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 Herrstedt⁵ • Matti Aapro⁶ • Leonard Chiu^{3,7} • Henry Lam³ • Elizabeth Prsic² • Michael Lock⁴ • Carlo DeAngelis^{3,8} • Rudolph M. Navari⁹

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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, chemotherapyinduced 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-HT_{2a}, 5-HT_{2c}, 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 metaanalysis 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 postchemotherapy) 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:

- HEC studies, as determined by the MASCC/ESMO classification [33]
- 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
- 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
- Studies with an open-controlled design, where the control arm includes antiemetics not included in the olanzapinecontaining 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 metaanalysis(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 (olanzapinecontaining) 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 opendesign studies using a control arm with different antiemetics than used in the investigational (olanzapinecontaining) 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

Evaluable sizeAge range \mathbb{R} MaleChemotherapy emetogenicityanzapine for the prophylaxis of chemotherapy-induced nauses and vomiting \mathbb{R} MaleChemotherapy emetogenicity6)24139-8132HEC & MEC8)24139-8132HEC & MEC8)1422-7850HEC & MEC9)1439-7673HEC9)1422-7850HEC8)17NRHEC9)1839-76739)1922-71779)10122-71771023-7177HEC50)10122-7177118429-767312100NRNR138429-80014100NRNR15338028-89201/541100NR101249118430-8012478NR13478NR1430-8001536361636961724961829-8028196451-601929842014481929961929NR1929141929141929141924-7921 <tr< th=""><th>I able I Study defilographics</th><th></th><th></th><th></th><th></th><th></th></tr<>	I able I Study defilographics					
& WEC	Study	Evaluable sample size	Age range	% Male	Chemotherapy emetogenicity	Intervention's additional/substitute drug regimens, relative to comparative arm
6] 241 39-81 32 HEC 4[47] 44 22-78 50 HEC & MEC 8] 14 421 NR 37 HEC 8] 14 22-78 50 HEC & MEC 8] 14 22-78 50 HEC 8] 17 NR 37 HEC 10 84 39-76 73 HEC CSO [51] 101 52-71 77 HEC CSO [51] 101 52-71 77 HEC [53] 84 29-80 0 MEC 2017 [54] 100 NR NR HEC 1 478 NR NR HEC 1 64 51-60 48 HEC 1 64 51-60 48 HEC 1 64 73 MEC 141 1 209 0 0 MEC 1 <t< td=""><td>Studies reporting on olanzapine for a Tan et al., 2009 [45]</td><td>the prophylaxis of chemothe 229</td><td>rapy-induced ni 18–74</td><td>ausea and vor 60</td><td>miting HEC & MEC</td><td>Day 1: addition of olanzapine 10 mg PO</td></t<>	Studies reporting on olanzapine for a Tan et al., 2009 [45]	the prophylaxis of chemothe 229	rapy-induced ni 18–74	ausea and vor 60	miting HEC & MEC	Day 1: addition of olanzapine 10 mg PO
[47] 44 22-78 50 HEC & MEC [8] 14 22-78 50 HEC & MEC [6] 17 NR 37 HEC [6] 17 NR 37 HEC [6] 17 NR 37 HEC [5] 84 39-76 73 HEC [53] 84 39-76 73 HEC [53] 84 29-80 0 MEC [54] 100 NR NR HEC [55] 50 NR NR HEC [53] 478 NR 0 MEC [54] 200 NR 0 MEC [61] 209 NR NR HEC<	Navari et al., 2011 [46]	241	39–81	32	НЕС	Days 2–5: olanzapine 10 mg PO, instead of dexamethasone 10 mg IV 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
J 84 39-76 73 HEC CSO) [51] 101 52-71 77 HEC CSO) [51] 101 52-71 77 HEC (53) 84 29-80 0 MEC (53) 50 NR NR 58 HEC (53) 50 NR NR 6 HEC (54) 478 NR 0 HEC J 64 51-60 48 HEC J 64 51-60 48 HEC J 209 0 0 MEC J 209 0 14 14 J 209 0 14 J 204 22-75 67 J 64 24-79 21 J 24-79 21 HEC J 24-79 21 HEC J 24-79 21 HEC J 24-79 21 HEC J 24-79 21 HEC<	Mizukami et al., 2014 [47] *Long et al., 2015 [48] Shumway et al., 2015 [49]	44 14 17	22–78 4–21 NR	50 NR 37	HEC & MEC HEC HEC	Day 4: olarizaptine 10 mg PO, instead of dexamentasone 4 mg PO BID Days 1–5: addition of olarizaptine 5 mg PO Olarizaptine, instead of aprepitant Days –2 to –1: addition of olarizaptine 5 mg PO Day 1: olarizaptine 10 mg PO, instead of aprepitant 125 mg PO Days 2–3: olarizaptine 10 mg PO, instead of aprepitant 80 mg PO Day 4: addition of olarizaptine 10 mg PO
(EJM) [52] 380 28-89 28 HEC (53) 84 29-80 0 MEC .2017 [54] 100 NR 50 NR 58 (35) 50 NR NR NR HEC (35) 50 NR NR NR HEC (35) 74) 100 NR NR NR HEC (35) 735 50 NR 0 HEC (35) 742 100 NR NR HEC (35) 705 56 30-80 0 MEC (31) 60] 93 91 51-60 48 HEC (32) 706 93 NR 4 HEC (33) 706 22-75 67 HEC (64) 239 NR 0 HEC (14) 24-79 21 21 HEC (63) 706 26-73 31 HEC (164) 141 24-79 21 HEC (164) 200 26-73 31 HEC	Wang et al., 2015 [50] Navari et al., 2016 (JCSO) [51]	84 101	39–76 52–71	73 77	HEC HEC	Days 1–8: addition of olanzapine 10 mg PO 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
.2017 [54] 100 NR 58 HEC & MEC [55] 50 NR NR HEC & MEC [51] 478 NR 0 HEC [51] 478 NR 0 HEC [53] 478 NR 0 HEC [1] 81 30-80 0 MEC [2] 64 51-60 48 HEC [2019 [60] 93 NR 4 HEC [61] 209 NR NR HEC [61] 209 NR 0 HEC [62] 39 NR 0 HEC [63] 706 22-75 67 HEC [64] 22-75 67 HEC HEC [64] 22-73 21 HEC	Navari et al., 2016 (NEJM) [52] *Mukesh et al., 2017 [53]	380 84	28–89 29–80	28 0	HEC MEC	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
i) 478 NR 0 HEC] 81 30-80 0 MEC] 81 30-80 0 MEC] 64 51-60 48 HEC 019 [60] 93 NR 4 HEC 2019 [60] 93 NR NR HEC .2019 [62] 39 NR NR HEC .2019 [63] 706 22-75 67 HEC .2010 [65] 64 24-79 21 HEC .2010 [65] 64 26-73 31 HEC	Mukhopadhyay et al., 2017 [54] *Sapkota et al., 2017 [55]	100 50	NR NR	58 NR	HEC & MEC HEC	Days 1–5: addition of olanzapine 10 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 mo PO
] 81 30-80 0 MEC] 64 51-60 48 HEC 2019 [60] 56 30-79 83 MEC 2019 [60] 93 NR 4 HEC 2019 [60] 93 NR NR HEC 2019 [61] 209 NR NR HEC 2019 [62] 39 NR 0 HEC 2019 [62] 39 NR 0 HEC 2019 [62] 39 NR 0 HEC 2010 [63] 706 22-75 67 HEC 2010 [65] 64 26-73 31 HEC	*Tran et al., 2017 [56]	478	NR	0	HEC	Days 1–3: olarization of and one prazole 20 mg PO instead of one prazole 20 mg PO BID and one prazole 20 mg PO BID, dexamethasone 4 mg PO BID and metoclopramide 20 mg PO TID Days 4–5: no use of ome prazole 20 mg PO BID, dexamethasone 4 mg PO BID, and DD
J 64 31-00 48 HEC 56 30-79 83 MEC 519 93 NR 4 HEC 9 61 209 NR 4 HEC 9 61 209 NR NR HEC 2019 621 39 NR 0 HEC 2013 706 22-75 67 HEC 202 141 24-79 21 HEC 203 56 4 26-73 31 HEC	Celio et al., 2019 [57]	81	30-80	0	MEC	Days 2–3: olarizapine 10 mg PO alone or olarizapine 10 mg PO in addition to dexamethasone 4 mg PO
209 NR NR HEC 39 NR 0 HEC 706 22-75 67 HEC 141 24-79 21 HEC 64 26-73 31 HEC 64 26-73 31 HEC	Dutat et al., 2019 [58] Jeon et al., 2019 [59] *Rumyantsev et al., 2019 [60]	64 56 93	30–79 NR	48 83 48	HEC HEC	Day 1: olarizaptine 10 mg PO, instead of natopendot 1 mg PO Days 2-4: olarizaptine 10 mg PO, instead of haloperidol 0.5 mg PO BID Days 1-4: addition of olarizaptine 10 mg PO Day 1: olarizaptine 5 mg PO, instead of aprepitant 125 mg PO Davs 2-3: olarizaptine 5 mg PO, instead of arrevitant 80 mg PO
39 NR 0 HEC 706 22-75 67 HEC 141 24-79 21 HEC 64 26-73 31 HEC 64 26-73 31 HEC	*Saldanha et al., 2019 [61]	209	NR	NR	HEC	Day 4: addition of olanzapine 5 mg PO Day 1-4: olanzapine 10 mg PO in addition to, or instead
120 32-/1 U HEC	Tienchaiananda et al., 2019 [62] Hashimoto et al., 2020 [63] Ithimakin et al., 2020 [64] Vimolchalao et al., 2020 [65] Yeo et al., 2020 [66]	39 706 141 64 120	NR 22-75 24-79 26-73 32-71	0 67 31 0	HEC HEC HEC HEC HEC	ot, aprepriatit statutator regimen Days 1-4: addition of olanzapine 10 mg PO Days 1-4: addition of olanzapine 5 mg PO Days 1-4: addition of olanzapine 10 mg PO Days 1-4: addition of olanzapine 10 mg PO Days 1-4: addition of olanzapine 10 mg PO

