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

MEDICINE REVIEW

1. Executive Summary

Date: November 2022
Medicine (INN): Olanzapine injection, orodispersible
Medicine (ATC): N05AH03
Indication (ICD10 code): Nausea and vomiting in palliative care R11 + (Z51.5)
Patient population: Adult palliative care patients with nausea and vomiting not responding to metoclopramide
Prevalence of condition: 62% to 71% (refs)
Level of Care: Hospital level (Adults)
Prescriber Level: Medical officer
Motivator/reviewer name(s): Trudy Leong, Dalene van Jaarsveld, Rene Krause
PTC affiliation: DVJ – Free State PTC; RK – Western Cape PTC

Key findings

- **Background:** Currently, haloperidol IM/SC/IV is the standard of care in the management of palliative nausea and vomiting where metoclopramide cannot be tolerated or is ineffective. Haloperidol injections have been discontinued from the South African market.
- We reviewed evidence for efficacy and safety of olanzapine in managing nausea and vomiting in adult palliative care patients.
- In a literature search conducted on 4 November 2022, we identified two systematic reviews that reported on 2 small randomised controlled trials (RCTs), which recruited participants with advanced cancer and malignant bowel obstruction, respectively. Both reviews were rated critically low on appraisal with AMSTAR 2.
- *Advanced cancer:* In a small randomised placebo controlled trial (n=30) Navari et al (2020) found that oral olanzapine 5mg reduced nausea scores by 8 (95% CI 7 to 8); p<0.001 compared to placebo, on an 11-point numerical rating scale (NRS) which rated nausea from 0 (no nausea) to 10 (severe nausea). Similarly, vomiting improved with a median of 2 fewer vomiting episodes per day (95% CI 2 fewer to 1 fewer vomiting episodes), p<0.001 Olanzapine exposure was not associated with excess sedation or other adverse effects (*very low quality evidence*).
- *Malignant bowel obstruction:* A small, underpowered, open-label RCT (n=16), reported in a letter by Kaneishi et al (2020), found similar reduction in nausea secondary to partial bowel obstructions, for a 3-day treatment course of olanzapine 5 mg/day compared to metoclopramide 20-30 mg/day. There was a change in score of −3.17 (NRS) for olanzapine and −2.38 (NRS) for metoclopramide, p=0.39 (*very low quality evidence*). Note that metoclopramide is a prokinetic and should therefore be avoided in patients with colic or abdominal pain.
- In summary, low to very low certainty evidence suggests that oral olanzapine may be considered in management of nausea and vomiting in advanced cancer or malignant bowel obstruction where metoclopramide is ineffective or not tolerated.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

Recommendation: Based on this review, the Adult Hospital Level Committee suggests that oral, oro-dispersable & IM olanzapine be used in adult palliative care patients with nausea and vomiting (N&V) not responding to metoclopramide, as a replacement to haloperidol.

Rationale: Haloperidol IM has been discontinued locally and an alternative for the management of N&V in palliative care patients is required. There is very little evidence to suggest that oral olanzapine may improve N&V and fatigue with no excessive sedation or adverse effects compared to placebo among adult patients with advanced cancer. Olanzapine may be as effective as metoclopramide in reducing N&V in malignant bowel syndrome.

Level of Evidence: Very low certainty evidence

Review indicator: New high-quality evidence of a clinically relevant benefit

NEMLC RECOMMENDATION – MEETING OF 23 FEBRUARY 2023:

NEMLC was in agreement with the recommendation by the Adult Hospital Level Committee & recommended oral, oro-dispersable & IM olanzapine be used in adult palliative care patients with nausea and vomiting (N&V) not responding to metoclopramide, as a replacement to haloperidol.

Monitoring and evaluation considerations

Research priorities

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

Dalene van Jaarsveld, Rene Krause, Trudy Leong

3. Author affiliation and conflict of interest details

DvJ (University of the Free State), RK (University of Cape Town), and TL (Cochrane-SA, Medical Research Council-SA; Right-To-Care as Secretariat support to the PHC/Adult Hospital Level Committee) have no conflict of interests to declare related to olanzapine.

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4. Introduction/ Background

Nausea and vomiting are regarded as one of the most distressing symptoms experiences by most palliative care patients (Leach, 2019). It is a common during the last days of life in patients with underlying cancer, heart failure, renal failure, AIDS, etc., and if not treated effectively, will cause deterioration in the patient's experience of quality of life and contribute to care giver distress.

