Supportive Care in Cancer (2021) 29:3439–3459
https://doi.org/10.1007/s00520-020-05935-7

REVIEW ARTICLE

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]

Received: 28 October 2020 / Accepted: 3 December 2020 / Published online: 13 January 2021

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

✉ Ronald Chow
ronald.chow@yale.edu

[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, Brimingham, 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 $(5\text{-}HT)_3$-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 $5\text{-}HT_{2a}$, $5\text{-}HT_{2c}$, $5\text{-}HT_3$, $5\text{-}HT_6$, and dopamine D_1, D_2, D_3, and D_4 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, chemotherapy emetogenicity, and the difference between the olanzapine 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 chemotherapy emetogenicity, 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 efficacy meta-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 children

In children, olanzapine was not statistically superior in the acute and overall phases, according to the one study by Long et al.

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).

Table 1 Study demographics

Study	Evaluable sample size	Age range	% Male	Chemotherapy emetogenicity	Intervention's additional/substitute drug regimens, relative to comparative arm
Studies reporting on olanzapine for the prophylaxis of chemotherapy-induced nausea and vomiting					
Tan et al., 2009 [45]	229	18–74	60	HEC & MEC	Day 1: addition of olanzapine 10 mg PO Days 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
*Long et al., 2015 [48]	14	4–21	NR	HEC	Olanzapine, instead of aprepitant
Shumway et al., 2015 [49]	17	NR	37	HEC	Days −2 to −1: 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
Wang et al., 2015 [50]	84	39–76	73	HEC	Days 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
*Mukesh et al., 2017 [53]	84	29–80	0	MEC	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
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	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
*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	Days 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
Jeon et al., 2019 [59]	56	30–79	83	MEC	Days 1–4: addition of olanzapine 10 mg PO
*Rumyantsev et al., 2019 [60]	93	NR	4	HEC	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
*Saldanha et al., 2019 [61]	209	NR	NR	HEC	Day 1–4: olanzapine 10 mg PO in addition to, or instead of, aprepitant standard regimen
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

Table 1 (continued)

Study	Evaluable sample size	Age range	% Male	Chemotherapy emetogenicity	Intervention's additional/substitute drug regimens, relative to comparative arm
Studies reporting on olanzapine for the rescue of breakthrough chemotherapy-induced nausea and vomiting					
Navari and Gray, 2009* [42]	100	37–85	NR	MEC	Day 1: dexamethasone 20 mg IV and olanzapine 5 mg PO BID, instead of prochlorperazine 10 mg IV and 10 mg PO BID or metoclopramide 20 mg IV and 10 mg PO BID Days 2–3: olanzapine 5 mg PO BID, instead of prochlorperazine 10 mg PO BID or metoclopramide 10 mg PO BID
Navari et al., 2013 [43]	56	38–79	46	HEC	Days 1–3: olanzapine 10 mg PO, instead of metoclopramide 10 mg PO TID
Nakagaki et al., 2017 [44]	62	20–68	41	HEC	Day 1: olanzapine 10 mg PO, instead of ondansetron 32 mg IV or palonosetron 0.25 mg IV Days 2–3: olanzapine 10 mg PO, instead of ondansetron 32 mg IV or none

BID twice a day, *HEC* highly emetogenic chemotherapy, *IV* intravenous, *MEC* moderately emetogenic chemotherapy, *NR* not reported, *PO* per os

*Conference abstract only

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).