Study	Evaluable sample size	Age range	% Male	Chemotherapy emetogenicity	Evaluable sample size Age range % Male Chemotrapy enterogementy intervention s'auditional/substitute drug regimens, relative to comparative arm
Studies reporting on olanzapine for the rescue of breakthrough chemotherapy-induced nausea and vomiting	he rescue of breakthrough cl	hemotherapy-in	duced nauses	1 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

*Conference abstract only

Table 1 (continued)

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

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itudy or Subgroup	Olanza Events	pine Total	Contr Events		Weight	Risk Ratio M-H, Random, 95%	Risk Ratio CI M-H, Random, 95% CI
.1.1 Children ong et al, 2015 ubtotal (95% CI)	7	10 10	6	9	100.0% 100.0%	1.05 [0.57, 1. 1.05 [0.57, 1.	94]
otal events	7	10	6	9	100.0%	1.03 [0.37, 1.	
leterogeneity. Not applicable est for overall effect: Z = 0.	15 (P = 0.	88)					
I. 1.2 Adults Javari et al, 2011	117	121	104	120	9.1%	1.12 [1.03, 1.	21]
fizukami et al, 2014 humway et al, 2015	22	22	19	22	5.9% 0.4%	1.15 [0.96, 1.	39]
lavari et al, 2016 (JSCO) lavari et al, 2016 (NEJM)	45 156	51 182	42 117	50 181	6.6% 7.7%	1.05 [0.90, 1. 1.33 [1.17, 1.	
lukesh et al, 2017 lukhopadhyay et al, 2017	38 49	42 50	38 47	42 50	7.2% 9.0%	1.00 [0.87, 1. 1.04 [0.96, 1.	13) -
apkota et al, 2017 Ielio et al, 2019	21 48	25 54	22 23	25 27	4.8% 5.9%	0.95 [0.76, 1. 1.04 [0.87, 1.	19] 25]
)ulal et al, 2019 eon et al, 2019	30 28	32 29	29 22	32 25	7.1% 6.5%	1.03 [0.90, 1. 1.10 [0.93, 1.	29]
aldanha et al, 2019 Tienchaiananda et al, 2019	104 15	141 20	47 7	68 19	5.8% 1.0%	1.07 [0.89, 1. 2.04 [1.07, 3.	36]
Hashimoto et al, 2020 Ihimakin et al, 2020	336 77	354 93	311 39	351 47	9.9% 6.6%	1.07 [1.02, 1. 1.00 [0.85, 1.	17) +
fimolchalao et al, 2020 feo et al, 2020	70 42	96 60	31 31	96 60	3.2% 3.5%	2.26 [1.65, 3. 1.35 [1.01, 1.	32]
otal events	1203	1380	932		100.0%	1.12 [1.05, 1.	•
leterogeneity: Tau ² = 0.01; 'est for overall effect: Z = 3.3	Chi ² = 59. 25 (P = 0.	58, df 001)	= 16 (P ·	< 0.00	001); l² =	73%	
.1.3 HEC							
lavari et al, 2011 humway et al, 2015	117	121	104	120 9	10.8% 0.6%	1.12 [1.03, 1. 1.88 [0.64, 5.	46]
lavari et al, 2016 (JSCO) lavari et al, 2016 (NEJM)	45 156	51 182	42 117	50 181	8.4% 9.5%	1.05 [0.90, 1. 1.33 [1.17, 1.	50]
lukhopadhyay et al, 2017 apkota et al, 2017	35 21	36 25	34 22	36 25	10.3% 6.4%	1.03 [0.93, 1. 0.95 [0.76, 1.	19]
lelio et al, 2019 Julal et al, 2019	48 30	54 32	23 29	27 32	7.5% 8.8%	1.04 [0.87, 1. 1.03 [0.90, 1.	25]
aldanha et al, 2019 'ienchaiananda et al, 2019	104 15	141 20	47 7	68 19	7.4% 1.5%	1.07 [0.89, 1. 2.04 [1.07, 3.	29]
lashimoto et al, 2020 Ihimakin et al, 2020	336 77	354 93	311 39	351 47	11.6% 8.3%	1.07 [1.02, 1. 1.00 [0.85, 1.	12] 17] -
rimolchalao et al, 2020 reo et al, 2020	70 42	96 60	31 31	96 60	4.4% 4.7%	2.26 [1.65, 3. 1.35 [1.01, 1.	
otal events	1101	1273	840	1121	100.0%	1.13 [1.04, 1.	
Heterogeneity: Tau ² = 0.01; Test for overall effect: Z = 2.1	Chi ² = 58.	27, df 003)		< 0.00	001); l ² =	78%	
.1.4 MEC							
fukesh et al, 2017 fukhopadhyay et al, 2017	38 14	42 14	38 13	42 14	44.1% 22.8%	1.00 [0.87, 1. 1.07 [0.89, 1.	30] —
eon et al, 2019 Subtotal (95% CI)	28	29 85	22	25 81	33.1% 100.0%	1.10 [0.93, 1. 1.05 [0.96, 1.	291
otal events leterogeneity: Tau ² = 0.00;	80 Chi ² = 0.8	2, df =	73 2 (P = 0	1.66); I ²	= 0%		
est for overall effect: Z = 1.	00 (P = 0.	32)					
1.1.5 HEC/MEC 1izukami et al, 2014	22	22	19	22	100.0%	1.15 [0.96, 1.	39] -
Subtotal (95% CI) Total events	22	22	19	22	100.0%	1.15 [0.96, 1.	39]
leterogeneity: Not applicable est for overall effect: Z = 1.1		13)					
.1.6 Olanzapine 10mg							
lavari et al, 2011 humway et al, 2015	117 5	121 8	104 3	120 9	9.6% 0.7%	1.12 [1.03, 1. 1.88 [0.64, 5.	
lavari et al, 2016 (JSCO) lavari et al, 2016 (NEJM)	45 156	51 182	42 117	50 181	7.9% 8.7%	1.05 [0.90, 1. 1.33 [1.17, 1.	23]
lukesh et al, 2017 lukhopadhyay et al, 2017	38 49	42 50	38 47	42 50	8.3% 9.6%	1.00 [0.87, 1. 1.04 [0.96, 1.	15] +
apkota et al, 2017 Telio et al, 2019	21 48	25 54	22	25 27	6.3% 7.3%	0.95 [0.76, 1. 1.04 [0.87, 1.	19]
oulal et al, 2019 eon et al, 2019	30 28	32 29	29 22	32	8.2% 7.8%	1.03 [0.90, 1. 1.10 [0.93, 1.	19] -
ialdanha et al, 2019 Tienchaiananda et al, 2019	104 15	141 20	47	68 19	7.2%	1.07 [0.89, 1. 2.04 [1.07, 3.	29]
ihimakin et al, 2020 /imolchalao et al, 2020	38	20 46 96	39 31	19 47 96	1.7% 7.2% 4.6%	1.00 [0.83, 1. 2.26 [1.65, 3.	20]
'eo et al, 2020 iubtotal (95% CI)	42	60 957	31	60	4.6% 4.9% 100.0%	1.35 [1.01, 1. 1.13 [1.04, 1.	32] 241
otal events leterogeneity: Tau ² = 0.02;	806 (bi ² = 61		602 = 14 (P -				···
Test for overall effect: $Z = 2$.	73 (P = 0.	006)					
I .1.7 Olanzapine 5mg fizukami et al, 2014	22	22	19	22	5.3%	1.15 [0.96, 1.	39]
Hashimoto et al, 2020 Ihimakin et al, 2020	336 39	354 47	311 39	351 47	89.4% 5.3%	1.07 [1.02, 1. 1.00 [0.83, 1.	
ubtotal (95% CI) otal events	397	423	369	420	100.0%	1.07 [1.03, 1.	12]
Heterogeneity: $Tau^2 = 0.00$; Test for overall effect: $Z = 3.3$	$Chi^2 = 1.1$	9, df = 001)	2 (P = 0	0.55); I ²	= 0%		
.1.8 Double-Blind Placebo							
fizukami et al, 2014 Iavari et al, 2016 (NEJM)	22 156	22 182	19 117	22 181	13.8% 15.4%	1.15 [0.96, 1. 1.33 [1.17, 1.	50]
eon et al, 2019 Tienchaiananda et al, 2019	28	29	22	25	14.4%	1.10 [0.93, 1. 2.04 [1.07, 3.	29] +-
Hashimoto et al, 2020 Ihimakin et al, 2020	336 77	354 93	311 39	351 47	16.7% 14.5%	1.07 [1.02, 1. 1.00 [0.85, 1.	12]
rimakin et al, 2020 'imolchalao et al, 2020 'eo et al. 2020	70 42	93 96 60	39 31 31	47 96 60	14.5% 10.1% 10.6%	2.26 [1.65.3.	091
ubtotal (95% CI)		856			10.6% 100.0%	1.35 [1.01, 1. 1.26 [1.08, 1.	48]
'otal events leterogeneity: Tau ² = 0.04; 'est for overall effect: Z = 2.:	746 Chi ² = 55.	36, df	577 = 7 (P <	0.000	01); I ² = 8	37%	
est for overall effect: 2 = 2.:			= All Ar	ntieme	tics, Exce	pt Olanzapine)	
lukhopadhyay et al, 2017 Jelio et al. 2019	49 48	50 54	47 23	50 27	83.9% 16.1%	1.04 [0.96, 1.	
Subtotal (95% CI)	97	104	70	77	100.0%	1.04 [0.87, 1. 1.04 [0.97, 1.	12)
otal events leterogeneity: Tau ² = 0.00; "est for overall effect: Z = 1.	$Chi^2 = 0.0$	0, df = 271		0.99); I ²	= 0%		
.1.10 Open Controlled Des			1 = Anti	emetic	s Not In (Olanzapine Arm)	
lavari et al, 2011 humway et al, 2015	117 5	121 8	104 3	120 9	46.6% 0.2%	1.12 [1.03, 1. 1.88 [0.64, 5.	21]
	45 38	51 42	42 38	50 42	11.3% 14.5%	1.05 [0.90, 1. 1.00 [0.87, 1.	231
lavari et al, 2016 (JSCO) Iukesh et al, 2017	21	25	22	25	5.6%	0.95 [0.76, 1. 1.03 [0.90, 1.	19]
lukesh et al, 2017 'apkota et al, 2017		22	20	22			
fukesh et al, 2017 iapkota et al, 2017 Dulal et al, 2019 ialdanha et al, 2019	30 104	32 141 420	29 47	32 68 346	13.7% 8.0% 100.0%	1.07 [0.89, 1.	29]
fukesh et al, 2017 'apkota et al, 2017 Dulal et al, 2019	30 104 360	141 420	47 285	68 346	8.0% 100.0%	1.07 [0.89, 1. 1.07 [1.01, 1.	29]