Most palliative care symptom management guidelines, including the Adult Hospital Level Standard Treatment Guidelines (STGs) and Essential Medicine List STG (2019 edition), recommends metoclopramide as first line pharmacological therapy for nausea and vomiting in palliation. Currently, the STGs recommend haloperidol oral or administered intramuscularly or subcutaneously as a second-line option for those with retractable nausea and

vomiting with or without metoclopramide. Haloperidol injection has been withdrawn from the South African market and an alternative agent is required specifically in patients where the oral route is unsuitable.

Olanzapine is an atypical antipsychotic, and its antiemetic action is attributed to dopamine and serotonin antagonist properties. The palliative care formulary (7th edition, p 256) (3) recommends olanzapine as a second-line anti-emetic in patient where symptoms persist despite optimal first-line treatment. However, most RCT evidence is for olanzapine for chemotherapy-induced nausea and vomiting (Sutherland, 2018), and evidence for olanzapine as an antiemetic in palliative care settings (non-chemotherapy related nausea and vomiting in patients with advance disease) has been reported to be case series, case studies and observational studies (Saudemont, 2020).

An evidence review was conducted to study the safety and effectiveness of olanzapine in treating nausea and vomiting in adult palliative patients.

5. Purpose/Objective

Question: Is olanzapine safe and effective for the management of nausea and vomiting in adult palliative care patients compared to haloperidol?

-P: Adult palliative care patients with nausea and vomiting not responding to metoclopramide
-I: Olanzapine injection or orodispersible formulation for intractable nausea and vomiting (with or without metoclopramide)
-C: Haloperidol oral, parenteral
-O: Quality of life, numeric nausea and vomiting rating scores, other validated nausea and vomiting severity scales, number of emetic episodes during trial period, nausea and vomiting diaries, number of breakthrough nausea and vomiting, serious adverse events other adverse effects including somnolence or fatigue

Study designs: Systematic reviews of randomized controlled trials (RCTs) and RCTs, and if these are not available observational studies and guidelines

6. Methods:

a. Data sources

Systematic reviews were sought in PUBMED and Epistemonikos.

b. Search strategy

A search strategy was developed for PubMed and adapted to other databases (Appendix 1).

c. Screening, data extraction and evidence synthesis

Records were screened, followed by text screening by one reviewer (TL). A step-wise approach was taken, screening for systematic reviews, and if these were not available followed by RCTs, then observational studies. Any discrepancies were resolved by consensus. Eligible systematic reviews were appraised using the AMSTAR II Checklist (Shea, 2017). Risk of bias of RCTs were assessed using the Cochrane's RoB 2.0 Tool (Higgins, 2022). Data extraction for included reviews was done by one reviewer (TL) and data was extracted in Table 1. For dichotomous outcomes, risk ratios (RR) with 95% confidence intervals (CI) were reported and reported results from the review were described. Where available, the GRADE (level of certainty) of the evidence was reported (Guyatt, 2008).

d. Excluded studies

Rationale for excluding studies is described in Appendix 3.

7. Results:

a. Search results

PubMed and Epistemonikos was searched on 4 November 2022, and 29 records were identified for screening. Four duplicates were removed, and 8 were irrelevant. 17 full-text studies were assessed for eligibility; 15 studies were excluded. There were two systematic reviews selected for evidence synthesis. Refer to the Prisma Flow Chart in Appendix 2.

b. Description of systematic reviews

Two systematic reviews that informed Multinational Association for Supportive Care in Cancer guidelines were identified for inclusion:

1) *Davis et al, 2021*: Review within the "MASCC antiemetics in advanced cancer updated guideline" (Davis, 2021a)
2) *Davis et al, 2021*: Review within the "Medical management of malignant bowel obstruction in patients with advanced cancer: 2021 MASCC guideline update" (Davis, 2021b)

Davis, 2021a (advanced cancer): For the updated guideline for antiemetics in advanced cancer, Davis et al reviewed RCT evidence for the pharmacological management of nausea and vomiting in advanced cancer patients. Studies related to chemotherapy-related nausea and vomiting, non-pharmacological management of nausea and vomiting in advanced cancer and malignant bowel obstruction were excluded. The review was assessed to be of critically low quality using the AMSTAR 2 tool. See Table 1). Primary outcome was not stated in the review. Outcomes assessed were reduction in chronic generalized nausea and vomiting in advanced cancer and nausea and vomiting associated with opioid therapy