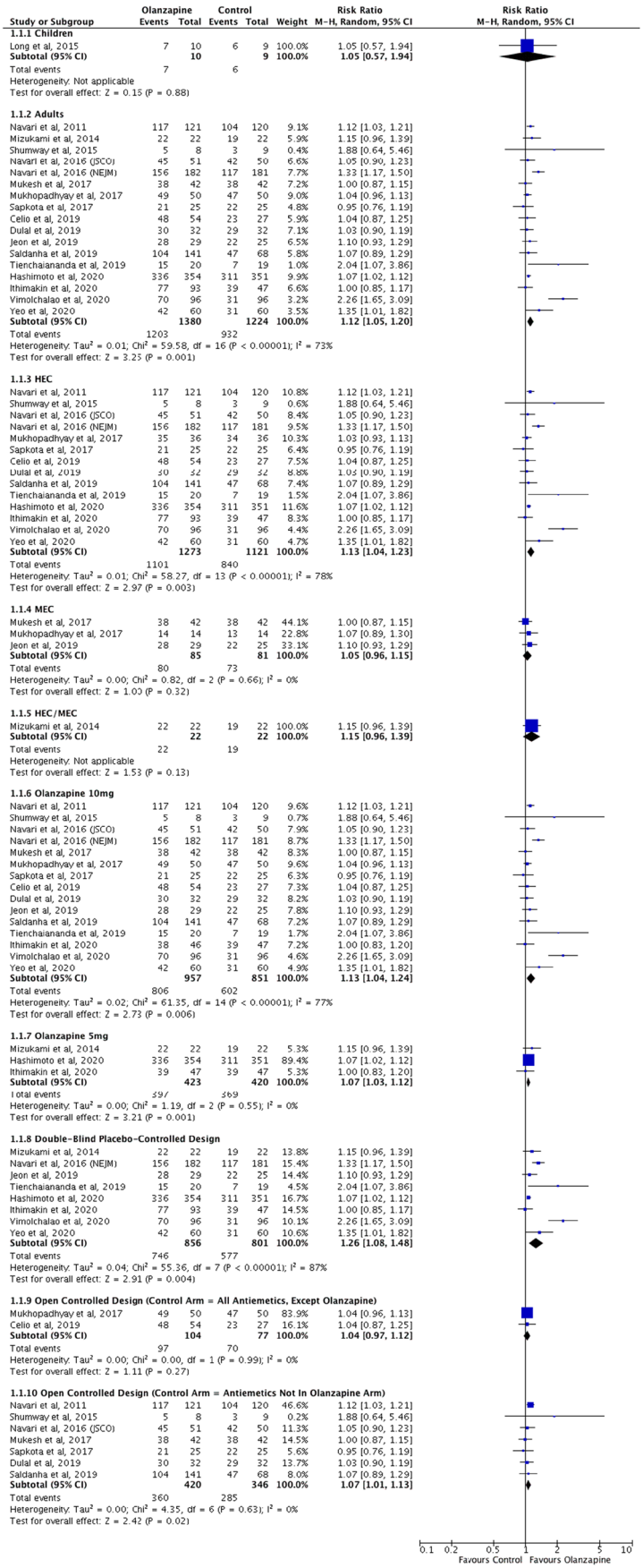
Discussion

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]. This

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


Olanzapine Control Risk Ratio Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI
1.1.1 Children
Long et al, 2015 7 10 6 9 100.0% 1.05 [0.57, 1.94]
Subtotal (95% CI) 10 9 100.0% 1.05 [0.57, 1.94]
Total events 7 6
Heterogeneity: Not applicable
Test for overall effect: Z = 0.15 (P = 0.88)
1.1.2 Adults
Navari et al, 2011 117 121 104 120 9.1% 1.12 [1.03, 1.21]
Mizukami et al, 2014 22 22 19 22 5.9% 1.15 [0.96, 1.39]
Shumway et al, 2015 5 8 3 9 0.4% 1.88 [0.64, 5.46]
Navari et al, 2016 (JSCO) 45 51 42 50 6.6% 1.05 [0.90, 1.23]
Navari et al, 2016 (NEJM) 156 182 117 181 7.7% 1.33 [1.17, 1.50]
Mukesh et al, 2017 38 42 38 42 7.2% 1.00 [0.87, 1.15]
Mukhopadhyay et al, 2017 49 50 47 50 9.0% 1.04 [0.96, 1.13]
Sapkota et al, 2017 21 25 22 25 4.8% 0.95 [0.76, 1.19]
Celio et al, 2019 48 54 23 27 5.9% 1.04 [0.87, 1.25]
Dulal et al, 2019 30 32 29 32 7.1% 1.03 [0.90, 1.19]
Jeon et al, 2019 28 29 22 25 6.5% 1.10 [0.93, 1.29]
Saldanha et al, 2019 104 141 47 68 5.8% 1.07 [0.89, 1.29]
Tienchaiananda et al, 2019 15 20 7 19 1.0% 2.04 [1.07, 3.86]
Hashimoto et al, 2020 336 354 311 351 9.9% 1.07 [1.02, 1.12]
Ithimakin et al, 2020 77 93 39 47 6.6% 1.00 [0.85, 1.17]
Vimolchalao et al, 2020 70 96 31 96 3.2% 2.26 [1.65, 3.09]
Yeo et al, 2020 42 60 31 60 3.5% 1.35 [1.01, 1.82]
Subtotal (95% CI) 1380 1224 100.0% 1.12 [1.05, 1.20]
Total events 1203 932
Heterogeneity: Tau² = 0.01; Chi² = 59.58, df = 16 (P < 0.00001); I² = 73%
Test for overall effect: Z = 3.25 (P = 0.001)
1.1.3 HEC
Navari et al, 2011 117 121 104 120 10.8% 1.12 [1.03, 1.21]
Shumway et al, 2015 5 8 3 9 0.6% 1.88 [0.64, 5.46]
Navari et al, 2016 (JSCO) 45 51 42 50 8.4% 1.05 [0.90, 1.23]
Navari et al, 2016 (NEJM) 156 182 117 181 9.5% 1.33 [1.17, 1.50]
Mukhopadhyay et al, 2017 35 36 34 36 10.3% 1.03 [0.93, 1.13]
Sapkota et al, 2017 21 25 22 25 6.4% 0.95 [0.76, 1.19]
Celio et al, 2019 48 54 23 27 7.5% 1.04 [0.87, 1.25]
Dulal et al, 2019 30 32 29 32 8.8% 1.03 [0.90, 1.19]
Saldanha et al, 2019 104 141 47 68 7.4% 1.07 [0.89, 1.29]
Tienchaiananda et al, 2019 15 20 7 19 1.5% 2.04 [1.07, 3.86]
Hashimoto et al, 2020 336 354 311 351 11.6% 1.07 [1.02, 1.12]
Ithimakin et al, 2020 77 93 39 47 8.3% 1.00 [0.85, 1.17]
Vimolchalao et al, 2020 70 96 31 96 4.4% 2.26 [1.65, 3.09]
Yeo et al, 2020 42 60 31 60 4.7% 1.35 [1.01, 1.82]
Subtotal (95% CI) 1273 1121 100.0% 1.13 [1.04, 1.23]
Total events 1101 840
Heterogeneity: Tau² = 0.01; Chi² = 58.27, df = 13 (P < 0.00001); I² = 78%
Test for overall effect: Z = 2.97 (P = 0.003)
1.1.4 MEC
Mukesh et al, 2017 38 42 38 42 44.1% 1.00 [0.87, 1.15]
Mukhopadhyay et al, 2017 14 14 13 14 22.8% 1.07 [0.89, 1.30]
Jeon et al, 2019 28 29 22 25 33.1% 1.10 [0.93, 1.29]
Subtotal (95% CI) 85 81 100.0% 1.05 [0.96, 1.15]
Total events 80 73
Heterogeneity: Tau² = 0.00; Chi² = 0.82, df = 2 (P = 0.66); I² = 0%
Test for overall effect: Z = 1.03 (P = 0.32)
1.1.5 HEC/MEC
Mizukami et al, 2014 22 22 19 22 100.0% 1.15 [0.96, 1.39]
Subtotal (95% CI) 22 22 100.0% 1.15 [0.96, 1.39]
Total events 22 19
Heterogeneity: Not applicable
Test for overall effect: Z = 1.53 (P = 0.13)
1.1.6 Olanzapine 10mg
Navari et al, 2011 117 121 104 120 9.6% 1.12 [1.03, 1.21]
Shumway et al, 2015 5 8 3 9 0.7% 1.88 [0.64, 5.46]
Navari et al, 2016 (JSCO) 45 51 42 50 7.9% 1.05 [0.90, 1.23]
Navari et al, 2016 (NEJM) 156 182 117 181 8.7% 1.33 [1.17, 1.50]
Mukesh et al, 2017 38 42 38 42 8.3% 1.00 [0.87, 1.15]
Mukhopadhyay et al, 2017 49 50 47 50 9.6% 1.04 [0.96, 1.13]
Sapkota et al, 2017 21 25 22 25 6.3% 0.95 [0.76, 1.19]
Celio et al, 2019 48 54 23 27 7.3% 1.04 [0.87, 1.25]
Dulal et al, 2019 30 32 29 32 8.2% 1.03 [0.90, 1.19]
Jeon et al, 2019 28 29 22 25 7.8% 1.10 [0.93, 1.29]
Saldanha et al, 2019 104 141 47 68 7.2% 1.07 [0.89, 1.29]
Tienchaiananda et al, 2019 15 20 7 19 1.7% 2.04 [1.07, 3.86]
Ithimakin et al, 2020 38 46 39 47 7.2% 1.00 [0.83, 1.20]
Vimolchalao et al, 2020 70 96 31 96 4.6% 2.26 [1.65, 3.09]
Yeo et al, 2020 42 60 31 60 4.9% 1.35 [1.01, 1.82]
Subtotal (95% CI) 957 851 100.0% 1.13 [1.04, 1.24]
Total events 806 602
Heterogeneity: Tau² = 0.02; Chi² = 61.35, df = 14 (P < 0.00001); I² = 77%
Test for overall effect: Z = 2.73 (P = 0.006)
1.1.7 Olanzapine 5mg
Mizukami et al, 2014 22 22 19 22 5.3% 1.15 [0.96, 1.39]
Hashimoto et al, 2020 336 354 311 351 89.4% 1.07 [1.02, 1.12]
Ithimakin et al, 2020 39 47 39 47 5.3% 1.00 [0.83, 1.20]
Subtotal (95% CI) 423 420 100.0% 1.07 [1.03, 1.12]
Total events 397 369
Heterogeneity: Tau² = 0.00; Chi² = 1.19, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 3.21 (P = 0.001)
1.1.8 Double-Blind Placebo-Controlled Design
Mizukami et al, 2014 22 22 19 22 13.8% 1.15 [0.96, 1.39]
Navari et al, 2016 (NEJM) 156 182 117 181 15.4% 1.33 [1.17, 1.50]
Jeon et al, 2019 28 29 22 25 14.4% 1.10 [0.93, 1.29]
Tienchaiananda et al, 2019 15 20 7 19 4.5% 2.04 [1.07, 3.86]
Hashimoto et al, 2020 336 354 311 351 16.7% 1.07 [1.02, 1.12]
Ithimakin et al, 2020 77 93 39 47 14.5% 1.00 [0.85, 1.17]
Vimolchalao et al, 2020 70 96 31 96 10.1% 2.26 [1.65, 3.09]
Yeo et al, 2020 42 60 31 60 10.6% 1.35 [1.01, 1.82]
Subtotal (95% CI) 856 801 100.0% 1.26 [1.08, 1.48]
Total events 746 577
Heterogeneity: Tau² = 0.04; Chi² = 55.36, df = 7 (P < 0.00001); I² = 87%
Test for overall effect: Z = 2.91 (P = 0.004)
1.1.9 Open Controlled Design (Control Arm = All Antiemetics, Except Olanzapine)
Mukhopadhyay et al, 2017 49 50 47 50 83.9% 1.04 [0.96, 1.13]
Celio et al, 2019 48 54 23 27 16.1% 1.04 [0.87, 1.25]
Subtotal (95% CI) 104 77 100.0% 1.04 [0.97, 1.12]
Total events 97 70
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.11 (P = 0.27)
1.1.10 Open Controlled Design (Control Arm = Antiemetics Not In Olanzapine Arm)
Navari et al, 2011 117 121 104 120 46.6% 1.12 [1.03, 1.21]
Shumway et al, 2015 5 8 3 9 0.2% 1.88 [0.64, 5.46]
Navari et al, 2016 (JSCO) 45 51 42 50 11.3% 1.05 [0.90, 1.23]
Mukesh et al, 2017 38 42 38 42 14.5% 1.00 [0.87, 1.15]
Sapkota et al, 2017 21 25 22 25 5.6% 0.95 [0.76, 1.19]
Dulal et al, 2019 30 32 29 32 13.7% 1.03 [0.90, 1.19]
Saldanha et al, 2019 104 141 47 68 8.0% 1.07 [0.89, 1.29]
Subtotal (95% CI) 420 346 100.0% 1.07 [1.01, 1.13]
Total events 360 285
Heterogeneity: Tau² = 0.00; Chi² = 4.35, df = 6 (P = 0.63); I² = 0%
Test for overall effect: Z = 2.42 (P = 0.02)
0.1 0.2 0.5 1 2 5 10
Favours Control Favours Olanzapine