1.2

1.2								
tudy or Subgroup	Olanzap Events		Contr Events		Weight M	Risk Ratio I-H, Random, 95% CI		Ratio om, 95% Cl
Javari et al. 2011	93	121	88	120	8.5%			_
fizukami et al, 2014	22	22	16	22	5.8%	1.05 [0.91, 1.21] 1.36 [1.05, 1.77]		_ _
humwayet al, 2015 Javari et al, 2016 (JSCO)	6 39	9 51	5 37	9 50	1.4% 6.6%	1.20 [0.57, 2.53] 1.03 [0.83, 1.29]		
lavari et al, 2016 (NEJM)	109	163	88	168	7.7%	1.28 [1.07, 1.53]		
flukesh et al, 2017 flukhopadhyay et al, 2017	31 48	42 50	35 21	42 50	6.6% 4.5%	0.89 [0.71, 1.11] 2.29 [1.64, 3.18]	-	
apkota et al, 2017	19 45	25 54	18	25 27	4.6% 6.8%	1.06 [0.76, 1.47]	-	<u> </u>
Ielio et al, 2019 Dulal et al, 2019	45	32	22 27	32	6.9%	1.02 [0.82, 1.27] 1.00 [0.81, 1.23]	_	F
eon et al, 2019	20 105	29 1 41	12 48	25 68	2.8% 7.6%	1.44 [0.89, 2.31] 1.05 [0.88, 1.26]	_	
'aldanha et al, 2019 Hashimoto et al, 2020	280	354	231	351	9.8%	1.20 [1.10, 1.32]		+
ihimakin et al, 2020 fimolchalao et al. 2020	68 65	93 96	34 38	47 96	6.8% 5.4%	1.01 [0.81, 1.25] 1.71 [1.29, 2.27]	-	
'eo et al, 2020	56	60	45	60	8.2%	1.24 [1.06, 1.46]		
ubtotal (95% CI) otal events	1033	1342	765	1192	100.0%	1.17 [1.07, 1.29]		•
Heterogeneity: Tau ² = 0.02; lest for overall effect: Z = 3	$Chi^2 = 44$			= 0.00	01); $I^2 = 66$	5%		
L.2.2 HEC								
Javari et al, 2011	93	121	88	120	10.5%	1.05 [0.91, 1.21]	-	-
humwayet al, 2015	6 39	9 51	5 37	9 50	1.4% 7.8%	1.20 [0.57, 2.53]		
Javari et al, 2016 (JSCO) Javari et al, 2016 (NEJM)	109	163	88	168	9.3%	1.03 [0.83, 1.29] 1.28 [1.07, 1.53]	_	
lukhopadhyay et al, 2017	34 19	36 25	14	36 25	3.7% 5.1%	2.43 [1.60, 3.69]	_	
apkota et al, 2017 Jelio et al, 2019	45	25 54	18 22	27	5.1% 8.1%	1.06 [0.76, 1.47] 1.02 [0.82, 1.27]	_	_
Dulal et al, 2019 aldanha et al, 2019	27 105	32 141	27 48	32 68	8.2% 9.2%	1.00 [0.81, 1.23] 1.05 [0.88, 1.26]	_	_
lashimoto et al, 2020	280	354	231	351	12.4%	1.20 [1.10, 1.32]		+
himakin et al, 2020 ïmolchalao et al, 2020	68 65	93 96	34 38	47 96	8.1% 6.2%	1.01 [0.81, 1.25]	-	-
eo et al, 2020	56	60	45	60	10.0%	1.24 [1.06, 1.46]		
ubtotal (95% CI) otal events	946	1235	695	1089	100.0%	1.17 [1.06, 1.28]		•
leterogeneity: Tau ^z = 0.02;	$Chi^2 = 32$			= 0.00	1); I ² = 63%	6		
est for overall effect: Z = 3	. 66 (F = 0.							
.2.3 MEC lukesh et al. 2017	31	42	35	42	39.2%	0.89 0.71. 1.11		L
ukhopadhyay et al, 2017	14	14	7	14	29.7%	1.93 [1.16, 3.23]	-	
eon et al, 2019 ubtotal (95% CI)	20	29 85	12	25 81	31.1% 100.0%	1.44 [0.89, 2.31] 1.30 [0.78, 2.17]		
otal events	65		54					-
leterogeneity: Tau ² = 0.16; est for overall effect: Z = 0	Chr = 10. .99 (P = 0.	.00, ar .32)	= 2 (P =	0.007); l* = 80%			
.2.4 HEC/MEC								
lizukami et al, 2014	22	22	16		100.0%	1.36 [1.05, 1.77]		
ubtotal (95% CI) otal events	22	22	16	22	100.0%	1.36 [1.05, 1.77]		•
leterogeneity: Not applicabl	e							
est for overall effect: Z = 2	.31 (P = 0.	.02)						
L.2.5 Olanzapine 10mg Navari et al, 2011	93	121	88	120	9.6%	1.05 [0.91, 1.21]	-	_
humwayet al, 2015	б	9	5	9	1.9%	1.20 [0.57, 2.53]		
Vavari et al, 2016 (JSCO) Vavari et al, 2016 (NEIM)	39 109	5 1 163	37 88	50 168	7.9% 8.9%	1.03 [0.83, 1.29] 1.28 [1.07, 1.53]	-	—
fukesh et al, 2017	31	42	35	42	7.9%	0.89 [0.71, 1.11]	-	-
1ukhopadhyay et al, 2017 'apkota et al, 2017	48 19	50 25	21 18	50 25	5.8% 5.8%	2.29 [1.64, 3.18] 1.06 [0.76, 1.47]	_	
Ielio et al, 2019	45	54	22	27	8.1%	1.02 [0.82, 1.27]	-	-
Dulal et al, 2019 eon et al, 2019	27 20	32 29	27 12	32 25	8.2% 3.8%	1.00 [0.81, 1.23] 1.44 [0.89, 2.31]	-	
aldanha et al, 2019	105 33	141 46	48 34	68 47	8.8% 7.3%	1.05 [0.88, 1.26]	-	-
ihimakin et al, 2020 'imolchalao et al, 2020	33 65	46 96	34	96	6.7%	0.99 [0.77, 1.28] 1.71 [1.29, 2.27]		¯ _
'eo et al, 2020 iubtotal (95% CI)	56	60 919	45	60 819	9.3% 100.0%	1.24 [1.06, 1.46] 1.16 [1.04, 1.30]		→
otal events	696		518					•
Heterogeneity: Tau ² = 0.03; Test for overall effect: Z = 2			= 13 (P	< 0.00	01); I ² = 69	9%		
.2.6 Olanzapine 5mg								
lizukami et al, 2014	22	22	16	22	14.7%	1.36 [1.05, 1.77]		
lashimoto et al, 2020 himakin et al, 2020	280 35	354 47	231 34	351 47	68.4% 16.9%	1.20 [1.10, 1.32]	_	
ubtotal (95% CI)		423		420	10.9% 100.0%	1.03 [0.81, 1.31] 1.19 [1.07, 1.33]	_	♦
otal events leterogeneity: Tau ² = 0.00;	337 Chi ² = 2.4	13. df =	281 2 (P = 1	0.301	² = 18%			
est for overall effect: Z = 3					x 0-9			
.2.7 Double-Blind Placeb	o-Controll	led Des	ign					
lizukami et al, 2014 Iavari et al, 2016 (NEJM)	22 109	22 163	16 88	22 168	10.0% 16.6%	1.36 [1.05, 1.77] 1.28 [1.07, 1.53]		
eon et al, 2019	20	29	12	25	3.7%	1.44 [0.89, 2.31]	-	<u>⊢</u> •
lashimoto et al, 2020 himakin et al, 2020	280 68	354 93	231 34	351 47	28.7% 13.3%	1.20 [1.10, 1.32] 1.01 [0.81, 1.25]	_	-
imolchalao et al, 2020	65	96	38	96	9.0%	1.71 [1.29, 2.27]		
eo et al, 2020 ubtotal (95% CI)	56	60 817	45	60 769	18.7% 100.0%	1.24 [1.06, 1.46] 1.26 [1.14, 1.38]		•
otal events	620		464					
leterogeneity: Tau ² = 0.01; 'est for overall effect: Z = 4	cm* = 10. .63 (P < 0.	.02, df .00001)	= v (P =	0.12);	r* = 40%			
.2.8 Open Controlled Des				ntieme	tics, Except	Olanzapine)		
ukhopadhyay et al, 2017	48	50	21	50	49.0%	2.29 [1.64, 3.18]	-	
elio et al, 2019 ubtotal (95% CI)	45	54 104	22		51.0% 100.0%	1.02 [0.82, 1.27] 1.52 [0.63, 3.63]	_	
otal events	93		43					
leterogeneity: Tau ² = 0.38; 'est for overall effect: Z = 0	Chr = 19. .93 (P = 0.	.∋o, df .35)	= 1 (P <	U.000	UI); I° = 95	70		
.2.9 Open Controlled Des			= Antie	metics	Not in Ola	nzapine Arm)		
Javari et al, 2011	93	121	88	120	31.3%	1.05 [0.91, 1.21]	-	•
humway et al, 2015 Javari et al, 2016 (ISCO)	б 39	9 51	5 37	9 50	1.2% 13.2%	1.20 [0.57, 2.53] 1.03 [0.83, 1.29]		
lukesh et al, 2017	31	42	35	42	13.1%	0.89 [0.71, 1.11]	-	ŀ
iapkota et al, 2017 Dulai et al, 2019	19 27	25 32	18 27	25 32	6.1% 14.9%	1.06 [0.76, 1.47] 1.00 [0.81, 1.23]		•
aldanha et al, 2019	105	141	48	68	20.2%	1.05 [0.88, 1.26]	-	-
ubtotal (95% CI)		421	258	346	100.0%	1.02 [0.94, 1.11]	•	ſ
otal events	320							
'otal events leterogeneity: Tau² = 0.00;	$Chi^2 = 2.0$	07, df =	б(Р=	0.91);	² = 0%			
otal events	$Chi^2 = 2.0$)7, df = .64)	б (Р =	0.91);	2 = 0%			
otal events leterogeneity: Tau ² = 0.00;	$Chi^2 = 2.0$)7, df = .64)	б (Р = I	0.91);	2 = 0%		0.1 0.2 0.5	1 2 5 1 Favours Olanzapine