For haloperidol compared to olanzapine, the reviewers found limited RCT evidence, with a paucity of head-to-head studies. However, a single well conducted, small placebo-controlled RCT (n=30) showed that olanzapine 5 mg was superior to placebo, amongst patients with advanced cancer with nausea and vomiting unrelated to chemotherapy or radiation (Navari, 2020). At day 7, there was an 8-point reduction in nausea scores in the olanzapine-treated group (95% CI 7 to 8) compared to the placebo arm, $p<0.001$ (using an 11-point numerical rating score, NRS 0 no nausea, 10 severe nausea). Vomiting, fatigue, pain, and well-being improved, and there was no excessive sedation or other toxic effects associated with olanzapine that was reported. The study was assessed to be of moderate risk of bias as one study participant in the placebo group withdrew from the study at day 5, due to persistent nausea and vomiting. Authors suggested further research with larger studies. See Table 2)

Davis, 2021b (MBO): The systematic review within the "Medical management of malignant bowel obstruction in patients with advanced cancer: 2021 MASCC guideline update", focused on RCTs for the pharmacologic management of nausea and vomiting in malignant bowel obstruction (MBO) only. Studies on non-pharmacological management and surgical management of MBO were excluded.

The review was assessed to be of critically low quality using the AMSTAR 2 tool. One small placebo controlled RCT of olanzapine was included in the review. (Table 1 and 2)

The small RCT (n=16), reported in a letter (Kaneishi, 2020) showed that olanzapine may be as effective as metoclopramide in reducing nausea secondary to partial bowel obstructions (though, metoclopramide is a prokinetic and should be avoided if there is colic or abdominal pain). Patients with incomplete bowel obstruction and an average nausea score >4 (using NRS) were randomized to olanzapine 5 mg daily or metoclopramide 20–30 mg daily for 3 days. The primary outcome was mean nausea score for 3 days. There was no difference in the reduction in nausea, with a change in nausea score of −3.17 (NRS) for olanzapine vs −2.38 (NRS) for metoclopramide, p=0.39; assessed by systematic reviewers as low quality evidence due to lack of blinding and uncertainty about testing equi-effective doses. Because as the study was assessed as high risk of bias as open-label, study protocol was not available and most of the study details were not reported in the publication, the quality of the evidence was downgraded to very low quality. This was a small, underpowered open-label pilot trial and further research is needed.

Table 1: AMSTAR assessment of systematic reviews

Systematic review	Recommendation(s)	Appraisal AMSTAR 2
Davis et al, 2021a. MASCC antiemetics in advanced cancer updated guideline. Support Care Cancer. 2021 Dec;29(12):8097-8107. doi: 10.1007/s00520-021-06437-w	• Metoclopramide recommended as first-line antiemetic; *moderate quality evidence, consistent findings* • Haloperidol recommended as first-line antiemetic; *moderate quality evidence, consistent findings* • Olanzapine recommended as a second-line antiemetic; *moderate quality evidence, generally consistent findings*	Critically low-quality review. See Appendix 4
Davis, 2021b. Medical management of malignant bowel obstruction (MBO) in patients with advanced cancer: 2021 MASCC guideline update. Support Care Cancer. 2021 Dec;29(12):8089-8096 doi: 10.1007/s00520-021-06438-9	• Octreotide recommended as a front-line treatment for inoperable MBO; *high quality evidence, consistent findings* • Metoclopramide suggested as an active antiemetic in the management of MBO; *low quality evidence, generally consistent findings* • Olanzapine suggested as an active antiemetic in the management of MBO; *low quality evidence, generally consistent findings* • Haloperidol suggested as an active antiemetic in the management of MBO; *low to very low quality evidence, generally consistent findings*	Critically low-quality review. See Appendix 4

Haloperidol, conventionally has been used to treat breakthrough nausea and vomiting from MBO in randomized trials but has not be compared with other antiemetics (Davis, 2021b).

