

**SOUTH AFRICAN PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 22: MEDICINES FOR PALLIATIVE CARE
NEMLC RECOMMENDATIONS FOR MEDICINE MANAGEMENT (2016 – 2018)**

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

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.

Preamble to the chapter describes a few general principles of palliative care and states that where down-referral management is required that the patient be down-referred with a care plan.

Palliative care delivery model: Some palliative care conditions (e.g. diarrhoea, nausea and vomiting) could be managed at primary level of care. However, conditions such as respiratory secretions, anorexia, fatigue etc. are short-term conditions for terminally ill patient populations that are best managed by specially trained palliative care teams. The benefits of treatment for anorexia for example are likely to be minimal and short-lived, with a high potential for adverse effects – patients must be carefully selected for treatment; for many/most patients, pharmacological intervention is inappropriate. So the Primary Health Care (PHC) Committee was of the opinion that these patients should not be managed at all PHC facilities, and rather managed via down-referral mechanisms for the time being. As per the National Strategic Plan, palliative care healthcare workers are still to be trained and the infrastructure for delivery of palliative care is still to be developed.

Recommendations:

- Palliative care STGs for end of life settings (i.e. anorexia and cachexia; fatigue and respiratory secretions) not be included in the PHC palliative care chapter, but referred to secondary level of care (with guidance described in the respective Adult Hospital STGs)
- Text be included in the foreword of this chapter regarding down-referral processes with care plans and management by trained palliative care teams where appropriate and if available.

Chapter layout:

22.1 Gastrointestinal conditions
22.1.1 Constipation
22.1.2 Diarrhoea
22.1.3 Nausea and vomiting
22.2 Neuropsychiatric conditions
22.2.1 Anxiety
22.2.2 Delirium

¹ Minutes of the NEMLC meeting of 6 April 2017

22.2.3 Depression
 22.3 Respiratory conditions
 22.3.1 Dyspnoea
 22.4 End of life care

SECTION	MEDICINE	ADDED/DELETED/AMENDED/NOT ADDED/ RETAINED
22.1.1 Constipation	Sennosides A and B, oral	Added
	Lactulose, oral	Added
	Glycerine, suppositories	Not added
	Phosphate enemas	Not added
	Bisacodyl suppositories	Not added
	Sorbitol, oral	Not added
	Lactulose, oral	Retained
For management of opioid-induced constipation:	Bisacodyl suppositories	Not added
	Glycerine suppositories	Not added
22.1.2 Diarrhoea	Loperamide, oral	Added
	Sugar salt solution (Oral rehydration solution)	Cross-reference added to Section 2.9.1 Diarrhoea, acute in children.
22.1.3 Nausea and vomiting	Metoclopramide, oral	Added
	Ondansetron, oral	Not added
	Haloperidol	Not added
	Cyclizine	Not added
	Dexamethasone/Betamethasone	Not added
	Lorazepam:	Not added
22.2.1 Anxiety	Fluoxetine, oral	Added
	Citalopram, oral	Added
	Diazepam, oral	Added
	Lorazepam, sublingual	Not added
	Clonidine	Not added
22.2.2 Delirium	Haloperidol, IM	Not added;
	Diazepam, IV	Added with dosing for elderly, frail patients, liver disease
	Midazolam, IM	Added with dosing for elderly, frail patients, liver disease
22.2.3 Depression	Fluoxetine, oral	Added
	Citalopram, oral	Added
	Amitriptyline	Added
22.3.1 Dyspnoea	Morphine syrup	Added
	Oxygen (home-based)	Not added

An external comment that the STGs and EML need to be expanded to include general guidance and not only guidance regarding medicine treatment was not accepted, as the PHC Committee had recommended that this section wouldn't be a textbook, and were advised by the Palliative Care Technical Working Group that other National Department of Health guidelines would be developed.

22.1.1 CONSTIPATION

Sorbitol, oral: not added

Lactulose, oral: retained

An external commenter suggested that sorbitol was cheaper than lactulose.

A MCC-registered sorbitol product could not be sourced and the current tender price for lactulose is R29.13 (150 ml) and R 84.43 (500 ml)².

