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

Ronald Chow 1,2,3,4, Jørn Herrstedt 5, Matti Aapro 6, Leonard Chiu 3,7, Henry Lam 3, Elizabeth Prsic 2, Michael Lock 4, Carlo DeAngelis 3,8, Rudolph M. Navari 9

Abstract

Introduction The aim of this study is to rigorously review the efficacy and safety of olanzapine in defined hematology oncology settings including (1) the setting of highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC) settings (2) at 5 mg and 10 mg doses, and (3) for response rates for use in the acute, delayed, and overall settings post-MEC and HEC.

Methods Ovid MEDLINE, Embase, and Cochrane Central Register of Controlled Trials were searched through April 23, 2020. The primary efficacy endpoints were the rate of complete response, in the acute (0–24 h post-chemotherapy), delayed (24–120 h post-chemotherapy), and overall (0–120 h post-chemotherapy) phases. The secondary efficacy endpoints were the rates of no nausea and no emesis, for each phase. Safety endpoints were the rate of no serious adverse events (i.e., no grade 3 or 4 toxicities), as assessed by Common Terminology Criteria for Adverse Events (CTCAE) criteria. The Mantel-Haenszel, random-effects analysis model was used to compute risk ratios and accompanying 95% confidence intervals for each endpoint. For endpoints that statistically favored one arm, absolute risk differences were computed to assess whether there is a 10% or greater difference, used as the threshold for clinical significance by MASCC/ESMO. Fragility indices were also calculated for each statistically significant endpoint, to quantitatively assess the robustness of the summary estimate. A cumulative meta-analysis was conducted for each efficacy meta-analysis with more than 5 studies, also using the Mantel-Haenszel random-effects analysis model.

Results Three studies reported on olanzapine for the rescue of breakthrough chemotherapy-induced nausea and vomiting (CINV); 22 studies reported on olanzapine in the prophylactic setting. For studies reporting on HEC patients, olanzapine-containing regimens were statistically and clinically superior in seven of nine efficacy endpoints in the prophylaxis setting. When olanzapine is administered at a 10 mg dose, it is statistically and clinically superior to control patients in eight of nine endpoints among adults. Olanzapine may be effective in the MEC setting and when administered at 5-mg doses, but the paucity of data leads to notable uncertainty.

Conclusion Further RCTs are needed in the setting of MEC patients and administration of olanzapine at a lower 5-mg dose, which may be given to reduce the sedative effect of olanzapine at 10 mg.

Keywords Olanzapine  Antiemetics  Nausea  Vomiting  Meta-analysis  Systematic review

---

1 Yale School of Public Health, Yale University, New Haven, CT, USA
2 Yale New Haven Hospital, Yale University, New Haven, CT, USA
3 Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada
4 London Health Sciences Centre, University of Western Ontario, London, Ontario, Canada
5 Zealand University Hospital, Roskilde, Denmark and University of Copenhagen, Copenhagen, Denmark
6 Genolier Cancer Center, Genolier, Switzerland
7 Columbia University Vagelos College of Physicians and Surgeons, New York, NY, USA
8 Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada
9 Cancer Care Program, Central and South America, World Health Organization, Birmingham, AL, USA
Introduction

For cancer patients undergoing chemotherapy, chemotherapy-induced nausea and vomiting (CINV) are two prevalent and potentially treatment-limiting side effects [1]. Female patients and younger patients have been reported to be at greater risk [2–4]. Patients who have experienced vomiting during previous chemotherapy and those with high expectations of severe nausea prior to chemotherapy are at greater risk as well [5].

CINV is classified according to its time of incidence as either acute (0–24 h post-chemotherapy) or delayed (24–120 h post-chemotherapy). CINV that occurs during the course of chemotherapy despite a prophylactic regimen is termed as breakthrough CINV [6, 7].

Only two groups of antiemetics have been developed to target specific biochemical CINV pathways. These include neurokinin (NK)1-receptor antagonists (e.g., aprepitant, rolapitant, and netupitant), and serotonergic (5-HT)3-receptor antagonists (e.g., ondansetron, palonosetron), whereas dopamine (D)2-receptor antagonists (e.g., prochlorperazine, metoclopramide) initially were developed for different indications [8–11]. Olanzapine was approved by the US Food and Drug Administration as an antipsychotic [12], but has been used off-label as an antiemetic due to its potential to bind to multiple receptors in the CINV pathway, specifically serotonergic 5-HT2A, 5-HT2C, 5-HT3, 5-HT6, and dopamine D1, D2, D3, and D4 receptors [13].

Several phase I–II trials first investigated the efficacy and safety of olanzapine [14–19]. A systematic review and meta-analysis of early phase trials reported that 97.2% and 83.1% of patients achieved complete response (defined as no emesis and no use of rescue antiemetics) in the acute and delayed phase, respectively [20].

A number of phase III randomized controlled trials were subsequently undertaken and published, and multiple systematic reviews and meta-analyses have been conducted [21–27]. However, no review has separately analyzed antiemetics for highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC) patients, an important distinction that leads to different clinical guideline recommendations. Notably, the American Society of Clinical Oncology (ASCO) [28] currently recommends olanzapine as part of a four-drug regimen for HEC patients, while the National Comprehensive Cancer Network (NCCN) [29] and the Multinational Association of Supportive Care in Cancer (MASCC)/the European Society for Medical Oncology (ESMO) [30] recommend the four-drug regimen as an option in HEC patients. None of these guidelines, however, recommend olanzapine for MEC patients [28, 30]. Furthermore, each of the published reviews has methodological limitations when appraised using AMSTAR-2, a critical appraisal tool for systematic reviews [31] (Appendix 1 Electronic Supplementary Material).

Given the growing interest in olanzapine and the need for a more rigorous review, the aim of this study is to review the efficacy and safety of olanzapine for the prophylaxis and rescue of CINV through a systematic review and meta-analysis. Furthermore, given the large body of existing data, the aim of this review will be to determine the shortfalls of existing literature to provide future direction for olanzapine research in the CINV setting through a cumulative meta-analysis and fragility assessment.

Methods

The protocol for this review has been included in Appendix 2 Electronic Supplementary Material. The reporting of this review is conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [32].

Search strategy

In the interest of conducting a rigorous and comprehensive review, a de novo search strategy was developed to search databases from their beginnings. Ovid MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were searched from their beginning to April 24, 2020. Search restrictions were placed, so only English-language clinical trials were identified (Appendix 3 Electronic Supplementary Material).

Study selection

Two independent in-duplicate screenings were conducted. Where disagreements occurred, discussion of discrepancies occurred and consensus achieved, with the input of a senior author if required. Cohen’s kappa coefficient was calculated, to report the concordance.

Studies were first screened by title and abstract (level 1 screening). Studies were included after level 1 if they reported on olanzapine in a clinical trial for the setting of CINV. These abstracts then underwent full-text screening (level 2 screening) and were eligible for assessment of quantitative synthesis if they compared an olanzapine-containing regimen in one trial arm to a non-olanzapine-containing regimen in the other trial arm(s). Reference lists of included articles after level 2 screening were also assessed, to identify other potentially relevant randomized controlled trials. Studies with less than 5 patients per arm and non-randomized trials were excluded.

Data extraction

As with study selection, data extraction was conducted in duplicate and independently. Disagreements were resolved via discussion, to achieve consensus.
Study demographics of age range, percentage male, chemotherapyemetogenicity, and the difference between the olanzapinedos regimen and the comparative regimen were noted. The primary efficacy endpoints were the rate of complete response, in the acute (0–24 h post-chemotherapy), delayed (24–120 h post-chemotherapy), and overall (0–120 h post-chemotherapy) phases. The secondary efficacy endpoints were the rates of no nausea and no emesis, for each phase. Safety endpoints were the rate of no serious adverse events (i.e., no grade 3 or 4 toxicities, as assessed by Common Terminology Criteria for Adverse Events (CTCAE) criteria), as reported by authors. Grades 1 and 2 toxicities were not extracted for analysis, due to the paucity of data.

When a trial had two olanzapine-containing arms, the data across the two olanzapine arms were summed for analysis and compared to the non-olanzapine-containing arm.

Meta-analysis

The Mantel-Haenszel, random-effects analysis model was used to compute risk ratios (RRs) and accompanying 95% confidence intervals for each endpoint. A p value of less than 0.05 was considered statistically significant in the test for overall effect.

Studies were first separately meta-analyzed by regimen intent—whether olanzapine was administered for prophylaxis or for management of breakthrough nausea. It was then analyzed by age, separating studies reporting on adult and children. Adult studies were further meta-analyzed according to chemotherapyemetogenicity, olanzapine dosage, comparative regimens, and study quality; meta-analyses were conducted for the following subgroups of adult studies:

1. HEC studies, as determined by the MASCC/ESMO classification [33]
2. MEC studies, as determined by the MASCC/ESMO classification [33]
3. Olanzapine, administered as 10 mg daily PO
4. Olanzapine, administered as 5 mg daily PO
5. Studies with a double-blind, placebo-controlled design, where the control arm includes a placebo and all antiemetics of the olanzapine-containing arm except for olanzapine itself
6. Studies with an open-controlled design, where the control arm includes all the antiemetics of the olanzapine-containing arm except for olanzapine itself
7. Studies with an open-controlled design, where the control arm includes antiemetics not included in the olanzapine-containing arm

For endpoints that statistically favored one arm and had more than 3 included trials, absolute risk differences (RD) were computed to assess whether there is a 10% or greater difference, deemed to be the threshold for clinical significance by MASCC/ESMO [34]. These analyses were performed using Review Manager (RevMan 5.4) by Cochrane IMS.

Fragility assessment

Fragility indices were calculated for each statistically significant endpoint by subgroup, to quantitatively assess the robustness of the summary estimate. Determination of the index involves a series of iterative calculations, until the simulated study results change from statistically significant to statistically insignificant according to the Fisher’s exact test. Essentially, the index is the number of control patients that would need to change from a nonevent to an event outcome, to change the statistical conclusion of a trial [35]. These analyses were conducted using Stata 16.