Table 2: Characteristics of included studies

Author, date	*Type of study*	Population (n)	Comparators	Primary outcome	Effect sizes	Comments
Davis et al, 2021a. MASCC antiemetics in advanced cancer updated guideline. Support Care Cancer. 2021 Dec;29(12):8097-8107. doi: 10.1007/s00520-021-06437-w	Systematic review of 1 SR and 3 RCTs, assessed as critically low quality. Only 1 RCT was related to olanzapine (Navari, 2020) – which is described below					
Navari et al, 2020. Olanzapine for the treatment of advanced cancer-related chronic nausea and/or vomiting: a randomized pilot trial. JAMA Oncol 6(6):895–899 doi:10.1001/jamaoncol.2020.1052	Double-blind, placebo-controlled, multi-center RCT *Inclusion criteria* - outpatients with advanced cancer with persistent nausea/vomiting without history of chemo- or radiotherapy in previous 14 days. - Chronic nausea present for at least 1 week (worst daily nausea score> 3 on a NRS 0-10 scale). *Funding:*	n=30 (n_1=15; n_2=15) Adults: 16 women, 14 men Mean age: 63 (39-79) years. Baseline median nausea scores: 9 out of 10 (range, 8-10).	*Intervention:* Olanzapine 5 mg/d, orally, days 1-7 (n_1=15) vs. *Placebo* (n_2=15)	Primary outcome: Reduction in nausea and vomiting (using NRS) Other outcomes: Nausea, appetite, fatigue, sedation, pain, well-being numeric rating scores; number of emesis episodes	**Olanzapine vs placebo:** Primary outcome: *Change in nausea scores (NRS):* –8 (95% CI –8 to –7), p<0.001 Other outcomes (difference between study groups): *Vomiting episodes/day:* Median –2 (95% CI –2 to –1), p<0.001 *Alternative antiemetic doses/day:* difference not reported *Appetite scores (NRS):* Median (range) 5 (95% CI 5 to 6), p<0.001 *Fatigue scores (NRS):* –3 (95% CI–4 to –1), p=0.004 *Sedation scores (NRS):* –1 (95% CI–2 to 0), p=0.08 *Pain sores (NRS):* –1 (–2 to 0), p=0.01 *Well-being scores (NRS):* 5 (4 to 5), p<0.01	Small pilot RCT, consistent with the results of other pilot studies (Passik, 2002; Harder, 2019; Macintosh, 2013) One study participant in the placebo group withdrew from the study at day 5, due to persistent nausea and vomiting Overall risk of bias assessment: **Some concerns** • *Randomisation:* **Low risk** • *Deviations from intervention:* **Low risk** • *Missing outcome data:* **Some concerns** • *Measurement of outcome:* **Low risk** • *Selection of the reported results:* **Low risk**

Davis, 2021b. Medical management of malignant bowel obstruction in patients with advanced cancer: 2021 MASCC guideline update. Support Care Cancer. 2021 Dec;29(12):8089-8096 doi: 10.1007/s00520-021-06438-9	Systematic review of 1 SR and 3 RCTs, assessed as critically low quality. Only 1 RCT was related to olanzapine (Kaneishi, 2020) – which is described below					
Kaneishi, 2020. Olanzapine versus Metoclopramide for Treatment of Nausea and Vomiting in Advanced Cancer Patients with Incomplete Malignant Bowel Obstruction. Journal of Palliative Medicine. 2020 Jul 1;23(7):880-881. doi.org/10.1089/jpm.2020.0101	Open-label pilot RCT *Inclusion criteria:* - advanced cancer - average nausea score of >4/10 due to incomplete malignant bowel obstruction (iMBO) *Funding:* Grant for Research Advancement on Palliative Medicine from the Japanese Society for Palliative Medicine	n=16 Number of participants per comparator group not reported	*Intervention:* Olanzapine 5 mg/d x 3days vs. Metoclopramide 20–30 mg/d x 3 days	Outcomes: -Change in mean nausea scores (NRS) for 3 days - rate of 30% reduction in NRS score - number of vomiting episodes - satisfaction rating of patients - preference to continue with the treatment - frequency of severe toxicities - adverse events	**Olanzapine vs placebo:** *Change in mean nausea scores over 3days:* -3.17 vs -2.38; p=0.39 *Rate of 30% reduction in NRS score:* 87.5% vs 50%; p = 0.11 *Mean difference in vomiting episodes/ day:* 2.25 vs 0.85; p=0.83 *Patient satisfaction rate:* 87.5% vs 75% *Preference to continue treatment:* 100% vs 50% *Frequency of severe toxicities:* Most symptoms were of low grade, and no patient chose to stop anti- emetic therapy *Adverse events:* Both olanzapine & metoclopramide caused drowsiness and dizziness	Lack of blinding and uncertainty about testing equi-effective doses; *low certainty evidence*. Study results reported in a letter to editor of a journal. Baseline demographics of comparator groups were not reported. Small pilot study, suggest the potential efficacy of olanzapine and metoclopramide against nausea and vomiting in patients with advanced cancer who have iMBO. Overall risk of bias assessment: **High risk** • *Randomisation:* Some concerns • *Deviations from intervention:* **High risk** • *Missing outcome data:* **High risk** • *Measurement of outcome:* **High risk** • *Selection of the reported results:* Some concerns