For management of opioid-induced constipation:

An external commenter suggested that suppositories (in addition to oral treatment) are necessary to treat constipation in palliative care (no evidence provided).

Bisacodyl suppositories: not added

Glycerine suppositories: not added

Recommendation: Glycerine and bisacodyl suppositories not be included on the PHC EML.

Rationale: Glycerine suppositories for adults are not currently on the National EML, but the Adult Hospital Level Committee is currently reviewing this. The PHC Committee upheld NEMLC's approval for not including bisacodyl suppositories on the PHC EML. Patients would be referred to secondary level for required management of constipation with suppositories (with access at PHC through down-referral mechanisms where appropriate). Pragmatic implication is that as an essential medicine, these suppositories would be required to be stocked at every primary level facility for this single indication.

Level of Evidence: III Expert opinion

Recommendations previously accepted by NEMLC on 2 November 2017³

NEMLC report of 2 November 2017:

Sennosides A and B, oral: added

Lactulose, oral: added

Glycerine suppositories: not added

Phosphate enemas: not added

Bisacodyl suppositories: not added

Sennosides, lactulose, oral: Recommendations for sennosides A and B, oral and lactulose, oral was aligned with the constipation STG in the PHC gastro-intestinal chapter. However, no available RCT evidence could be sourced for combination therapy (sennosides + lactulose) for managing constipation in palliative care; though combination therapy is standard of care in most guidelines.

Recommendation: Combination therapy sennosides A and B, oral with lactulose, oral be recommended for constipation in palliative care where appropriate.

Rationale: Aligned with guidelines⁴.

Level of Evidence: III Guidelines

Glycerine suppositories; phosphate enema: The PHC Committee was of the opinion that children who were unable to swallow and require suppositories or enemas for management of constipation need to be referred to secondary level of care. Down-referral processes would then be required for continuum of care of this select patient population.

Recommendation: Glycerine suppositories and phosphate enemas not be included on the Primary Health Care EML as an essential medicine.

Rationale: Children who are unable to swallow and who require suppositories or enemas for management of constipation is a small population group and should be managed at secondary level of care with down-referral for continuum of care.

Level of Evidence: III Expert opinion

² Contract circular RTT300-2017

³ NEMLC report and respective NEMLC minutes for the PHC palliative care chapter, 2 November 2017.

⁴ 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>

Bisacodyl suppositories (Refer to the medicine review for detailed information): Evidence for bisacodyl suppositories compared to other laxatives is limited and of low quality. However, guidelines recommend this agent as second line option.

Recommendation: *Bisacodyl suppositories not be included in the EML for primary level of care. However, this medicine could be considered for use at hospital level where short-term use would be restricted specifically in patients who cannot swallow. The PHC Committee was of the opinion that it was not appropriate to initiate management at primary level of care, but should be initiated by palliative care teams and accessed at primary level of care should down-referral mechanism if required.*

Rationale:*Use of bisacodyl suppositories for constipation in palliative care would be limited to a small population of patients: adult palliative care patients who cannot swallow. This agent should be accessed through a down-referral mechanism from secondary level of care. There is no evidence of superiority to alternate laxatives that are currently included in the primary health care EML.*

Level of Evidence: III Expert opinion

(Note: Medicine review to be forwarded to Adult Hospital Level Committee).

22.1.2 DIARRHOEA

Sugar salt solution (Oral rehydration solution): *added*

An external commenter mistakenly thought that the STG advised against rehydration of children with diarrhoea, despite the wording 'rehydrate the patient as appropriate if necessary'. To clarify this, the PHC ERC added a cross-reference to the GIT chapter.

Recommendation: Cross-reference was made to Section 2.9.1 Diarrhoea, acute in children and Section 2.9.3 Diarrhoea, acute, without blood, in adults.

Level of Evidence: III Expert opinion

Loperamide, oral:*added*

Oral rehydration solution:*not added*

Adult management was aligned with diarrhoea STGs in the PHC gastro-intestinal chapter. However, vigorous rehydration for children is not considered appropriate. Terminally ill children should be down-referred from secondary level of care with a care plan.