Cumulative meta-analysis

A cumulative meta-analysis was conducted for each efficacymeta-analysis with more than 5 studies, also using the Mantel-Haenszel random-effects analysis model. These analyses will allow for the assessment of the impact of each trial on the meta-analysis summary effect size and 95% CI. These analyses were conducted using Comprehensive Meta-Analysis (Version 3) by Biostat.

Assessment of bias

The Cochrane Risk of Bias tool was used to assess the quality of included randomized controlled trials. Four reviewers (RC, LC, ML, CD) independently assessed bias, after which discussion and consensus was used to resolve any discrepancies. Funnel plots were generated to visually assess for publication bias, for each phase of the three efficacy endpoints where there are 5 or more trials; these were generated using Comprehensive Meta-Analysis (Version 3) by Biostat.

Results

Included studies

From the search strategies, 312 records were identified. After removing duplicate records and adding records identified from included trials, 178 records underwent level 1 screening. A total of 34 full-text articles were assessed for eligibility through level 2 screening, at which points 6 were excluded with reason—three were not a randomized controlled trial [36–38], one did not investigate olanzapine in the CINV setting [39], and two did not have an appropriate treatment regimen for inclusion in our review [40, 41]. Of the remaining 28
articles, 25 randomized controlled trials had extractable data and were included in this systematic review and meta-analysis (Appendix 4 Electronic Supplementary Material). Concordance, as measured by Cohen’s Kappa, for level 1 screening was 0.86, and 0.84 for level 2 (Appendix 5 Electronic Supplementary Material).

Three studies reported on olanzapine for the rescue of breakthrough CINV [42–44]; 22 studies reported on olanzapine in the prophylactic setting [45–66]. Only seven studies (one reporting on rescue of breakthrough CINV, and six reporting on prophylactic CINV) had no corresponding full-text articles [42, 48, 53, 55, 56, 60, 61]. One study reported on olanzapine for children [48]. Among the adult prophylactic studies, 15 reported exclusively on HEC patients [46, 49–52, 55, 56, 58, 60–66], three exclusively on MEC patients [53, 57, 59], and three on a patient population that consists of both HEC and MEC patients [45, 47, 54]. Eight studies compared olanzapine to a double-blind placebo-controlled regimen [47, 52, 59, 62–66] and thirteen used an opened controlled study design—nine studies used a control arm with antiemetics different from the antiemetics in the investigational (olanzapine-containing) arm [46, 49, 51, 53, 55, 56, 58, 60, 61] and four used a control arm with the same antiemetics as in the investigational (olanzapine-containing) arm except for olanzapine [45, 50, 54, 57]. 17 adult prophylactic studies used 10 mg doses of olanzapine [45, 46, 49–59, 61, 62, 65, 66], and 3 studies used 5 mg [47, 60, 63]; 1 used a mix of 5 mg and 10 mg [64] (Table 1).

Quality of included studies

The risk of bias assessment for each included study is reported in Appendix 6 Electronic Supplementary Material. Over half of all included studies had high risk of bias, due to concerns around lack of blinding.

Assessment for publication bias of olanzapine for the prophylaxis of CINV

Funnel plots are presented in Appendix 7, 8 Electronic Supplementary Material. There are no obvious asymmetries, suggesting no obvious concerns of publication bias in this body of literature.

Efficacy of olanzapine for the prophylaxis of CINV in adults

Complete response

Acute phase Olanzapine was statistically better than comparative regimens in the acute phase. Among HEC studies, studies using 10 mg olanzapine dosages, studies using a double-blind placebo-controlled design, and open-design studies comparing olanzapine to control regimens of antiemetics not included in the investigational arm, olanzapine was still statistically superior (Fig. 1.1). Olanzapine was clinically superior (risk difference greater than 10%) overall, in HEC studies, studies using 10 mg olanzapine doses, and for studies comparing olanzapine in a double-blind placebo-controlled design (Table 2).

Delayed phase Olanzapine was also statistically and clinically superior in the delayed phase. This statistical and clinical superiority prevails in analyses of HEC studies, studies using 10-mg olanzapine doses, studies administering 5-mg of olanzapine, and studies assessing olanzapine in double-blind placebo control studies (Fig. 1.2; Table 2).

Overall phase Olanzapine was statistically and clinically superior in the overall phase among all studies, HEC studies, 10-mg olanzapine studies, 5-mg olanzapine studies, and double-blind placebo-controlled studies (Fig. 1.3; Table 2).

Nausea control

For the acute, delayed, and overall phases, olanzapine was statistically superior to comparative regimens. This observation was similarly noted among HEC studies, studies where 10 mg of olanzapine was administered, and double-blind placebo-controlled trials. Olanzapine was also statistically and clinically superior to open-design studies using a control arm with different antiemetics than used in the investigational (olanzapine-containing) arm in the delayed and overall phases (Fig. 2; Table 2).

Emesis control

Neither olanzapine nor control arms were statistically superior to the comparator arm in the acute phase. Olanzapine was both statistically and clinically superior in the delayed and overall phases. Olanzapine was statistically and clinically better in the delayed phase among HEC trials and 10-mg olanzapine trials (Fig. 3; Table 2).
| Study                         | Evaluable sample size | Age range | % Male | Chemotherapy emetogenicity | Intervention’s additional/substitute drug regimens, relative to comparative arm |
|-------------------------------|-----------------------|-----------|--------|----------------------------|---------------------------------------------------------------------------------|
| Tan et al., 2009 [45]         | 229                   | 18–74     | 60     | HEC & MEC                 | Day 1: addition of olanzapine 10 mg PO Day 2–5: olanzapine 10 mg PO, instead of dexamethasone 10 mg IV |
| Navari et al., 2011 [46]      | 241                   | 39–81     | 32     | HEC                       | Day 1: olanzapine 10 mg PO, instead of aprepitant 125 mg PO; dexamethasone 20 mg IV, instead of dexamethasone 12 mg IV Days 2–3: olanzapine 10 mg PO, instead of aprepitant 80 mg PO and dexamethasone 4 mg PO BID Day 4: olanzapine 10 mg PO, instead of dexamethasone 4 mg PO BID |
| Mizukami et al., 2014 [47]    | 44                    | 22–78     | 50     | HEC & MEC                 | Days 1–5: addition of olanzapine 5 mg PO Olanzapine, instead of aprepitant Days 2–4: addition of olanzapine 5 mg PO Day 1: olanzapine 10 mg PO, instead of aprepitant 125 mg PO Days 2–3: olanzapine 10 mg PO, instead of aprepitant 80 mg PO Day 4: addition of olanzapine 10 mg PO |
| Long et al., 2015 [48]        | 14                    | 4–21      | NR     | HEC                       | Olanzapine, instead of aprepitant Days 1–5: addition of olanzapine 5 mg PO |
| Shumway et al., 2015 [49]     | 17                    | NR        | 37     | HEC                       | Day 1: olanzapine 10 mg PO, instead of aprepitant 125 mg PO Days 2–3: olanzapine 10 mg PO, instead of aprepitant 80 mg PO Day 4: addition of olanzapine 10 mg PO |
| Wang et al., 2015 [50]        | 84                    | 39–76     | 73     | HEC                       | Day 1–8: addition of olanzapine 10 mg PO |
| Navari et al., 2016 (JCSO) [51]| 101                   | 52–71     | 77     | HEC                       | Day 1: olanzapine 10 mg PO, instead of fosaprepitant 150 mg IV Days 2–3: olanzapine 10 mg PO, instead of dexamethasone 4 mg PO BID Day 4: olanzapine 10 mg PO |
| Navari et al., 2016 (NEJM) [52]| 380                   | 28–89     | 28     | HEC                       | Days 1–4: addition of olanzapine 10 mg PO Day 1: olanzapine 10 mg PO, instead of aprepitant 125 mg PO Days 2–3: olanzapine 10 mg PO, instead of aprepitant 80 mg PO Day 1: olanzapine 10 mg PO, instead of aprepitant 180 mg PO Days 2–3: olanzapine 10 mg PO, instead of aprepitant 80 mg PO Day 4: addition of olanzapine 10 mg PO |
| Mukesh et al., 2017 [53]      | 84                    | 29–80     | 0      | MEC                       | Day 1: olanzapine 10 mg PO, instead of aprepitant 125 mg PO |
| Mukhopadhyay et al., 2017 [54]| 100                   | NR        | 58     | HEC & MEC                 | Days 1–5: addition of olanzapine 10 mg PO |
| Sapkota et al., 2017 [55]     | 50                    | NR        | NR     | HEC                       | Days 1–5: addition of olanzapine 10 mg PO |
| Tran et al., 2017 [56]        | 478                   | NR        | 0      | HEC                       | Days 1–3: olanzapine 10 mg PO and omeprazole 20 mg PO instead of omeprazole 20 mg PO BID, dexamethasone 4 mg PO BID and metoclopramide 20 mg PO TID Days 4–5: no use of omeprazole 20 mg PO BID, dexamethasone 4 mg PO BID and metoclopramide 20 mg PO TID |
| Celio et al., 2019 [57]       | 81                    | 30–80     | 0      | MEC                       | Day 2–3: olanzapine 10 mg PO alone or olanzapine 10 mg PO in addition to dexamethasone 4 mg PO |
| Dulal et al., 2019 [58]       | 64                    | 51–60     | 48     | HEC                       | Day 1: olanzapine 10 mg PO, instead of haloperidol 1 mg PO Days 2–4: olanzapine 10 mg PO, instead of haloperidol 0.5 mg PO BID Days 1–4: addition of olanzapine 10 mg PO |
| Jeon et al., 2019 [59]        | 56                    | 30–79     | 83     | MEC                       | Day 1: olanzapine 5 mg PO, instead of aprepitant 125 mg PO Days 2–3: olanzapine 5 mg PO, instead of aprepitant 80 mg PO Day 4: addition of olanzapine 5 mg PO |
| Rumyantsev et al., 2019 [60]  | 93                    | NR        | 4      | HEC                       | Day 1–4: addition of olanzapine 10 mg PO in addition to, or instead of, apreptant standard regimen |
| Saldanha et al., 2019 [61]    | 209                   | NR        | NR     | HEC                       | Days 1–4: addition of olanzapine 10 mg PO |
| Tienchaiananda et al., 2019 [62]| 39                    | NR        | 0      | HEC                       | Days 1–4: addition of olanzapine 10 mg PO |
| Hashimoto et al., 2020 [63]   | 706                   | 22–75     | 67     | HEC                       | Days 1–4: addition of olanzapine 5 mg PO |
| Ithimakin et al., 2020 [64]   | 141                   | 24–79     | 21     | HEC                       | Days 1–4: addition of olanzapine 10 mg PO or olanzapine 5 mg PO |
| Vimolchalao et al., 2020 [65] | 64                    | 26–73     | 31     | HEC                       | Days 1–4: addition of olanzapine 10 mg PO |
| Yeo et al., 2020 [66]         | 120                   | 32–71     | 0      | HEC                       | Days 1–4: addition of olanzapine 10 mg PO |
Cumulative meta-analysis and fragility assessment of olanzapine for the prophylaxis of CINV

Across all three time phases, the meta-analysis results for complete response are the most robust; results reporting on emetic control are the least robust of the three efficacy endpoints (Appendix 9 Electronic Supplementary Material). The most recent trials did not lead to a noticeable effect on the meta-analysis’ summary estimate for the endpoints of complete response and nausea control (Appendix 10, 11 Electronic Supplementary Material).

