.com/files/Annual%20Reports/CMSAR2018_19.pdf
- StatsSA mid-year population estimates of 2021.
- Platz E, et al. Assessment and prevalence of pulmonary oedema in contemporary acute heart failure trials: a systematic review. Eur J Heart Fail. 2015 Sep;17(9):906-16.
- Contract circular HP06-2021SVP, June 2022

VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [x] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [x]	No evidence of values and acceptability was reviewed/sought. The Committee expects minor variability in how patients value critical outcomes such as death and avoiding serious adverse events. Acceptable to stakeholders in the hospital setting (district level). However, removing morphine from practice for pulmonary oedema may result in some resistance or lack of behavior change, especially in the prehospital setting.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [x] Uncertain [ ]	Removing morphine will likely result in increased equity across settings where morphine was not available or had unequal access.

Version	Date	Reviewer(s)	Recommendation and Rationale
1.0	13 April 2022	ID, VN, CH, GT, MM, TL	

References:

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Appendix 1: Search Strategy

Ovid MEDLINE

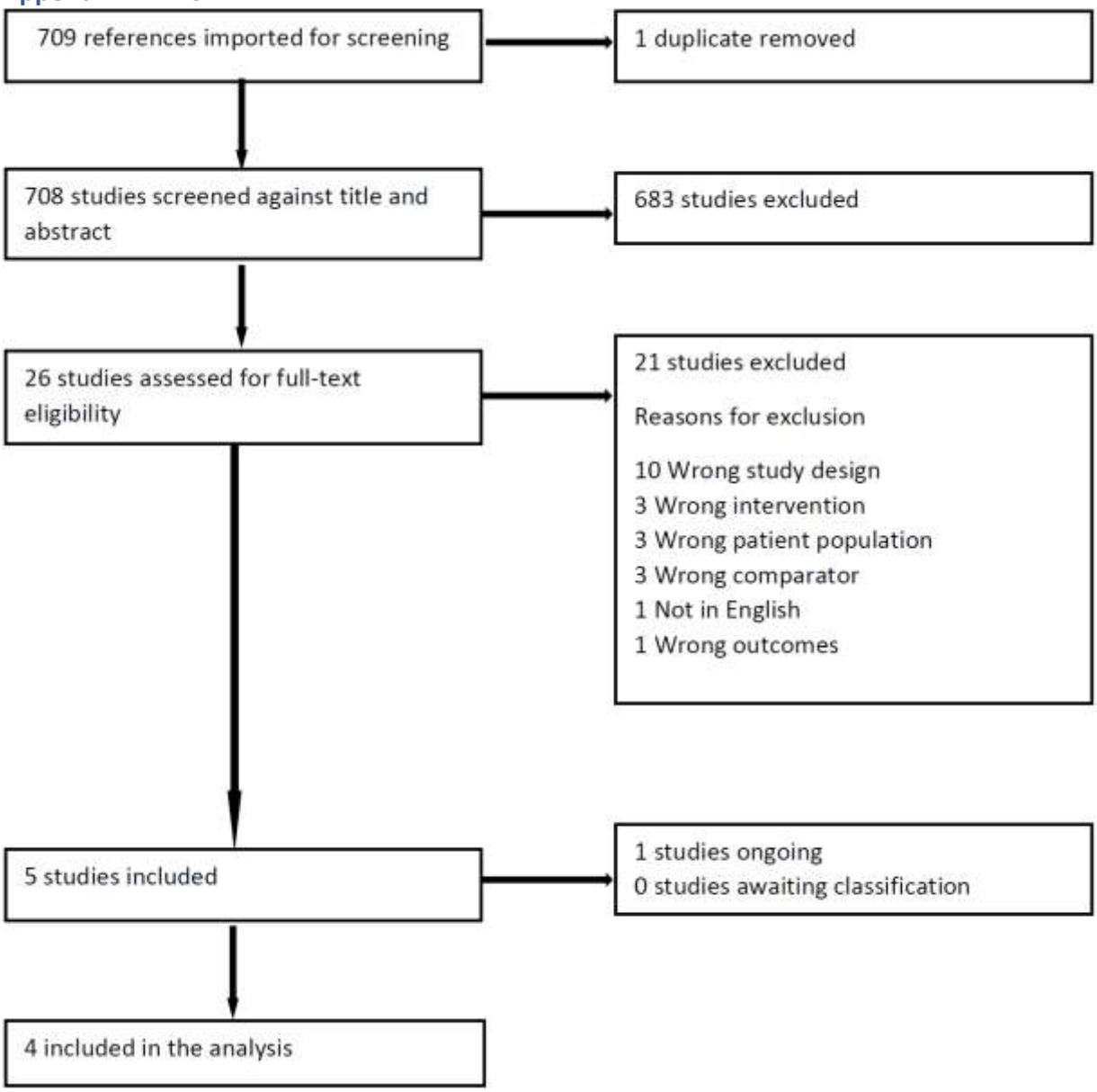
1	Pulmonary Edema/	17628
2	(pulmonary adj2 (edema or oedema)).tw.	19427
3	decompensated heart failure.mp.	3870
4	decompensated cardiac failure.mp.	37
5	exp Heart Failure/	135224
6	1 or 2 or 3 or 4 or 5	161564
7	Morphine/	39357
8	morphin*.tw.	55512
9	7 or 8	62460
10	6 and 9	332
11	randomized controlled trial.pt.	558117
12	controlled clinical trial.pt.	94685
13	(randomized or placebo or randomly or trial or groups).ab.	3175308
14	drug therapy.fs.	2440064
15	11 or 12 or 13 or 14	5255383
16	exp animals/ not humans.sh.	4955382
17	15 not 16	4572999
18	10 and 17	152
19	Meta-Analysis as Topic/	20787
20	meta-analysis/ or "systematic review"/	257861
21	meta analy*.tw.	223648
22	metaanaly*.tw.	2381
23	(systematic adj (review* or overview*)).tw.	232823
24	19 or 20 or 21 or 22 or 23	389013
25	10 and 24	7
26	18 or 25	152