Fig. 1 (continued)

	Olanza vents		Cont Events		Weight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% CI
1.3.1 Children Long et al, 2015	4	10	3	9	100.0%	1.20 [0.36, 3.97] 1.20 [0.36, 3.97]	
Subtotal (95% CI) Total events	4	10	з	9	100.0%	1.20 [0.36, 3.97]	
Heterogeneity: Not applicable Test for overall effect: Z = 0.30	(P = 0	.77)					
1.3.2 Adults Navarietal. 2011	93	121	88	120	8.5%	1.05 [0.91, 1.21]	1
Navarret al, 2011 Mizukami et al, 2014 Shumway et al, 2015	22 4	22	15 2	22	8.5% 6.0% 0.6%	1.05 [0.91, 1.21] 1.45 [1.09, 1.94] 2.00 [0.48, 8.31]	
Navari et al, 2016 (JSCO) Navari et al, 2016 (NEJM)	39 103	51 162	37 69	50 170	7.1%	1.03 [0.83, 1.29] 1.57 [1.26, 1.94]	+
Mukesh et al, 2017 Mukhopadhyay et al, 2017	29 47	42	35	42	6.8% 5.1%	0.83 [0.65, 1.06] 2.35 [1.66, 3.32]	
Tran et al, 2017 Dulai et al, 2019	418 26	478 32	330 25	478 32	9.6% 6.7%	1.27 [1.18, 1.36] 1.04 [0.81, 1.33]	-
jeon et al, 2019 Rumyantsev et al, 2019	20	29 47	12	25	3.6%	1.44 [0.89, 2.31] 1.37 [1.00, 1.87]	
Saldanha et al, 2019 Hashimoto et al, 2020	96 276	141 354	41 223	68 351	7.2%	1.13 [0.90, 1.41] 1.23 [1.11, 1.35]	
Ithimakin et al, 2020 Vimolchalao et al, 2020	62 65	93	33	47 96	6.9% 4.8%	0.95 [0.75, 1.20] 2.71 [1.87, 3.93]	+
Yeo et al, 2020 Subtotal (95% CI)	39	60 1787	23	60	4.8% 100.0%	1.70 [1.17, 2.46] 1.28 [1.15, 1.44]	→
	1374 1 ² = 68	.58. df	1002 = 15 (P				
Test for overall effect: Z = 4.32	(P < 0	.0001)	(
1.3.3 HEC Navari et al, 2011	93	121	88	120	10.6%	1.05 [0.91, 1.21]	+
Shumwayet al, 2015 Navariet al, 2016 (JSCO)	4 39	9 51	2 37	9 50	0.7% 8.7%	2.00 [0.48, 8.31] 1.03 [0.83, 1.29]	-
Navari et al, 2016 (NEJM) Mukhopadhyay et al, 2017	103 33	162 36	69 13	170 36	8.9% 4.5%	1.57 [1.26, 1.94] 2.54 [1.63, 3.96]	-
Tran et al, 2017 Dulai et al, 2019	418 26	478 32	330 25	478 32	12.0% 8.1%	1.27 [1.18, 1.36] 1.04 [0.81, 1.33]	+
Rumyantsev et al, 2019 Saldanha et al, 2019	35 96	47 141	25 41	46 68	6.7% 8.7%	1.37 [1.00, 1.87] 1.13 [0.90, 1.41]	+
Hashimoto et al, 2020 Ithimakin et al, 2020	276 62	354 93	223 33	351 47	11.6% 8.4%	1.23 [1.11, 1.35] 0.95 [0.75, 1.20]	_ *
Vimolchalao et al, 2020 Yeo et al, 2020 Subtotal (95% CI)	65 39	96 60	24 23	96 60	5.6% 5.6%	2.71 [1.87, 3.93] 1.70 [1.17, 2.46] 1.30 [1.15, 1.46]	
Total events	1289	1680	933		100.0%		•
Heterogeneity: Tau ² = 0.03; Ch Test for overall effect: Z = 4.34	i ² = 53	.29, df .000 1)	= 12 (P	< 0.00	001); l ² =	77%	
1.3.4 MEC							
Mukesh et al, 2017 Mukhopadhyay et al, 2017	29 14	42 14	35	42 14	38.1% 30.4%	0.83 [0.65, 1.06] 1.93 [1.16, 3.23]	*†_ - •-
leon et al, 2019 Subtotal (95% CI)	20	29 85	12	25 81	31.6% 100.0%	1.44 [0.89, 2.31] 1.27 [0.73, 2.22]	
Total events Heterogeneity: Tau ² = 0.19; Ch	63 i ² = 11	26, df	54 = 2 (P =	0.004); I ² = 823	ĸ	
Test for overall effect: Z = 0.86 1.3.5 HEC/MEC	(P = 0	39)					
Mizukami et al, 2014	22	22 22	15	22 22	100.0%	1.45 [1.09, 1.94]	1
Subtotal (95% CI) Total events	22	~~	15	~~	100.0%	1.45 [1.09, 1.94]	-
Heterogeneity: Not applicable Test for overall effect: Z = 2.51	(P = 0	.01)					
1.3.6 Olanzapine 10mg	<u>-</u>		~~		10.000	1 05 10 04	
Navari et al, 2011 Shumway et al, 2015 Navari et al, 2015 (ISCO)	93 4 20	121 9	88 2	120 9	10.1%	1.05 [0.91, 1.21] 2.00 [0.48, 8.31]	
Navari et al, 2016 (JSCO) Navari et al, 2016 (NEJM)	39 103	51 162	37 69	50 170	9.0% 9.1%	1.03 [0.83, 1.29] 1.57 [1.26, 1.94]	
Mukesh et al, 2017 Mukhopadhyay et al, 2017	29 47	42 50	35 20	42 50	8.7%	0.83 [0.65, 1.06] 2.35 [1.66, 3.32]	
Tran et al, 2017 Dulai et al, 2019 Joan et al, 2019	418 26	478 32	330 25	478	10.9% 8.6% 5.3%	1.27 [1.18, 1.36] 1.04 [0.81, 1.33]	÷.
leon et al, 2019 Saldanha et al, 2019 Ithimakin et al, 2020	20 96 30	29 141 46	12 41	25 68 47	9.0%	1.44 [0.89, 2.31] 1.13 [0.90, 1.41]	
ithimakin et al, 2020 Vimolchalao et al, 2020	65	46 96 60	33 24	47 96 60	8.0% 6.6%	0.93 [0.70, 1.23] 2.71 [1.87, 3.93]	
Yeo et al, 2020 Subtotal (95% CI) Total events	39 1009	1317 1317	23 739		6.7% 100.0%	1.70 [1.17, 2.46] 1.29 [1.11, 1.50]	◆
rotarevents Heterogeneity: Tau ² = 0.05; Ch Test for overall effect: Z = 3.29	i ² = 67		= 12 (P	< 0.00	001); I ² =	82%	
1.3.7 Olanzapine Smg	., ±0						
Mizukami et al, 2014 Rumyantsev et al, 2019	22 35	22 47	15 25	22 46	16.7% 14.9%	1.45 [1.09, 1.94] 1.37 [1.00, 1.87]	
Hashimoto et al, 2020 Ithimakin et al, 2020	276 32	354 47	223	351 47	49.9%	1.23 [1.11, 1.35] 0.97 [0.74, 1.27]	
Subtotal (95% CI) Total events	365	470	296	466	100.0%	1.23 [1.07, 1.41]	◆
Heterogeneity: Tau ² = 0.01; Ch Test for overall effect: Z = 2.94	i ² = 4.1		3 (P =	0.20); I	² = 36%		
1.3.8 Double-Blind Placebo-C			ign				
Mizukami et al, 2014 Navari et al, 2016 (NEJM)	22 103	22 162	15 69	22 170	14.4% 16.4%	1.45 [1.09, 1.94] 1.57 [1.26, 1.94]	
leon et al, 2019 Hashimoto et al, 2020	20 276	29 354	12 223	25 351	9.9% 18.9%	1.44 [0.89, 2.31] 1.23 [1.11, 1.35]	
thimakin et al, 2020 Vinnolchalao et al, 2020	62 65	93 96	33 24	47 96	15.9% 12.3%	0.95 [0.75, 1.20] 2.71 [1.87, 3.93]	+
Yeo et al, 2020 Subtotal (95% CI)	39	60 816	23	60	12.3% 100.0%	1.70 [1.17, 2.46] 1.46 [1.18, 1.81]	→
Total events Heterogeneity: Tau ² = 0.06; Ch	587 1 ² = 30	0.63, df	399 = 6 (P -	0.000	1); I ² = 8	0%	
Test for overall effect: Z = 3.50	(P = 0	.0005)					
1.3.9 Open Controlled Design Mukhopadhyay et al, 2017	(Cont 47	50	= All A 20	50	100.0%	2.35 [1.66, 3.32]	
Subtotal (95% CI) Total events	47	50	20		100.0%	2.35 [1.66, 3.32]	-
Heterogeneity: Not applicable Test for overall effect: Z = 4.83	(P < 0	.00001	I				
1.3.10 Open Controlled Desig	ın (Con	trol Arr	n = Ant				
Navari et al, 201 1 Shumway et al, 2015	93 4	121 9	88 2	120 9	17.8% 0.7%	1.05 [0.91, 1.21] 2.00 [0.48, 8.31]	
	39 29	51 42	37 35	50 42	13.0% 12.0%	1.03 [0.83, 1.29] 0.83 [0.65, 1.06]	- +
Navari et al, 2016 (JSCO) Mukesh et al, 2017		478	330	478 32	22.5% 11.8%	1.27 [1.18, 1.36] 1.04 [0.81, 1.33]	_ ⊥ •
Navari et al, 2016 (JSCO) Mukesh et al, 2017 Tran et al, 2017 Dulal et al, 2019	418 26	32	25				
Navari et al, 2016 (JSCO) Mukesh et al, 2017 Tran et al, 2017 Dulal et al, 2019 Rumyantsev et al, 2019 Saldanha et al, 2019		47 141	25 25 41	46 68	9.0% 13.1%	1.37 [1.00, 1.87] 1.13 [0.90, 1.41]	
Navari et al, 2016 (JSCO) Mukesh et al, 2017 Tran et al, 2017 Dulal et al, 2019 Rumyantsev et al, 2019	26 35 96 7 4 0	47 141 921	25 41 583	46 68 845	9.0% 13.1% 100.0%	1.37 [1.00, 1.87] 1.13 [0.90, 1.41] 1.10 [0.98, 1.24]	•