Olanzapine for the rescue of breakthrough CINV

Olanzapine was statistically superior to comparative regimens with respect to complete control, nausea control, and emetic control, according to the one study reporting on each outcome (Fig. 4). Olanzapine was also clinically superior in all these aforementioned endpoints—RD = 0.33 (95% CI: 0.10–0.56) for complete response in the acute phase, RD = 0.38 (95% CI: 0.18–0.57) for complete response in the overall phase, RD = 0.45 (95% CI: 0.28–0.62) for nausea control in the overall phase, and RD = 0.39 (95% CI: 0.21–0.56) for emetic control in the overall phase.

Safety of olanzapine for the prophylaxis of CINV

Olanzapine is as safe as comparative regimens; the risk of serious adverse events is not statistically significant for olanzapine relative to other regimens (Appendix 12, 13 Electronic Supplementary Material).

Discussion

This review is the most rigorous systematic review to date investigating olanzapine in the CINV setting. A protocol was developed prior to the commencement, risk of bias for studies were assessed, and publication bias was assessed; some or all of these three methodological elements were omitted in prior reviews [21–27].

This review also has the highest statistical power and appraises all the clinically important endpoints. The most recent reviews by Zhou et al. in 2020 included 11 studies with 1107 patients [21]; other reviews by Bahbah et al. in 2019 and Sutherland et al. in 2018 included 9 RCTs with 1572 patients, and 14 trials with 1917 participants, respectively [22, 23].

Fig. 1 Efficacy of olanzapine regimens compared to others for the prophylaxis of chemotherapy-induced nausea and vomiting (CINV)—Complete response. 1.1 Acute phase. 1.2 Delayed phase. 1.3 Overall phase
1.1

| Study or Subgroup | Sample | Control | Effect Size | Risk Ratio | 95% CI |
|-------------------|--------|---------|-------------|------------|--------|
| **Overall**       |        |         |             |            |        |
|                   | 250    | 299    |             | 1.06       | 0.99-1.13 |
| **Heterogeneity** |        |         |             |            |        |
|                   | 1.05   | 0.99-1.13 |        |            |        |

**1.2 Adults**

| Study or Subgroup | Sample | Control | Effect Size | Risk Ratio | 95% CI |
|-------------------|--------|---------|-------------|------------|--------|
|                   | 117    | 109    |             | 1.05       | 0.97-1.13 |
| **Heterogeneity** |        |         |             |            |        |
|                   | 1.05   | 0.97-1.13 |        |            |        |

**1.3 HNC**

| Study or Subgroup | Sample | Control | Effect Size | Risk Ratio | 95% CI |
|-------------------|--------|---------|-------------|------------|--------|
|                   | 117    | 109    |             | 1.05       | 0.97-1.13 |
| **Heterogeneity** |        |         |             |            |        |
|                   | 1.05   | 0.97-1.13 |        |            |        |

**1.4 Oesophagus**

| Study or Subgroup | Sample | Control | Effect Size | Risk Ratio | 95% CI |
|-------------------|--------|---------|-------------|------------|--------|
|                   | 117    | 109    |             | 1.05       | 0.97-1.13 |
| **Heterogeneity** |        |         |             |            |        |
|                   | 1.05   | 0.97-1.13 |        |            |        |

**1.5 Head and Neck**

| Study or Subgroup | Sample | Control | Effect Size | Risk Ratio | 95% CI |
|-------------------|--------|---------|-------------|------------|--------|
|                   | 117    | 109    |             | 1.05       | 0.97-1.13 |
| **Heterogeneity** |        |         |             |            |        |
|                   | 1.05   | 0.97-1.13 |        |            |        |

**1.6 Small Bowel**

| Study or Subgroup | Sample | Control | Effect Size | Risk Ratio | 95% CI |
|-------------------|--------|---------|-------------|------------|--------|
|                   | 117    | 109    |             | 1.05       | 0.97-1.13 |
| **Heterogeneity** |        |         |             |            |        |
|                   | 1.05   | 0.97-1.13 |        |            |        |

**1.7 Lung**

| Study or Subgroup | Sample | Control | Effect Size | Risk Ratio | 95% CI |
|-------------------|--------|---------|-------------|------------|--------|
|                   | 117    | 109    |             | 1.05       | 0.97-1.13 |
| **Heterogeneity** |        |         |             |            |        |
|                   | 1.05   | 0.97-1.13 |        |            |        |

**1.8 Stomach**

| Study or Subgroup | Sample | Control | Effect Size | Risk Ratio | 95% CI |
|-------------------|--------|---------|-------------|------------|--------|
|                   | 117    | 109    |             | 1.05       | 0.97-1.13 |
| **Heterogeneity** |        |         |             |            |        |
|                   | 1.05   | 0.97-1.13 |        |            |        |

**1.9 Uterus**

| Study or Subgroup | Sample | Control | Effect Size | Risk Ratio | 95% CI |
|-------------------|--------|---------|-------------|------------|--------|
|                   | 117    | 109    |             | 1.05       | 0.97-1.13 |
| **Heterogeneity** |        |         |             |            |        |
|                   | 1.05   | 0.97-1.13 |        |            |        |

**1.10 Colon**

| Study or Subgroup | Sample | Control | Effect Size | Risk Ratio | 95% CI |
|-------------------|--------|---------|-------------|------------|--------|
|                   | 117    | 109    |             | 1.05       | 0.97-1.13 |
| **Heterogeneity** |        |         |             |            |        |
|                   | 1.05   | 0.97-1.13 |        |            |        |

**1.11 Prostate**

| Study or Subgroup | Sample | Control | Effect Size | Risk Ratio | 95% CI |
|-------------------|--------|---------|-------------|------------|--------|
|                   | 117    | 109    |             | 1.05       | 0.97-1.13 |
| **Heterogeneity** |        |         |             |            |        |
|                   | 1.05   | 0.97-1.13 |        |            |        |

**1.12 Ovarian**

| Study or Subgroup | Sample | Control | Effect Size | Risk Ratio | 95% CI |
|-------------------|--------|---------|-------------|------------|--------|
|                   | 117    | 109    |             | 1.05       | 0.97-1.13 |
| **Heterogeneity** |        |         |             |            |        |
|                   | 1.05   | 0.97-1.13 |        |            |        |

**1.13 Male Breast**

| Study or Subgroup | Sample | Control | Effect Size | Risk Ratio | 95% CI |
|-------------------|--------|---------|-------------|------------|--------|
|                   | 117    | 109    |             | 1.05       | 0.97-1.13 |
| **Heterogeneity** |        |         |             |            |        |
|                   | 1.05   | 0.97-1.13 |        |            |        |

**1.14 Female Breast**

| Study or Subgroup | Sample | Control | Effect Size | Risk Ratio | 95% CI |
|-------------------|--------|---------|-------------|------------|--------|
|                   | 117    | 109    |             | 1.05       | 0.97-1.13 |
| **Heterogeneity** |        |         |             |            |        |
|                   | 1.05   | 0.97-1.13 |        |            |        |

**1.15 Cervix**

| Study or Subgroup | Sample | Control | Effect Size | Risk Ratio | 95% CI |
|-------------------|--------|---------|-------------|------------|--------|
|                   | 117    | 109    |             | 1.05       | 0.97-1.13 |
| **Heterogeneity** |        |         |             |            |        |
|                   | 1.05   | 0.97-1.13 |        |            |        |

**1.16 Bladder**

| Study or Subgroup | Sample | Control | Effect Size | Risk Ratio | 95% CI |
|-------------------|--------|---------|-------------|------------|--------|
|                   | 117    | 109    |             | 1.05       | 0.97-1.13 |
| **Heterogeneity** |        |         |             |            |        |
|                   | 1.05   | 0.97-1.13 |        |            |        |

**1.17 Rectum**

| Study or Subgroup | Sample | Control | Effect Size | Risk Ratio | 95% CI |
|-------------------|--------|---------|-------------|------------|--------|
|                   | 117    | 109    |             | 1.05       | 0.97-1.13 |
| **Heterogeneity** |        |         |             |            |        |
|                   | 1.05   | 0.97-1.13 |        |            |        |

**1.18 Other**

| Study or Subgroup | Sample | Control | Effect Size | Risk Ratio | 95% CI |
|-------------------|--------|---------|-------------|------------|--------|
|                   | 117    | 109    |             | 1.05       | 0.97-1.13 |
| **Heterogeneity** |        |         |             |            |        |
|                   | 1.05   | 0.97-1.13 |        |            |        |

**1.9 Overall**

| Study or Subgroup | Sample | Control | Effect Size | Risk Ratio | 95% CI |
|-------------------|--------|---------|-------------|------------|--------|
|                   | 250    | 299    |             | 1.06       | 0.99-1.13 |
| **Heterogeneity** |        |         |             |            |        |
|                   | 1.05   | 0.99-1.13 |        |            |        |