Conclusion

A review of available RCT evidence of low quality, suggests that oral olanzapine 5mg/daily may reduce nausea scores and vomiting episodes compared to placebo amongst adult patients with advanced cancer and is safe. Amongst patients with malignant bowel obstruction, very low quality evidence there was no difference in the reduction of nausea with olanzapine compared to metoclopramide. Currently, haloperidol injections (discontinued from the South African market), administered IM/SC/IV is the standard of care in the management of palliative nausea and vomiting where metoclopramide cannot be tolerated or is ineffective. Thus, based on low to very low certainty evidence (pilot studies conducted in high income countries), olanzapine oral may be considered as an alternative to metoclopramide in advanced cancer or malignant bowel obstruction. However, research is required to sufficiently address the question of olanzapine for palliation, noting that there is a need for evidence from low-income settings.

Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** *a.* *Nausea/vomiting in advanced cancer* High [ ] Moderate [ ] Low [ ] Very low [x]	*a.* *Nausea/vomiting in advanced cancer* **Olanzapine** (oral) **vs placebo:** Very low certainty evidence
	b. *Nausea/vomiting in MBO* High [ ] Moderate [ ] Low [ ] Very low [X] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	*b.* *Nausea/vomiting in MBO* **Olanzapine vs metoclopramide:** Very low certainty evidence
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** *a.* *Nausea/vomiting in advanced cancer* Large [ ] Moderate [X] Small [ ] None [ ]	*a.* *Nausea/vomiting in advanced cancer* **Olanzapine vs placebo:** • Nausea scores reduced (an 11-point numerical rating score, NRS: 0 no nausea, 10 severe nausea) by 8 (95% CI 7 to 8); p<0.001 vs placebo • Vomiting episodes improved with a median of –2 (95% CI –2 to –1), p<0.001
	b. *Nausea/vomiting in MBO* Large [ ] Moderate [ ] Small [ ] None [x]	*b.* *Nausea/vomiting in MBO* **Olanzapine** (oral) **vs metoclopramide:** • No difference in the reduction in nausea, with a change in score of −3.17 (NRS) for olanzapine vs −2.38 (NRS) for metoclopramide, p=0.39 • Vomiting episodes – not reported
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** *a.* *Nausea/vomiting in advanced cancer* High [ ] Moderate [ ] Low [ ] Very low [x]	*a.* *Nausea/vomiting in advanced cancer* **Olanzapine** (oral) **vs placebo:** very Low certainty evidence
	b. *Nausea/vomiting in MBO* High [ ] Moderate [ ] Low [ ] Very low [X]	*b.* *Nausea/vomiting in MBO* **Olanzapine vs metoclopramide:** Very low certainty evidence
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** *a.* *Nausea/vomiting in advanced cancer* Large [ ] Moderate [ ] Small [ ] None [X]	*a.* *Nausea/vomiting in advanced cancer* **Olanzapine** (oral) **vs placebo:** No sedation or adverse effects reported.
	b. *Nausea/vomiting in MBO* Large [ ] Moderate [ ] Small [ ] None [ ]	*b.* *Nausea/vomiting in MBO* **Olanzapine vs metoclopramide:** Not reported
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** *a.* *Nausea/vomiting in advanced cancer* Favours intervention [x] Favours control [ ] Intervention = Control *or* Uncertain [ ]	*a.* *Nausea/vomiting in advanced cancer* **Olanzapine** (oral) **vs placebo:** Favours intervention

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
	b. Nausea/vomiting in MBO Favours intervention: [ ] Favours control: [ ] Intervention = Control *or* Uncertain: [X]	*b. Nausea/vomiting in MBO* **Olanzapine vs metoclopramide:** Uncertain
THERAPEUTIC INTERCHANGE	n/a	
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes: [X] No: [ ] Uncertain: [ ]	Olanzapine is currently SAHPRA-registered (including generic products). Olanzapine has also been considered as an alternative to haloperidol injection for the management of aggressive disruptive disorders and delirium in adult patients (due to the current discontinuation of haloperidol injection from the South African market).
RESOURCE USE	**How large are the resource requirements?** More intensive: [ ] Less intensive: [ ] Uncertain: [ ]	**Price of medicines/ treatment course** Direct price comparison using maximum doses for 3 days AND patient cannot swallow: **A: Standard of care** — **Single dose** — **3-day course** Haloperidol IM/SC/IV — R 45,68 — R 411,12 *Haloperidol IM/SC/IV 5mg 8hrly x 3 days* *Previous S21 price* **B: Olanzapine alternative** **Single dose**: ***100% SEP*** R 8,91; ***60% SEP*** R 5,35 **3-day course**: ***100% SEP*** R26,74; ***60% SEP*** R16,04 Olanzapine orodispersible Olanzapine IM: ***100% SEP*** R 72,84; ***60% SEP*** R 43,71 **3-day course**: ***100% SEP*** R218,53; ***60% SEP*** R131,12 *Olanzapine alternative treatment: Olazapine ODT or IM 5 mg daily x 3 days*
VALUES, PREFERENCES, ACCEPTABILITY	**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: [ ] No: [ ] Uncertain: [X]	
EQUITY	**Would there be an impact on health inequity?** Yes: [ ] No: [ ] Uncertain: [ ]	