Fig. 1 (continued)

 Table 2
 Absolute risk difference

 between olanzapine and other
 regimens for statistically

 significant differences
 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

Study or Subgroup	Olanza Events		Contr Events		Weight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M–H, Random, 95% Cl
2.1.1 Adults Fan 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]	Ŧ
5humwayet al, 2015 Wang et al, 2015	3 28	9 42	5 19	10 42	1.0% 4.8%	0.67 [0.22, 2.03] 1.47 [0.99, 2.19]	
Navari et al, 2015 (ISCO)	20 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]	
dukesh et al, 2017	35 48	42 50	29 43	42 50	7.3% 9.6%	1.21 [0.95, 1.54]	<u></u>
fukhopadhyay et al, 2017 Celio et al. 2019	48 46	54	43 21	27	9.8%	1.12 [0.98, 1.27] 1.10 [0.87, 1.38]	
Dulal et al, 2019	27	32	26	32	7.7%	1.04 [0.83, 1.30]	+-
aldanha et al, 2019	98 10	141 20	43 2	68 19	7.9%	1.10 [0.89, 1.36]	+
Tienchaiananda et al, 2019 thimakin et al, 2020	52	93	21	47	0.7% 5.2%	4.75 [1.19, 18.92] 1.25 [0.87, 1.80]	
/imolchalao et al, 2020	48	96	21	96	4.3%	2.29 [1.49, 3.51]	
(eo et al, 2020 Subtotal (95% CI)	46	60 1115	32	60 952	6.7% 100.0%	1.44 [1.09, 1.89] 1.21 [1.08, 1.36]	
otal events	842	,	585	552	100.070	1.21 [1.00, 1.50]	•
leterogeneity: Tau ² = 0.03; C est for overall effect: Z = 3.3	hi ² = 67.	46, df 0009)		0.000	001); l ² =	79%	
2.1.2 HEC							
an et al, 2009	53	56	40	46	11.0%	1.09 [0.96, 1.24]	<u> </u> ∙-
lavari et al, 2011 humway et al, 2015	105 3	121 9	104 5	120 10	11.4% 1.5%	1.00 [0.91, 1.11] 0.67 [0.22, 2.03]	_
Vang et al, 2015	28	42	19	42	6.3%	1.47 [0.99, 2.19]	
lavari et al, 2016 (JSCO)	44	51	39	50	10.0%	1.11 [0.92, 1.33]	+
lavari et al, 2016 (NEJM) :elio et al, 2019	135 46	183 54	82 21	181 27	10.1% 9.2%	1.63 [1.36, 1.95] 1.10 [0.87, 1.38]	
Julai et al, 2019	27	32	26	32	9.3%	1.04 [0.83, 1.30]	<u> </u>
aldanha et al, 2019	98 10	141	43	68	9.5%	1.10 [0.89, 1.36]	+
'ienchaiananda et al, 2019 himakin et al. 2020	10 52	20 93	2 21	19 47	1.0% 6.7%	4.75 [1.19, 18.92] 1.25 [0.87, 1.80]	
himakin et al, 2020 'imolchalao et al, 2020	52 48	93 96	21	47 96	5.8%	2.29 [1.49, 3.51]	
'eo et al, 2020	46	60	32	60	8.3%	1.44 [1.09, 1.89]	
otal events	695	958	455	798	100.0%	1.24 [1.08, 1.43]	●
leterogeneity: Tau ² = 0.04; C est for overall effect: 2 = 2.9	$2hi^2 = 57$			0.000	001); l² =	79%	
.1.3 MEC	·• (i = •.	005,					
Fan et al, 2009	64	65	58	62	69.4%	1.05 [0.98, 1.13]	• _
dukesh et al, 2017 Subtotal (95% CI)	35	42 107	29	42 104	30.6% 100.0%	1.21 [0.95, 1.54] 1.10 [0.92, 1.30]	
otal events	99		87			2.20 [0.52, 2.30]	T
Heterogeneity: Tau ² = 0.01; C Test for overall effect: Z = 1.0				. 14); 1²	= 54%		
2.1.4 HEC/MEC							L
lukhopadhyay et al, 2017 Subtotal (95% CI)	48	50 50	43	50	100.0% 100.0%	1.12 [0.98, 1.27] 1.12 [0.98, 1.27]	_
otal events	48	50	43	50	100.0%	1.12 [0.98, 1.27]	•
Heterogeneity: Not applicable Test for overall effect: Z = 1.7		001	12				
	2 (r = 0.	09)					
1.1.5 Olanzapine 10mg an et al, 2009	117	121	98	108	10.3%	1.07 [0.99, 1.14]	-
Vavari et al, 2011	105	121	104	120	9.9%	1.00 [0.91, 1.11]	+
humway et al, 2015	3	9	5	10	1.0%	0.67 [0.22, 2.03]	
Vang et al, 2015 Iovani et al, 2016 (ISCO)	28 44	42	19	42	4.8%	1.47 [0.99, 2.19]	
Vavari et al, 2016 (JSCO) Vavari et al, 2016 (NEJM)	135	51 183	39 82	50 181	8.5% 8.5%	1.11 [0.92, 1.33] 1.63 [1.36, 1.95]	° →-
lukesh et al, 2017	35	42	29	42	7.3%	1.21 [0.95, 1.54]	+
fukhopadhyay et al, 2017 Celio et al, 2019	48 46	50 54	43 21	50 27	9.5% 7.6%	1.12 [0.98, 1.27]	<u> </u>
.ello et al, 2019 Dulai et al, 2019	46	32	21	32	7.6%	1.10 [0.87, 1.38] 1.04 [0.83, 1.30]	—
aldanha et al, 2019	98	141	43	68	7.9%	1.10 [0.89, 1.36]	+
'ienchaiananda et al, 2019	10	20	2	19	0.7%	4.75 [1.19, 18.92]	
thimakin et al, 2020 /imolchalao et al, 2020	30 48	46 96	21 21	47 96	5.0% 4.4%	1.46 [1.00, 2.14] 2.29 [1.49, 3.51]	
'eo et al, 2020	48 46	60	32	60	6.7%	1.44 [1.09, 1.89]	
ubtotal (95% CI)		1068		952	100.0%	1.23 [1.09, 1.38]	◆
otal events leterogeneity: Tau ² = 0.03; C	820 Thi ² = 70	61, df	585 = 14 (P <	0.000	001); l ² =	80%	
est for overall effect: Z = 3.3	9 (P = 0.	0007)					
2.1.6 Olanzapine 5mg thimakin et al, 2020	22	47	21		100.0%	1.05 [0.67, 1.63]	_ _
iubtotal (95% CI)	~~	47		47	100.0%	1.05 [0.67, 1.63]	-
otal events leterogeneity. Not applicable			21				
est for overall effect: Z = 0.2							
1.1.7 Double-Blind Placebo- lavari et al, 2016 (NEJM)	-Controll 135	ed Des 183	ign 82	181	34.9%	1.63 [1.36, 1.95]	<u> </u>
ienchaiananda et al, 2019	10	20	2	19	2.3%	4.75 [1.19, 18.92]	
himakin et al, 2020 Iimelshelee et al, 2020	52 48	93 96	21	47	19.9%	1.25 [0.87, 1.80]	+•
'imolchalao et al, 2020 'eo et al, 2020	48 46	96 60	21 32	96 60	16.5% 26.5%	2.29 [1.49, 3.51] 1.44 [1.09, 1.89]	
ubtotal (95% CI)		452			100.0%	1.62 [1.31, 2.01]	
otal events leterogeneity: Tau ² = 0.03; C	291 Thi ² = 7.6	6, df =	158 4 (P = 0	. 10); 12	= 48%		
lest for overall effect: Z = 4.3							
2.1.8 Open Controlled Desig Tan et al, 2009	117	121	98	108	55.8%	1.07 [0.99, 1.14]	_
Vang et al, 2015	28	42	19	42	4.1%	1.47 [0.99, 2.19]	<u> </u>
lukhopadhyay et al, 2017 Jelio et al, 2019	48 46	50 54	43 21	50 27	29.1% 11.1%	1.12 [0.98, 1.27] 1.10 [0.87, 1.38]	
ubtotal (95% CI)	-0	267	21		100.0%	1.10 [1.01, 1.19]	•
'otal events leterogeneity: Tau² = 0.00; C	239 Ihi ² = 3.9	9, df =	181 3 (P = 0	.26); I²	= 25%		
est for overall effect: Z = 2.2	4 (P = 0.	03)					
2.1.9 Open Controlled Desig Navari et al, 2011	n (Contr 105	ol Arm 121	= Antier 104	netics 120	Not In O 53.3%	lanzapine Arm) 1.00 [0.91, 1.11]	
Navanietal, 2011 Thumwayetal, 2015	105	121	104	120	53.3% 0.4%	0.67 [0.22, 2.03]	T
lavari et al, 2016 (JSCO)	44	51	39	50	15.5%	1.11 [0.92, 1.33]	+ - -
lukesh et al, 2017	35	42	29	42	8.8%	1.21 [0.95, 1.54]	_ <u>t</u>
	27 98	32 141	26 43	32 68	10.4% 11.6%	1.04 [0.83, 1.30] 1.10 [0.89, 1.36]	—
Dulal et al, 2019				222	100.0%	1.05 [0.97, 1.13]	L
)ulal et al, 2019 aldanha et al, 2019 iubtotal (95% CI)		396		322	100.0%	1.05 [0.57, 1.15]	T
Dulal et al, 2019 Iaidanha et al, 2019 Iubtotal (95% CI) Total events	312		246 5 (R = 0			1.05 [0.97, 1.15]	
iulal et al, 2019 aldanha et al, 2019 ubtotal (95% CI)	312 Thi ² = 3.3	8, df =				1.05 [0.57, 1.15]	Ĭ

