SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 24: MEDICINES USED IN PALLIATIVE CARE
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2017 -2020)

Background

NEMLC had previously recommended that chapters for palliative care be developed for PHC and Hospital level (adult and paediatric management) at the meeting of the 6 April 2017. NEMLC had "acknowledged the WHO position paper and the list of conditions recommended by the International Association for Hospice and Palliative Care (IAHPC) requiring pharmacological management. Although the evidence base is limited, NEMLC would assess each motivation on evidence based medicine principles".[1]

General

Objective: The chapter essentially describes medicine treatment in palliative care, with referral to the National Guidelines on Palliative Care for guidance on management of the palliative care patient.

End-of life care: Please note that the recommendations in this chapter are directed at end-of-life care, which is a component of palliative care. The approach to end-of-life care may differ from supportive palliative care, but cross-referrals to respective sections for supportive palliative care are included in the STGs, e.g.: Section 15.4: Depressive disorder, major.

Continuity of care: For continuity of care from primary level of care, the STGs cross reference to the PHC STGs for primary management of conditions, where appropriate.

Differentiation between palliative care at primary and secondary levels of care: Despite the approval of a national strategic policy for palliative care; concerns regarding adequate infrastructure and service delivery platforms at primary level of care limits recommendations for palliative care at this level of care. Medicines and care plans will be down referred from secondary level until service delivery is operational at primary level of care.

Chapter layout:

[1] Minutes of the NEMLC meeting of 6 April 2017

Medicine recommendations, with supporting evidence and rationale are listed below. Kindly review the medicine amendments in the context of this new chapter.

CONDITION	MEDICINE	MEDICINE ADDED/NOT ADDED
24.1.1 Anorexia and cachexia	Betamethasone, oral/IV	Not added
	Prednisone, oral	Added
24.1.2 Constipation		
- First line options	Sennosides A and B, oral, 13.5 mg	Added (aligned with PHC STGs and EML)
	Lactulose, oral	Added (aligned with PHC STGs and EML)
- Severe constipation, unable to swallow	Glycerine suppositories	Added
	Bisacodyl suppositories	Added
	Phosphate enemas	Not added
24.1.3 Nausea and vomiting	Metoclopramide, oral	Added
	Metoclopramide, IM/IV	Added
	Cyclizine, suppositories	Not added
-If ineffective or contra-indicated (i.e. inoperable bowel obstruction):	Haloperidol, oral	Added
	Haloperidol, IM/IV/SC	Added
- Drug-induced parkinsonism	Anticholinergic agents	Added as a therapeutic class
	Orphenadrine, oral	Added as an example of anticholinergic therapeutic class
-If haloperidol not tolerated or inoperable bowel obstruction	Promethazine, IM/IV	Added
	Ondansetron, oral/IM/SC	Not added
24.2.1 Anxiety		
- Acute management of anxiety:	Benzodiazepines	Added as a therapeutic class
	Diazepam, oral	Added as example of benzodiazepine therapeutic class
	Diazepam, IV	Directions for use amended
- Longer term management	SSRIs	Added as a therapeutic class
	Citalopram, oral	Added as example of SSRI therapeutic class
	Fluoxetine, oral	Added as example of SSRI therapeutic class
24.2.2 Delirium	Haloperidol, oral	Added
	Haloperidol, SC/IV	Added
	Lorazepam, oral	Added
	Midazolam, SC/IV	Added
24.2.3 Depression	Citalopram, oral	Added
	Fluoxetine, oral	Not added
	Amitriptyline	Added
24.2.4 Fatigue	Betamethasone, oral/IV	Not added
	Prednisone, oral	Added
24.4.1 Dyspnoea	Oxygen	Added
	Morphine, oral solution	Directions for use amended
24.4.2 Respiratory secretions	Hyoscine buthylbromide (butylscopalamine), SC/IM	Added
24.5 Sedation in palliative care	Lorazepam, oral	Retained
	Haloperidol, oral	Retained and dose amended
	Midazolam, SC/IM	Added
	Propofol	Not added

24.1.1 ANOREXIA AND CACHEXIA

Betamethasone, oral/IV: *not added*
Prednisone, oral: *added*
Refer to the NEMLC approved medicine review done by Primary Health Care (PHC) Committee for detailed information (Betamethasone for anorexia in palliative care, July 2017). Management to take place at secondary level rather than primary level of care. There is limited RCT evidence[2], with recommendations mostly guided by expert opinion[3].
Level of Evidence: III Expert opinion.