**1.10 Overall**

| Study or Subgroup | Sample | Control | Effect Size | Risk Ratio | 95% CI |
|-------------------|--------|---------|-------------|------------|--------|
|                   | 250    | 299    |             | 1.06       | 0.99-1.13 |
| **Heterogeneity** |        |         |             |            |        |
|                   | 1.05   | 0.99-1.13 |        |            |        |
1.2

| Study or Subgroup | Oxaliplatin | Control | Risk Ratio | Risk Ratio |
|-------------------|------------|---------|------------|------------|
|                   | M-H, Random | M-H, Random | M-H, Random, 95% CI | M-H, Random, 95% CI |
| L2.2 HNC        |            |         |            |            |
| Nooter et al. 2021 | 23 124 | 89 120 | 0.89 | 1.19 (0.88, 1.61) |
| Yi et al. 2021    | 8 56   | 42 52  | 0.86 | 1.21 (0.76, 1.94) |
| L2.3 MEC        |            |         |            |            |
| Munnell et al. 2017 | 18 43  | 45 48  | 0.79 | 1.28 (0.88, 1.28) |
| L2.4 HIC/MEC    |            |         |            |            |
| Minto et al. 2014 | 22 22   | 16 16  | 1.23 | 1.73 (0.96, 3.08) |
| Subtotal (95% CI) | 45 65   | 100 100 | 1.35 (1.10, 1.65) |

Fig. 1 (continued)

 Springer
1.3

1.3.1 Children

| Study or Subgroup | Olanzapine Events | Total | Control Events | Total | Weight | Risk Ratio | M-H Random, Risk, YS (CI) | Risk Ratio | M-H Random, Risk, YS (CI) |
|-------------------|-------------------|-------|----------------|-------|--------|------------|---------------------------|------------|---------------------------|
| Long et al. 2015  | 4                 | 10    | 3              | 9     | 100.0% | 1.20 (0.95, 1.50) | 1.20 (0.94, 1.55) |
| Subtotal (% CI)   | 10                | 9     | 100.0%         | 10    | 100.0% | 1.20 (0.98, 1.49) |
| Total events     | 4                 | 3     | 100.0%         | 4     | 100.0% | 1.20 (0.98, 1.49) |
| Heterogeneity:   | Not applicable    |       |                |       |        |             |                           |            |                           |

1.3.2 Adults

| Study or Subgroup | Olanzapine Events | Total | Control Events | Total | Weight | Risk Ratio | M-H Random, Risk, YS (CI) | Risk Ratio | M-H Random, Risk, YS (CI) |
|-------------------|-------------------|-------|----------------|-------|--------|------------|---------------------------|------------|---------------------------|
| Navari et al. 2018 | 9                 | 28    | 11             | 11    | 100.0% | 1.24 (1.02, 1.51) | 1.24 (0.99, 1.54) |
| Mawson et al. 2014 | 3                 | 12    | 5              | 5     | 60.0%  | 1.37 (1.04, 1.81) | 1.37 (1.02, 1.87) |
| Navari et al. 2016 (SCID) | 9         | 35   | 11             | 11   | 70.0%  | 1.20 (0.89, 1.61) | 1.20 (0.88, 1.55) |
| Navari et al. 2016 (NPH) | 10     | 61    | 12             | 12   | 80.0%  | 1.27 (1.07, 1.51) | 1.27 (1.06, 1.49) |
| Mawson et al. 2017 | 6                 | 24    | 6              | 6     | 33.3%  | 1.24 (0.93, 1.67) | 1.24 (0.91, 1.65) |
| Wang et al. 2017  | 3                 | 12    | 5              | 5     | 60.0%  | 1.37 (1.04, 1.81) | 1.37 (1.02, 1.87) |
| Total 2017       | 15                | 54    | 9              | 9     | 100.0% | 1.27 (1.05, 1.54) | 1.27 (1.04, 1.51) |
| Dalal et al. 2019 | 2                 | 6     | 2              | 2     | 50.0%  | 1.50 (0.92, 2.48) | 1.50 (0.90, 2.48) |
| Salter et al. 2019 | 12                | 42    | 9              | 9     | 100.0% | 1.27 (1.05, 1.55) | 1.27 (1.04, 1.51) |
| Salter et al. 2020 | 3                 | 12    | 5              | 5     | 60.0%  | 1.37 (1.04, 1.81) | 1.37 (1.02, 1.87) |
| Ferrante et al. 2020 | 29            | 104    | 10             | 10     | 100.0% | 1.27 (1.05, 1.55) | 1.27 (1.04, 1.51) |
| Total 2020       | 43                | 163   | 18             | 18     | 100.0% | 1.27 (1.05, 1.55) | 1.27 (1.04, 1.51) |
| Subtotal (% CI) | 43                 | 163   | 18             | 18     | 100.0% | 1.27 (1.05, 1.55) | 1.27 (1.04, 1.51) |
| Total events     | 52                | 177   | 27             | 27     | 100.0% | 1.27 (1.05, 1.55) | 1.27 (1.04, 1.51) |
| Heterogeneity:   | Not applicable    |       |                |       |        |             |                           |            |                           |

Support Care Cancer (2021) 29:3439–3459

Fig. 1 (continued)
review summarizes the results across 25 studies, which reported on 4275 patients. One study reported the effect of olanzapine on children, and three studies reported on olanzapine for the rescue of breakthrough CINV; the remaining 23 studies reported on olanzapine for the prophylaxis of CINV in adults, across 4217 patients. Zhou et al. reported on acute and delayed emetic control with or without nausea control, Bahbah et al. meta-analyzed complete response and nausea control rates, and Sutherland et al. summarized instances where patients successfully experienced no nausea and no emesis; our review reports on complete response, nausea control, and emetic control.

### Table 2 Absolute risk difference between olanzapine and other regimens for statistically significant differences

| Endpoint | Risk difference (95% confidence interval) | Clinically significant? |
|----------|------------------------------------------|-------------------------|
| Complete response, acute phase - adults | 0.10 (0.05, 0.15) | Yes |
| Complete response, acute phase - HEC | 0.11 (0.05, 0.17) | Yes |
| Complete response, acute phase - olanzapine 10 mg | 0.10 (0.04, 0.17) | Yes |
| Complete response, acute phase - double-blind placebo-controlled design | 0.17 (0.07, 0.27) | Yes |
| Complete response, acute phase - open controlled design (control arm = antiemetics not in olanzapine arm) | 0.06 (0.01, 0.11) | No |
| Complete response, delayed phase - adults | 0.12 (0.05, 0.20) | Yes |
| Complete response, delayed phase - HEC | 0.12 (0.05, 0.20) | Yes |
| Complete response, delayed phase - olanzapine 10 mg | 0.11 (0.02, 0.20) | Yes |
| Complete response, delayed phase - olanzapine 5 mg | 0.14 (0.03, 0.24) | Yes |
| Complete response, delayed phase - double-blind placebo-controlled design | 0.16 (0.10, 0.22) | Yes |
| Complete response, overall phase - adults | 0.17 (0.10, 0.24) | Yes |
| Complete response, overall phase - HEC | 0.18 (0.10, 0.25) | Yes |
| Complete response, overall phase - olanzapine 10 mg | 0.16 (0.07, 0.25) | Yes |
| Complete response, overall phase - olanzapine 5 mg | 0.15 (0.04, 0.26) | Yes |
| Complete response, overall phase - double-blind placebo-controlled design | 0.22 (0.12, 0.33) | Yes |
| No nausea, acute phase - adults | 0.13 (0.07, 0.19) | Yes |
| No nausea, acute phase - HEC | 0.14 (0.06, 0.21) | Yes |
| No nausea, acute phase - olanzapine 10 mg | 0.14 (0.07, 0.20) | Yes |
| No nausea, acute phase - double-blind placebo-controlled design | 0.26 (0.19, 0.33) | Yes |
| No nausea, delayed phase - adults | 0.19 (0.12, 0.26) | Yes |
| No nausea, delayed phase - HEC | 0.19 (0.11, 0.26) | Yes |
| No nausea, delayed phase - olanzapine 10 mg | 0.19 (0.12, 0.26) | Yes |
| No nausea, delayed phase - double-blind placebo-controlled design | 0.19 (0.11, 0.27) | Yes |
| No nausea, delayed phase - open controlled design (control arm = antiemetics not in olanzapine arm) | 0.16 (0.03, 0.28) | Yes |
| No nausea, overall phase - adults | 0.20 (0.13, 0.26) | Yes |
| No nausea, overall phase - HEC | 0.21 (0.14, 0.28) | Yes |
| No nausea, overall phase - olanzapine 10 mg | 0.20 (0.13, 0.27) | Yes |
| No nausea, overall phase - double-blind placebo-controlled design | 0.20 (0.11, 0.29) | Yes |
| No nausea, overall phase - open controlled design (control arm = antiemetics not in olanzapine arm) | 0.15 (0.05, 0.26) | Yes |
| No emesis, delayed phase - adults | 0.20 (0.13, 0.26) | Yes |
| No emesis, delayed phase - HEC | 0.17 (0.09, 0.25) | Yes |
| No emesis, delayed phase - olanzapine 10 mg | 0.20 (0.13, 0.26) | Yes |
| No emesis, overall phase - adults | 0.19 (0.11, 0.28) | Yes |
| No emesis, overall phase - HEC | 0.25 (0.13, 0.37) | Yes |
| No emesis, overall phase - olanzapine 10 mg | 0.19 (0.11, 0.28) | Yes |

**Fig. 2** Efficacy of olanzapine regimens compared to others for the prophylaxis of chemotherapy-induced nausea and vomiting (CINV)—no nausea. 2.1 Acute phase. 2.2 Delayed phase. 2.3 Overall phase
### 2.1

#### Gliosarcoma

| Study or Subgroup | Control | Risk Ratio |
|------------------|---------|-----------|
|                  | Events  | Total     | H-n, Nafnet, 95% CI |
|                  | 177     | 265       | 0.80 (0.56, 1.15) |
|                  | Events  | Total     | H-n, Nafnet, 95% CI |
|                  | 177     | 265       | 0.80 (0.56, 1.15) |

#### Osteosarcoma

| Study or Subgroup | Control | Risk Ratio |
|------------------|---------|-----------|
|                  | Events  | Total     | H-n, Nafnet, 95% CI |
|                  | 177     | 265       | 0.80 (0.56, 1.15) |
|                  | Events  | Total     | H-n, Nafnet, 95% CI |
|                  | 177     | 265       | 0.80 (0.56, 1.15) |