Embase

1	lung edema/	51465
2	(pulmonary adj2 (edema or oedema)).tw.	31414
3	decompensated heart failure.mp.	8216
4	decompensated cardiac failure.mp.	73
5	exp Heart Failure/	597104
6	1 or 2 or 3 or 4 or 5	641888
7	Morphine/	116360
8	morphin*.tw.	78128
9	7 or 8	130930
10	6 and 9	3362
11	(random* or factorial* or placebo* or assign* or allocat* or crossover*).tw.	2281083
12	((blind* or mask*) and (single or double or triple or treble)).tw.	301379
13	crossover procedure/	69726
14	double blind procedure/ or single blind procedure/	237518
15	randomization/ or placebo/	471387
16	parallel design/ or Latin square design/	15682
17	randomized controlled trial/	697078
18	exp ANIMAL/ or exp NONHUMAN/ or exp ANIMAL EXPERIMENT/ or exp ANIMAL MODEL/	32230501
19	exp human/	24589730
20	18 not 19	7640771
21	11 or 12 or 13 or 14 or 15 or 16 or 17	2588211
22	21 not 20	2254143
23	10 and 22	360
24	exp Meta Analysis/	237876
25	((meta adj analy*) or metaanalys*).tw.	289477
26	(systematic adj (review* or overview*)).tw.	283463

27	"systematic review"/	331371
28	24 or 25 or 26 or 27	559508
29	10 and 28	106
30	23 or 29	417
Cochrane Database of Systematic Reviews		
#231	MeSH descriptor: [Pulmonary Edema] explode all trees	273
#232	(pulmonary edema):ti,ab,kw	1925
#233	("pulmonary œdema"):ti,ab,kw	262
#234	MeSH descriptor: [Heart Failure] explode all trees	10224
#235	(decompensated heart failure):ti,ab,kw	1337
#236	(decompensated cardiac failure):ti,ab,kw	407
#237	#231 or #232 or 233 or #234 or #235 or #236	25707
#238	MeSH descriptor: [Morphine Derivatives] explode all trees	7372
#239	(morphin*):ti,ab,kw	15665
#240	#238 or #239	17651
#241	#240 and #237	208