Betamethasone for anorexia in palliative

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

NEMLC MEETING OF 12 APRIL 2018:
NEMLC recommended that generally for palliative end of life care patients, minimal invasive treatment is preferred. Thus, oral treatment be recommended, wherever possible.
In addition, due to the supply challenges associated with oral betamethasone and dexamethasone formulations in South Africa, NEMLC recommended that prednisone, oral be recommended for anorexia, where there is a profound impact on quality of life, and when treating the underlying cause is not possible or effective.
Limited evidence suggests that oral methylprednisolone improved appetite and performance status[4].
NEMLC Recommendation: Prednisone, oral (at an equivalent dose – ratio of 1:5) be recommended for anorexia at end-of-life, where there is a profound impact on quality of life, and when treating the underlying cause is not possible or effective.

Level of Evidence: II Systematic review of low quality studies[5]

24.1.2 CONSTIPATION

First line treatment options:
Sennosides A and B, oral, 13.5 mg: *added*
Lactulose, oral: *added*
Aligned with Canadian Canadian Consensus Development Group for Constipation in Patients with Advanced Progressive Illness[6]
Level of Evidence: III Guidelines

Severe constipation in patients who are unable to swallow:
Bisacodyl suppositories: *added*
Glycerine suppositories: *added*

Bisacodyl suppositories: Refer to the NEMLC approved medicine review, below done by PHC Committee for

[2] Miller S, McNutt L, McCann MA, McCorry N. Use of corticosteroids for anorexia in palliative medicine: a systematic review. J Palliat Med. 2014 Apr;17(4):482-5. https://www.ncbi.nlm.nih.gov/pubmed/24702642
[3] Back I., Watson M., Lucas C., Hoy A. and Armstrong P. 2012. Anorexia, cachexia and asthenia. Palliative Care Guidelines Plus [Online]. Available: http://book.pallcare.info/index.php?p=pdf&op_target=print&id=339&media=pdf&pdffmt=1&dg=1 [Accessed 23 November 2017].
[4] Yavuzsen T, Davis MP, Walsh D, LeGrand S, Lagman R. Systematic review of the treatment of cancer-associated anorexia and weight loss. J Clin Oncol. 2005 Nov 20;23(33):8500-11. https://www.ncbi.nlm.nih.gov/pubmed/16293879
[5] Yavuzsen T, Davis MP, Walsh D, LeGrand S, Lagman R. Systematic review of the treatment of cancer-associated anorexia and weight loss. J Clin Oncol. 2005 Nov 20;23(33):8500-11. https://www.ncbi.nlm.nih.gov/pubmed/16293879.
[6] Librach SL, Bouvette M, De Angelis C, Farley J, Oneschuk D, Pereira JL, Syme A; Canadian Consensus Development Group for Constipation in Patients with Advanced Progressive Illness. Consensus recommendations for the management of constipation in patients with advanced, progressive illness. J Pain Symptom Manage. 2010 Nov;40(5):761-73. https://www.ncbi.nlm.nih.gov/pubmed/21075273

detailed information for bisacodyl suppositories (August 2017). Recommendations aligned with Guidelines[7] [8].

Bisacodyl supp for constipation in palli

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Level of Evidence: III Guidelines, Expert opinion

Glycerine suppositories: Included in the STG as an alternative option as it is standard practice.
Level of Evidence: III Standard of care

Phosphate enemas: *not added*
External comment was received to consider phosphate enemas. However, there is no RCT evidence for rectal formulations for management of palliative constipation. Systematic review[9] of the published literature showed that phosphate enemas commonly associated with water and electrolyte disturbances, moreso if there was comorbid conditions and amongst the younger and elderly patient.
Price of phosphate enema is more expensive than glycerine suppository – per dose: Phosphate enema (175ml) is R17.77[10] vs ±R 8.50 glycerine (1.698ml) suppository – (pack of 12 is R ± 102.00[11]).
Recommendation: Phosphate enemas not be recommended for palliative constipation.
Rationale: Safety and price of phosphate enema precludes it from being included in the Adult Hospital Level STGs and EML for management of constipation in palliative care.
Level of Evidence: III Systematic review of case reports, Expert opinion