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	November 2022	TL, DVJ, RK	NEMLC recommended oral, oro-dispersable & IM olanzapine be used in adult palliative care patients with nausea and vomiting (N&V) not responding to metoclopramide, as a replacement to haloperidol. Haloperidol IM has been

			discontinued locally and an alternative for the management of N&V in palliative care patients is required. Olanzapine may be as effective as metoclopramide in reducing N&V in malignant bowel syndrome.

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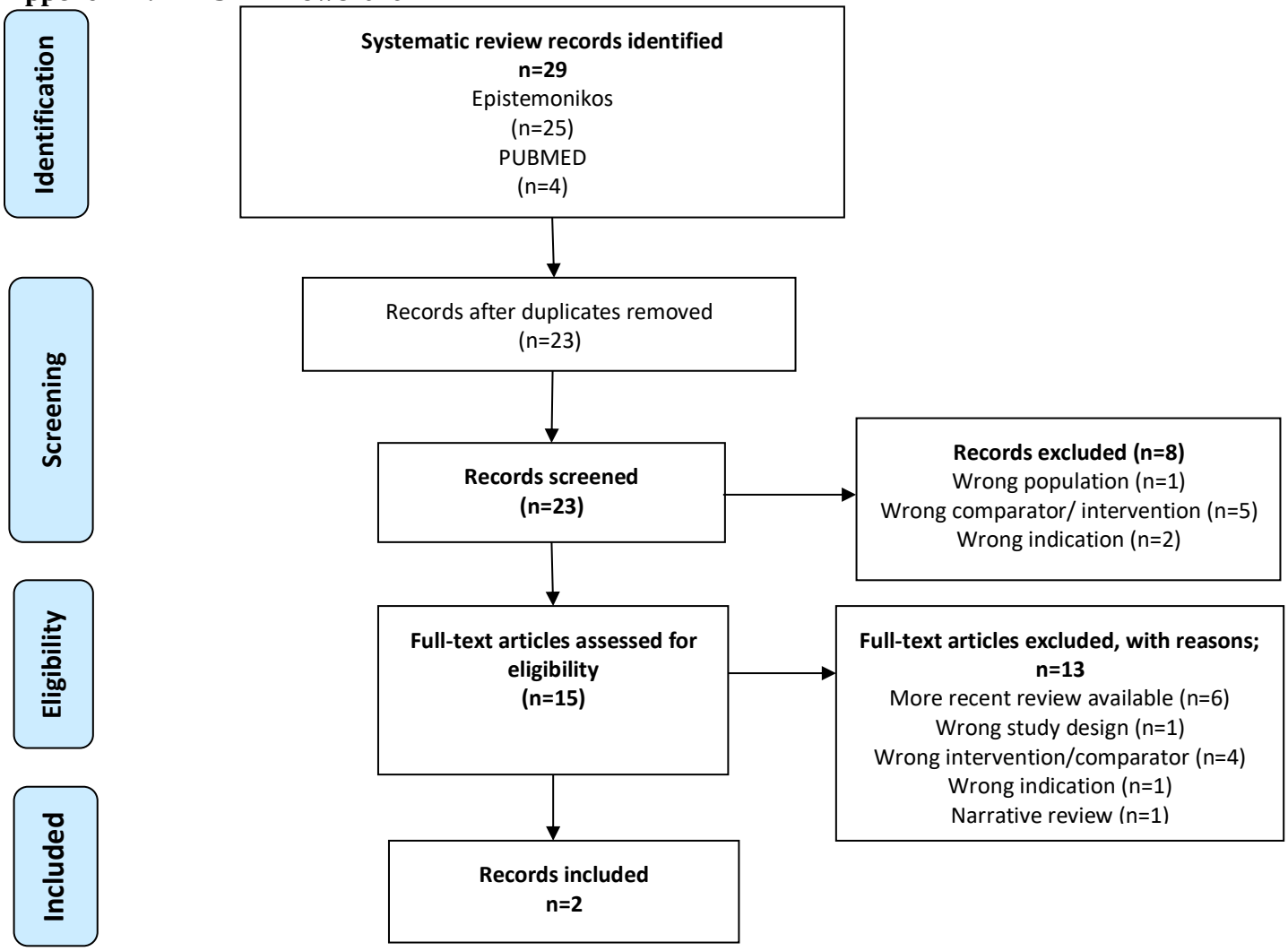
Appendix 1: Search strategy

