South Africa National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Medicines for palliative care

MEDICINE REVIEW:

1. Executive Summary

Date: July 2017
Medicine (INN): Promethazine
Medicine (ATC): Antihistamines for systemic use, (R06A)
Indication (ICD10 code): The treatment of nausea and vomiting in palliative care patients with complete and inoperable bowl obstruction (R11 + (Z51.5))
Patient population: Patients with intractable nausea and vomiting to complete and inoperable bowl obstruction at end of life
Prevalence of condition: Unknown
Level of Care: Palliative care: doctor or professional nurse
Prescriber Level: Secondary and primary level of care
Current standard of Care: n/a
Efficacy estimates: (preferably NNT): n/a
Motivator/reviewer name(s): MFPC van Jaarsveld
PTC affiliation: Free State

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

MFPC van Jaarsveld

3. Author affiliation and conflict of interest details

Department of Internal Medicine University of Free State; No conflict of interests declared.

4. Introduction/ Background

There is in general very poor evidence to guide the treatment of nausea and vomiting (N&V) in palliative care. Most guidelines are based on expert opinion and past experience. Treatment of Nausea and vomiting in palliative care setup in patient with increased intra-cranial pressure is an area where no RCT or systematic review could be found. However, the currently recommended pharmacologic management of N&V in palliative care is based on the mechanistic approached, targeting the most relevant neurotransmitter involved in the emetogenesis for a specific patient, notwithstanding the evidence that this approaches could not be proven superior to empiric treatment (1). This forms the basis for the use of agents with effect on histamine and cholinergic receptors; most commonly in situations where metoclopramide and haloperidol is ineffective or contra-indicated; both medicines mediicnehave little effect on these receptors. Therefore, promethazine, classified as an anti-histamine agent with anti-cholinergic properties remains in palliative guidelines an important medicine to use oral, deep IM or IV to treat N&V refractory to haloperidol and other anti-secretoric agents in patient with complete inoperable bowl obstruction to primary or secondary malignancies.

5. Purpose/Objective i.e. PICO question

-P*:* Patient which intractable N&V due to complete inoperable bowl obstruction.

-I*:* Promethazine

-C*:* Treatment of underlying cause is not possible or effective. Refractory to other anti-emetics used with/without adjunct corticosteroids.

-O*:* Reduced nausea and vomiting with improved quality of life

6. Methods:

a. Data sources

Search strategy: Medline, PubMed, Embase and Cochrane electronic databases were used to search for articles using the following MeSH search key words: anti-histamine agents, cyclizine, promethazine, nausea, vomiting, antiemetics, bowel obstruction, 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.

b. Evidence synthesis

Authors	Type of Study	Subjects	Results	Comment
SYSTEMATIC REVIEWS				
Glare et al 2004 (1)	Systematic Review (21 studies: 2 systematic reviews, 7 RCTs, 12 uncontrolled studies or case series)		Highly hetrogenous RCTs precluded any quantitative data synthesis and the 7 RCTs were prone to bias. Uncontrolled studies showed a high response rate to standard regimens (75 to 93% for both nausea and vomiting), but RCTs showed lower response rate (23 to 36% for nausea, 18 to 52% for vomiting). 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; but there is conflicting evidence for the efficacy of serotonin antagonists vs standard treatments (e.g. metoclopramide, dopamine antagonists and dexamethasone). Limited or no evidence for commonly used medicines such as haloperidol, cyclizine, and methotrimeprazine.	The management of nausea in advanced cancer will continue to be based on expert opinion rather than evidence.
Keeley 2009 (2)	Systematic review of RCTs, systematic reviews, comparative cohort studies)	Cancer patients and non-cancer patients with other chronic diseases for palliation of N&V	Antihistamines: No systematic review or RCTs were found.	Although antihistamines (cyclizine, prochlorperazine) are used for the control of nausea and vomiting in people with cancer, there is no evidence from well-conducted trials that they are beneficial. Despite the lack of robust RCT evidence, antihistamines are used for N&V in cancer patients, for motion sickness, mechanical bowel obstruction, and raised intracranial pressure.
Benze et al (2012b) (3)	Systematic review (75 studies: 5HT3 receptor antagonists, steroids, antihistamines, anticholinergics, somatostatin	Palliative care patients with far advanced cancer not receiving chemotherapy or radiotherapy, AIDS, COPD,	Evidence for any medicine used as an antiemetic is low. Concerning 5HT3 receptor antagonists, data are insufficient for recommendations on the treatment of patients with AIDS and MS due to the small size of included patient groups. For patients with cancer contradictory results were published: the larger studies showed a positive effect of 5HT3 receptor antagonists and better efficacy, as compared to metoclopramide, dexamethasone and neuroleptics. 5HT3	Recommendations in the literature are mainly based on studies in patients with cancer. Regarding symptom control of N&V in patients with COPD, progressive heart failure and ALS no studies were undertaken in patients receiving palliative care.