24.1.3 NAUSEA AND VOMITING

Metoclopramide, oral: *added*
Metoclopramide, IM/IV: *added*
Cyclizine suppositories: *not added*

Metoclopramide, oral: Aligned with Primary Health Care STGs and EML, 2018 edition - Chapter 22: Medicines for palliative care; whilst parenteral formulation was considered appropriate for secondary level of care.
Cyclizine suppositories was reviewed in the previous Adult Hospital Level review cycle and was not accepted, as there was insufficient evidence to recommend inclusion to the EML. In addition, usage creep of suppositories for other indications was considered to be a concern.

If ineffective or contra-indicated (i.e. inoperable bowel obstruction):
Haloperidol, oral: *added*
Haloperidol, IM/IV/SC: *added*

Haloperidol, oral: Refer to the medicine review, haloperidol for nausea and vomiting in palliative care, December 2017.

[7] Canadian Agency for Drugs and Technologies in Health (CADTH). Rapid response report - Routine Bowel Care for Patients in Long-Term or Palliative Care: Guidelines; 2015 Dec 7. [Internet]. Canadian [cited 2017 October 30]. Available from: https://www.cadth.ca/sites/default/files/pdf/htis/dec-2015/RB0940%20Bowel%20Care%20in%20LTC%20Final.pdf
[8] Larkin,PJ ,Sykes,NP,Centeno,C,Ellershaw,JE, Elsner,F, Eugene,B.Gootjes,JRG,Naba,M,Noguera,IA,Ripamonti,C, Zucco,F, ,Zuurmond, WWA .The management of constipation in palliative care: clinical practice recommendationsPalliative Medicine. Vol 22, Issue 7, pp. 796 – 807.http://dx.doi.org/10.1177%2F0269216308096908
[9] Mendoza J, Legido J, Rubio S, Gisbert JP. Systematic review: the adverse effects of sodium phosphate enema. Aliment Pharmacol Ther. 2007 Jul 1;26(1):9-20. https://www.ncbi.nlm.nih.gov/pubmed/17555417
(Retrieved and circulated post meeting)
[10] Contract circular HP08-2017SSP.
[11] Price at Clicks for OTC product [Accessed 2 July 2019] - https://clicks.co.za/lennon_glycerine-suppositories-for-adults-12-suppositories/p/349951

Haloperidol for nausea and vomitin

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommended for palliative nausea and vomiting, where metoclopramide is contra-indicated or ineffective.
Rationale: There is no RCT evidence for haloperidol in this clinical setting. However, a recent Pharmacovigilance case series study suggests haloperidol is effective in this setting.
Note: Sole pharmaceutical supplier has discontinued haloperidol 0.5 mg from the South African market; however the 1.5 mg and 2.5 mg formulations are still currently available. Both tablet strengths are scored.
Level of Evidence: III Pharmacovigilance case series study[12]

Haloperidol, parenteral
Recommended as either IM/IV/SC; noting that generally patients at end-of-life are wasted. Aligned with SAMF (2016)[13], International practice[14] and evidence from a pharmacokinetic study that suggests that the pharmacokinetics of haloperidol (oral and subcutaneous) in terminally ill patients was comparable to other patients.[15]
Level of Evidence: III Guidelines

Drug induced parkinsonism
Anticholinergic agents: *added as a therapeutic class*
Orphenadrine, oral: *added as an example of anticholinergic therapeutic class*
The following text was added, aligned with the mental health care chapter:

Drug-induced parkinsonism:
- Anticholinergic agent, e.g.:
- Orphenadrine, oral, 50–150 mg daily according to individual response
  - Usual dose: 50 mg 8 hourly.
  - Maximum dose: 150 mg daily.
  - Use with caution in the elderly as it may cause confusion and urinary retention.

Note: Anticholinergic medicines (e.g. orphenadrine) should not be added prophylactically to antipsychotics to prevent extrapyramidal side effects.

