

**South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Palliative Care**

MEDICINE REVIEW:

1. Executive Summary

Date: November December 2017
Medicine (INN): Haloperidol
Medicine (ATC): N05AD01
Indication (ICD10 code): The treatment of nausea and vomiting in palliative care patients R11 + (Z51.5)
Patient population: Patients with intractable nausea and vomiting at end of life not effectively controlled by other anti-emetics.
Prevalence of condition: Unknown
Level of Care: Palliative care: doctor or professional nurse
Prescriber Level: Hospital and primary health care/palliative care
Current standard of Care: Metoclopramide
Efficacy estimates: (preferably NNT): n/a
Motivator/reviewer name(s): MFPC van Jaarsveld, TD Leong
PTC affiliation: Free State

2. Name of author(s)/motivator(s)

MFPC van Jaarsveld, TD Leong

3. Author affiliation and conflict of interest details

MFPC van Jaarsveld: Department of Internal Medicine University of Free State, Co-opted expert to the Adult Hospital Level Committee (2017-2020); No conflict of interests.

TD Leong: National Department of Health, Essential Drugs Programme; Secretariat to the Adult Hospital Level Committee (2017-2020); No conflict of interests.

4. Introduction/ Background

Nausea and vomiting is a common and distressing symptom during End of Life care and play a major role in quality of life of the patient. The choice of medicine used in treatment is based on the underlying pathophysiology and at end of life, many different etiological factors contribute to nausea and vomiting and single drug use is most often not effective in controlling this devastating symptom. Therefore, combination agents are commonly used to effectively address nausea and vomiting. There is in general very poor evidence to guide the treatment of nausea and vomiting (N&V) in palliative care and most guidelines is based on expert opinion and past experience. It is also important to note that patients at end of life experience combination of symptoms and careful consideration of all the symptoms and best treatment options available to alleviate these symptoms; taking in consideration the side effect profile, route of administration and drug-drug interactions play a critical role in choice of drug-combination.

5. Purpose/Objective i.e. PICO question

-**P(patient/population)**: Patient which intractable N&V not responding to metoclopramide alone, where metoclopramide is contra-indicated or patients with N&V and end of life restlessness/delirium.

-**I(intervention)**: Treatment of underlying cause is not possible or effective, and where end of life restlessness/ delirium contributes to poor quality of life.

-**C(comparator)**: Refractory to metoclopramide.

-**O(outcome)**: Reduce nausea and vomiting and addressing restlessness/delirium and potentially lower dosage of metoclopramide is needed, therefore improving quality of life

6. Methods:

i) Search described in the WHO EML review

a. **Data sources**: Medline, PubMed and Embase electronic databases were used to search for systematic review articles.

b. **Search strategy**: MeSH search key words: nausea, vomiting, antiemetics, palliative care, hospices, hospice care, terminal care. The search was limited to studies in humans published in English. The WHO EML was also used to identify articles not included during the search process.

ii) Second search strategy

a. **Data source**: Tripdatabase

b. **Search strategy**: Search terms: haloperidol, nausea, vomiting, palliative care, restricted to systematic reviews.

c. **Excluded studies**: Three systematic reviews were retrieved, but the following two were excluded:

Systematic review	Reason for exclusion
Perkins P, Dorman S. Haloperidol for the treatment of nausea and vomiting in palliative care patients. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD006271.	Cochrane review update in 2015
Maltoni M, Scarpi E, Rosati M, Derni S, Fabbri L, Martini F, Amadori D, Nanni O. Palliative sedation in end-of-life care and survival: a systematic review. J Clin Oncol. 2012 Apr 20;30(12):1378-83.	Indication: Palliative sedation.

7. Evidence Synthesis

Authors	Type of Study	Subjects	Results	Comment
Glare et al, 2004	Systematic review	21 studies: 2 systematic reviews, 7 RCTs and 12 uncontrolled studies or case series.	Two methods of antiemetic choice (the inferred mechanism or empirical) were equally effective. Reasonably strong evidence for the use of metoclopramide in cancer-associated dyspepsia and steroids in malignant bowel obstruction. Conflicting evidence about the efficacy of serotonin antagonists compared with standard treatments (e.g. metoclopramide, dopamine antagonists and dexamethasone). There was little or no evidence of the efficacy of some commonly used and seemingly effective drugs such as haloperidol, cyclizine, and methotrimeprazine.	The management of nausea in advanced cancer will continue to be based on expert opinion rather than evidence. A few recommendations based on the results of this review (graded- see full article for supporting evidence) Metoclopramide is effective in the management of nausea in advanced cancer (grade of recommendation: A) Haloperidol may be effective in the management of nausea in advanced cancer (grade of recommendation: C) Other standard antiemetics recommended for the management of nausea in advanced cancer, including cyclizine, steroids and methotrimeprazine may be effective in the management of nausea in advanced cancer (grade of recommendation: B)
Davis & Hallerberg, 2010	Systematic review of antiemetics for emesis in cancer unrelated to chemotherapy and radiation	93 articles included: 14 RCTs; prospective single-drug studies that used guidelines based on the aetiology of emesis, cohort, retrospective and case series or single-patient reports. Studies involving treatment of emesis related to bowel obstruction were included. Studies involving chemotherapy, radiation, or post operation related emesis were excluded.	Metoclopramide had modest evidence (grade of recommendation: B) based on RCTs and prospective cohort studies. Octreotide, dexamethasone, and hyoscine butylbromide are effective in reducing symptoms of bowel obstruction, based on prospective studies and/or one RCT. There was no evidence that either multiple antiemetics or antiemetic choices based on the aetiology of emesis were any better than a single antiemetic. There is poor evidence for dose response, intra-class or inter-class drug switch, or antiemetic combinations in those individuals failing to respond to the initial antiemetic.	Most studies were of low quality, based either on lack of blinding, lack of description of the method of randomization, concealment, and/or attrition. (grade of recommendation: C)