2.2

Study or Subgroup 2.2.1 Adults	Olanzap Events		Contr Events		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% Cl
Fan et al, 2009	93	121	50	108	8.9%	1.66 [1.33, 2.08]	
Vavari et al, 2011	83	121	46	120	8.5% 1.3%	1.79 [1.38, 2.31]	
ihumwayetal, 2015 Vangetal, 2015	4 35	9 42	2	9 42	1.3%	2.00 [0.48, 8.31] 1.59 [1.16, 2.19]	
lavari et al, 2016 (JSCO)	36	51	20	50	7.0%	1.76 [1.20, 2.59]	
lavari et al, 2016 (NEJM) Iukesh et al, 2017	75 24	177 42	45 23	177 42	7.9% 7.0%	1.67 [1.23, 2.26] 1.04 [0.71, 1.53]	
lukhopadhyay et al, 2017	38	50	19	50	6.9%	2.00 [1.36, 2.94]	
elio et al, 2019 Julal et al, 20 1 9	32 22	54 32	20 24	27 32	7.8% 7.9%	0.80 [0.58, 1.10] 0.92 [0.67, 1.25]	
aldanha et al, 2019	98	141	40	68	8.9%	1.18 [0.94, 1.48]	+
'ienchaiananda et al, 2019 himakin et al, 2020	6 37	20 93	0 16	19 47	0.4% 5.9%	12.38 [0.75, 205.75] 1.17 [0.73, 1.87]	
'imolchalao et al, 2020	40	96	13	96	5.0%	3.08 [1.76, 5.38]	
'eo et al, 2020 Subtotal (95% CI)	46	60 1109	38	60 947	8.8% 100.0%	1.21 [0.95, 1.54] 1.42 [1.20, 1.69]	
otal events	669		378				-
leterogeneity: Tau ² = 0.08; 'est for overall effect: Z = 3.:			= 14 (P <	: 0.00	001); F =	73%	
2.2.2 HEC							
an et al, 2009	39	56 121	14 46	46 120	7.4% 10.0%	2.29 [1.43, 3.66]	
Vavari et al, 2011 Thumway et al, 2015	83 4	121	46	120	10.0%	1.79 [1.38, 2.31] 2.00 [0.48, 8.31]	
Vang et al, 2015	35	42	22	42	9.3%	1.59 [1.16, 2.19]	_ _
lavari et al, 2016 (JSCO) lavari et al, 2016 (NEJM)	36 75	51 177	20 45	50 177	8.4% 9.4%	1.76 [1.20, 2.59] 1.67 [1.23, 2.26]	
elio et al, 2019	32	54	20	27	9.3%	0.80 [0.58, 1.10]	
Dulal et al, 2019 Taldanha et al. 2019	22 98	32 141	24 40	32 68	9.4% 10.4%	0.92 [0.67, 1.25] 1.18 [0.94, 1.48]	
ienchaiananda et al, 2019	ę	20	0	19	0.5%	12.38 [0.75, 205.75]	
himakin et al, 2020 Imolchalao et al, 2020	37 40	93 96	16 13	47 96	7.4% 6.4%	1.17 [0.73, 1.87] 3.08 [1.76, 5.38]	
'eo et al, 2020	46	60	38	60	10.3%	1.21 [0.95, 1.54]	
otal events	553	952	300	793	100.0%	1.46 [1.18, 1.79]	
leterogeneity: Tau ² = 0.09; i 'est for overall effect: Z = 3.1	$Chi^2 = 48.4$			0.00	001); l ² =	75%	
.2.3 MEC							
an et al, 2009 Inizate et al. 2017	54	65	36	62	61.2%	1.43 [1.13, 1.82]	
lukesh et al, 2017 Subtotal (95% CI)	24	42 107	23	42 104	38.8% 100.0%	1.04 [0.71, 1.53] 1.27 [0.93, 1.72]	
fotal events	, 78		59				-
Heterogeneity: $Tau^2 = 0.02$; Test for overall effect: $Z = 1.5$	Chi≤ = 1.9 52 (P = 0.1	4, df = 13)	1 (P = 0	. 16); I '	= 49%		
.2.4 HEC/MEC							
lukhopadhyay et al, 2017	38	50	19		100.0%	2.00 [1.36, 2.94]	│
otal events	38	50	19	50	100.0%	2.00 [1.36, 2.94]	-
Heterogeneity: Not applicable	2		13				
Test for overall effect: Z = 3.1	эт (P = 0.0	JUU4)					
2.2.5 Olanzapine 10mg Fan et al, 2009	93	121	50	108	9.0%	1.66 [1.33, 2.08]	
Vavari et al, 2011	83	121	46	120	8.6%	1.79 [1.38, 2.31]	
ihumwayetal, 2015 ∦angetal, 2015	4 35	9 42	222	9 42	1.3% 7.8%	2.00 [0.48, 8.31] 1.59 [1.16, 2.19]	
Vavari et al, 2016 (JSCO)	36	51	20	50	7.0%	1.76 [1.20, 2.59]	
Navari et al, 2016 (NE J M)	75 24	177 42	45 23	177 42	8.0% 7.0%	1.67 [1.23, 2.26] 1.04 [0.71, 1.53]	
Mukesh et al, 2017 Mukhopadhyay et al, 2017	38	50	19	50	7.0%	2.00 [1.36, 2.94]	
Celio et al, 2019	32	54	20	27	7.9%	0.80 [0.58, 1.10]	
Dulai et al, 2019 Taidanha et al, 2019	22 98	32 141	24 40	32 68	7.9% 8.9%	0.92 [0.67, 1.25] 1.18 [0.94, 1.48]	-
Fienchaiananda et al, 2019	б	20	0	19	0.4%	12.38 [0.75, 205.75]	
thimakin et al, 2020 /imolchalao et al, 2020	18 40	46 96	16 13	47 96	5.3% 5.1%	1.15 [0.67, 1.97] 3.08 [1.76, 5.38]	
reo et al, 2020	46	60	38	60	8.8%	1.21 [0.95, 1.54]	
Subtotal (95% CI) Fotal events	650	1062	378	947	100.0%	1.42 [1.20, 1.70]	◆
Heterogeneity: Tau ² = 0.08; Fest for overall effect: Z = 3.:	Chi ² = 51.2			0.00	00 1); I ² =	73%	
2.2.6 Olanzapine 5mg							
thimakin et al, 2020 Subtotal (95% CI)	19	47 47	16	47 47	100.0%	1.19 [0.70, 2.01]	
Subtotal (95% CI) Fotal events	19	47	16	4/	100.0%	1.19 [0.70, 2.01]	
Heterogeneity: Not applicable Fest for overall effect: Z = 0.1	2	521	**				
2.2.7 Double-Blind Placebo			ign				
lavari et al, 2016 (NEJM)	75	177	45	177	27.3%	1.67 [1.23, 2.26]	
"ienchaiananda et al, 2019 thimakin et al, 2020	6 37	20 93	0 16	19 47	1.8% 22.2%	12.38 [0.75, 205.75] 1.17 [0.73, 1.87]	
/imolchalao et al, 2020	40	96	13	96	19.6%	3.08 [1.76, 5.38]	
'eo et al, 2020 Subtotal (95% CI)	46	60 446	38	60 399	29.2% 100.0%	1.21 [0.95, 1.54] 1.64 [1.11, 2.42]	
fotal events	204		112				
Heterogeneity: Tau ² = 0.12; Test for overall effect: $Z = 2$.	Chi ² = 14.9 49 (P = 0.0	97, df = 01)	= 4 (P =	0.005)	; I ² = 733	36	
2.2.8 Open Controlled Desi			= All An	tieme	ics. Exce	pt Olanzanine)	
Fan et al, 2009	93	121	50	108	27.2%	1.66 [1.33, 2.08]	
Vang et al, 2015 Aukhonochov et al. 2017	35	42	22	42	24.9%	1.59 [1.16, 2.19]	_ _
fukhopadhyay et al, 2017 Telio et al, 2019	38 32	50 54	19 20	50 27	22.9% 25.0%	2.00 [1.36, 2.94] 0.80 [0.58, 1.10]	_ _
Subtotal (95% CI)		267			100.0%	1.43 [0.98, 2.09]	-
Fotal events Heterogeneity: Tau ² = 0.12; ; Fest for overall effect: Z = 1.3			111 = 3 (P =	0.0003	8); I ² = 8-	4%	
			- Arel	notic-	Not in O	lanzaning Arm	
2.2.9 Open Controlled Desi Navari et al, 2011	gn (Contro 83	121	= Antier 46	netics 120	21.3%	lanzapine Arm) 1.79 [1.38, 2.31]	
humway et al, 2015	4	9	2	9	2.9%	2.00 [0.48, 8.31]	
Vavari et al, 2016 (JSCO) Nukesh et al, 2017	36 24	51 42	20 23	50 42	16.9% 17.0%	1.76 [1.20, 2.59] 1.04 [0.71, 1.53]	
Dulal et al, 2019	22	32	24	32	19.5%	0.92 [0.67, 1.25]	
ialdanha et al, 2019 Subtotal (95% CI)	98	141 396	40	68 321	22.3% 100.0%	1.18 [0.94, 1.48] 1.31 [1.01, 1.69]	
Fotal events	267		155				-
Heterogeneity: Tau ² = 0.06; Fest for overall effect: Z = 2.1	Chi ² = 16.2 03 (P = 0.4	27, df: 04)	= 5 (P =	0.006)	; 1² = 693	36	
							0.1 0.2 0.5 1 2 5 :

0.1 0.2 0.5 1 2 5 10 Favours Control Favours Olanzapine

Fig. 2 (continued)