Level of Evidence: III Guidelines[16], Expert opinion

If haloperidol not tolerated or inoperable bowel obstruction
Promethazine, IM/IV: *added as an example of the antihistamine therapeutic class*

Promethazine IM/IV: Refer to the medicine review, promethazine for nausea and vomiting in palliative care (July 2017):

Promethazine for nausea and vomitin

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommended for intractable nausea and vomiting in patients with inoperable bowel obstruction, not responsive to haloperidol. Antihistamines considered for this indication includes promethazine, IM/IV and cyclizine, oral.
Rationale: Aligned with guidelines (Wiffen, P. Palliative Care Formula 5th edition, 2014).
Level of Evidence: III Guidelines

[12] Digges M, Hussein A, Wilcock A, Crawford GB, Boland JW, Agar MR, Sinnarajah A, Currow DC, Johnson MJ. Pharmacovigilance in Hospice/Palliative Care: Net Effect of Haloperidol for Nausea or Vomiting. J Palliat Med. 2018 Jan;21(1):37-43.
[13] SAMF, 2016
[14] Doyle D, Woodruff R. The IAHPC Manual of Palliative Care. 3rd ed. IAHPC Press, 2013. Available from: https://hospicecare.com/what-we-do/publications/manual-of-palliative-care/ [Accessed August 2019]
[15] Franken LG, Mathot RAA, Masman AD, Baar FPM, Tibboel D, van Gelder T, Koch BCP, de Winter BCM. Population pharmacokinetics of haloperidol in terminally ill adult patients. Eur J Clin Pharmacol. 2017 Oct;73(10):1271-1277. https://www.ncbi.nlm.nih.gov/pubmed/28681176
[16] SAMF, 2016

Promethazine, parenteral not recommended for subcutaneous use. The STG text was corrected, accordingly. The Adult Hospital Level Committee recommends that a review of the evidence for agents that can be administered subcutaneously, where haloperidol is contraindicated be reviewed in the next cycle.

Ondansetron, oral/IM/SC: *not added*
Ondansetron as an option not recommended as this medicine should not be used where there is subacute intestinal obstruction.
Level of Evidence: III Guidelines[17]

24.2.1 ANXIETY

Acute management of anxiety:
Benzodiazepines: *added as a therapeutic class*
Diazepam, oral: *added as example of benzodiazepine therapeutic class*
Lorazepam, oral: *added as example of benzodiazepine therapeutic class*

Benzodiazepines for acute management are the preferred agents in the terminally ill as opposed to SSRIs that require administration for weeks to produce an effect. Cochrane review[18]concluded that no firm conclusion could be drawn about the effectiveness of medicine therapy for anxiety in adult cancer patients receiving palliative care, and recommendations be aligned with guidelines, as there is a paucity of evidence.
Diazepam, oral: Caution of use in liver impairment aligned with SAMF, 2016.
Lorazepam, oral: Aligned with guidelines, and option to administer crushed oral tablets sublingually added to the STG, as pharmacokinetic study[19] showed comparative systemic availability vs administration of oral tablets.
Level of evidence: III Guidelines, Pharmacokinetic study, Expert opinion

SSRIs: *added as a therapeutic class*
Citalopram, oral: *added as an example of SSRI therapeutic class*
Fluoxetine, oral: *added as an example of SSRI therapeutic class*
SSRIs (Fluoxetine and citalopram, oral): Aligned with Adult Hospital Mental Health Conditions chapter. Citalopram preferred as first line therapy rather than fluoxetine, as drug-drug interactions needs consideration in this patient cohort. Citalopram has reduced potential for drug interactions and is indicated for panic disorder. Fluoxetine added as second-line option for non-responders, as meta-analysis[20] suggests that all SSRIs except citalopram superior to placebo, in reducing anxiety by 50% using the relevant anxiety scale.
Level of evidence: I Meta-analysis, Guidelines[21]

Diazepam, IV: *directions for use amended*
STG text amended to include caution for lower dosing of diazepam IV in liver dysfunction aligned with the SAMF, 2016, as follows:

CAUTION
Benzodiazepines, especially diazepam IV, can cause respiratory depression. Patients in liver failure require lower doses. **Monitor patients closely**.In the short-term, benzodiazepines can aggravate delirium.