#### Neuroblastoma

| Study or Subgroup | Control | Risk Ratio |
|------------------|---------|-----------|
|                  | Events  | Total     | H-n, Nafnet, 95% CI |
|                  | 177     | 265       | 0.80 (0.56, 1.15) |
|                  | Events  | Total     | H-n, Nafnet, 95% CI |
|                  | 177     | 265       | 0.80 (0.56, 1.15) |

#### Renal Cell Carcinoma

| Study or Subgroup | Control | Risk Ratio |
|------------------|---------|-----------|
|                  | Events  | Total     | H-n, Nafnet, 95% CI |
|                  | 177     | 265       | 0.80 (0.56, 1.15) |
|                  | Events  | Total     | H-n, Nafnet, 95% CI |
|                  | 177     | 265       | 0.80 (0.56, 1.15) |

#### Soft Tissue Sarcoma

| Study or Subgroup | Control | Risk Ratio |
|------------------|---------|-----------|
|                  | Events  | Total     | H-n, Nafnet, 95% CI |
|                  | 177     | 265       | 0.80 (0.56, 1.15) |
|                  | Events  | Total     | H-n, Nafnet, 95% CI |
|                  | 177     | 265       | 0.80 (0.56, 1.15) |

#### Neuroendocrine Tumors

| Study or Subgroup | Control | Risk Ratio |
|------------------|---------|-----------|
|                  | Events  | Total     | H-n, Nafnet, 95% CI |
|                  | 177     | 265       | 0.80 (0.56, 1.15) |
|                  | Events  | Total     | H-n, Nafnet, 95% CI |
|                  | 177     | 265       | 0.80 (0.56, 1.15) |

#### Hemangioblastoma

| Study or Subgroup | Control | Risk Ratio |
|------------------|---------|-----------|
|                  | Events  | Total     | H-n, Nafnet, 95% CI |
|                  | 177     | 265       | 0.80 (0.56, 1.15) |
|                  | Events  | Total     | H-n, Nafnet, 95% CI |
|                  | 177     | 265       | 0.80 (0.56, 1.15) |

#### Other Tumors

| Study or Subgroup | Control | Risk Ratio |
|------------------|---------|-----------|
|                  | Events  | Total     | H-n, Nafnet, 95% CI |
|                  | 177     | 265       | 0.80 (0.56, 1.15) |
|                  | Events  | Total     | H-n, Nafnet, 95% CI |
|                  | 177     | 265       | 0.80 (0.56, 1.15) |

#### Overall

| Study or Subgroup | Control | Risk Ratio |
|------------------|---------|-----------|
|                  | Events  | Total     | H-n, Nafnet, 95% CI |
|                  | 177     | 265       | 0.80 (0.56, 1.15) |
|                  | Events  | Total     | H-n, Nafnet, 95% CI |
|                  | 177     | 265       | 0.80 (0.56, 1.15) |

#### Overall

| Study or Subgroup | Control | Risk Ratio |
|------------------|---------|-----------|
|                  | Events  | Total     | H-n, Nafnet, 95% CI |
|                  | 177     | 265       | 0.80 (0.56, 1.15) |
|                  | Events  | Total     | H-n, Nafnet, 95% CI |
|                  | 177     | 265       | 0.80 (0.56, 1.15) |
### 2.2

| Study or Subgroup | Objective | Total Events | Weight | Risk Ratio M–H, Random, 95% CI | Risk Ratio M–H, Random, 95% CI |
|------------------|-----------|--------------|--------|-------------------------------|-------------------------------|
| **Total events** |           |              |        | 1.109                         | 0.971                         |
| **Het for M & H**|           |              |        | 0.001                         | 0.006                         |
| **Total events**|           |              |        | 1.109                         | 0.971                         |
| **Het for M & H**|           |              |        | 0.001                         | 0.006                         |

**Note:** For overall effect, $I^2 = 3.58 \%$ (p = 0.0001).

### 2.2.2 NEC

| Study or Subgroup | Objective | Total Events | Weight | Risk Ratio M–H, Random, 95% CI | Risk Ratio M–H, Random, 95% CI |
|------------------|-----------|--------------|--------|-------------------------------|-------------------------------|
| **Total events** |           |              |        | 1.109                         | 0.971                         |
| **Het for M & H**|           |              |        | 0.001                         | 0.006                         |
| **Total events**|           |              |        | 1.109                         | 0.971                         |
| **Het for M & H**|           |              |        | 0.001                         | 0.006                         |

**Note:** For overall effect, $I^2 = 3.58 \%$ (p = 0.0001).

### 2.2.4 NEC/MEC

| Study or Subgroup | Objective | Total Events | Weight | Risk Ratio M–H, Random, 95% CI | Risk Ratio M–H, Random, 95% CI |
|------------------|-----------|--------------|--------|-------------------------------|-------------------------------|
| **Total events** |           |              |        | 1.109                         | 0.971                         |
| **Het for M & H**|           |              |        | 0.001                         | 0.006                         |
| **Total events**|           |              |        | 1.109                         | 0.971                         |
| **Het for M & H**|           |              |        | 0.001                         | 0.006                         |

**Note:** For overall effect, $I^2 = 3.58 \%$ (p = 0.0001).

### 2.2.5 Cholestasis (SJP)

| Study or Subgroup | Objective | Total Events | Weight | Risk Ratio M–H, Random, 95% CI | Risk Ratio M–H, Random, 95% CI |
|------------------|-----------|--------------|--------|-------------------------------|-------------------------------|
| **Total events** |           |              |        | 1.109                         | 0.971                         |
| **Het for M & H**|           |              |        | 0.001                         | 0.006                         |
| **Total events**|           |              |        | 1.109                         | 0.971                         |
| **Het for M & H**|           |              |        | 0.001                         | 0.006                         |

**Note:** For overall effect, $I^2 = 3.58 \%$ (p = 0.0001).

### 2.2.6 Double-Blind Placebo-Controlled Design

| Study or Subgroup | Objective | Total Events | Weight | Risk Ratio M–H, Random, 95% CI | Risk Ratio M–H, Random, 95% CI |
|------------------|-----------|--------------|--------|-------------------------------|-------------------------------|
| **Total events** |           |              |        | 1.109                         | 0.971                         |
| **Het for M & H**|           |              |        | 0.001                         | 0.006                         |
| **Total events**|           |              |        | 1.109                         | 0.971                         |
| **Het for M & H**|           |              |        | 0.001                         | 0.006                         |

**Note:** For overall effect, $I^2 = 3.58 \%$ (p = 0.0001).

### 2.2.7 Open Controlled Design (C-armetol Amn = All Antidepressants, Except Cholestasis)

| Study or Subgroup | Objective | Total Events | Weight | Risk Ratio M–H, Random, 95% CI | Risk Ratio M–H, Random, 95% CI |
|------------------|-----------|--------------|--------|-------------------------------|-------------------------------|
| **Total events** |           |              |        | 1.109                         | 0.971                         |
| **Het for M & H**|           |              |        | 0.001                         | 0.006                         |
| **Total events**|           |              |        | 1.109                         | 0.971                         |
| **Het for M & H**|           |              |        | 0.001                         | 0.006                         |

**Note:** For overall effect, $I^2 = 3.58 \%$ (p = 0.0001).

### 2.2.8 Open Controlled Design (C-armetol Amn = Antidepressants Not Including Cholestasis)

| Study or Subgroup | Objective | Total Events | Weight | Risk Ratio M–H, Random, 95% CI | Risk Ratio M–H, Random, 95% CI |
|------------------|-----------|--------------|--------|-------------------------------|-------------------------------|
| **Total events** |           |              |        | 1.109                         | 0.971                         |
| **Het for M & H**|           |              |        | 0.001                         | 0.006                         |
| **Total events**|           |              |        | 1.109                         | 0.971                         |
| **Het for M & H**|           |              |        | 0.001                         | 0.006                         |

**Note:** For overall effect, $I^2 = 3.58 \%$ (p = 0.0001).
Fig. 2 (continued)
3.1

### 3.1.1 Adults

| Study or Subgroup       | Olanzapine Events | Control Events | Total Events | Weight | Risk Ratio (M-H, Random, 95% CI) |
|-------------------------|-------------------|----------------|--------------|--------|---------------------------------|
| Tan et al, 2009         | 114               | 121            | 101          | 108    | 39.4% 1.01 (0.94, 1.08)          |
| Shumway et al, 2015     | 5                 | 8              | 3            | 9      | 4.1% 1.88 (0.64, 5.46)          |
| Wang et al, 2015        | 38                | 42             | 33           | 42     | 32.1% 1.15 (0.96, 1.39)         |
| Yeo et al, 2020         | 43                | 60             | 31           | 60     | 24.5% 1.39 (1.04, 1.86)         |
| **Subtotal (95% CI)**   | **231**           | **219**        | **200**      | **168**| **100.0% 1.17 (0.93, 1.47)**   |
| Total events            | 137               | 168            |              |        |                                 |

*Heterogeneity: Tau² = 0.03; Chi² = 12.36, df = 3 (P = 0.006); I² = 76%*

Test for overall effect: Z = 1.32 (P = 0.19)

### 3.1.2 HEC

| Study or Subgroup       | Olanzapine Events | Control Events | Total Events | Weight | Risk Ratio (M-H, Random, 95% CI) |
|-------------------------|-------------------|----------------|--------------|--------|---------------------------------|
| Tan et al, 2009         | 51                | 56             | 41           | 46     | 40.8% 1.02 (0.90, 1.16)         |
| Shumway et al, 2015     | 5                 | 8              | 3            | 9      | 2.9% 1.88 (0.64, 5.46)          |
| Wang et al, 2015        | 38                | 42             | 33           | 42     | 33.8% 1.15 (0.96, 1.39)         |
| Yeo et al, 2020         | 43                | 60             | 31           | 60     | 22.6% 1.39 (1.04, 1.86)         |
| **Subtotal (95% CI)**   | **166**           | **157**        | **137**      | **108**| **100.0% 1.16 (0.96, 1.40)**   |
| Total events            | 137               | 168            |              |        |                                 |