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2.3							
Study or Subgroup	Olanzapi Events		Contro Events		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% Cl
2.3.1 Adults Tan et al, 2009 Navari et al, 2011	93 83	121 121	48 46	108 120	11.9% 11.4%	1.73 [1.37, 2.18] 1.79 [1.38, 2.31]	
Shumway et al, 2015 Navari et al, 2016 (JSCO)	2 36	9 51	3 21	10 50	1.3% 9.2%	0.74 [0.16, 3.48] 1.68 [1.16, 2.44]	
Navari et al, 2016 (NEJM)	66	177	39	178	9.8%	1.70 [1.22, 2.38]	_
Mukesh et al, 2017 Dulal et al, 2019	23 22	42 32	23 23	42 32	8.8% 10.2%	1.00 [0.68, 1.48] 0.96 [0.70, 1.32]	
Rumyantsev et al, 2019 Saldanha et al, 2019	21 89	47 141	11 33	46 68	5.6% 11.1%	1.87 [1.02, 3.42] 1.30 [0.99, 1.71]	
Tienchaiananda et al, 2019	б	20	0	19	0.4%	12.38 [0.75, 205.75]	
lthimakin et al, 2020 Vimolchalao et al, 2020	30 39	93 96	13 11	47 96	6.3% 5.6%	1.17 [0.67, 2.02] 3.55 [1.93, 6.50]	
Yeo et al, 2020 Subtotal (95% CI)		60 1010	20	60 876	8.3% 100.0%	1.75 [1.15, 2.66] 1.53 [1.28, 1.84]	
Total events Heterogeneity: $Tau^2 = 0.06$; (0.002	2); I ² = 6	1%	
Test for overall effect: Z = 4.5 2.3.2 HEC	>7 (P < 0.0	0001					
Tan et al, 2009	39	56	13	46	8.4%	2.46 [1.51, 4.03]	
Navari et al, 2011 Shumway et al, 2015	83 2	121 9	46 3	120 10	12.8% 1.6%	1.79 [1.38, 2.31] 0.74 [0.16, 3.48]	
Navari et al, 2016 (JSCO)	36	51	21	50	10.6%	1.68 [1.16, 2.44]	_
Navari et al, 2016 (NEJM) Dulal et al, 2019	66 22	177 32	39 23	178 32	11.2% 11.6%	1.70 [1.22, 2.38] 0.96 [0.70, 1.32]	
Rumyantsev et al, 2019	21	47 141	11 33	46 68	6.8% 12.4%	1.87 [1.02, 3.42]	
Saldanha et al, 2019 Tienchaiananda et al, 2019	89 6	20	33 0	68 19	0.5%	1.30 [0.99, 1.71] 12.38 [0.75, 205.75]	
Ithimakin et al, 2020 Vimelsheleo et al, 2020	30 39	93 96	13 11	47 96	7.6% 6.8%	1.17 [0.67, 2.02] 3.55 [1.93, 6.50]	
Vimolchalao et al, 2020 Yeo et al, 2020	35	60	20	60	9.7%	1.75 [1.15, 2.66]	
Subtotal (95% CI) Total events	468	903	233	772	100.0%	1.64 [1.33, 2.02]	•
Heterogeneity: $Tau^2 = 0.07$; (Test for overall effect: $Z = 4.6$			= 11 (P =	0.007	2); I ² = 63	2%	
2.3.3 MEC		~~	25	~	E 7 001	1 47 14 45 4	_
Tan et al, 2009 Mukesh et al, 2017	54 23	65 42	35 23	62 42	57.8% 42.2%	1.47 [1.15, 1.88] 1.00 [0.68, 1.48]	+
Subtotal (95% CI) Total events	77	107	58	104	100.0%	1.25 [0.86, 1.82]	◆
Heterogeneity: $Tau^2 = 0.05$;) Test for overall effect: $Z = 1.3$	$Chi^2 = 2.77$			10); l²	= 64%		
2.3.4 Olanzapine 10mg							
Tan et al, 2009 Navari et al, 2011	93 83	121 121	48 46	108 120	12.6% 12.1%	1.73 [1.37, 2.18] 1.79 [1.38, 2.31]	
Shumway et al, 2015	2	9	3	10	1.4%	0.74 [0.16, 3.48]	
Navari et al, 2016 (JSCO) Navari et al, 2016 (NEJM)	36 66	51 177	21 39	50 178	9.8% 10.5%	1.68 [1.16, 2.44] 1.70 [1.22, 2.38]	
Mukesh et al, 2017	23	42	23	42	9.5%	1.00 [0.68, 1.48]	_ _
Dulal et al, 2019 Saldanha et al, 2019	22 89	32 141	23 33	32 68	10.9% 11.7%	0.96 [0.70, 1.32] 1.30 [0.99, 1.71]	
Tienchaiananda et al, 2019 Ithimakin et al, 2020	6 16	20 46	0 13	19 47	0.4% 6.0%	12.38 [0.75, 205.75] 1.26 [0.68, 2.31]	
Vimolchalao et al, 2020	39	96	11	96	6.1%	3.55 [1.93, 6.50]	
Yeo et al, 2020 Subtotal (95% CI)	35	60 916	20	60 830	8.9% 100.0%	1.75 [1.15, 2.66] 1.52 [1.26, 1.84]	
Total events Heterogeneity: Tau ² = 0.06; (510 518 - 39.7		280	0.00-	20:18 - 6:		
Test for overall effect: Z = 4.3			= 11 (r =	0.002	2), 1 = 0.	576	
2.3.5 Olanzapine 5mg Rumyantsev et al, 2019	21	47	11	45	51.7%	1.87 [1.02, 3.42]	
Ithimakin et al, 2020 Subtotal (95% CI)	14	47 94	13	47 93	48.3% 100.0%	1.08 [0.57, 2.04] 1.43 [0.83, 2.46]	
Total events	35		24			1.45 [0.05, 2.46]	
Heterogeneity: Tau ² = 0.05; (Test for overall effect: Z = 1.3			1 (P = 0.	22); I²	= 34%		
2.3.6 Double-Blind Placebo				170	20.10	1 70 (1 22 2 2 20)	_
Navari et al, 2016 (NEJM) Tienchaiananda et al, 2019	66 6	177 20	39 Q	178 19	30.1% 1.8%	1.70 [1.22, 2.38] 12.38 [0.75, 205.75]	