A: PUBMED Date: 4 November 2022 Search strategy: (((olanzapine) AND (nausea)) AND (palliative care)) AND (vomiting) Filters applied: Systematic reviews Records retrieved: 4 Excluded: 2 Selected: 2
B: Epistemonikis Date: 4 November 2022 Search strategy: (title:((title:(olanzapine) OR abstract:(olanzapine)) AND (title:(nausea) OR abstract:(nausea)) AND (title:(vomiting) OR abstract:(vomiting))) OR abstract:((title:(olanzapine) OR abstract:(olanzapine)) AND (title:(nausea) OR abstract:(nausea)) AND (title:(vomiting) OR abstract:(vomiting)))) Filters applied: Systematic reviews, published last 5 years Records retrieved: 25 Excluded: 21 (6 records were duplicates)

Appendix 2: PRISMA flowchart



Appendix 3: List of excluded studies

Author, year	Study (systematic review)	Reason for exclusion
Chelkeba, 2017	Olanzapine for chemotherapy-induced nausea and vomiting: systematic review and meta-analysis. Pharm Pract (Granada). 2017 Jan-Mar;15(1):877	More recent review retrieved
Walsh, 2017	2016 Updated MASCC/ESMO consensus recommendations: Management of nausea and vomiting in advanced cancer. Support Care Cancer. 2017 Jan;25(1):333-340	More recent guidelines and supporting review retrieved
Saudemont, 2020	The use of olanzapine as an antiemetic in palliative medicine: a systematic review of the literature. BMC Palliat Care. 2020 Apr 22;19(1):56.	Wrong study designs (considered only if SRs of RCTs or RCTs are not available).
Chow, 2021	Olanzapine for the prophylaxis and rescue of chemotherapy-induced nausea and vomiting: a systematic review, meta-analysis, cumulative meta-analysis and fragility assessment of the literature. Support Care Cancer. 2021 Jul;29(7):3439-3459.	Control arm included other agents besides haloperidol, and did not stratify effect of olanzapine per comparator
Yoodee, 2017	Efficacy and safety of olanzapine for the prevention of chemotherapy-induced nausea and vomiting: A systematic review and meta-analysis. Crit Rev Oncol Hematol. 2017 Apr;112:113-125.	More recent review retrieved
Wang, 2021	The Balance Between the Effectiveness and Safety for Chemotherapy-Induced Nausea and Vomiting of Different Doses of Olanzapine (10 mg Versus 5 mg): A Systematic Review and Meta-Analysis. Front Oncol. 2021 Sep 30;11:705866. https://pubmed.ncbi.nlm.nih.gov/34660273/	Wrong comparator
Patel, 2022	Interventions for the prevention of acute phase chemotherapy-induced nausea and vomiting in adult and pediatric patients: a systematic review and meta-analysis. Support Care Cancer. 2022 Aug 12.	Intervention group not specific to olanzapine
Herrstedt, 2017	Updated MASCC/ESMO Consensus Recommendations: Prevention of Nausea and Vomiting Following High Emetic Risk Chemotherapy. Support Care Cancer. 2017 Jan;25(1):277-288.	More recent guidelines and supporting review retrieved
Qiu, 2021	Cost-Effectiveness of Aprepitant in Preventing Chemotherapy-Induced Nausea and Vomiting: A Systematic Review of Published Articles. Front Public Health. 2021 Aug 25;9:660514.	Wrong intervention
Yokoe, 2019	Effectiveness of Antiemetic Regimens for Highly Emetogenic Chemotherapy-Induced Nausea and Vomiting: A Systematic Review and Network Meta-Analysis. Oncologist. 2019 Jun;24(6):e347-e357.	Wrong indication
Zhou , 2020	Olanzapine combined with 5-hydroxytryptamine type 3 receptor antagonist (5-HT3 RA) plus dexamethasone for prevention and treatment of chemotherapy-induced nausea and vomiting in high and moderate emetogenic chemotherapy: a systematic review and meta-analysis of randomised controlled trials. ESMO Open. 2020 Feb;5(1):e000621.	Wrong intervention
Bai, 2020	Asian and North American patients with bipolar disorder have similar efficacy, tolerability, and safety profile during clinical trials with atypical antipsychotics? J Affect Disord. 2020 Jan 15;261:259-270.	Wrong indication
Sutherland, 2018	Olanzapine for the prevention and treatment of cancer-related nausea and vomiting in adults. Cochrane Database Syst Rev. 2018 Sep 21;9(9):CD012555.	More recent review retrieved
Yang, 2017	Efficacy of olanzapine for the prophylaxis of chemotherapy-induced nausea and vomiting: a meta-analysis. Br J Clin Pharmacol. 2017 Jul;83(7):1369-1379.	More recent 2021 review retrieved