*Heterogeneity: Tau² = 0.02; Chi² = 6.81, df = 3 (P = 0.08); I² = 56%*

Test for overall effect: Z = 1.56 (P = 0.12)

### 3.1.3 MEC

| Study or Subgroup       | Olanzapine Events | Control Events | Total Events | Weight | Risk Ratio (M-H, Random, 95% CI) |
|-------------------------|-------------------|----------------|--------------|--------|---------------------------------|
| Tan et al, 2009         | 63                | 65             | 60           | 62     | 100.0% 1.00 (0.94, 1.07)        |
| **Subtotal (95% CI)**   | **65**            | **62**         | **63**       | **60** | **100.0% 1.00 (0.94, 1.07)**   |
| Total events            | 63                | 60             |              |        |                                 |

*Heterogeneity: Not applicable*

Test for overall effect: Z = 0.05 (P = 0.96)

### 3.1.4 Olanzapine 10mg

| Study or Subgroup       | Olanzapine Events | Control Events | Total Events | Weight | Risk Ratio (M-H, Random, 95% CI) |
|-------------------------|-------------------|----------------|--------------|--------|---------------------------------|
| Tan et al, 2009         | 114               | 121            | 101          | 108    | 39.4% 1.01 (0.94, 1.08)         |
| Shumway et al, 2015     | 5                 | 8              | 3            | 9      | 4.1% 1.88 (0.64, 5.46)          |
| Wang et al, 2015        | 38                | 42             | 33           | 42     | 32.1% 1.15 (0.96, 1.39)         |
| Yeo et al, 2020         | 43                | 60             | 31           | 60     | 24.5% 1.39 (1.04, 1.86)         |
| **Subtotal (95% CI)**   | **231**           | **219**        | **200**      | **168**| **100.0% 1.17 (0.93, 1.47)**   |
| Total events            | 137               | 168            |              |        |                                 |

*Heterogeneity: Tau² = 0.03; Chi² = 12.36, df = 3 (P = 0.006); I² = 76%*

Test for overall effect: Z = 1.32 (P = 0.19)

### 3.1.5 Double-Blind Placebo-Controlled Design

| Study or Subgroup       | Olanzapine Events | Control Events | Total Events | Weight | Risk Ratio (M-H, Random, 95% CI) |
|-------------------------|-------------------|----------------|--------------|--------|---------------------------------|
| Yeo et al, 2020         | 43                | 60             | 31           | 60     | 100.0% 1.39 (1.04, 1.86)        |
| **Subtotal (95% CI)**   | **60**            | **60**         | **43**       | **31** | **100.0% 1.39 (1.04, 1.86)**   |
| Total events            | 43                | 31             |              |        |                                 |

*Heterogeneity: Not applicable*

Test for overall effect: Z = 2.20 (P = 0.03)

### 3.1.6 Open Controlled Design (Control Arm = All Antiemetics, Except Olanzapine)

| Study or Subgroup       | Olanzapine Events | Control Events | Total Events | Weight | Risk Ratio (M-H, Random, 95% CI) |
|-------------------------|-------------------|----------------|--------------|--------|---------------------------------|
| Tan et al, 2009         | 114               | 121            | 101          | 108    | 68.6% 1.01 (0.94, 1.08)         |
| Wang et al, 2015        | 38                | 42             | 33           | 42     | 31.4% 1.15 (0.96, 1.39)         |
| **Subtotal (95% CI)**   | **163**           | **150**        | **152**      | **134**| **100.0% 1.05 (0.92, 1.20)**   |
| Total events            | 152               | 134            |              |        |                                 |

*Heterogeneity: Tau² = 0.01; Chi² = 2.08, df = 1 (P = 0.15); I² = 52%*

Test for overall effect: Z = 0.73 (P = 0.46)

### 3.1.7 Open Controlled Design (Control Arm = Antiemetics Not In Olanzapine Arm)

| Study or Subgroup       | Olanzapine Events | Control Events | Total Events | Weight | Risk Ratio (M-H, Random, 95% CI) |
|-------------------------|-------------------|----------------|--------------|--------|---------------------------------|
| Shumway et al, 2015     | 5                 | 8              | 3            | 9      | 100.0% 1.88 (0.64, 5.46)        |
| **Subtotal (95% CI)**   | **8**             | **9**          | **5**        | **3**  | **100.0% 1.88 (0.64, 5.46)**   |
| Total events            | 5                 | 3              |              |        |                                 |

*Heterogeneity: Not applicable*

Test for overall effect: Z = 1.15 (P = 0.25)

---

**Fig. 3** Efficacy of olanzapine regimens compared to others for the prophylaxis of chemotherapy-induced nausea and vomiting (CINV)—no emesis. **3.1** Acute phase. **3.2** Delayed phase. **3.3** Overall phase.
### 3.2

| Study or Subgroup | Olanzapine | Control | Risk Ratio |
|------------------|------------|---------|------------|
|                  | Events     | Total   | Total      | Weight | M–H, Random, 95% CI | M–H, Random, 95% CI |
| **3.2.1 Adults** |            |         |            |        |                   |                     |
| Tan et al, 2009  | 112        | 121     | 73         | 108    | 38.4%              | 1.37 [1.19, 1.58]    |
| Wang et al, 2015 | 6          | 9       | 5          | 9      | 1.4%               | 1.22 [0.57, 2.53]    |
| Yeo et al, 2020  | 50         | 60      | 46         | 60     | 31.3%              | 1.22 [1.04, 1.42]    |
| **Subtotal (95% CI)** | 232        | 221     | 100.0%     |        |                    | 1.26 [1.16, 1.38]    |
| Total events     | 214        | 158     |            |        |                   |                     |
| **3.2.2 HEC**    |            |         |            |        |                   |                     |
| Tan et al, 2009  | 44         | 56      | 26         | 46     | 12.9%              | 1.39 [1.04, 1.85]    |
| Wang et al, 2015 | 6          | 9       | 5          | 9      | 1.9%               | 1.20 [0.57, 2.53]    |
| Yeo et al, 2020  | 56         | 60      | 46         | 60     | 44.3%              | 1.22 [1.04, 1.42]    |
| **Subtotal (95% CI)** | 167        | 157     | 100.0%     |        |                    | 1.22 [1.10, 1.35]    |
| Total events     | 146        | 111     |            |        |                   |                     |
| **3.2.3 MEC**    |            |         |            |        |                   |                     |
| Tan et al, 2009  | 58         | 65      | 47         | 62     | 100.0%             | 1.18 [1.00, 1.39]    |
| **Subtotal (95% CI)** | 65         | 62      | 100.0%     |        |                    | 1.18 [1.00, 1.39]    |
| Total events     | 58         | 47      |            |        |                   |                     |
| **3.2.4 Olanzapine 10mg** | | | | | | |
| Tan et al, 2009  | 112        | 121     | 73         | 108    | 38.4%              | 1.37 [1.19, 1.58]    |
| Wang et al, 2015 | 6          | 9       | 5          | 9      | 1.4%               | 1.20 [0.57, 2.53]    |
| Yeo et al, 2020  | 56         | 60      | 46         | 60     | 31.3%              | 1.22 [1.04, 1.42]    |
| **Subtotal (95% CI)** | 232        | 219     | 100.0%     |        |                    | 1.26 [1.16, 1.38]    |
| Total events     | 214        | 158     |            |        |                   |                     |
| **3.2.5 Double-Blind Placebo-Controlled Design** | | | | | | |
| Yeo et al, 2020  | 56         | 60      | 46         | 60     | 100.0%             | 1.22 [1.04, 1.42]    |
| **Subtotal (95% CI)** | 56         | 46      | 100.0%     |        |                    | 1.22 [1.04, 1.42]    |
| Total events     | 56         | 46      |            |        |                   |                     |
| **3.2.6 Open Controlled Design (Control Arm = All Antiemetics, Except Olanzapine)** | | | | | | |
| Tan et al, 2009  | 112        | 121     | 73         | 108    | 53.4%              | 1.37 [1.19, 1.58]    |
| Wang et al, 2015 | 40         | 42      | 34         | 42     | 28.9%              | 1.18 [1.00, 1.38]    |
| **Subtotal (95% CI)** | 163        | 150     | 100.0%     |        |                    | 1.28 [1.09, 1.49]    |
| Total events     | 152        | 107     |            |        |                   |                     |
| **3.2.7 Open Controlled Design (Control Arm = Antiemetics Not In Olanzapine Arm)** | | | | | | |
| Wang et al, 2015 | 6          | 9       | 5          | 9      | 100.0%             | 1.20 [0.57, 2.53]    |
| **Subtotal (95% CI)** | 9          | 9       | 100.0%     |        |                    | 1.20 [0.57, 2.53]    |
| Total events     | 6          | 5       |            |        |                   |                     |

Fig. 3 (continued)
### 3.3

#### 3.3.1 Adults

| Study or Subgroup | Olanzapine Events | Control Events | Weight | Risk Ratio M–H, Random, 95% CI |
|-------------------|-------------------|----------------|--------|--------------------------------|
| Tan et al, 2009   | 102               | 121            | 73     | 108 69.7% 1.25 [1.07, 1.45]     |
| Shumway et al, 2015 | 4                 | 9              | 2      | 9    1.1% 2.00 [0.48, 8.31]      |
| Jeon et al, 2019  | 20                | 29             | 14     | 25   12.1% 1.23 [0.81, 1.88]     |
| Yeo et al, 2020   | 41                | 60             | 24     | 60   17.0% 1.71 [1.20, 2.44]     |
| **Subtotal (95% CI)** | **219**           | **202**        | **100.0%** | **1.32 [1.13, 1.54]**      |
| **Total events** | **167**           | **113**        |        |                               |

Heterogeneity: Tau² = 0.00, Chi² = 3.23, df = 3 (P = 0.36); I² = 7%
Test for overall effect: Z = 3.59 (P = 0.0003)