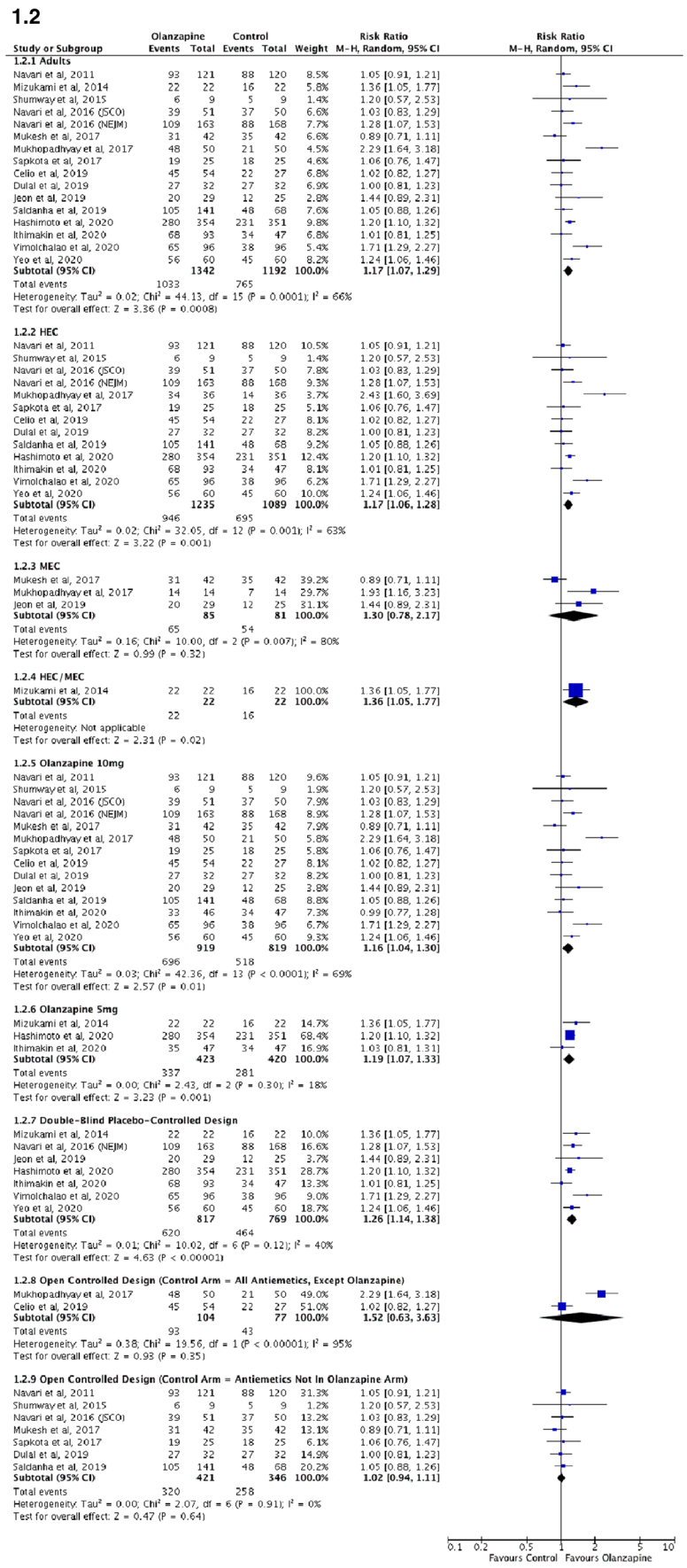


Fig. 1 (continued)

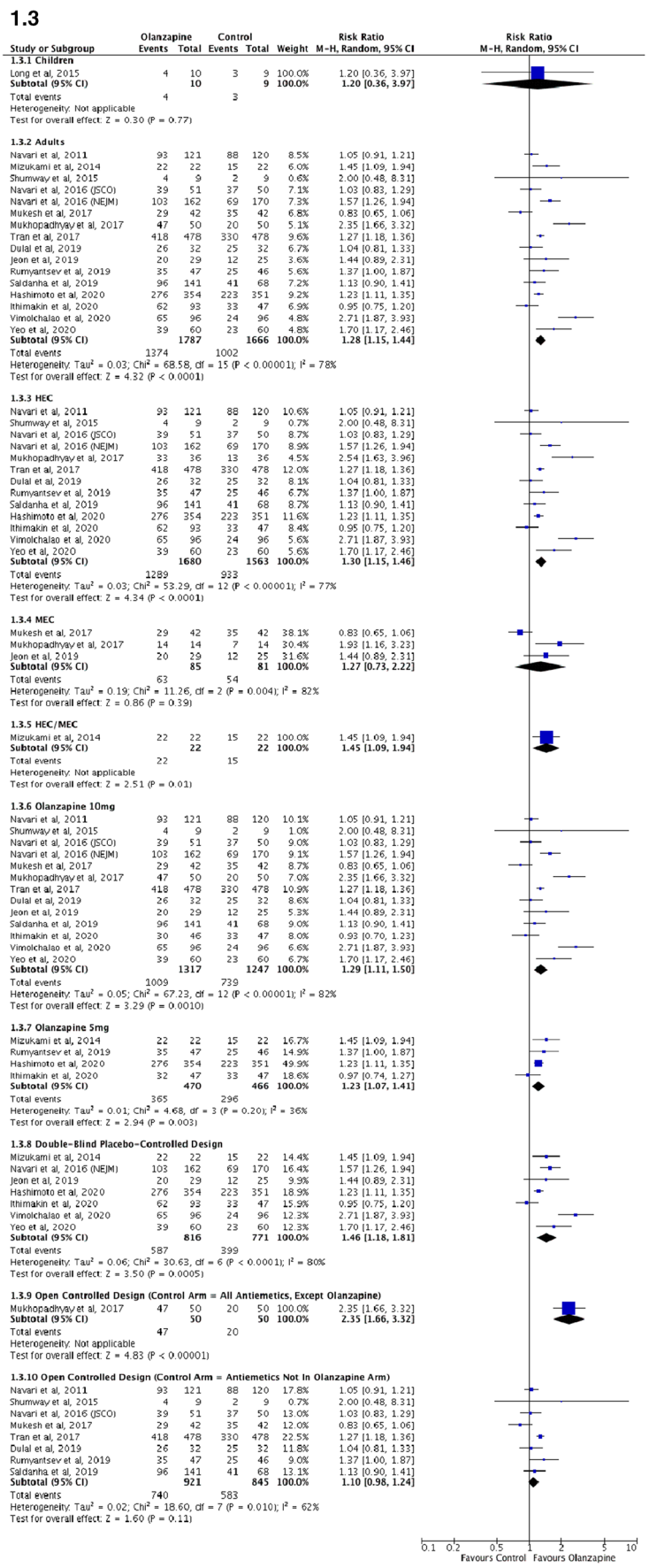


Fig. 1 (continued)

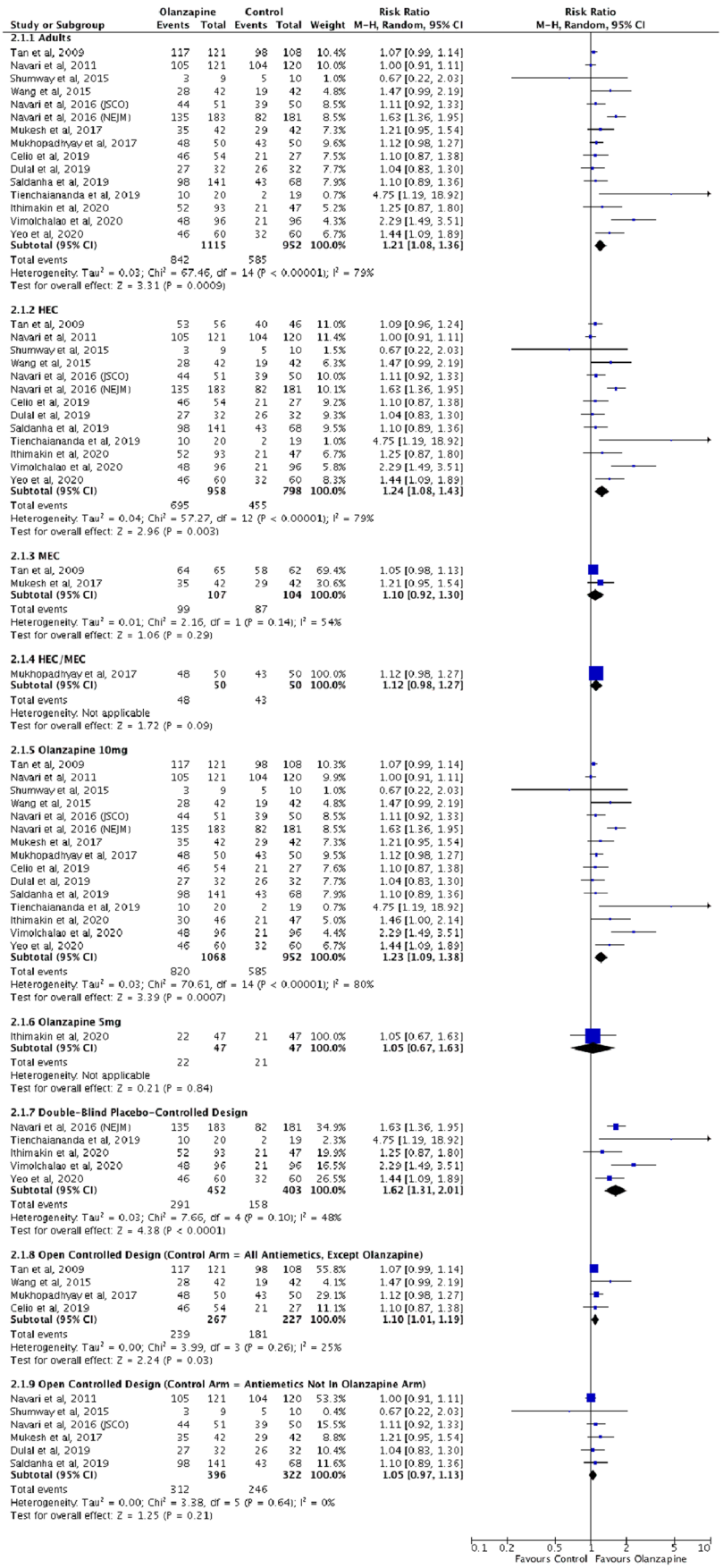
Table 2 Absolute risk difference between olanzapine and other regimens for statistically significant differences