Level of Evidence: III Standard practice, Expert opinion

22.1.3 NAUSEA AND VOMITING

Metoclopramide, oral: *added*

Ondansetron, oral: *not added*

Haloperidol: *not added*

Cyclizine: *not added*

Dexamethasone/Betamethasone: *not added*

Lorazepam: *not added*

Metoclopramide, oral: Palliation recommendations for adults aligned with the nausea and vomiting STG in the PHC gastro-intestinal chapter; and children recommendations aligned to the Paediatric Hospital level STG, 2016 and a weight-band table for metoclopramide dosing in children was developed:

Children:

- Metoclopramide, oral, 0.1 mg/kg/dose, 8–12 hourly.

Weight kg	Dose mg	Syrup 5 mg/5 mL	Age months/years
>9–11 kg	1 mg	1 mL	>12–18 months
>11–14 kg	1.2 mg	1.2 mL	>2–3 years
>14–17.5 kg	1.6 mg	1.6 mL	>3–5 years
>17.5–25 kg	2 mg	2 mL	>5–7 years

>25–35 kg	3 mg	3 mL	>7–11 years
>35–55 kg	4.5 mg	4.5 mL	>11–15 years

Level of Evidence: III Guidelines

Ondansetron: The PHC Committee was of the opinion that ondansetron would mostly be indicated for nausea and vomiting associated with chemotherapy and thus, should not be included in the PHC EML. Down-referral management to provide access to the relevant medicines.

Haloperidol, cyclizine, steroids, lorazepam: The PHC Committee was of the opinion that management with these medicines should be at secondary level of care; with access via down-referral mechanisms, as the underlying conditions for which they are indicated are unlikely to be diagnosed at PHC level.

Gastroparesis: Although management is mentioned in the endocrine chapter, the PHC Committee was of the opinion that palliative care patients with gastroparesis should be managed at secondary level of care with down-referral.

22.2.1 ANXIETY

Fluoxetine, oral: *added*

Citalopram, oral: *added*

Diazepam, oral: *added*

Lorazepam, sublingual: *not added*

Clonidine: *not added*

*Cochrane review*⁵ concluded that no firm conclusion could be drawn about the effectiveness of medicine therapy for anxiety in adult cancer patients receiving palliative care; and recommendation was added to the STG to offer referral for psychotherapy if available.

SSRIs: Medicine management aligned with the PHC and Adult Hospital level (2015) mental health care chapters, with referral of children to secondary level of care for management (and continued access to medicines via down referral).

Benzodiazepines: Medicine management aligned with the PHC (2014) and Adult Hospital level (2015) mental health care chapters, with referral of children to secondary level of care for management (and continued access to medicines via down referral); noting that diazepam is available as a 5 mg tablet:

Lorazepam, sublingual; clonidine: Motivation for these medicines for palliation in children were not considered as all children are referred to secondary level of care for management (with continued access to medicines via down referral); until the service delivery platform for palliative care has been developed and implemented.

22.2.2 DELIRIUM

Diazepam, IV: *added with dosing for elderly, frail patients and patients with liver disease*

The following text was added, aligned with the SAMF 2016:

Elderly or frail patients, or those with liver impairment:

- Diazepam, IV, 5 mg
 - If no response, give a 2nd dose.
 - Do not administer at a rate over 5 mg/minute.

Level of Evidence: III Guidelines

⁵ Salt S, Mulvaney CA, Preston NJ. Drug therapy for symptoms associated with anxiety in adult palliative care patients. Cochrane Database Syst Rev. 2017 May 18;5:CD004596. <https://www.ncbi.nlm.nih.gov/pubmed/28521070>

Midazolam, oral: *added with dosing for elderly, frail patients and patients with liver disease*

The dose of 7.5-15 mg was retained, as 7.5 mg was estimated to be equivalent to 5 mg diazepam – dose recommended in the frail and elderly – please see above.

Level of Evidence: III Guidelines⁶

Haloperidol: *not added*

An external comment to add haloperidol was not accepted, as no further evidence was forwarded, following tabling of evidence that was accepted by NEMLC at the meeting of 2 November 2017:

Cochrane review⁷ concluded that there is insufficient evidence to determine the role of medicine treatment for delirium in terminally ill patients.