Level of Evidence: III Guidelines

[17] SAMF, 2016.
[18] Salt S, Mulvaney CA, Preston NJ. Drug therapy for symptoms associated withanxiety in adult palliative care patients. Cochrane Database Syst Rev. 2017 May 18;5:CD004596. https://www.ncbi.nlm.nih.gov/pubmed/28521070
[19]Greenblatt DJ, Divoll M, Harmatz JS, Shader RI. Pharmacokinetic comparison of sublingual lorazepam with intravenous, intramuscular, and oral lorazepam. J Pharm Sci. 1982 Feb;71(2):248-52.
[20] Bandelow B, Reitt M, Rover C, Michaelis S, Gorlich Y, Wedekind D. Efficacy of treatments for anxiety disorders: a meta-analysis. Int Clin Psychopharmacol. 2015;30(4):183-92. https://www.ncbi.nlm.nih.gov/pubmed/25932596
[21] SAMF, 2016.

24.2.2 DELIRIUM

Haloperidol, oral: *added*
Haloperidol, SC/IV: *added*
Lorazepam, oral: *added*
Midazolam, SC/IV: *added*

Antipsychotic (haloperidol), oral/IV/SC: Low doses generally recommended as first line in guidelines, due to associated side-effects[22] [23]. However, a RCT[24] 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[25] 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

Haloperidol followed by haloperidol +lorazepam, oral:

- Hiu et al (2017)[26]: RCT (n=93) of advanced hospitalised cancer patients with agitated delerium showed that lorazepam added to haloperidol vs haloperidol resulted in greater reduction of agitation at 8 hours:
    - Results (ITT, but attrition bias):
        - Addition of lorazepam to haloperidol vs haloperidol alone resulted in a significantly greater reduction in agitation at 8 hours: −4.1 (-4.8 to -3.4) vs −2.3 (-2.9 to -1.6); p<0.001; points on the 10-point Richmond Agitation Sedation Scale).
- SAMF, 2016: Doses for haloperidol and lorazepam aligned with SAMF, 2016.

Level of Evidence: II RCT of low quality, Guidelines

Midazolam doses: Lower doses of midazolam SC/IV are used in palliative care, to assist anxiety associated with delirium, but not cognition; aligned with guidelines.[27] [28]

Level of Evidence: III Guidelines

Management of delirium in the elderly, non-responsive to haloperidol

Haloperidol is not recommended for delirium at primary level of care (PHC STGs and EML, 2018) – see rationale below:

[22] Grassi L, Caraceni A, Mitchell AJ, Nanni MG, Berardi MA, Caruso R, Riba M. Management of delirium in palliative care: a review. Curr Psychiatry Rep. 2015 Mar;17(3):550. https://www.ncbi.nlm.nih.gov/pubmed/25663153

[23] BCGuidelines.ca. Palliative Care for the Patient with Incurable Cancer or Advanced Disease - Part 2: Pain and Symptom Management, 22 February 2017 [Internet] [cited 23 November 2017]. Available at: https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/palliative-pain-management

[24] Agar MR, Lawlor PG, Quinn S, Draper B, Caplan GA, Rowett D, Sanderson C, Hardy J, Le B, Eckermann S, McCaffrey N, Devilee L, Fazekas B, Hill M, Currow DC. Efficacy of Oral Risperidone, Haloperidol, or Placebo for Symptoms of Delirium Among Patients in Palliative Care: A Randomized Clinical Trial. JAMA Intern Med. 2017 Jan 1;177(1):34-42. https://www.ncbi.nlm.nih.gov/pubmed/27918778

[25] Candy B, Jackson KC, Jones L, Leurent B, Tookman A, King M. Drug therapy for delirium in terminally ill adult patients. Cochrane Database Syst Rev. 2012 Nov 14;11:CD004770.https://www.ncbi.nlm.nih.gov/pubmed/23152226