#### 3.3.2 HEC

| Study or Subgroup | Olanzapine Events | Control Events | Weight | Risk Ratio M–H, Random, 95% CI |
|-------------------|-------------------|----------------|--------|--------------------------------|
| Tan et al, 2009   | 44                | 56             | 26     | 46   58.8% 1.39 [1.04, 1.85]     |
| Shumway et al, 2015 | 4                 | 9              | 2      | 9    2.4% 2.00 [0.48, 8.31]      |
| Yeo et al, 2020   | 41                | 60             | 24     | 60   38.8% 1.71 [1.20, 2.44]     |
| **Subtotal (95% CI)** | **125**           | **115**        | **100.0%** | **1.52 [1.22, 1.89]**      |
| **Total events** | **89**            | **52**         |        |                               |

Heterogeneity: Tau² = 0.00, Chi² = 0.97, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 3.71 (P = 0.0002)

#### 3.3.3 MEC

| Study or Subgroup | Olanzapine Events | Control Events | Weight | Risk Ratio M–H, Random, 95% CI |
|-------------------|-------------------|----------------|--------|--------------------------------|
| Tan et al, 2009   | 58                | 65             | 47     | 62   87.0% 1.18 [1.00, 1.39]     |
| Jeon et al, 2019  | 20                | 29             | 14     | 25   13.0% 1.23 [0.81, 1.88]     |
| **Subtotal (95% CI)** | **94**           | **87**        | **100.0%** | **1.18 [1.02, 1.38]**      |
| **Total events** | **78**            | **61**        |        |                               |

Heterogeneity: Tau² = 0.00, Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 2.16 (P = 0.03)

#### 3.3.4 Olanzapine 10mg

| Study or Subgroup | Olanzapine Events | Control Events | Weight | Risk Ratio M–H, Random, 95% CI |
|-------------------|-------------------|----------------|--------|--------------------------------|
| Tan et al, 2009   | 102               | 121            | 73     | 108 69.7% 1.25 [1.07, 1.45]     |
| Shumway et al, 2015 | 4                 | 9              | 2      | 9    1.1% 2.00 [0.48, 8.31]      |
| Jeon et al, 2019  | 20                | 29             | 14     | 25   12.1% 1.23 [0.81, 1.88]     |
| Yeo et al, 2020   | 41                | 60             | 24     | 60   17.0% 1.71 [1.20, 2.44]     |
| **Subtotal (95% CI)** | **219**           | **202**        | **100.0%** | **1.32 [1.13, 1.54]**      |
| **Total events** | **167**           | **113**        |        |                               |

Heterogeneity: Tau² = 0.00, Chi² = 3.23, df = 3 (P = 0.36); I² = 7%
Test for overall effect: Z = 3.59 (P = 0.0003)

#### 3.3.5 Double-Blind Placebo-Controlled Design

| Study or Subgroup | Olanzapine Events | Control Events | Weight | Risk Ratio M–H, Random, 95% CI |
|-------------------|-------------------|----------------|--------|--------------------------------|
| Jeon et al, 2019  | 20                | 29             | 14     | 25   43.5% 1.23 [0.81, 1.88]     |
| Yeo et al, 2020   | 41                | 60             | 24     | 60   56.5% 1.71 [1.20, 2.44]     |
| **Subtotal (95% CI)** | **89**           | **85**        | **100.0%** | **1.48 [1.08, 2.04]**      |
| **Total events** | **61**            | **38**        |        |                               |

Heterogeneity: Tau² = 0.01, Chi² = 1.37, df = 1 (P = 0.24); I² = 27%
Test for overall effect: Z = 2.40 (P = 0.02)

#### 3.3.6 Open Controlled Design (Control Arm = All Antiemetics, Except Olanzapine)

| Study or Subgroup | Olanzapine Events | Control Events | Weight | Risk Ratio M–H, Random, 95% CI |
|-------------------|-------------------|----------------|--------|--------------------------------|
| Tan et al, 2009   | 102               | 121            | 73     | 108 100.0% 1.25 [1.07, 1.45]     |
| **Subtotal (95% CI)** | **121**           | **108**        | **100.0%** | **1.25 [1.07, 1.45]**      |
| **Total events** | **102**           | **73**        |        |                               |

Heterogeneity: Not applicable
Test for overall effect: Z = 2.86 (P = 0.004)

#### 3.3.7 Open Controlled Design (Control Arm = Antiemetics Not In Olanzapine Arm)

| Study or Subgroup | Olanzapine Events | Control Events | Weight | Risk Ratio M–H, Random, 95% CI |
|-------------------|-------------------|----------------|--------|--------------------------------|
| Shumway et al, 2015 | 4                 | 9              | 2      | 9    100.0% 2.00 [0.48, 8.31]      |
| **Subtotal (95% CI)** | **9**           | **9**        | **100.0%** | **2.00 [0.48, 8.31]**      |
| **Total events** | **4**            | **2**        |        |                               |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.95 (P = 0.34)
For studies reporting on HEC patients, olanzapine is statistically and clinically superior in seven of nine efficacy endpoints in the prophylaxis setting; only complete emetic control in the acute and overall phases were not statistically different from comparative regimens. Meta-analysis results among studies employing 10-mg doses and among studies comparing olanzapine to placebo-controlled regimens indicated olanzapine as statistically and clinically superior in eight of nine efficacy endpoints for prophylaxis of CINV, with the exception of complete emetic control in the acute phase. These results support the international clinical guidelines [28–30] in their recommendation of 10-mg olanzapine in addition to standard antiemetic regimens for the prophylaxis of CINV among HEC patients.

Furthermore, this review includes important subgroup analyses not previously conducted among prophylactic studies, namely meta-analyzing studies reporting on MEC patients and 5-mg olanzapine dosing. Olanzapine is both statistically and clinically superior in only three of six efficacy endpoints where a 5-mg dosage is employed—complete response in the acute, delayed, and overall phases. However, it is important to note that over 800 patients across 4 studies were meta-analyzed for the efficacy endpoints of complete response; there was much less statistical power relative to meta-analyses looking at HEC patients alone. Furthermore, even for the efficacy endpoints of complete response, these meta-analysis results are much more fragile and less certain than those pertaining to olanzapine administered at 10-mg dose studies. Olanzapine may potentially be superior to comparative regimens when administered in 5-mg doses as indicated by point estimates, but the paucity of data results in low statistical power to find these differences statistically significant. Olanzapine has also recently been reported to be effective at 5-mg doses in controlling nausea and vomiting, unrelated to chemotherapy, for patients with advanced cancer [67]. More RCTs are needed in the CINV setting, to evaluate the efficacy of 5-mg olanzapine doses compared to non-olanzapine-containing regimens. Studies comparing 5-mg doses to 10-mg doses are also encouraged; an abstract recently presented by Mukhopadhyay et al. suggests that 5-mg and 10-mg doses may have similar efficacy, although it has no description of drop out patients or chemotherapy regimens in either arm, and no statistical calculations were published [39].

In the MEC setting, olanzapine is reported to be statistically and clinically superior in two of nine efficacy endpoints only—no nausea in the delayed phase, and no emesis in the overall phase. However, as with the results from the meta-analysis of 5-mg doses, there is a paucity of data in this setting.
The results are less robust compared to those in the HEC setting, with the recent clinical trials having noticeable impacts on the summary effect size. More RCTs in this setting would allow for a better understanding of olanzapine’s true efficacy for MEC patients.

Olanzapine is reported to be clinically and statistically superior than other regimens for the rescue of breakthrough CINV. However, this review’s results are only supported by one included study for each efficacy endpoint. Results should be interpreted with caution. In both the prophylactic and rescue setting, olanzapine is reported to be equally as safe as other regimens. However, this too should be interpreted with caution, as the key adverse event of sedation is not routinely reported—many studies commonly reported only on serious (i.e., grade 3 or greater toxicity) adverse events, an observation also noted by our group several years ago [26]. It has been well-documented that olanzapine is a strong sedative, and patients commonly experience fatigue, drowsiness, and reduced general activity [20]. In the interest of reducing adverse events, further exploring the reduction of the dosage of olanzapine (i.e. more RCTs reporting on 5-mg olanzapine doses) is encouraged.

This review was not without limitations. Ideally, the protocol would have been registered on PROSPERO; given the COVID 19 pandemic, this was not a feasible option—protocol registration would have required several months, while in hindsight our review was already completed. There were numerous instances where there were high levels of heterogeneity; a random-effects model was applied in all circumstances to try to appropriately account for this. As well, as is the nature of meta-analyses, the results suffer from any intrinsic biases from included RCTs; over half of the studies have notable concerns of bias due to lack of blinding.

In conclusion, olanzapine is effective and safe for the prophylaxis and rescue of CINV. It has been well-documented in the HEC setting and when administered at 10-mg doses; it is statistically and clinically superior to comparative regimens, but its sedative properties can make it difficult to use in outpatient settings. It is unclear if olanzapine is effective in the MEC setting and when administered at a lower 5-mg dose, and further RCTs are needed for a more definitive conclusion. The sedative effect associated with 10 mg of olanzapine further corroborates the need for more investigations into using olanzapine at lower doses.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00520-020-05935-7.

Authors’ contributions All authors contributed substantially to conception and design, or acquisition of data, or analysis and interpretation of data. All authors contributed in drafting the article or revising it critically for important intellectual content. All authors approved the version to be published.

Data availability N/A

Compliance with ethical standards

Conflict of interest Dr Lock reports consulting fees from Ferring, Abbvie, Sanofi, and AstraZeneca in the past 10 years outside the submitted work. Dr Herrstedt reports personal fees from SOBI and GSK outside the submitted work. Dr Aapro reports personal fees and non-financial support from the Multinational Association for Supportive Care in Cancer, personal fees and non-financial support from European Society of Medical Oncology, personal fees and non-financial support from the European Cancer Organisation, grants and personal fees from Helsinn, personal fees from Tesaro, grants and personal fees from Sandoz, personal fees from Merck USA, personal fees from Vifor, personal fees from Pfizer, personal fees from Taiho, and personal fees from Kyowa Kirin, outside the submitted work. The other authors declare that they have no conflict of interest.