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

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.

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


Olanzapine
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
2.1.1 Adults
Tan et al, 2009 117 121 98 108 10.4% 1.07 [0.99, 1.14]
Navari et al, 2011 105 121 104 120 10.0% 1.00 [0.91, 1.11]
Shumway et al, 2015 3 9 5 10 1.0% 0.67 [0.22, 2.03]
Wang et al, 2015 28 42 19 42 4.8% 1.47 [0.99, 2.19]
Navari et al, 2016 (JSCO) 44 51 39 50 8.5% 1.11 [0.92, 1.33]
Navari et al, 2016 (NEJM) 135 183 82 181 8.5% 1.63 [1.36, 1.95]
Mukesh et al, 2017 35 42 29 42 7.3% 1.21 [0.95, 1.54]
Mukhopadhyay et al, 2017 48 50 43 50 9.6% 1.12 [0.98, 1.27]
Cello et al, 2019 46 54 21 27 7.5% 1.10 [0.87, 1.38]
Dulal et al, 2019 27 32 26 32 7.7% 1.04 [0.83, 1.30]
Saldanha et al, 2019 98 141 43 68 7.9% 1.10 [0.89, 1.36]
Tienchaiananda et al, 2019 10 20 2 19 0.7% 4.75 [1.19, 18.92]
Ithimakin et al, 2020 52 93 21 47 5.2% 1.25 [0.87, 1.80]
Vimolchalao et al, 2020 48 96 21 96 4.3% 2.29 [1.49, 3.51]
Yeo et al, 2020 46 60 32 60 6.7% 1.44 [1.09, 1.89]
Subtotal (95% CI) 1115 952 100.0% 1.21 [1.08, 1.36]
Total events 842 585
Heterogeneity: Tau² = 0.03; Chi² = 67.46, df = 14 (P < 0.00001); I² = 79%
Test for overall effect: Z = 3.31 (P = 0.0009)
2.1.2 HEC
Tan et al, 2009 53 56 40 46 11.0% 1.09 [0.96, 1.24]
Navari et al, 2011 105 121 104 120 11.4% 1.00 [0.91, 1.11]
Shumway et al, 2015 3 9 5 10 1.5% 0.67 [0.22, 2.03]
Wang et al, 2015 28 42 19 42 6.3% 1.47 [0.99, 2.19]
Navari et al, 2016 (JSCO) 44 51 39 50 10.0% 1.11 [0.92, 1.33]
Navari et al, 2016 (NEJM) 135 183 82 181 10.1% 1.63 [1.36, 1.95]
Cello et al, 2019 46 54 21 27 9.2% 1.10 [0.87, 1.38]
Dulal et al, 2019 27 32 26 32 9.3% 1.04 [0.83, 1.30]
Saldanha et al, 2019 98 141 43 68 9.5% 1.10 [0.89, 1.36]
Tienchaiananda et al, 2019 10 20 2 19 1.0% 4.75 [1.19, 18.92]
Ithimakin et al, 2020 52 93 21 47 6.7% 1.25 [0.87, 1.80]
Vimolchalao et al, 2020 48 96 21 96 5.8% 2.29 [1.49, 3.51]
Yeo et al, 2020 46 60 32 60 8.3% 1.44 [1.09, 1.89]
Subtotal (95% CI) 958 798 100.0% 1.24 [1.08, 1.43]
Total events 695 455
Heterogeneity: Tau² = 0.04; Chi² = 57.27, df = 12 (P < 0.00001); I² = 79%
Test for overall effect: Z = 2.96 (P = 0.003)
2.1.3 MEC
Tan et al, 2009 64 65 58 62 69.4% 1.05 [0.98, 1.13]
Mukesh et al, 2017 35 42 29 42 30.6% 1.21 [0.95, 1.54]
Subtotal (95% CI) 107 104 100.0% 1.10 [0.92, 1.30]
Total events 99 87
Heterogeneity: Tau² = 0.01; Chi² = 2.16, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 1.06 (P = 0.29)
2.1.4 HEC/MEC
Mukhopadhyay et al, 2017 48 50 43 50 100.0% 1.12 [0.98, 1.27]
Subtotal (95% CI) 50 50 100.0% 1.12 [0.98, 1.27]
Total events 48 43
Heterogeneity: Not applicable
Test for overall effect: Z = 1.72 (P = 0.09)
2.1.5 Olanzapine 10mg
Tan et al, 2009 117 121 98 108 10.3% 1.07 [0.99, 1.14]
Navari et al, 2011 105 121 104 120 9.9% 1.00 [0.91, 1.11]
Shumway et al, 2015 3 9 5 10 1.0% 0.67 [0.22, 2.03]
Wang et al, 2015 28 42 19 42 4.8% 1.47 [0.99, 2.19]
Navari et al, 2016 (JSCO) 44 51 39 50 8.5% 1.11 [0.92, 1.33]
Navari et al, 2016 (NEJM) 135 183 82 181 8.5% 1.63 [1.36, 1.95]
Mukesh et al, 2017 35 42 29 42 7.3% 1.21 [0.95, 1.54]
Mukhopadhyay et al, 2017 48 50 43 50 9.5% 1.12 [0.98, 1.27]
Cello et al, 2019 46 54 21 27 7.6% 1.10 [0.87, 1.38]
Dulal et al, 2019 27 32 26 32 7.7% 1.04 [0.83, 1.30]
Saldanha et al, 2019 98 141 43 68 7.9% 1.10 [0.89, 1.36]
Tienchaiananda et al, 2019 10 20 2 19 0.7% 4.75 [1.19, 18.92]
Ithimakin et al, 2020 30 46 21 47 5.0% 1.46 [1.00, 2.14]
Vimolchalao et al, 2020 48 96 21 96 4.4% 2.29 [1.49, 3.51]
Yeo et al, 2020 46 60 32 60 6.7% 1.44 [1.09, 1.89]
Subtotal (95% CI) 1068 952 100.0% 1.23 [1.09, 1.38]
Total events 820 585
Heterogeneity: Tau² = 0.03; Chi² = 70.61, df = 14 (P < 0.00001); I² = 80%
Test for overall effect: Z = 3.39 (P = 0.0007)
2.1.6 Olanzapine 5mg
Ithimakin et al, 2020 22 47 21 47 100.0% 1.05 [0.67, 1.63]
Subtotal (95% CI) 47 47 100.0% 1.05 [0.67, 1.63]
Total events 22 21
Heterogeneity: Not applicable
Test for overall effect: Z = 0.21 (P = 0.84)
2.1.7 Double-Blind Placebo-Controlled Design
Navari et al, 2016 (NEJM) 135 183 82 181 34.9% 1.63 [1.36, 1.95]
Tienchaiananda et al, 2019 10 20 2 19 2.3% 4.75 [1.19, 18.92]
Ithimakin et al, 2020 52 93 21 47 13.9% 1.25 [0.87, 1.80]
Vimolchalao et al, 2020 48 96 21 96 16.5% 2.29 [1.49, 3.51]
Yeo et al, 2020 46 60 32 60 26.5% 1.44 [1.09, 1.89]
Subtotal (95% CI) 452 403 100.0% 1.62 [1.31, 2.01]
Total events 291 158
Heterogeneity: Tau² = 0.03; Chi² = 7.66, df = 4 (P = 0.10); I² = 48%
Test for overall effect: Z = 4.38 (P < 0.0001)
2.1.8 Open Controlled Design (Control Arm = All Antiemetics, Except Olanzapine)
Tan et al, 2009 117 121 98 108 55.8% 1.07 [0.99, 1.14]
Wang et al, 2015 28 42 19 42 4.1% 1.47 [0.99, 2.19]
Mukhopadhyay et al, 2017 48 50 43 50 29.1% 1.12 [0.98, 1.27]
Cello et al, 2019 46 54 21 27 11.1% 1.10 [0.87, 1.38]
Subtotal (95% CI) 267 227 100.0% 1.10 [1.01, 1.19]
Total events 239 181
Heterogeneity: Tau² = 0.00; Chi² = 3.99, df = 3 (P = 0.26); I² = 25%
Test for overall effect: Z = 2.24 (P = 0.03)
2.1.9 Open Controlled Design (Control Arm = Antiemetics Not In Olanzapine Arm)
Navari et al, 2011 105 121 104 120 53.3% 1.00 [0.91, 1.11]
Shumway et al, 2015 3 9 5 10 0.4% 0.67 [0.22, 2.03]
Navari et al, 2016 (JSCO) 44 51 39 50 15.5% 1.11 [0.92, 1.33]
Mukesh et al, 2017 35 42 29 42 8.8% 1.21 [0.95, 1.54]
Dulal et al, 2019 27 32 26 32 10.4% 1.04 [0.83, 1.30]
Saldanha et al, 2019 98 141 43 68 11.6% 1.10 [0.89, 1.36]
Subtotal (95% CI) 396 322 100.0% 1.05 [0.97, 1.13]
Total events 312 246
Heterogeneity: Tau² = 0.00; Chi² = 3.38, df = 5 (P = 0.64); I² = 0%
Test for overall effect: Z = 1.25 (P = 0.21)
0.1 0.2 0.5 1 2 5 10
Favours Control Favours Olanzapine