[26] Hui D, Frisbee-Hume S, Wilson A, Dibaj SS, Nguyen T, De La Cruz M, Walker P, Zhukovsky DS, Delgado-Guay M, Vidal M, Epner D, Reddy A, Tanco K, Williams J, Hall S, Liu D, Hess K, Amin S, Breitbart W, Bruera E. Effect of Lorazepam With Haloperidol vs Haloperidol Alone on Agitated Delirium in Patients With Advanced Cancer Receiving Palliative Care: A Randomized Clinical Trial. JAMA. 2017 Sep 19;318(11):1047-1056. https://www.ncbi.nlm.nih.gov/pubmed/28975307

[27] NHS Scotland. Scottish Palliative Care Guidelines – Delirium, 15 April 2014. [Internet] [Accessed 23 November 2017] Available at: http://www.palliativecareguidelines.scot.nhs.uk/guidelines/symptom-control/Delirium.aspx

[28] Bush SH, Tierney S, Lawlor PG. Clinical Assessment and Management of Delirium in the Palliative Care Setting. Drugs. 2017 Oct;77(15):1623-1643. https://www.ncbi.nlm.nih.gov/pubmed/28864877

EXTRACT FROM THE PHC NEMLC REPORT, 2 NOVEMBER 2017

Haloperidol is generally recommended as first line treatment in guidelines[29]. There is very limited evidence for efficacy, but there is risk of harm (i.e. increased agitation)[30]. A recent study (n=249) showed that placebo improved symptoms significantly more than haloperidol[31] and authors suggested that eliminating precipitants and supportive measures are more important than treatment with antipsychotics. A systematic review[32] showed that antipsychotics (haloperidol and risperidone) had no significant effect on delirium incidence amongst geriatric patients, post-operatively, vs. placebo, with high heterogeneity of studies (OR 0.56; 95% CI 0.23 to 1.29; I^2=93%).

Recommendations:

- Antipsychotics not be recommended for delirium in palliative care. Management to include interventions that are patient-centred and low risk such as frequent reorientation, etc.
- Benzodiazepines, short-course, be recommended for patients who are acutely distressed.

Rationale: Evidence shows that placebo improved delirium symptoms more than antipsychotics (risperidone, haloperidol) and increased the use of rescue midazolam amongst palliative care patients.

However, the study population of the randomised controlled trial (RCT)[33] that showed that placebo was better than antipsychotics, was elderly persons with a mean age 75 years.

NEMLC Recommendation: Benzodiazepines be recommended for management of delirium in the elderly or where there is no response or resistance to haloperidol.

24.2.3 DEPRESSION

SSRIs: *added as a therapeutic class*
Citalopram, oral: *added as an example of SSRI therapeutic class*
Fluoxetine, oral: *not added as an example of SSRI therapeutic class*
SSRIs (Fluoxetine and citalopram, oral): Aligned with Adult Hospital Mental Health Conditions chapter. Citalopram preferred rather than fluoxetine, as drug-drug interactions needs consideration in this patient cohort.
Level of evidence: III Guidelines[34]

24.2.4 FATIGUE

Betamethasone, oral/IV: *added*
The PHC medicine review of corticosteroids for fatigue was approved by NEMLC; not for use at primary level of care but rather at secondary level of care. (Refer to the review: Betamethasone for fatigue in palliative care, July 2017).

Cochrane review[35]: Authors of the 2016 review concluded, "*Due to the limited evidence, we cannot recommend a specific drug for the treatment of fatigue in palliative care patients. Some drugs, which may be beneficial for the treatment of fatigue associated with palliative care such as amantadine, methylphenidate, and*

[29]Grassi L, Caraceni A, Mitchell AJ, Nanni MG, Berardi MA, Caruso R, Riba M. Management of delirium in palliative care: a review. Curr Psychiatry Rep. 2015 Mar;17(3):550.
[30] Crawford GB, Agar MM, Quinn SJ, Phillips J, Litster C, Michael N, Doogue M, Rowett D, Currow DC. Pharmacovigilance in hospice/palliative care: net effect of haloperidol for delirium. J Palliat Med. 2013 Nov;16(11):1335-41.
[31] Agar MR, Lawlor PG, Quinn S, Draper B, Caplan GA, Rowett D, Sanderson C, Hardy J, Le B, Eckermann S, McCaffrey N, Devilee L, Fazekas B, Hill M, Currow DC. Efficacy of Oral Risperidone, Haloperidol, or Placebo for Symptoms of Delirium Among Patients in Palliative Care: A Randomized Clinical Trial. JAMA Intern Med. 2017 Jan 1;177(1):34-42.
[32] Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM. Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis. J Am Geriatr Soc. 2016 Apr;64(4):705-14.
[33] Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM. Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis. J Am Geriatr Soc. 2016 Apr;64(4):705-14.
[34] SAMF, 2016.
[35] Mücke M; Mochamat, Cuhls H, Peuckmann-Post V, Minton O, Stone P, Radbruch L. Pharmacological treatments for fatigue associated with palliative care. Cochrane Database Syst Rev. 2015 May 30;(5):CD006788. https://www.ncbi.nlm.nih.gov/pubmed/26026155