Appendix 2: PRISMA



Appendix 3

Table 1: Characteristics of included studies

Citation	Study design	Population	Treatment	Main Findings	Comments
Lin Y, Chen Y, Yuan J, Pang X, Liu H, Dong S, Chen Q. Intravenous morphine use in acute heart failure increases adverse outcomes: a meta-analysis. Rev. Cardiovasc. Med. 2021 Sep 24;22(3):865-72.	Systematic review and Meta-analysis	5 studies (3 propensity-matched cohorts, 2 retrospective analysis (1 unpublished)). Total n=149,967 (intravenous morphine group, n=22,072; no-morphine group, n=127,895) All studies provided the primary clinical endpoints, 4 studies provided secondary endpoints; 3 studies had follow-up durations from 30 days to 12 months Patients with AHF	Intravenous morphine used in treatment group (dosage≥0.5 mg/kg) vs no morphine used in the control group.	**In-hospital mortality** OR = 2.14, 95% CI: 0.88–5.23, p = 0.095, I^2 = 97.1 %; Very low certainty of evidence <u>Total group:</u> 2899/22072 in intervention group 3180/127895 in control group. <u>Sub group analysis in score matching studies</u>: 178/1165 in intervention group 132/1165 in control group (OR=1.41, 95% CI: 1.11–1.80, p =0.005, I^2 = 0%) **ICU Length of stay** Not reported **Hospital Length of stay** Not reported	All included studies represented a low risk of bias in selective outcome reporting and outcome assessment. The scores of NOS for study quality assessment of included studies ranged from 7 to 9. However, the funnel plot asymmetry for in-hospital mortality and invasive mechanical ventilation indicated publication bias. Between-study heterogeneity in in-hospital mortality was $I2$ = 97.1%. Accordingly, subgroup analyses including score-matching studies only were conducted, for which in-hospital mortality was $I2$ = 0%, suggesting low heterogeneity.
Gao D, David C, Rosa MM, Costa J, Pinto F, Caldeira D. The Risk of Mortality Associated With Opioid With Acute Heart Failure: Systematic Review and Meta-analysis. J Cardiovasc Pharmacol Volume 77, Number 2, February 2021	Systematic Review and Meta-analysis	6 studies (observational retrospective studies) Total n=151735 Patients with AHF defined as acute signs/or symptoms of low cardiac output and/or congestion, either de novo or as a heart failure exacerbation, or as reported by investigators irrespective of the details reported.	Treatment: IV morphine Control: Standard of care was not stated.	**In-hospital mortality** OR 1.78; 95% CI 1.01–3.13. very low certainty of Evidence, 151 735 participants, 6 studies Sensitivity analysis (OR 1.46; 95% CI 1.19–1.79; I^2= 0%. Total n=151735 Intervention n=22649 Control n=129086 **30-day mortality** OR 1.56; 95% CI 1.14–2.15 Very low certainty of evidence, 986 participants, 6 studies Total n=986 Intervention n=493 Control n=493 **ICU length of stay** No reported **Hospital length of stay** Not reported	Opioids seem to be associated with a higher risk of in-hospital mortality; however, the true effect may be substantially different from the estimated effect. Opioids seem to be associated with a higher risk of 30-d mortality, however the true effect may be substantially different from the estimated effect.

Gil V, Domínguez—Rodríguez A, Masip J, Peacock WF, Miró O. Morphine Use in the Treatment of Acute Cardiogenic Pulmonary Edema and its Effects on Patient Outcome: A Systematic Review. Current Heart Failure Reports (2019) 16:81–88 https://doi.org/10.1007/s11897-019-00427-0	Systematic Review (7 studies)	1 randomized controlled trial 1 non-randomized controlled trial 5 observational studies Total n=150639 Intervention n=22080 Control n=128559 Unable to determine total number of males and females as not all studies provide this information	Treatment: Morphine with or without other drugs Control: Other drugs without morphine, but the drugs were not stated.	All studies with the exception of Sachetti et al. evaluated mortality in the patients. The conclusion from the review was that administration of morphine to patients with acute pulmonary oedema could lead to worse outcomes in the patients ranging from increased length of hospital stay to death	A meta-analysis not performed but a narrative review of each study was done
Zhang D, Lai W, Liu X, Shen Y, Hong K. The safety of morphine in patients with acute heart failure: A systematic review and meta-analysis. Clin Cardiol. 2021;44(9):1216-1224. https://doi.org/10.1002/clc.23691	Systematic review and meta-analysis	Seven studies (all retrospective case-control studies) Total n=172226 Morphine group n=22967 Control group n=149259 Mean age range from 73 to 81 years Sample size range from 181 to 147 362.	Treatment Morphine and intravenous morphine. Dosage not stated Control treatment was not stated.	**In-hospital mortality** Five studies Total n=170993 Morphine n=22338 Control n= 148655 (OR: 1.94; 95% CI 0.93 to 4.03; p = 0.08, I^2 = 96%) **7-day and 30-day all-cause mortality** Three studies included Total n= 9904 Morphine n= 1175 Control n=8729 **For 7 day all-cause mortality** (OR: 1.69; 95% CI 0.89 to 3.22; p = 0.11, I^2 = 61%) **For 30-day all-cause mortality** OR: 1.59; 95% CI 1.16 to 2.17; p = 0.004, I^2 = 0% **SAE** Risk of invasive mechanical ventilation 4 studies Total n=167847 Morphine n=22047 Control n= 145800 OR 2.72; 95% CI 1.09 to 6.80; p = 0.03, I^2 = 93% **ICU length of stay** Not reported **Hospital length of stay** Not reported	Publication bias could not be ascertained as the number of included studies was less than 10 The Newcastle-Ottawa Scale (NOS) for observational studies was used to assess the quality of the studies based on selection of the population, the comparability of the study, and the assessment of the outcome. The study scored an average of 6.43 For the in-hospital mortality, risk of invasive mechanism and 7-day all-cause mortality outcomes the results showed significant heterogeneity There was no heterogeneity for the 30-day all-cause mortality outcome