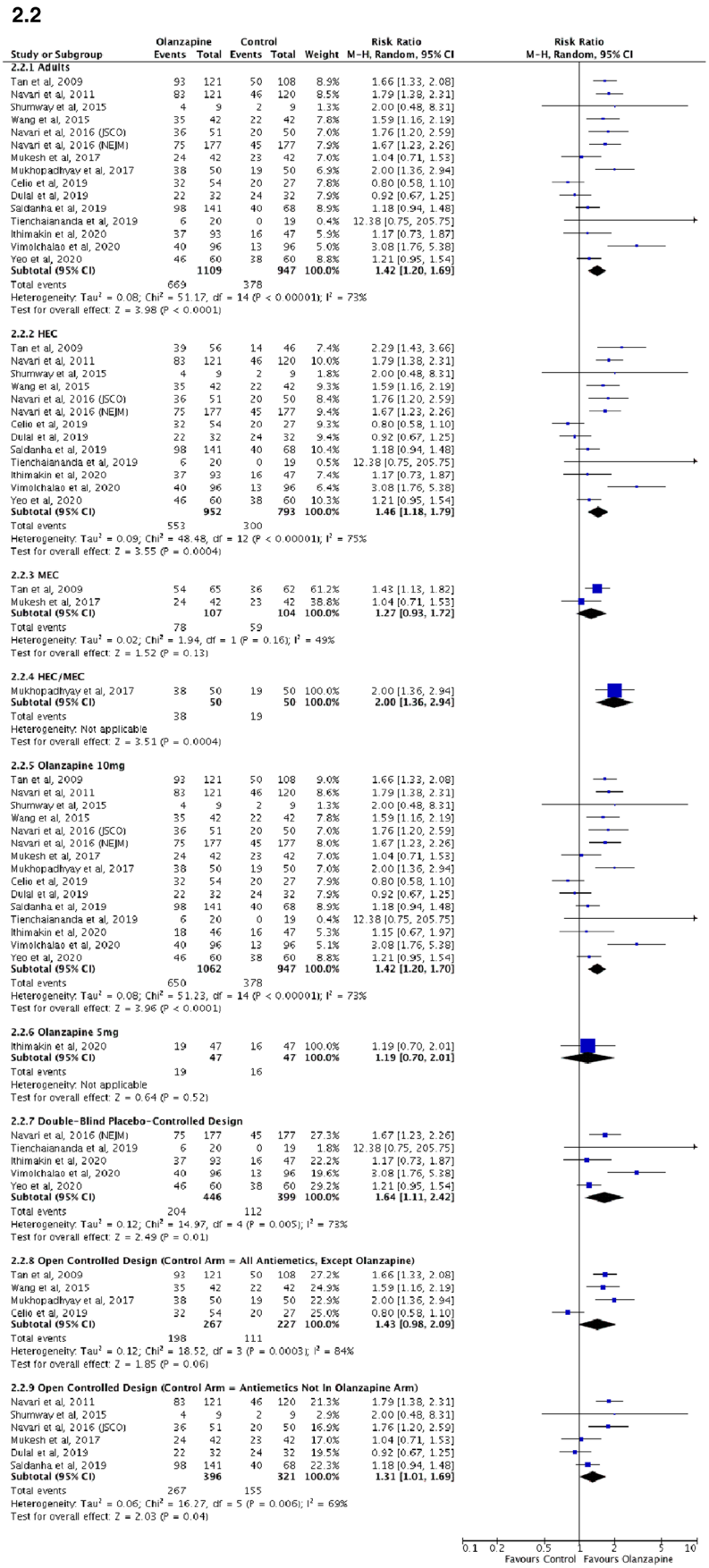


Fig. 2 (continued)

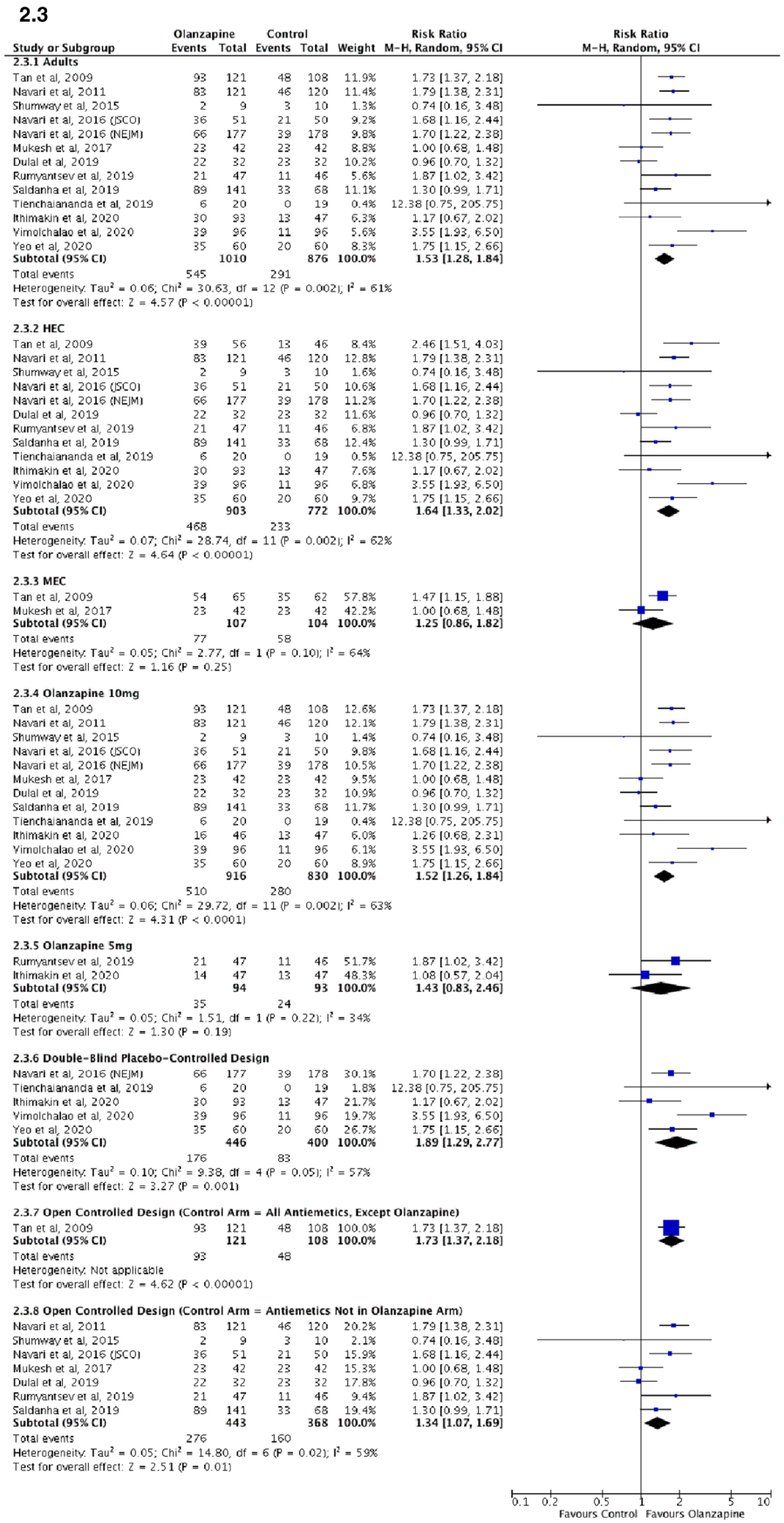


Fig. 2 (continued)