modafinil, should be further researched".

Recommendation: Corticosteroids recommended, aligned with clinical practice[36].

Level of Evidence: III Expert opinion

Betamethasone for fatigue in palliative

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

NEMLC MEETING OF 12 APRIL 2018:

NEMLC recommended that generally for palliative end of life care patients, minimal invasive treatment is preferred. Thus, oral treatment be recommended, wherever possible.

In addition, due to the supply challenges associated with oral betamethasone and dexamethasone formulations in South Africa, NEMLC recommended that prednisone, oral be recommended for fatigue at end-of-life, when treating the underlying cause is not possible or effective. Thus, the recommended medicine will fulfil the definition of an essential medicine within the Constitutional framework.

Level of Evidence: III Expert opinion

24.4.1 DYSPNOEA

Morphine solution, oral: *added*

Oxygen: *added*

Cross-reference to Primary Health Care chapter: Medicines for palliative care; section 22.3.1: Dyspnoea for primary management as morphine oral solution; whilst the Adult Hospital level STG essentially provides guidance for management with oxygen in patients with dyspnoea.

Refer to PHC medicine review: Morphine for dyspnoea in palliative care, September 2017:

Morphine for dyspnoea in palliati

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

24.4.2 RESPIRATORY SECRETIONS

Hyoscine buthylbromide (butylscopalamine), SC/IM: *added*

Refer to medicine review: Hyoscine for death rattle in palliative care, July 2017:

Hyoscine for death rattle in palliative ca

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: The Adult Hospital Level Committee recommends that the consideration be made for the inclusion of hyoscine butylbromide injection in palliative care for "death rattle".

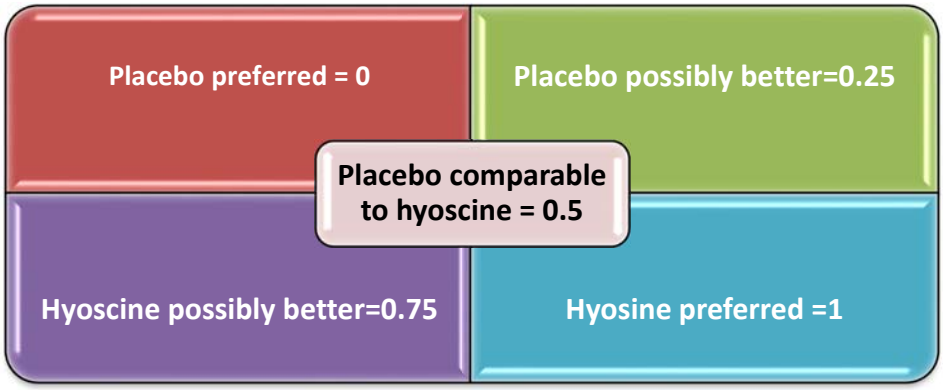
Rationale: Despite the lack of evidence of benefit for hyoscine to reduce respiratory secretions in the terminally ill patient, parenteral hyoscine is standard of care in many international guidelines[37] to reduce "death rattle". The Adult Hospital Level Committee also considered ethics and other value judgements (as

[36] Radbruch L, Strasser F, Elsner F, Gonçalves JF, Løge J, Kaasa S, Nauck F, Stone P; Research Steering Committee of the European Association for Palliative Care (EAPC). Fatigue in palliative care patients -- an EAPC approach. Palliat Med. 2008 Jan;22(1):13-32. https://www.ncbi.nlm.nih.gov/pubmed/18216074