Appendix 4

Table 2: Characteristics of excluded studies

Citation	Type or record	Reason for exclusion
Agewall S. *Morphine in acute heart failure*. J Thorac Dis 2017;9(7):1851-1854.	Journal article	Wrong study design
Berger PE, et al.. *ARE narcotics harmful in the treatment of acute pulmonary edema? A critically appraised topic*. Scientific Abstracts (163). CJEM.JCMU 2010;12(3): 277.	Conference abstract	Wrong study design
Dominquez-Rodriquez A, , et al. Study Design and Rationale of *A"Multicenter, Open-labelled, Randomized Controlled Trial Comparing Midazolam Versus Morphine in Acute Pulmonary Edema":* MIMO Trial. Cardiovasc Drugs Ther 2017; 31:209-213	Protocol	Wrong comparator
Dominquez-Rodriquez A, et al. *Influence of morphine treatment on in-hospital mortality among patients with acute heart failure*. Med Intensiva 2017;41:382-384.	Letter	Wrong comparator
Ellingsrud C, et al *Morphine in the treatment of acute pulmonary edema*. Tidsskr Nor Legeforen 23-24, 2014; 134:2272-2275.	Journal article	Wrong study design
Graham CA, et al. *Morphine should be abandoned as a treatment for acute cardiogenic pulmonary oedema*. Emergency Medicine Australasia 2009;21:160.	Letter	Wrong study design
Hall M, et al. *Is Morphine indicated in acute pulmonary oedema*. Emerg Med J 2005; 22:391-392.	Letter	Wrong study design
Herlitz J, et al. *Is pre-hospital treatment of chest pain optimal in acute coronary syndrome? The relief of both pain and anxiety is needed*. International Journal of Cardiology 2011;(149): 147–151.	Journal article	Wrong study design
Holm M, et al.. *The Movement Trial*. J Am Heart Assoc. 2019;8:1-11.	Journal article	Wrong intervention
Johnson MJ, et al.. *Morphine for the relief of breathlessness in patients with chronic heart failure – a pilot study*. The European Journal of Heart Failure 2002; (4):753–756.	Journal article	Wrong patient population
Johnson MJ, et al. *Oral modified release morphine for breathlessness in chronic heart failure: a randomized placebo-controlled trial*. ESC Heart Failure 2019: 6:1149-1160.	Journal article	Wrong intervention
Kubica J, et al.. *Morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction: the randomized, double-blind, placebo-controlled IMPRESSION trial*. European Heart Journal 2016; 37:245–252.	Journal article	Wrong patient population
León-Delgado M, et al.. *Opioids for the management of dyspnea in patients with heart failure: a systematic review of the literature*. Colombian Journal of Anesthesiology 2019; 47(1): 49-56	Journal article	Wrong comparator
Mattu A, et al. *Prehospital Management of Congestive Heart Failure*. Heart Failure Clin 5 2009; 19–24.	Journal article	Wrong study design
Orso D, et al. *Is morphine safe in acute decompensated heart failure? A systematic review of the literature*. European Journal of Internal Medicine 2019; 69:e8–e10.	Journal article	Wrong study design
Oxberry SG, et al.. *Short-term opioids for breathlessness in stable chronic heart failure: a randomized controlled trial*. European Journal of Heart Failure 2011;13:1006–1012.	Journal article	Wrong patient population
Oxberry SG, et al.. *Minimally clinically important difference in chronic breathlessness: Every little helps*. American Heart Journal 2012; 164(2):229-235.	Journal article	Wrong outcomes
Oxberry SG, et al. *Repeat Dose Opioids May Be Effective for Breathlessness in Chronic Heart Failure if Given for Long Enough*. Journal of Palliative Medicine 2013; 16(3): 250-255.	Journal article	Wrong intervention
Poole-Wilson PA. *Treatment of Acute Heart Failure. Out with the Old, in With the New*. JAMA 2002; 287(12):1578-1580.	Journal article	Wrong study design
Triposkiadis F, et al.. *Current drugs and medical treatment algorithms in the management of acute decompensated heart failure.* Expert Opin Investig Drugs 2009; 18(6):695-707.	Journal article	Wrong study design
Vicicevic Z. Is it necessary to use Morphine in acute pulmonary edema? Lijec Vjesn 2003; 125(47):1-2.	Journal article	Not in English