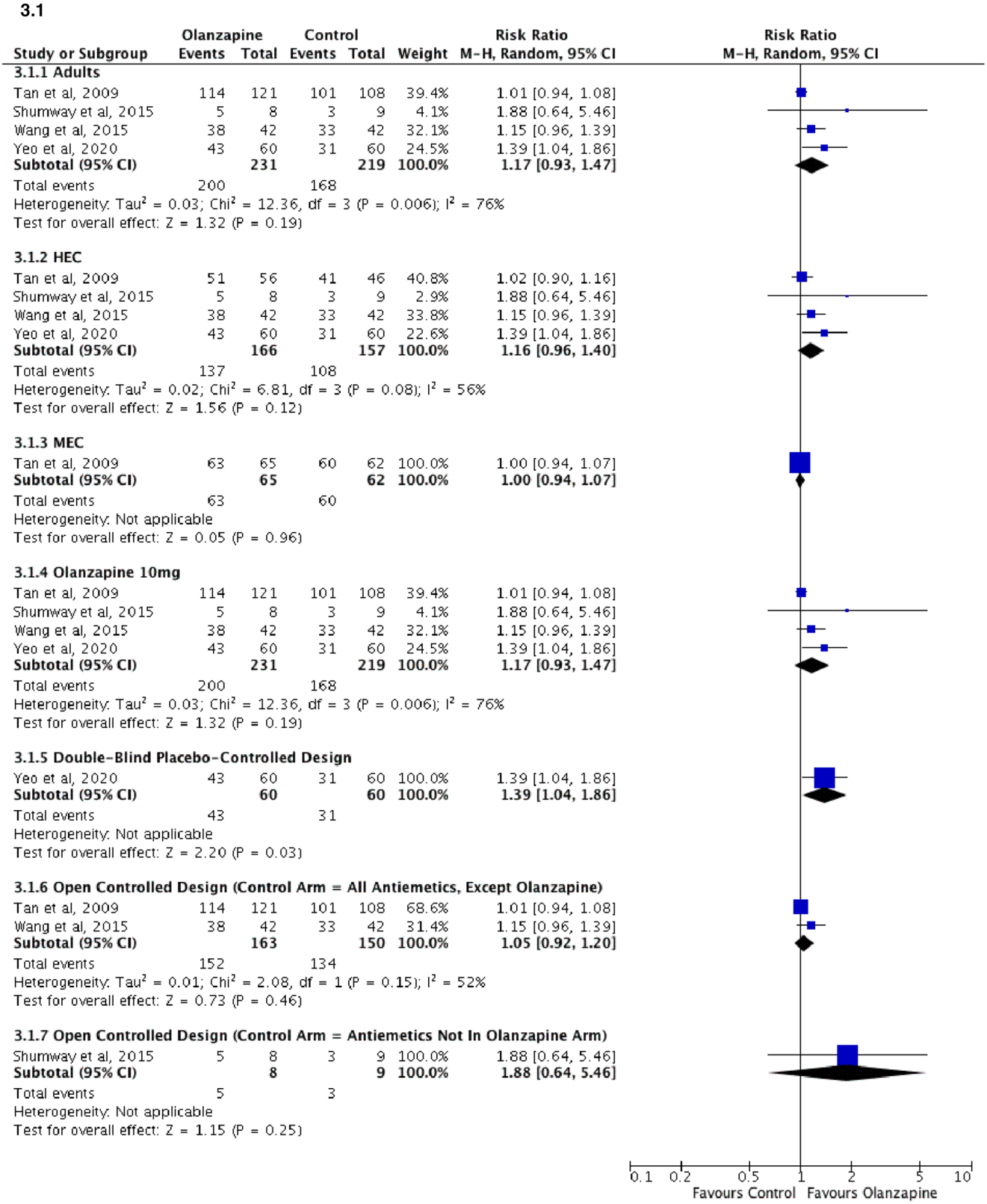


Fig. 3 Efficacy of olanzapine regimens compared to others for the prophylaxis of chemotherapy-induced nausea and vomiting (CINV)—no emesis. **3.1** Acute phase. **3.2** Delayed phase. **3.3** Overall phase

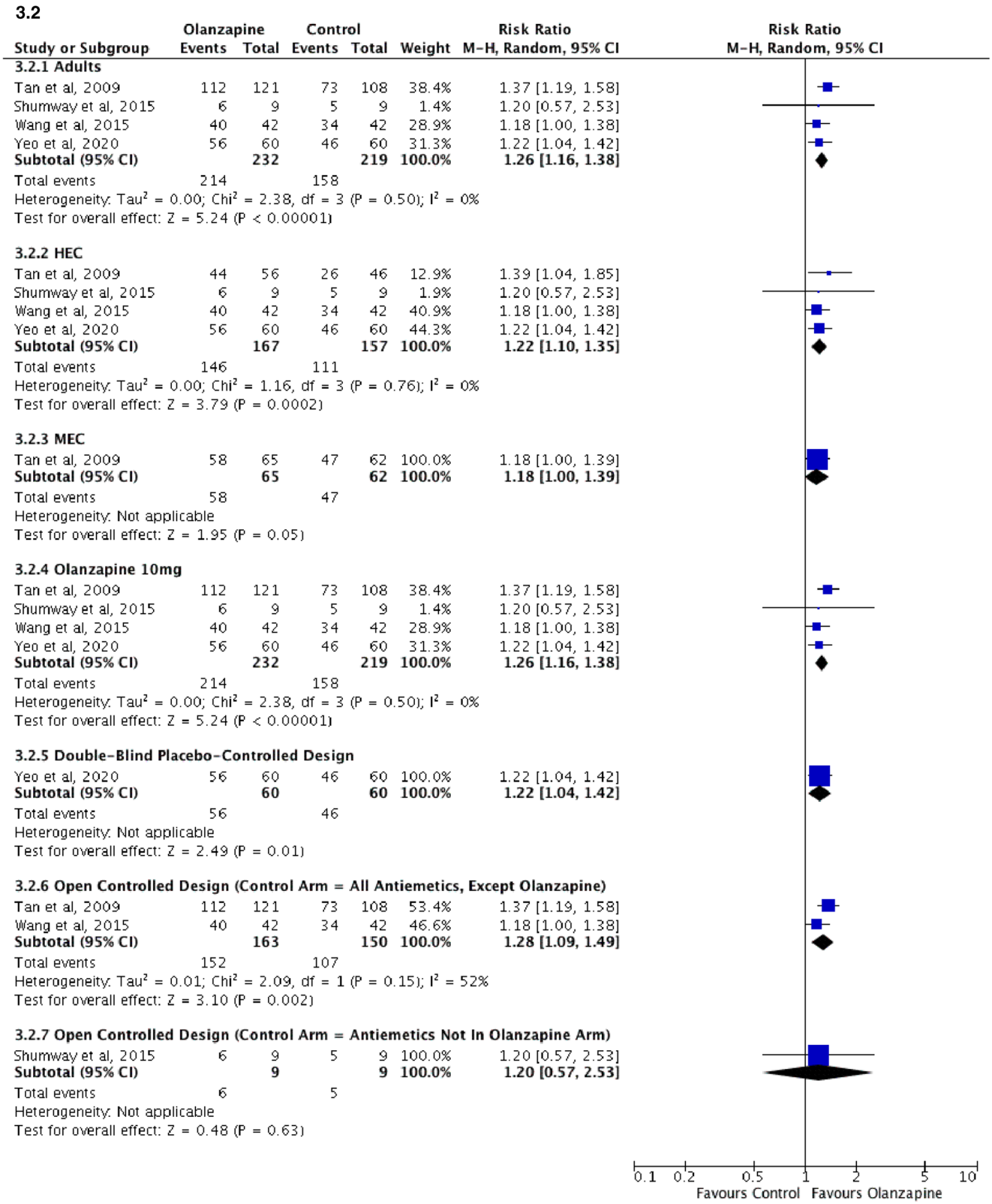


Fig. 3 (continued)