Ethics approval N/A

Consent to participate N/A

Consent to publication N/A

Code availability N/A

References

1. Cohen L, de Moor CA, Eisenberg P et al (2007) Chemotherapy-induced nausea and vomiting: incidence and impact on patient quality of life at community oncology settings. Support Care Cancer 15: 491–503
2. Pollera CF, Giannarelli D (1989) Prognostic factors influencing cisplatin-induced emesis: definition and validation of a predictive logistic model. Cancer 64:1117–1122
3. du Bois A, Meerpohl HG, Vach W et al (1992) Course, patterns and risk-factors for chemotherapy-induced emesis in cisplatin-pretreated patients: a study with ondansetron. Eur J Cancer 28: 450–457
4. Osoba D, Zee B, Pater J, Warr D, Latreille J, Kaizer L (1997) Determinants of postchemotherapy nausea and vomiting in patients with cancer. J Clin Oncol 15:116–123
5. Molassiotis A, Aapro M, Dicato M, Gascon P, Novoa SA, Isambert N, Burke TA, Gu A, Roila F (2014) Evaluation of risk factors predicting chemotherapy-related nausea and vomiting: results from a European prospective observational study. J Pain Symptom Manag 47:839–848
6. Chow R, Warr DG, Navari RM, Tsao M, Milakovic M, Popovic M, Chiu L, Lam H, DeAngelis C (2018) Efficacy and safety of 1-day versus 3-day dexamethasone for the prophylaxis of chemotherapy-induced nausea and vomiting: a systematic review and meta-analysis of randomized controlled trials. J Hosp Manag Health Policy 2:25
7. Chow R, Valdez C, Chow N, Zhang D, Im J, Sodhi E, Lock M (2020) Oral cannabinoid for the prophylaxis of chemotherapy-induced nausea and vomiting – a systematic review and meta-analysis. Support Care Cancer 28:2095–2103
8. Gralla RJ, Itri LM, Pisko SE, Squillante AE, Kelsen DP, Braun DW Jr, Bordin LA, Braun TJ, Young CW (1981) Antiemetic efficacy of high-dose metoclopramide: randomized trials with placebo and prochlorperazine in patients with chemotherapy-induced nausea and vomiting. N Engl J Med 305:905–909
40. Minatogawa H, Iwata N, Kawaguchi T et al (2019) Phase III study of comparing dexamethasone on day 1 with day 1-4 with combined neurokinin-1 receptor antagonist, palonosetron and olanzapine in cisplatin-based chemotherapy. Support Care Cancer 27(Suppl 1): S38–S39

41. Mukhopadhyay S, Dutta P, Bhattacharyya B et al (2018) Low dose olanzapine in chemotherapy induced nausea and vomiting: The ideal 8 pm antiemetic? Support Care Cancer 26(Suppl 1):S79

42. Navari RM, Gray SE (2009) Treatment of chemotherapy-induced breakthrough nausea and vomiting. J Clin Oncol 27:e20536. https://doi.org/10.1200/JCO.2009.27.15_suppl.e20536

43. Navari RM, Nagy CK, Gray SE (2013) The use of olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. Support Care Cancer 21:1655–1663

44. Nakagaki M, Barras M, Curley C, Butler JP, Kennedy GA (2017) A randomized trial of olanzapine versus palonosetron versus infused ondansetron for the treatment of breakthrough chemotherapy-induced nausea and vomiting in patients undergoing hematopoietic stem cell transplantation. Support Care Cancer 25:607–613

45. Tan L, Liu J, Liu X, Chen J, Yan Z, Yang H, Zhang D (2009) Clinical research of olanzapine for prevention of chemotherapy-induced nausea and vomiting. J Exp Clin Cancer Res 28:131

46. Navari RM, Gray SE, Kerr AC (2011) Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. J Support Oncol 9:188–195

47. Mizukami N, Yamazaki M, Koike K, Watanabe A, Ichihara K, Masumori N, Yamakage M (2014) Olanzapine for the prevention of chemotherapy-induced nausea and vomiting in patients receiving highly or moderately emetogenic chemotherapy: a randomized, double-blind, placebo-controlled study. J Pain Symptom Manag 47:542–550

48. Long C, Knoderer H, Mueller E (2015) A pilot study comparing the efficacy of olanzapine or aprepitant in an antiemetic regimen for highly emetogenic chemotherapy. Pediatr Blood Cancer 62(Suppl 2):S104

49. Shumway NM, Terrazzino SE, Jones CG (2015) A randomized pilot study comparing olanzapine (Zyprexa) to aprepitant (Emend) for treatment of chemotherapy-induced nausea and vomiting. J Pain Manag 8:233–241

50. Wang X, Wang L, Wang H, Zhang H (2015) Effectiveness of olanzapine combined with ondansetron in prevention of chemotherapy-induced nausea and vomiting of non-small cell lung cancer. Cell Biochem Biophys 72:471–473

51. Navari RM, Nagy CK, Le-Rademacher JL et al (2016) Olanzapine versus fosaprepitant for the prevention of concurrent chemotherapy radiotherapy-induced nausea and vomiting. J Community Support Oncol 14:141–147

52. Navari RM, Qin R, Rudyk KJ, Liu H, Powell SF, Bajaj M, Dietrich L, Biggs D, Lafky JM, Loprinzi CL (2016) Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. N Engl J Med 375:134–142

53. Mukesh S, Sathya M, Akshay JK (2017) Olanzapine versus aprepitant in the prevention of chemotherapy induced nausea and vomiting (CINV) in breast cancer patients. J Clin Oncol 35:e21670. https://doi.org/10.1200/JCO.2017.35.15_suppl.e21670

54. Mukhopadhyay S, Gagandeep K, Alice KP et al (2017) Role of olanzapine in chemotherapy-induced nausea and vomiting on platinum-based chemotherapy patients: a randomized controlled study. Support Care Cancer 25:145–154

55. Sapkota S, Mahaseet R, Jha K (2017) The use of olanzapine compared to aprepitant as antiemetic for prevention of chemotherapy induced nausea and vomiting in highly emetogenic chemotherapy – a randomized trial. Eur J Cancer 72:S168. https://doi.org/10.1016/S0959-8049(17)30623-8

56. Tran T, Nguyen N, Pham V et al (2017) Olanzapine and omeprazole combination is simple, safe and effective for delayed nausea and vomiting control in adjuvant chemotherapy for early stage breast cancer. Support Care Cancer 25:572

57. Celio L, Salvatore G, Lepori S et al (2019) Short-course olanzapine to prevent delayed emesis following carboplatin/paclitaxel for gynecologic cancer: a randomised study. Tumori J 105:253–258

58. Dulal S, Paudel BD, Neupane P, Shah A, Acharya B, Poudyal BS, Shilpakar R, Wood LA (2019) Randomized phase II trial to compare the efficacy of haloperidol and olanzapine in the control of chemotherapy-induced nausea and vomiting in Nepal. J Glob Oncol 5:1–6. https://doi.org/10.1200/JGO.18.00245

59. Jeon SY, Han HS, Bae WK, Park MK, Shim H, Lee SC, Go SI, Yun HJ, Im YJ, Song EK (2019) A randomized double-blind, placebo-controlled study of the safety and efficacy of olanzapine for the prevention of chemotherapy-induced nausea and vomiting in patients receiving moderately emetogenic chemotherapy: results of the Korean South West Oncology Group (KSWOG) study. Cancer Res Treat 51:90–97

60. Rumyansev AS, Glazkova E, Nasyrova R, Ignatova E, Chitina L, Popova A, Chekini D, Kochetkova Y, Kit S, Elsnuakaev K, Menshikova S, Sekhina O, Pokatea I, Tyulyandina A, Stenima M, Frolova MA, Bulanov A, Fedyanin M, Tryakin A, Tjalandin S (2019) Olanzapine (OLN) versus aprepitant (APR) in patients receiving high-emetogenic chemotherapy: final results of randomized phase II trial. J Clin Oncol 37:11504. https://doi.org/10.1200/JCO.2019.37.15_suppl.11504

61. Saldanha SC, Dasappa L, Jacob LA, Babu SM, Lokesh KN, Reduresha AH, Lakavalli RK, Kumar J (2019) Efficacy of olanzapine combination in prevention of nausea & vomiting in highly emetogenic chemotherapy. Ann Palliat Med 8:73–80

62. Tienclarnandna P, Nipondhkit W, Maneenil K, Sa-nguansai S, Payapwattanawong S, Laohavinij S, Maneenavakhajorn J (2019) A randomized, double-blind, placebo-controlled study evaluating the efficacy in combination olanzapine, ondansetron and dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving doxorubicin plus cyclophosphamide. Eur J Cancer 80:46–52

63. Hashimoto H, Abe M, Tokuyama O, Mizutani H, Uchitomi Y, Yamaguchi T, Hoshina Y, Sakata Y, Takahasi TV, Nakashima K, Nakao M, Takei D, Zenda S, Mizukami K, Iwasa S, Sakurai M, Yamamoto N, Ohe Y (2020) Olanzapine 5 mg plus standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting (J-FORCE): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 21:242–249

64. Ithimakin S, Theeratrakul P, Laorchaoenkit A, Nimmanit K, Akewanlop C, Soparatpanaissarn N, Techarwathanawanna S, Korphaisarn K, Dancharavijitr P (2020) Randomized, placebo-controlled study of aprepitant versus a combination of olanzapine with ondansetron plus dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving high-emetogenic chemotherapy. Support Care Cancer 28:5335–5342. https://doi.org/10.1007/s00520-020-05380-6

65. Vimolchalao V, Sakdejayont S, Wongchanapai P, Sukprakun S, Angspatt P, Thawinwisan W, Chenaksara P, Sriruampong V, Vinayanguwatikun C, Parinyanitikun N, Poovorawan N, Tananasivin S (2020) The efficacy and safety of the addition of olanzapine to ondansetron and dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving high-emetogenic chemotherapy. Int J Clin Oncol 25:396–402

66. Yeo W, Lau TKH, Li L, Lai KT, Pang E, Cheung M, Chan VTC, Wong A, Soo WMT, Yeung VTY, Tse T, Lam DCM, Yeung EWM, Ng KPK, Tang NLS, Tong M, Suen JJS, Mo FK (2020) A randomized study of olanzapine-containing versus standard...
67. Navari RM, Pywell CM, Le-Rademacher JG et al (2020) Olanzapine for the treatment of advanced cancer-related chronic nausea and/or vomiting. JAMA Oncol 6:895–899. https://doi.org/10.1001/jamaoncol.2020.1052

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.