Walsh et al, 2016	Consensus recommendations, based on available systematic reviews	Available systematic reviews on antiemetic drug effectiveness were used. One generic systematic review of antiemetics in advanced cancer (to 2009) (Davis & Hallerberg (2010) was updated to February 2016.	The medicine of choice for managing nausea and vomiting in advanced cancer is metoclopramide titrated to effect. Alternative options include haloperidol, levomepromazine, or olanzapine. For bowel obstruction, the recommendation is to use octreotide given alongside an antiemetic (haloperidol) and where octreotide is not an option to use an anticholinergic anti-secretory agent. For opioid-induced nausea and vomiting, no recommendation could be made. Agreement on recommendations was reached between panel members, and these were voted in favor unanimously by the larger antiemetic committee membership (n = 37).	The evidence base in this field is minimal with largely poor quality trials or uncontrolled trials and case studies. The level of evidence in most studies is low.
Murray-Brown et al 2015	Cochrane review (1 published RCT, 1 conference abstract)	RCTs of haloperidol for the treatment of n & v, or both, in adults receiving palliative care or suffering from an incurable progressive medical condition. RCTs excluded: n & v secondary to pregnancy or surgery.	Authors concluded that "There is incomplete evidence from published RCTs to determine the effectiveness of haloperidol for nausea and vomiting in palliative care. Other than the trial of ABH gel vs placebo, we did not identify any fully published RCTs exploring the effectiveness of haloperidol for nausea and vomiting in palliative care patients for this update, but two trials are underway". The one small RCT showed that ABH gel containing haloperidol, diphenhydramine and lorazepam was not significantly better than placebo; but topical haloperidol is poorly absorbed. Two RCTs underway at the time of Cochrane review update and a conference abstract of one ongoing trial suggests that haloperidol is effective for 65% of patients.	Limited published RCT evidence is available. The next Cochrane update to review results from two ongoing RCTs. It is noted that there are a number of unpublished RCTs.

8. Evidence quality:

WHO EML Grading of Recommendations Assessment, Development and Evaluation (GRADE 2007)

<i>Code</i>	<i>Quality of Evidence</i>	<i>Definition</i>
A	High	Further research is very unlikely to change our confidence in the estimate of effect. <ul style="list-style-type: none">• Several high-quality studies with consistent results.• In special cases: one large, high-quality multi-centre trial
B	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. <ul style="list-style-type: none">- One high-quality study- Several studies with some limitations
C	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. <ul style="list-style-type: none">- One or more studies with severe limitations
D	Very Low	Any estimate of effect is very uncertain. <ul style="list-style-type: none">- Expert opinion- No direct research evidence- One or more studies with very severe limitations

There is limited published RCT evidence to support or refute use of haloperidol for palliative nausea and vomiting to refute. Results from two ongoing trials are awaited.

Büttner et al (2004) pooled data from published and unpublished RCTs of haloperidol in postoperative nausea and vomiting, gastrointestinal disorders, and prophylaxis against chemotherapy-induced emesis, suggests a NNT for haloperidol 2 mg, IM in gastroenterology of 3 (2 to 4), but no conclusions could be drawn for chemotherapy and radiation therapy. Of note is industry funding of most RCTs and that trials were deemed to be of low methodological quality.

A recent prospective, multicenter, consecutive case series by Digges et al (2018) using Australian modified Karnofsky Performance Scale showed that haloperidol, administered orally or IM was effective in palliative nausea and vomiting with low-grade short-term harms. At 48 hours, 57 (39%) patients had \geq reduction in vomiting score and improved nausea reported in 105 (70%) patients. At day seven, mild/moderate harms were reported that included constipation 15 (25%); dry mouth 13 (21%); and somnolence 12 (19%).