Appendix 5: Certainty assessment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsist-ency	Indirectness	Imprecision	Other considerations	Morphine	SOC	Relative (95% CI)	Absolute (95% CI)		
In-hospital mortality												
6	observational studies	serious[a]	serious[b]	not serious	not serious[c]	none	794/22649 (3.5%)	2582/129086[g] (2.0%)	**OR 1.78 (1.01 to 3.13)**	**15 more per 1,000 (from 0 fewer to 40 more)**	⊕⊕◯◯ Low	CRITICAL
SAE												
4	observational studies	not serious[d]	serious[e]	not serious	serious[f]	none	1632/22047 (7,4%)	4083/145800[g] (2,8%)	**OR 2.72 (1.09 to 6.80)**	**45 more per 1,000 (from 2 more to 136 more)**	⊕⊕◯◯ Low	CRITICAL

CI: confidence interval; **OR:** odds ratio; **SOC:** standard of care

Explanations

a. Serious risk of bias: At least one domain of bias in most studies was graded as serious according to ROBINS-I tool

b. With the exception of Peacock, confidence intervals show overlapping, point estimates have a some variation and there is a significant heterogeneity in the pooling. Peacock is a study that comprises a greater sample size (147k vs. 6k, the 2nd greatest) in comparison with the aforementioned studies, and is the only study conducted in a nation that does not abide by ESC guidelines. Inconsistency may be dampened with the exclusion of Peacock as observed following the jackknife sensitivity analysis, however as no concrete justification for the discrepancy was found

c. No imprecision: Not downgraded, very low baseline risk (rare events <2%), further changes in relative effects are unlikely to result in meaningful changes in absolute effects. Furthermore, not downgrading for imprecision as to not double downgrade/penalise for both inconsistency and imprecision.

d. No serious ROB: NCOS was used, low risk of bias for this outcome of included studies

e. Serious inconsistency: Significant heterogeneity across studies specifically Oscar (2017) and Sacchetti (1999)

f. Serious imprecision: Absolute effect does not cross the null threshold, potentially large relative effect (OR >2.5) with IOS met, however absolute effect ranges from trivial harms to possible large harms.

g. Baseline risk calculated from references 16 (for in-hospital mortality)and 27 (for SAE) as this data was not provided as generic inverse variance methods was used

Appendix 6: Overall AMSTAR score for each of the included studies

STUDY	AMSTAR RESULT
Lin Y, Chen Y, Yuan J, Pang X, Liu H, Dong S, Chen Q. Intravenous morphine use in acute heart failure increases adverse outcomes: a meta-analysis. Rev. Cardiovasc. Med. 2021 Sep 24;22(3):865-72.	Critically Low quality review
Gao D, David C, Rosa MM, Costa J, Pinto FJ, Caldeira D. The risk of mortality associated with opioid use in patients with acute heart failure: systematic review and meta-analysis. Journal of Cardiovascular Pharmacology. 2021 Feb 1;77(2):123-9.	Moderate quality review
Gil V, Domínguez-Rodríguez A, Masip J, Peacock WF, Miró Ò. Morphine use in the treatment of acute cardiogenic pulmonary edema and its effects on patient outcome: a systematic review. Current heart failure reports. 2019 Aug;16(4):81-8.	Critically Low quality review
Zhang D, Lai W, Liu X, Shen Y, Hong K. The safety of morphine in patients with acute heart failure: A systematic review and meta-analysis. Clinical cardiology. 2021 Sep;44(9):1216-24.	Moderate quality review

Appendix 7: Ongoing studies

Ongoing studies

A Multicenter, Open-Labeled, Randomized Controlled Trial Comparing Midazolam Versus Morphine in Acute Pulmonary Edema": MIMO Trial(26)

