**PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST**

**CHAPTER 22: MEDICINES FOR PALLIATIVE CARE**

**RECOMMENDATIONS FROM THE NEMLC MEETING: 2 NOVEMBER 2017**

**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]](#footnote-2)

**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:

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| 22.1 Gastrointestinal conditions22.1.1 Constipation22.1.2 Diarrhoea22.1.3 Nausea and vomiting22.2 Neuropsychiatric conditions22.2.1 Anxiety22.2.2 Delirium22.2.3 Depression22.3 Respiratory conditions22.3.1 Dyspnoea22.4 End of life care |

**A: NEW SECTIONS(S)**

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| **SECTION** | **CONDITION** | **MEDICINE**  | **MEDICINE ADDED/NOT ADDED** |
| **22.1.1** | **Constipation** | Sennosides A and B, oral | Added |
| Lactulose, oral | Added |
| Glycerine, suppositries | Not added |
| Phosphate enemas | Not added |
| Bisacodyl suppositories | Not added |
| **22.1.2** | **Diarrhoea** | Loperamide, oral | Added |
| Oral rehydration solution | Not added |
| **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 |
| Midazolam, IM | Added |
| **22.2.3** | **Depression** | Fluoxetine, oral | Added |
| Citalopram, oral | Added |
| Amitriptyline | Added |
| **22.3.1** | **Dyspnoea** | Morphine syrup | Added |
| Oxygen (home-based) | Not added |
| **Not added**  | **Fatigue** | Betamethasone/dexamethasone, oral | Not added |
| **Anorexia/cachexia** | Not added |

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| **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*

*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 guidelines[[2]](#footnote-3).

**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**

*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 appropiate 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).

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| **22.1.2 DIARRHOEA** |

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**

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| **22.1.3NAUSEA 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 withthe 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:

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| Children:* Metoclopramide, oral, 0.1 mg/kg/dose, 8–12 hourly.

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| **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 |

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**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.

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| **22.2.1ANXIETY** |

Fluoxetine, oral:*added*

Citalopram, oral: *added*

Diazepam, oral:*added*

Lorazepam, sublingual:*not added*

Clonidine: *not added*

*Cochrane review[[3]](#footnote-4)*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 (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).

*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.

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| **22.2.2DELIRIUM** |

Haloperidol, IM: *not added*

Midazolam, IM: *added*

Diazepam, IV:*added*

*Cochrane review[[4]](#footnote-5)* concluded that there is insufficient evidence to determine the role of medicine treatment for delirium in terminally illpatients.

*Haloperidol* is generally recommended as first line treatment in guidelines[[5]](#footnote-6). There is very limited evidence for efficacy, but there is risk of harm (i.e. increased agitation)[[6]](#footnote-7). A recent study (n=249) showed that placebo improved symptoms significantly more than haloperidol[[7]](#footnote-8) and authors suggested that eliminating precipitants and supportive measures are more important than treatment with antipsychotics. A systematic review[[8]](#footnote-9) 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 care[[9]](#footnote-10), Expert opinion.**

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| **22.2.3DEPRESSION** |

Fluoxetine, oral: *added*

Citalopram, oral: *added*

Amitryptiline, oral:*added*

Medicine management aligned with the PHC (2014) 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):

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| **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**

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| **22.3.1DYSPNOEA** |

Morphine syrup:*added*

(Refer to the medicine review for detailed information)

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 recommmended 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.

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| **FATIGUE** |

Betamethasone/dexamethasone, oral:*not added*

(Refer to the medicine review for detailed information).

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).

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| **ANOREXIA AND CACHEXIA** |

Betamethasone/dexamethasone, oral:*not added*

(Refer to the medicine review for detailed information).

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.

1. Minutes of the NEMLC meeting of 6 April 2017 [↑](#footnote-ref-2)
2. 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> [↑](#footnote-ref-3)
3. 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> [↑](#footnote-ref-4)
4. 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> [↑](#footnote-ref-5)
5. 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. [↑](#footnote-ref-6)
6. Crawford 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. [↑](#footnote-ref-7)
7. 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 [↑](#footnote-ref-8)
8. 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. https://www.ncbi.nlm.nih.gov/pubmed/2700473 [↑](#footnote-ref-9)
9. 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> [↑](#footnote-ref-10)