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS										
QUALITY OF EVIDENCE	<p>What is the overall confidence in the evidence of effectiveness?</p> <p>Confident Not confident Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/></p>	<p>As in most areas of palliative care, there is no good quality evidence in literature that support the use of haloperidol in the treatment of nausea and vomiting at end of life. However, palliative care guidelines support the use of haloperidol mainly based on its past use for relieving symptoms of nausea and vomiting as well as restlessness/delirium at end of life stage using oral, IV IM or subcutaneous routes.</p>										
BENEFITS & HARMES	<p>Do the desirable effects outweigh the undesirable effects?</p> <p>Benefits outweigh harms Harms outweigh benefits Benefits = harms or Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>											
THERAPEUTIC INTERCHANGE	<p>Therapeutic alternatives available: n/a</p> <p>Yes No</p> <p><input type="checkbox"/> <input checked="" type="checkbox"/></p> <p>List the members of the group: n/a List specific exclusion from the group: n/a</p>	<p>Rationale for therapeutic alternatives included: n/a References: n/a</p> <p>Rationale for exclusion from the group: n/a References: n/a</p>										
VALUES & PREFERENCES / ACCEPTABILITY	<p>Is there important uncertainty or variability about how much people value the options?</p> <p>Minor Major Uncertain</p> <p><input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/></p> <p>Is the option acceptable to key stakeholders?</p> <p>Yes No Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>											
RESOURCE USE	<p>How large are the resource requirements?</p> <p>More intensive Less intensive Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/></p>	<p>Price of medicines</p> <table border="1"> <thead> <tr> <th>Medicine</th> <th>Cost (ZAR)</th> </tr> </thead> <tbody> <tr> <td>Haloperidol, 5mg/ml, 1ml inj</td> <td>R 43.71**</td> </tr> <tr> <td>Haloperidol 0.5 mg cap</td> <td>R 1.65*</td> </tr> <tr> <td>Haloperidol 1.5 mg tab</td> <td>R 0.18*</td> </tr> <tr> <td>Haloperidol 5 mg tab</td> <td>R 0.30*</td> </tr> </tbody> </table> <p>*Contract circular RT289-2019 (weighted average price) **SEP database, accessed November2019. https://mpr.code4sa.org/</p> <p>Additional resources: n/a</p>	Medicine	Cost (ZAR)	Haloperidol, 5mg/ml, 1ml inj	R 43.71**	Haloperidol 0.5 mg cap	R 1.65*	Haloperidol 1.5 mg tab	R 0.18*	Haloperidol 5 mg tab	R 0.30*
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Haloperidol 5 mg tab	R 0.30*											
EQUITY	<p>Would there be an impact on health inequity?</p> <p>Yes No Uncertain</p> <p><input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/></p>											

FEASIBILITY	Is the implementation of this recommendation feasible?			
	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	Uncertain <input type="checkbox"/>	

Type of recommendation	We recommend against the option and for the alternative <input type="checkbox"/>	We suggest not to use the option or to use the alternative <input type="checkbox"/>	We suggest using either the option or the alternative <input type="checkbox"/>	We suggest using the option <input checked="" type="checkbox"/>	We recommend the option <input type="checkbox"/>
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Recommendation: Based on this review, the Adult Hospital Level Committee recommends that haloperidol be recommended for palliative nausea and vomiting, where metoclopramide is contra-indicated or ineffective.

Rationale: There is no RCT evidence for haloperidol. However, a recent Pharmacovigilance case series study suggests haloperidol is effective in this setting.

Level of Evidence: III Pharmacovigilance case series study

Review indicator:

Evidence of efficacy <input checked="" type="checkbox"/>	Evidence of harm <input checked="" type="checkbox"/>	Price reduction <input type="checkbox"/>
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VEN status:

Vital <input type="checkbox"/>	Essential <input checked="" type="checkbox"/>	Necessary <input type="checkbox"/>
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NEMLC MEETING OF 5 DECEMBER 2019
NEMLC accepted the proposal as recommended by the Adult Hospital Level Committee, above.

Monitoring and evaluation considerations

Research priorities

References:

1. Cancer Care Alliance, UK. Network Supportive and Palliative Care Guidelines, 2006.
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4. De Lima L. International Association for Hospice and Palliative Care list of essential medicines for palliative care. Ann Oncol 2007; 18: 395-9.
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7. Walsh D, Davis M Ripamonti C Bruera E, Davies A and Molassiotis A. 2016 Updated MASCC/ESMO consensus recommendations: Management of nausea and vomiting in advanced cancer. *Support Care Cancer* 2017; 25:333–340
8. Murray-Brown F, Dorman S. Haloperidol for the treatment of nausea and vomiting in palliative care patients. *Cochrane Database Syst Rev*. 2015 Nov 2;(11):CD006271.
9. Büttner M, Walder B, von Elm E, Tramèr MR. Is low-dose haloperidol a useful antiemetic?: A meta-analysis of published and unpublished randomized trials. *Anesthesiology*. 2004 Dec;101(6):1454-63.
10. 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.