3.3

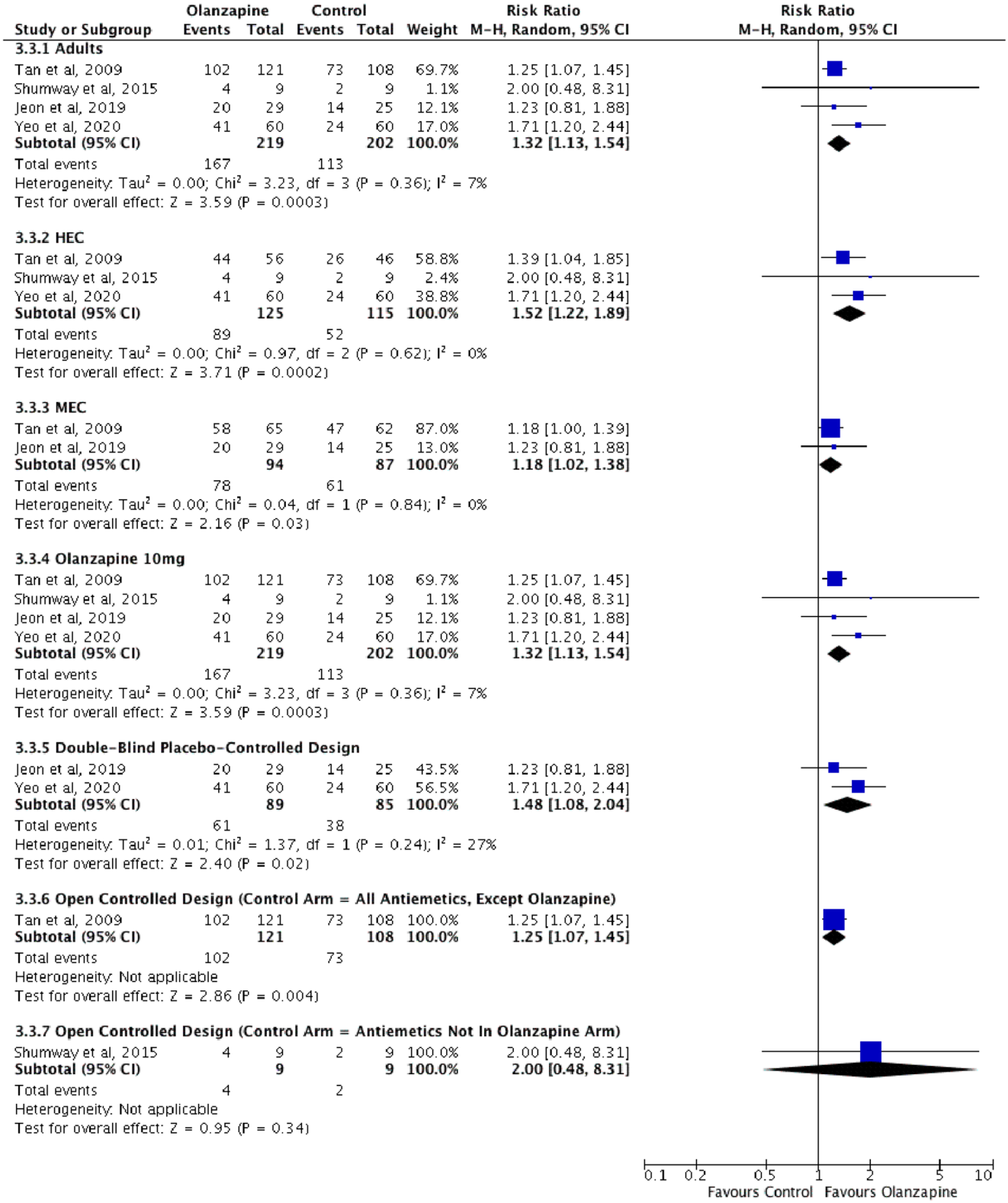


Fig. 3 (continued)

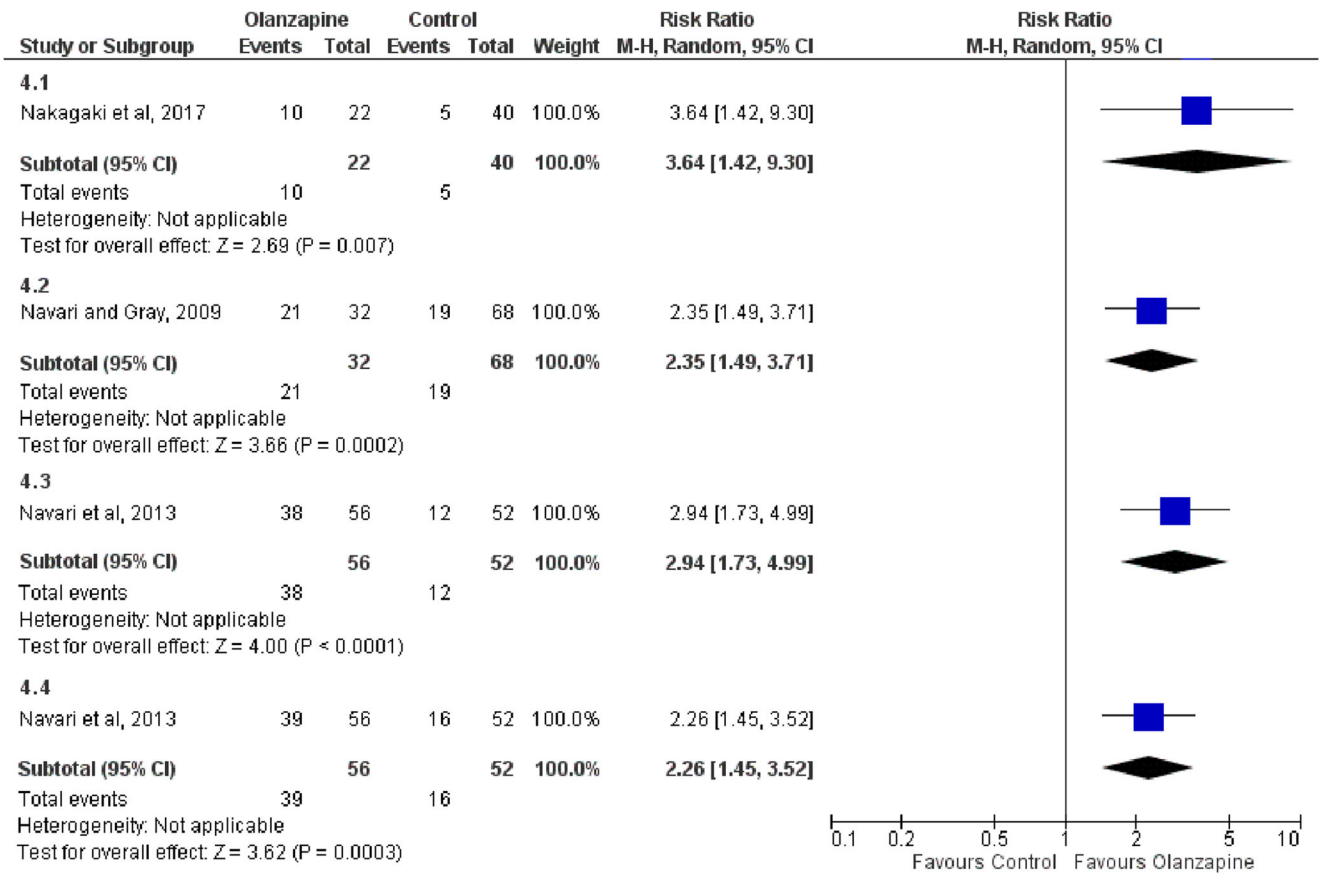


Fig. 4 Efficacy of olanzapine regimens compared to others for the rescue of breakthrough chemotherapy-induced nausea and vomiting (CINV). **4.1** Complete response - acute phase. **4.2** Complete response - overall phase. **4.3** No nausea - overall phase. **4.4** No Emesis - overall phase