	analogs and canabinoides).	progressive heart failure, ALS or MS.	receptor antagonists can be used if treatment with other antiemetics, such as metoclopramide and neuroleptics is not sufficient. Heterogeneous results were found for steroids, with a positive trend for patients with cancer. Data are insufficient for antihistamines and benzodiazepines. Only 1 article was retrieved for antihistamines: case reports concerning two palliative care patients with gastrointestinal cancer; with control of nausea in both, reduction of vomiting in one.	Data insufficient for recommendations on the treatment of patients with AIDS and MS due to the small size of included patient groups. The overall strength of evidence is low. More well designed studies in palliative care patients are needed in order to provide evidence-based therapy
Davis & Hallerberg (2010) (4)	Systematic review (93 articles included: 14 RCTs, and other studies: prospective single-drug studies, studies that used guidelines based on the aetiology of emesis, cohort, retrospective and case series or single-patient reports.	N&V in advanced cancer unrelated to chemotherapy and radiation or post operation related emesis, but including emesis related to bowel obstruction.	Metoclopramide had modest evidence based on RCTs and prospective cohort studies. (grade of recommendation: B). 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, intraclass or interclass 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 bias. (grade of recommendation: C)
Walsh et al 2016 (5)	Systematic review(s) informing guideline recommendations	N & V in advanced cancer	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. The medicine of choice for managing N & V 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 antisecretory agent.	The use of cyclizine or 5-HT3 receptor antagonists is poorly defined to date and may be used where dopamine antagonists are contraindicated or ineffective. (grade of recommendation: D).

			For opioid-induced N & V, no recommendation could be made. Data is insufficient for antihistamines or 5-HT3 receptor antagonists.	
OBSERVATIONAL STUDY				
Kumar G et al 2008 (6)	Retrospective analysis of patient case notes	63 patients with cancer admitted for palliation of N&V in an inpatient veteran hospice population	57 patients (90%) had no vomiting within 1 to 3 days of staring antiemetic medication; as reflected in nursing notes. Antiemetic cocktail includes metoclopramide 10 mg with 25 mg diphenhydramine and 4 mg dexamethasone.	Of the 63 patients, 12 were switched to oral cocktail within 2 days, 28 were switched within 3 to 5 days, 38 were switched within 6 to 10 days, and 25 were never switched. Dexamethasone has synergistic effects with metoclopramide; whilst diphenhydramine prevents EPSE of metoclopramide.

c. Evidence quality:

(GRADE 2007): Table 1 - Grading of Recommendations Assessment, Development and Evaluation

Code	*Quality of Evidence*	*Definition*
A	High	Further research is very unlikely to change our confidence in the estimate of effect. • 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. - 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. - One or more studies with severe limitations
D	Very Low	Any estimate of effect is very uncertain. - Expert opinion - No direct research evidence - One or more studies with very severe limitations

EVIDENCE TO DECISION FRAMEWORK

<table>
<tr><th></th><th>JUDGEMENT</th><th>SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE</td><td>What is the overall confidence in the evidence of effectiveness?