Brief Summary: Acute pulmonary edema (APE) is a common condition in the emergency room, associated with considerable mortality. The use of intravenous morphine in the treatment of APE remains controversial and Benzodiazepines have been suggested as an alternative for morphine to relieving dyspnoea and anxiety in the patients with APE. The Midazolam versus Morphine in APE trial (MIMO) is a multicenter, prospective, open-label, randomized study designed to evaluate the efficacy and safety of morphine in patients with APE.
Study type: Interventional (Clinical Trial)
Estimated enrollment: 136 participants
Allocation: Randomized
Intervention model: Parallel assignment
Masking: None (Open Label)
Primary purpose: Treatment

South African National Essential Medicine List
Primary Healthcare EML review process
Component: Emergencies & injuries

RAPID SCOPING REVIEW

Date: 21 October 2021

Key findings

- The purpose of this rapid scoping review was to determine if there is any new evidence since the previous review of the evidence in 2018 for burn dressings and mupirocin to trigger a formal review.
- No additional RCTs or relevant evidence from SRs since 2018 of burns dressings was found.
- No evidence signal to indicate any change to original 2018 NEMLC recommendations for local wound care (Povidone iodine, silver sulfadiazine, mupirocin, nano-crystalline dressings, *melaleuca alternifolia*) in patients with burns.
- No evidence for the effectiveness mupirocin.
- 2018 and 2019 recommendations remain unchanged.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

Recommendation: Current standard of care in the STG to be retained – topical povidone iodine for infected burns.
Rationale: No new evidence could be identified for alternative treatment options for septic burns.
Level of Evidence: Low to very low certainty
Review indicator: New evidence sufficient to change the recommendation

NEMLC RECOMMENDATION (MEETING OF 23 JUNE 2022):
NEMLC accepted the review and proposed recommendation, but recommended that the PHC/Adult Hospital Level Committee consider reviewing other dressings for wounds, noting that this topic would be prioritised in the topic prioritisation project plan and may be reviewed in the next review cycle. Furthermore, it was noted that wound dressings are not funded from the Provincial Pharmaceutical budgets.

Monitoring and evaluation considerations

Research priorities

1. Executive Summary

Date: 21 October 2021
Medicine (INN): Dressings for burns (antibiotics and chemotherapeutics for dermatological use)
Medicine (ATC): D06
Indication (ICD10 code): Burns T30.0-3/T31.0-9 + (Y34.99)
Patient population: Adults and paediatrics
Level of Care: Primary Healthcare
Prescriber Level: Nurse prescriber
Current standard of Care: Povidone iodine 5% cream
Efficacy estimates: n/a
Motivator/reviewer name(s): Dr Michael McCaul, Dr Clint Hendricks, Dr Gustav Thom
PTC affiliation: GT – KZN PPTC

2. Name of reviewer(s) : Michael McCaul (1), Clint Hendricks (2), Gustav Thom (3)

1) Division of Epidemiology and Biostatistics, Department of Global Health, Stellenbosch University. SA GRADE Network
2) Division of Emergency Medicine, University of Cape Town. Emergency Physician, Cape Town
3) District Clinical Specialist Team, Amajuba District, KZN

MM, CH, GT have no interests pertaining to topical preparations for management of burns.

3. Introduction/ Background

A proposal was made to add topical mucopirocin to the Adult Hospital Level and PHC STG for the management of septic burns. As the issue of topical preparations had been investigated and not added during the 2017-19 NEMLC review cycle it was necessary to ascertain whether new evidence had emerged since that would necessitate a new review.

4. Purpose/Objective:

To determine if new evidence has emerged since the 2018 (PHC, 21.3.2) and 2019 (Adult, 20.15) EML for dressings for burn care, specifically:

- Povidone iodine
- Silver sulfadiazine
- Mupirocin
- Nano-crystalline dressings
- Melaleuca alternifolia

5. Methods:

We conducted a rapid scoping review of the literature to determine whether there is any new evidence to trigger a formal review of burn dressings for adult and PHC level.

a. **Data sources** : Searched https://www.epistemonikos.org/ for updated or new systematic review of effect on 13 October 2021. Search terms included all intervention terms (as above, including dressings) and terms linked to the population (i.e. burns).

b. **Search strategy :** Title and abstract, and full text screening was done individually by MM, with a 2nd reviewer checking excluded studies (GT). Search strategy in Appendix 1. We used the search filers for systematic reviews and then for trials. We only included evidence (systematic reviews or RCTs) from 2018 onwards and checked CENTRAL for updated systematic reviews that originally supported the 2018 and 2019 Adult and PHC reviews.

c. **Search Yield:** We screened 74 articles, of which 10 were included in full text screening. Seven SRs were included in the narrative summary.