Chiu, 2021	Secondary and cumulative meta-analysis of olanzapine for antiemetic prophylaxis for chemotherapy-induced nausea and vomiting: do we still need to study its effectiveness? Ann Palliat Med. 2021 Mar;10(3):2540-2547.	Control arm included other agents besides haloperidol, and did not stratify effect of olanzapine per comparator
Alhifany, 2020	Efficacy of olanzapine, neurokinin-1 receptor antagonists, and thalidomide in combination with palonosetron plus dexamethasone in preventing highly emetogenic chemotherapy-induced nausea and vomiting: a Bayesian network meta-analysis. Support Care Cancer. 2020 Mar;28(3):1031-1039.	Wrong comparator
Jahn, 2022	The Prevention and Treatment of Nausea and Vomiting During Tumor Therapy. Dtsch Arztebl Int. 2022 May 27;119(21):382-392.	Narrative review
Xiao, 2022	A pooled analysis of adding olanzapine to guideline-recommended antiemetic therapy for breast cancer patients treated with an anthracycline and cyclophosphamide in prospective and retrospective studies. Support Care Cancer. 2022 Mar;30(3):2445-2453. 34775535.	Wrong population group (specific to breast cancer patients), wrong study design
Zhang, 2018	Olanzapine-Based Triple Regimens Versus Neurokinin-1 Receptor Antagonist-Based Triple Regimens in Preventing Chemotherapy-Induced Nausea and Vomiting Associated with Highly Emetogenic Chemotherapy: A Network Meta-Analysis. Oncologist. 2018 May;23(5):603-616.	Wrong intervention
Bahbah, 2019	Should Olanzapine be Advocated Over Conventional Anti-Emetics for the Prevention of Chemotherapy-Induced Nausea and Vomiting? An Updated Meta-Analysis of Randomized Control Trials. Current Enzyme Inhibition. 2019;	Control arm included other agents besides haloperidol, and did not stratify effect of olanzapine per comparator
Solmi, 2020	Safety of 80 antidepressants, antipsychotics, anti-attention-deficit/hyperactivity medications and mood stabilizers in children and adolescents with psychiatric disorders: a large scale systematic meta-review of 78 adverse effects. World Psychiatry. 2020 Jun;19(2):214-232.	Wrong indication

Appendix 4: AMSTAR 2 assessment

		Yes/ Partial Yes/ No	
No	**Criteria**	**Davis, 2021a**	**Davis, 2021b**
1	Research questions and inclusion criteria for the review included the components of PICO	Partial yes	Partial yes
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	No, not explicit	No, not explicit
3	Review authors explained selection of the study designs for inclusion in the review	No	No
4*	Review authors used a comprehensive literature search strategy	Partial yes	Partial yes
5	Review authors perform study selection in duplicate	Yes	Yes
6	Review authors perform data extraction in duplicate	Yes	Yes
7	Review authors provided a list of excluded studies and justify the exclusions	No	No
8*	Review authors described the included studies in adequate detail	Yes	Yes
9	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	No	No
10*	Review authors reported on the sources of funding for the studies included in the review?	No	No
11	For meta-analyses, review authors used appropriate methods for statistical combination of results	n/a	n/a
12*	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	n/a	n/a
13	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	No	No
14*	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	n/a	n/a
15	For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	No	No
16*	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	Yes	Yes

** Critical domains*

• *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
• *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review
• *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest
• *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies
(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

OVERALL ASSESMENT: Critically low
Rationale: More than one critical flaw (# 2,10)
Conclusion: The AMSTAR assessment suggests that both reviews have more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.