[37] Douglas C, Murtagh FEM, Chambers EJ, Howse M, Ellershaw J. Symptom management for the adult patient dying with advanced chronic kidney disease: A review of the literature and development of evidence-based guidelines by a United Kingdom Expert Consensus Group. Palliative medicine. 2009;23(2):103-10.

assessed by the HTA Core Model assessment), and proposes compassionate use of parenteral hyoscine for death rattle in terminally ill patients. This was accepted by the NEMLC at the meeting of 5 December 2019[38].
Level of Evidence: III Guidelines, Expert opinion

Considerations
Evidence: No evidence could be sourced to show that hyoscine butylbromide (or any intervention) is superior to placebo in decreasing secretions in the terminally ill. Guidelines recommend compassionate use of this agent for the benefit of the family and healthcare worker treating these patients.
Collaboration: A query was submitted to the International Network of Agencies for Health Technology Assessment (INAHTA) to determine if any work had been done for "death rattle" in palliative care. However, it was reported that this is the accepted norm internationally to improve the quality of life for patients and their caregivers/ family.
Value judgement: A comprehensive health technology assessment reviewing other domains (besides clinical effectiveness and costs and economic evaluation) piloting the European network for health technology assessment (EUnetHTA) HTA Core Model framework was done by the Adult Hospital Level Committee.
Similar to the AGREE II instrument, the HTA Core Model is a registered trademark and a methodological framework for collaborative production and sharing of HTA information. Considers benefit-risk balance, ethics and value judgments, and attempts to adhere to the definitions of HTA that emphasise the multidisciplinary nature of assessments, and it employs the nine domains. These domains were ranked according to priority by the Adult Hospital Level Committee for the assessment of hyoscine butylbromide, and elements in each domain were rated based on appropriate evidence, using the following scale:



The total weighted score for this assessment was 0.70, favouring hyoscine as ranked and measured by the Adult Hospital Level Committee (noting that the domain for ethical analysis scored the highest).

24.5 SEDATION IN PALLIATIVE CARE

Lorazepam, oral: *retained*
Haloperidol, oral: *retained and dose amended*
Section 23.1.3: Sedation in palliative care was moved from chapter 23: Sedation to chapter 24: Medicines for use in palliative care, with a cross reference.

The sole pharmaceutical supplier has discontinued haloperidol 0.5 mg from the South African market; however the 1.5 mg and 2.5 mg formulations are still currently available. Both tablet strengths are scored. Dose for haloperidol was amended as follows:

Dosing in frail, often elderly patients should be titrated to effect.
- Lorazepam, oral, 0.5 mg 4 hourly.

OR

Haloperidol, oral, ~~0.5~~ 0.75 mg 4 hourly.

Level of Evidence: III Guidelines[39]

[38] Minutes of the NEMLC meeting of 5 December 2019.
[39] SAMF, 2016

Patient unable to take oral medication or terminal sedation required:

Midazolam, IV/SC: *added*

Guidelines by Schildmann et al[40] suggests that midazolam was the mainstay of treatment for terminal/palliative sedation. No RCT evidence was reported to be available to support this recommendation, though. Dosing was aligned with the European association for palliative care (EAPC) recommended framework for the use of sedation in palliative care.[41]

Level of Evidence: III Guidelines

Propofol*: not added*

Not recommended due to associated cardiovascular toxicity, respiratory depression, pain on injection and requires intravenous access in this setting.

Level of Evidence: III Expert opinion

Report prepared by TD Leong: Secretariat to the Adult Hospital Level Committee (2017-2020)

- ***Note:*** *Information was sourced from NEMLC ratified minutes and NEMLC-approved documents.*

[40] Schildmann EK, Schildmann J, Kiesewetter I. Medication and monitoring in palliative sedation therapy: a systematic review and quality assessment of published guidelines. J Pain Symptom Manage. 2015 Apr;49(4):734-46. https://www.ncbi.nlm.nih.gov/pubmed/25242022

[41] Cherny NI, Radbruch L; Board of the European Association for Palliative Care. European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care. Palliat Med. 2009 Oct;23(7):581-93. https://www.ncbi.nlm.nih.gov/pubmed/19858355