d. Excluded studies:

Author, date	Type of study	Reason for exclusion
Rahimi 2021	SR	Biosynthetic Dressings not relevant
Li, 2020	SR	Nano-silver dressing combined with recombinant human epidermal growth factor. Not relevant.
Harshman, 2019	SR	Acute Emergency care (pre-burn center)
Wormald, 2020	SR	Hydrosurgical debridement. Not relevant

e. Evidence synthesis

Description of included SRs

We found 4 Cochrane Systematic Reviews and 3 non-Cochrane reviews. Three SRs were included (<2018) as they were part of the original evidence review in 2018/2019 (See Table 11: Characteristics of included reviews). Below we include original evidence from the 2018/2019 review, and additional evidence, with references.

Results of Systematic Reviews

We found no new RCTs addressing burn dressings. The 2013 Cochrane review informing the previous recommendations has not been updated. New SRs across topics provide no new evidence for povidone iodine, silver sulfadiazine, mupirocin, nano-crystalline dressings and melaleuca alternifolia.

Silver Sulfadiazine

Silver sulphadiazine was consistently associated with poorer healing outcomes than biosynthetic (skin substitute) dressings, silver-containing dressings and silicon-coated dressings. (Wasiak, 2013, Cochrane Review).

Silver sulfadiazine was associated with a statistically significant increase in burn wound infection vs. dressings/skin substitute (OR = 1.87; 95% CI: 1.09 to 3.19, I2 = 0%). Though, RCTs were at high, or unclear, risk of bias. Silver sulfadiazine was also associated with significantly longer length of hospital stay vs dressings/skin substitute (MD = 2.11 days; 95% CI: 1.93 to 2.28) (Barajas-Nava, 2013, Cochrane Review)

Similar results found in other SRs for SSD (Nimia, 2019 and Maciel, 2019). Moderate quality evidence indicates that there is no significant difference in wound healing between silver-containing foam dressing and SSD dressing (Chaganti, 2019).

Povidone iodine:

Cochrane review showed that there is probably no difference in infection rates between an iodine-based treatment vs moist exposed burn ointment (moderate certainty evidence) – Mean time to healing for wounds treated with povidone iodine vs chlorhexidine: MD - 2.21 days, 95% CI 0.34 to 4.08. (Norman, 2017, Cochrane Review)

Melaleuca alternifolia:

No available evidence could be sourced for cooling burns with Melaleuca alternifolia (tea tree oil) for the first 12 hours. There is also the associated risk of hypothermia for large burn wounds, if this is practiced

Nano-crystalline dressings:

Cochrane review showed that, "There is moderate certainty evidence that, on average, burns treated with nanocrystalline silver dressings probably have a slightly shorter mean time to healing than those treated with Vaseline gauze (difference in means -3.49 days, 95%CI -4.46 to -2.52; I2 = 0%; 2 studies, n=204), but low certainty evidence that there may be little or no difference in numbers of healing events at 14 days between burns treated with silver xenograft or paraffin gauze (RR 1.13, 95% CI 0.59 to 2.16 1 study; n=32) (Norman, 2017, Cochrane Review).

Mupirocin:

We found no RCTs or SRs of Mupirocin.

Facial Burns

Topical antimicrobial agents versus topical non-antimicrobial agents *(Hoogewerf, 2020)*

There is moderate-certainty evidence that there is probably little or no difference between antimicrobial agents and non-antimicrobial agents (SSD and MEBO) in time to complete wound healing (hazard ratio (HR) 0.84 (95% confidence interval (CI) 0.78 to 1.85, 1 study, 39 participants).

Topical antimicrobial agents versus other topical antimicrobial agent *(Hoogewerf, 2020)*

There is very low-certainty evidence regarding whether topical antimicrobial agents make a difference to wound infection (RR 0.73, 95% CI 0.46 to 1.17; 1 study, 15 participants).

Skin substitutes versus topical antimicrobial agents *(Hoogewerf, 2020)*

There is low-certainty evidence that a skin substitute may slightly reduce time to partial (i.e. greater than 90%) wound healing, compared with a non-specified antibacterial agent (MD –6.00 days, 95% CI –8.69 to –3.31; 1 study, 34 participants).

We are uncertain whether skin substitutes in general make any other difference in effects as the evidence is very low certainty. Outcomes included wound infection, pain, scar quality, adverse effects of treatment and length of hospital stay.