Confident [ ] Not confident [ ] Uncertain [x]</td><td>There is no good quality evidence in literature that support the use of promethazine in patients with complete inoperable bowl obstruction (e.g. primary or secondary malignancies). However, guidelines on palliative care support the use of anti-histamine (cyclizine) mainly based on its use in the palliative care setting.
(Wiffen, P. Palliative Care Formula 5th edition, 2014. http://www.palliativedrugs.com/)</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable effects?
Benefits outweigh harms [ ] Harms outweigh benefits [ ] Benefits = harms or Uncertain [X]</td><td></td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:
Yes [x] No [ ]

List the members of the group.
Other anti-histamine agents, e.g.: cyclizine

List specific exclusion from the group: n/a</td><td>Rationale for therapeutic alternatives included: see reference below
References: Benze G, et al, 2012 (3)
Note: Promethazine is contra-indicated for sub-cutaneous, as severe tissue injury may occur from peri-vascular extravastation (SAMF, 2016)

Rationale for exclusion from the group: n/a
References: n/a</td></tr>
<tr><td>VALUES & PREFERENCES / ACCEPTABILITY</td><td>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 [x] No [ ] Uncertain [ ]</td><td></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/24 hr
<table><tr><th>Medicine</th><th>Cost (ZAR) max dose</th></tr><tr><td>Promethazine 12.5-25mg, IM, 4-6 hourly (100 mg/24h)*</td><td>17.72</td></tr><tr><td>Cyclizine 50 mg, oral, 6-8 hourly (200 mg/24 h)**</td><td>2.62</td></tr></table>* Contract circular RT297-2019 – 2mg/2mL injection = R5.47
**Contract circular RT289-2019 – R0.656/ 50 mg tablet
Additional resources: n/a</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes [ ] No [x] Uncertain [ ]</td><td></td></tr>
</table>

FEASIBILITY	Is the implementation of this recommendation feasible?	
	Yes [x] No [ ] Uncertain [ ]	

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	X	☐	☐

Recommendation

Based on this evidence review, the Committee acknowledges evidence is limited, but recommends antihistamines for intractable nausea and vomiting in patients with inoperable bowel obstruction, not responsive to haloperidol.

Rationale: Aligned with guidelines -Wiffen, P. Palliative Care Formula 5th edition, 2014 (7).

Level of Evidence: III Guidelines

NEMLC MEETING OF 5 DECEMBER 2019

NEMLC accepted the proposal as recommended by the Adult Hospital Level Committee, above.

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
x	x	

VEN status:

Vital	Essential	Necessary
	x	

Monitoring and evaluation considerations

Research priorities

RCTs with high methodology quality for Palliative care research in general

References:

1. Glare P, Pereira G, Kristjanson LJ, Stockler M, Tattersall M. Systematic review of the efficacy of antiemetics in the treatment of nausea in patients with far-advanced cancer. Support Care Cancer. 2004 Jun;12(6):432-40. https://www.ncbi.nlm.nih.gov/pubmed/15108099
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cannabinoids in palliative care patients: a systematic review]. Schmerz. 2012b Sep;26(5):481-99. [Article in German – English translation] https://www.ncbi.nlm.nih.gov/pubmed/22983450
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5. 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. https://www.ncbi.nlm.nih.gov/pubmed/27534961
6. Kumar G, Hayes KA and Clark R. Efficacy of a Scheduled IV Cocktail of Antiemetics for the Palliation of Nausea and Vomiting in a Hospice Population. American Journal of Hospice & Palliative Medicine. 2008: 25(3). https://www.ncbi.nlm.nih.gov/pubmed/18573994
7. Wiffen, P. Palliative Care Formula 5th edition, 2014. http://www.palliativedrugs.com/
8. South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.