Haloperidol is generally recommended as first line treatment in guidelines⁸. There is very limited evidence for efficacy, but there is risk of harm (i.e. increased agitation)⁹. A recent study (n=249) showed that placebo improved symptoms significantly more than haloperidol¹⁰ and authors suggested that eliminating precipitants and supportive measures are more important than treatment with antipsychotics. A systematic review¹¹ 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; I²=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.

Antipsychotics: **Level of Evidence: I Systematic review, RCT**

Benzodiazepines: **Level of Evidence: III Standard of care¹², Expert opinion.**

This section cross-refers to section 21.2.4: Delirium with acute confusion and aggression in adults, for supportive palliative care as opposed to end-of-life palliative care.

22.2.3 DEPRESSION

Fluoxetine, oral: *added*

Citalopram, oral: *added*

Amitryptiline, oral: *added*

⁶ SAMF, 2016

⁷Candy 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>

⁸Grassi 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.

⁹Crawford GB, Agar M M, 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.

¹⁰Agar 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>

¹¹Neufeld 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. <https://www.ncbi.nlm.nih.gov/pubmed/2700473>

¹²Grassi 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>

Medicine management aligned with the PHC and Adult Hospital level (2015) mental health care chapters and caution regarding tricyclic antidepressants (TCAs) in palliation added to the text of the STG as follows (aligned with SAMF, 2016):

Note: Tricyclic antidepressants may cause dry mouth, constipation, urinary retention, and confusion, which might be especially problematic in palliative care patients. Use the lowest dose possible, and titrate slowly.

Level of Evidence: III Guidelines

22.3.1 DYSPNOEA

Morphine syrup: *added*

(Refer to the medicine review for detailed information)



Morphine
solution_Dyspnoea

Based on the evidence review, the Primary Health Care Committee recommends the addition of oral morphine for the management of palliative dyspnea in paediatric and adult patients receiving palliative care.

Rationale: Systematic review and metaanalysis of limited low quality RCTs suggests that oral opioids may be of benefit to palliate breathlessness in adults; however, studies were very small. There is a paucity of RCT data for the management of palliative dyspnoea in children; however morphine, oral is standard of care as recommended in a number of guidelines.

Level of Evidence: II Systematic review of low to very low RCTs, III Guidelines

Home-based oxygen: *not added*

As the Paediatric Hospital level STG (2016) recommends home-based oxygen; the need for oxygen for hypoxia be included as a referral criterion.

FATIGUE

Betamethasone/dexamethasone, oral: *not added*

(Refer to the medicine review for detailed information).



Betamethasone for
fatigue in palliative

There is very limited evidence and recommended use appears to be guided by expert opinion. There is no clear evidence of efficacy, or safety or evidence for dosage, duration of treatment, specific indications/contraindications. Primarily used short-term in specific patients who are terminally ill and the risk of adverse effects should be taken into consideration.

Recommendation:

- Dexamethasone/betamethasone not be included in the PHC EML, but considered for the Adult Hospital level EML. Not appropriate for initiation at PHC, but should be prescribed by palliative care teams, and accessed at PHC via down-referral mechanisms if necessary.

Level of Evidence: III Expert opinion

(Note: Medicine review to be forwarded to Adult Hospital Level Committee).

ANOREXIA AND CACHEXIA

Betamethasone/dexamethasone, oral: not added
(Refer to the medicine review for detailed information).



Betamethasone_An
orexia-PalliativeCare

Similar to use of these medicines in fatigue amongst palliative care patients, there is very limited evidence and medicine is generally used short term use in the terminally ill.

Recommendation:

- Dexamethasone/betamethasone not be included in the PHC EML, but considered for the Adult Hospital level EML. Not appropriate for initiation at PHC, but should be prescribed by palliative care teams, and accessed at PHC via down-referral mechanisms if necessary.

Level of Evidence: III Expert opinion

(Note: Medicine review to be forwarded to Adult Hospital Level Committee).

The PHC Committee identified the need for guidance on mouth care and management of pressure sores in palliation. Evidence pertaining to this will be reviewed, whilst the chapter is being disseminated for external comments.