Table of included studies

Author, date	***Type of study***	**n**	**Population**	**Comparators**	**Primary outcome**
Wasiak, 2013[1] (in original review)	Cochrane Systematic Review	30 RCTs, poor quality	Any age with superficial or partial thickness burns	hydrocolloid dressings; polyurethane film dressings; hydrogel dressings; silicon-coated nylon dressings; biosynthetic skin substitute dressings; antimicrobial (silver and iodine containing) dressings; fibre dressings; wound dressing pads	Time to healing No of dressings Pain QOL LOS Infection AE
Barajas-Navam 2013[2] (in original review)	Cochrane Systematic Review	36 RCTs (2117 participants)	People of any age or gender, with any type of burn injury	Systemic antibiotics given orally or parenterally Selective intestinal decontamination with antibiotics **Topical antibiotics, such as topical antimicrobial dressings or ointments** Local airway prophylaxis, such as aerosolised antibiotics.	Burn wound infection Invasive infection Infection-related mortality Adverse events wound healing rate Antibiotic resistance All-cause mortality LOS
Nimia, 2019[3]	Systematic Review	24 RCTs Low to unclear ROB	People with burns	SSD vs other dressings (with or without silver)	Infection control and wound healing
Marciel, 2019[4]	Systematic Review	11 RCTS	Burn patients hospitalized in the burn ward	New treatments vs SSD	Complete healing

Chaganti, 2019[5]	Systematic Review	3 RCTS	Patients with partial thickness burns	foam dressing vs SSD and non-foam dressing	Wound healing
Norman, 2017[6] (in original review)	Cochrane Systematic Review	56 RCTs (5807 participants)	people with any burn wound	topical treatments with antiseptic properties.	time to complete wound healing proportion of wounds completely healed during follow-up AEs QOL Pain Resource use
Hoogewerf, 2020[7]	Cochrane Systematic Review	12 RCTs (507 participants)	People with facial burns of any depth	Topical antimicrobial agents topical non-antimicrobial agents Skin substitutes Miscellaneous treatments	time to complete wound healing proportion of wounds completely healed during follow-up AEs QOL Pain Resource use

f. Evidence quality: Overall certainty of the evidence in the included SRs were low.

Appendix 1 – Search strategy

(title:(burn OR burns) OR abstract:(burn OR burns)) AND (title:(dressings OR dresssing OR "povione iodine" OR "silver sulfadiazine" OR mupirocin OR "nano-crystalline" OR "melaleuca alternifolia") OR abstract:(dressings OR dressing OR "povione iodine" OR "silver sulfadiazine" OR mupirocin OR "nano-crystalline" OR "melaleuca alternifolia"))

Version	Date	Reviewer(s)	Recommendation and Rationale
1	21 October 2021	MM, CH, GT	Povidone iodine, topical retained for management of septic burns, as no new evidence could be identified for alternative treatment options for septic burns.

References:

Included studies

1. Wasiak J, Cleland H, Campbell F, Spinks A. Dressings for superficial and partial thickness burns. *Cochrane Database Syst Rev*. 2013;2013(3). doi:10.1002/14651858.CD002106.pub4
2. Barajas-Nava LA, López-Alcalde J, Roqué i Figuls M, Solà I, Bonfill Cosp X. Antibiotic prophylaxis for preventing burn wound infection. *Cochrane Database Syst Rev*. 2013;2013(6). doi:10.1002/14651858.CD008738.pub2
3. Nímia HH, Carvalho VF, Isaac C, Souza FÁ, Gemperli R, Paggiaro AO. Comparative study of Silver Sulfadiazine with other materials for healing and infection prevention in burns: A systematic review and meta-analysis. *Burns*. 2019;45(2):282-292. doi:10.1016/j.burns.2018.05.014
4. Siqueira BS, Zanette GF. Versus Other Treatments : a Systematic Review and Meta-Analysis of. *An Bras Dermatol*. 2019;94(2):204-210.
5. Chaganti P, Gordon I, Chao JH, Zehtabchi S. A systematic review of foam dressings for partial thickness burns. *Am J Emerg Med*. 2019;37(6):1184-1190. doi:10.1016/j.ajem.2019.04.014
6. Norman G, Christie J, Liu Z, et al. Antiseptics for burns. *Cochrane Database Syst Rev*. 2017;2017(7). doi:10.1002/14651858.CD011821.pub2
7. Hoogewerf CJ, Hop MJ, Nieuwenhuis MK, Oen IMMH, Middelkoop E, Van Baar ME. Topical treatment for facial burns. *Cochrane Database Syst Rev*. 2020;2020(7). doi:10.1002/14651858.CD008058.pub3