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

9. Chow R, Tsao M, Chiu L, Popovic M, Milakovic M, Lam H, DeAngelis C (2018) Efficacy of the combination of neurokinin-1 receptor antagonist, palonosetron, and dexamethasone compared to others for the prophylaxis of chemotherapy-induced nauseas and vomiting: a systematic review and meta-analysis of randomized controlled trials. Ann Palliat Med 7:221–223
10. Jordan K, Blattermann L, Hinke A et al (2018) Is the addition of a neurokinin-1 receptor antagonist beneficial in moderately emetogenic chemotherapy? – A systematic review and meta-analysis. Support Care Cancer 26:21–32
11. Chow R, Warr DG, Navari RM, Tsao M, Popovic M, Chiu L, Milakovic M, Lam H, DeAngelis C (2018) Should palonosetron be a preferred 5-HT_3 receptor antagonist for chemotherapy-induced nausea and vomiting? An updated systematic review and meta-analysis. Support Care Cancer 26:2519–2549
12. Brymaster FP, Calligaro D, Falcone J et al (1996)Radio-receptor binding profile of the atypical antipsychotic olanzapine. Neuropsychopharmacology 14:87–96
13. Srivastava M, Brito-Dellan N, Davis MP, Leach M, Lagman R (2003) Olanzapine as an antiemetic in refractory nausea and vomiting in advanced cancer. J Pain Symptom Manag 25:578–582
14. Abe M, Hirashima Y, Kasamatsu Y, Kado N, Komeda S, Kuji S, Tanaka A, Takahashi N, Takekuma M, Hihara H, Ichikawa Y, Itonaga Y, Hirakawa T, Nasu K, Miyagi K, Murakami J, Ito K (2016) Efficacy and safety of olanzapine combined with aprepitant, palonosetron and dexamethasone for preventing nausea and vomiting by cisplatin-based chemotherapy in gynecological cancer: KCOG-G1303 phase II trial. Support Care Cancer 24:675–682
15. Park S, Choi C, Kwon M et al (2015) A phase II trial of palonosetron and olanzapine without dexamethasone for the prevention of chemotherapy-induced nausea and vomiting. Support Care Cancer 23(Suppl 1):S147
16. Navari RM, Einhorn L, Passik S et al (2005) A phase II trial of olanzapine for the prevention of chemotherapy-induced nausea and vomiting: a Hoosier Oncology Group study. Support Care Cancer 13:529–534
17. Navari RM, Einhorn L, Loehrer P et al (2007) A phase II trial of olanzapine for the prevention of chemotherapy-induced nausea and vomiting: a Hoosier Oncology Group study. Support Care Cancer 15:1285–1291
18. Passik S, Navari RM, Jong S et al (2004) A phase I trial of olanzapine (zyprexa) for the prevention of delayed emesis in cancer patients: a Hoosier Oncology Group Study. Cancer Investig 22: 383–388
19. Passik S, Lundberg J, Kirsh K et al (2002) A pilot exploration of the antiemetic activity of olanzapine for the relief of nausea in patients with advanced cancer and pain. J Pain Symptom Manag 23:526–532
20. Chow R, Chiu L, Navari R, Passik S, Chiu N, Popovic M, Lam H, Pasetka M, Chow E, DeAngelis C (2016) Efficacy and safety of olanzapine for the prophylaxis of chemotherapy-induced nausea and vomiting (CINV) as reported in phase I and II studies: a systematic review. Support Care Cancer 24:1001–1008
21. Zhou JG, Huang L, Jin SH et al (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 randomized controlled trials. ESMO Open 6:e000621
22. Bahbah EI, Abdalla AR, Abdelshafy K, Almohandes AD, Menshawy A, Elalem Aziz MA, Ebada MA, Hegab A, Negida A (2019) Should olanzapine be advocated over conventional antiemetics for the prevention of chemotherapy-induced nausea and vomiting? An updated meta-analysis of randomized control trials. Curr Enzym Inhib 15:80–90
23. Sutherland A, Naessens K, Plugge E, Ware L, Head K, Burton MJ, Wee B, Cochrane Pain, Palliative and Supportive Care Group (2018) Olanzapine for the prevention and treatment of cancer-related nausea and vomiting in adults. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD012555.pub2
24. Chelkeba L, Gidey K, Mamo A, Yohannes B, Matso T, Melaku T (2017) Olanzapine for chemotherapy-induced nausea and vomiting: systematic review and meta-analysis. Pharm Pract 15:877
25. Yoodee J, Permsuwan U, Nimworapan M (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 112:113–125
26. Chiu L, Chow R, Popovic M, Navari RM, Shumway NM, Chiu N, Lam H, Milakovic M, Pasetka M, Vuong S, Chow E, DeAngelis C (2016) Efficacy of olanzapine for the prophylaxis and rescue of chemotherapy-induced nausea and vomiting (CINV): a systematic review and meta-analysis. Support Care Cancer 24:2381–2392
27. Hocking CM, Kichenadasse G (2014) Olanzapine for chemotherapy-induced nausea and vomiting: a systematic review. Support Care Cancer 22:1142–1151
28. Hesketh PJ, Kris MG, Basch E et al (2017) Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 28:3240–3261
29. Berger MJ, Ettinger DS, Aston J, Barbour S, Bergsbaken J, Bierman PJ, Brandt D, Dolan DE, Ellis G, Kim EJ, Kirkegaard S, Kloth DD, Lagman R, Lim D, Loprinzi C, Ma CX, Maurer V, Michaud LB, Nabell LM, Noonan K, Roeland E, Rugo HS, Schwartzberg LS, Scullion B, Timoney J, Todaro B, Urba SG, Shead DA, Hughes M (2017) NCCN guidelines insights: antiemesis, versions 2.2017. J Natl Compr Cancer Netw 15:883–893
30. Herrstedt J (2018) The latest consensus on antiemetics. Curr Opin Oncol 30:233–239
31. Shea BJ, Wells G, Hamel C et al (2017) AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 358:j4008
32. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 339:b2700
33. Jordan K, Chan A, Gralla RJ, Jahn F, Rapoport B, Warr D, Hesketh PJ (2017) 2016 updated MASCC/ESMO consensus recommendations: emetic risk classification and evaluation of the emetogenicity of antineoplastic agents. Support Care Cancer 25:271–275
34. Roila F, Molassiotis A, Herrstedt J et al (2016) 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol 26:v119–v133
35. Walsh M, Srinathan SK, McAuley DF et al (2014) The statistical significance of randomized controlled trial results is frequently fragile: a case for a Fragility Index. J Clin Epidemiol 67:622–628
36. Babu G, Saldanha SG, Chinnaglriyappa LK et al (2016) The efficacy, safety and cost benefit of olanzapine versus aprepitant in highly emetogenic chemotherapy: a pilot study from South India. Chemother Res Pract 2016:1–5. https://doi.org/10.1144/2016/3439707
37. Flank J, Schechter T, Gibson P, Johnston DL, Orsey AD, Portwine C, Sung L, Dupuis LL (2018) Olanzapine for prevention of chemotherapy-induced nausea and vomiting in children and adolescents: a multi-center, feasibility study. Support Care Cancer 26: 549–555
38. Osman AAM, Elhassan MMA, AbdElrahim BHA et al (2018) Olanzapine for the prevention of chemotherapy-induced nausea and vomiting: a comparative study from Sudan. J Glob Oncol 4: 1–9. https://doi.org/10.1200/JGO.17.00216
39. Navari RM, Brenner MC (2010) Treatment of cancer-related anorexia with olanzapine and megestrol acetate: a randomized trial. Support Care Cancer 18:951–956

40. Minatogawa H, Izawa 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, Bhattacharya 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, Yamauchi 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 addition 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, Ruddy 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, Mahaseth 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:S72
57. Celio L, Salbene 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 MR, 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. Rumyantsev A, Glazkova E, Nasyrova R, Ignatova E, Chitia L, Popova A, Chekini D, Kochetkova Y, Kit S, Elsnukaeva K, Menshikova S, Sekhina O, Pokataev I, Tyulyandina A, Stenina M, Frolova MA, Bulanov A, Fedyanin M, Tryakin A, Tjulandin 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, Rudresha AH, Lakkavalli RK, Kumar J (2019) Efficacy of olanzapine combination in prevention of nausea & vomiting in highly emetogenic chemotherapy. Ann Oncol 30:v722
62. Tienchaiananda P, Nipondhkit W, Maneenil K, Sa-nguansai S, Payapwattanawong S, Laohavinij S, Maneechavakajorn J (2019) A randomized, double-blind, placebo-controlled study evaluating the efficacy of combination olanzapine, ondansetron and dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving doxorubicin plus cyclophosphamide. Ann Palliat Med 8:372–380
63. Hashimoto H, Abe M, Tokuyama O, Mizutani H, Uchitomi Y, Yamaguchi T, Hoshina Y, Sakata Y, Takahashi TY, 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, Laocharoenkiat A, Nimmannit A, Akewanlop C, Soparattanapaisarn N, Techawattanawanna S, Korphaisarn K, Danchaivijitr P (2020) Randomized, double-blind, placebo-controlled study of aprepitant versus two dosages 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, Sriuranpong V, Vinayanuwatikun C, Parinyanitikun N, Poovorawan N, Tanasanvimon 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 highly 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 FKF (2020) A randomized study of olanzapine-containing versus standard

antiemetic regimens for the prevention of chemotherapy-induced nausea and vomiting in Chinese breast cancer patients. Breast 50: 30–38

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