lthimakin et al, 2020 Vimolchalao et al, 2020	30 39	93 96	13 11	47 96	21.7% 19.7%	1.17 [0.67, 2.02] 3.55 [1.93, 6.50]	
Yeo et al, 2020	35	60	20	60	26.7%	1.75 [1.15, 2.66]	
Subtotal (95% CI) Total events	176	446	83	400	100.0%	1.89 [1.29, 2.77]	•
Heterogeneity: Tau ² = 0.10; 0	Chi ² = 9.38			05); I ²	= 57%		
Test for overall effect: Z = 3.2							
2.3.7 Open Controlled Desig Tan et al. 2009	gn (Contro 93	I Arm 121	= All Ant 48		tics, Exce 100.0%	pt Olanzapine) 1.73 [1.37, 2.18]	
Subtotal (95% CI)		121			100.0%	1.73 [1.37, 2.18]	
Total events Heterogeneity: Not applicable	93		48				
Test for overall effect: Z = 4.6	52 (P < 0.0	0001;	1				
2.3.8 Open Controlled Desig							
Navari et al, 2011 Shumway et al, 2015	83 2	121 9	46 3	120 10	20.2% 2.1%	1.79 [1.38, 2.31] 0.74 [0.16, 3.48]	
Navari et al, 2016 (JSCO)	36	51	21	50	15.9%	1.68 [1.16, 2.44]	_
Mukesh et al, 2017 Dulal et al, 2019	23 22	42 32	23 23	42 32	15.3% 17.8%	1.00 [0.68, 1.48] 0.96 [0.70, 1.32]	
Rumyantsev et al, 2019	21	47	11	46	9.4%	1.87 [1.02, 3.42]	
Saldanha et al, 2019 Subtotal (95% CI)	89	141 4 43	33	68 368	19.4% 100.0%	1.30 [0.99, 1.71] 1.34 [1.07, 1.69]	•
Total events Heterogeneity: Tau ² = 0.05; (276 Chi ² = 14.8	0 ef	160 = 6 (P = 0	1071	12 = 5.0%		-
Test for overall effect: $Z = 2.5$			- o (r = (V2],	, - J9%		
							Favours Control Favours Olanzapine

3.1						
	Olanzapi		Control		Risk Ratio	Risk Ratio
Study or Subgroup	Events T	Fotal E	vents Tot	al Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
3.1.1 Adults	114	1 7 1	101 10	0 30.40	1 01 (0 04 1 00)	L
Tan et al, 2009 Shumway et al, 2015	114 5	121 8	101 10 3	8 39.4% 9 4.1%	• • •	
Wang et al. 2015	38	42		2 32.1%	• • •	
Yeo et al, 2020	43	60		0 24.5%	. , .	
Subtotal (95% CI)		231		9 100.0%	1.17 [0.93, 1.47]	◆
Total events	200	40.00	168	0.0000	7 7.00	
Heterogeneity: Tau ² = Test for overall effect: 2				= 0.006); 1	* = /6%	
3.1.2 HEC						
Tan et al, 2009	51	56		6 40.8%		
Shumway et al, 2015	5	8		9 2.9%	• • •	
Wang et al, 2015 Yeo et al. 2020	38 43	42 60		2 33.8% 0 22.6%	• • •	
Subtotal (95% CI)	45	166		7 100.0%	1.16 [0.96, 1.40]	
Total events	137		108			•
Heterogeneity: Tau ² = Test for overall effect: 2				0.08); l ² =	56%	
3.1.3 MEC						
Tan et al, 2009 Subtotal (95% CI)	63	65 65		2 100.0% 2 100.0%		
Total events	63		60			Ī
Heterogeneity: Not app Test for overall effect: 2		= 0.96)			
3.1.4 Olanzapine 10m	g					
Tan et al, 2009	114	121	101 10	8 39.4%	1.01 [0.94, 1.08]	+
Shumway et al, 2015	5	8	3	9 4.1%		
Wang et al, 2015	38	42		2 32.1%		
Yeo et al, 2020 Subtotal (95% CI)	43	60 231		0 24.5% 9 100.0%		
Total events	200		168	5 100.070	1117 [0100, 1117]	-
Heterogeneity: Tau ² =	0.03; Chi ² =	= 12.36	, df = 3 (P	= 0.006); I	² = 76%	
Test for overall effect: 2	Z = 1.32 (P	= 0.19))			
3.1.5 Double-Blind Pl			-			
Yeo et al, 2020 Subtotal (95% CI)	43	60 60		0 100.0% 0 100.0%	• • •	
Total events	43	00	31	0 100.0%	1.39 [1.04, 1.60]	-
Heterogeneity. Not app			51			
Test for overall effect: 2		= 0.03)			
3.1.6 Open Controlled	l Design (C	ontrol	Arm = All	Antiemetic	s, Except Olanzapine)	
Tan et al, 2009	114	121	101 10			•
Wang et al, 2015	38	42		2 31.4%	1.15 [0.96, 1.39]	
Subtotal (95% CI) Total events	152	163	15 134	0 100.0%	1.05 [0.92, 1.20]	•
Heterogeneity: Tau ² = Test for overall effect: 2	0.01; Chi ² =		df = 1 (P =	0.15); l ² =	52%	
3.1.7 Open Controlled	l Design (C	ontrol	Arm = Ant	iemetics N	ot In Olanzapine Arm)	
Shumway et al, 2015 Subtotal (95% CI)	5	8 8	3	9 100.0% 9 100.0%		
Total events	5		3			
Heterogeneity: Not app						
Test for overall effect: 2	Z = 1.15 (P	= 0.25))			
						0.1 0.2 0.5 1 2 5 10 Favours Control Favours Olanzapine
						ravours control Favours Olanzapine

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							
Chudes on Culture	Olanza		Cont		Mainte	Risk Ratio	Risk Ratio
Study or Subgroup 3.2.1 Adults	Events	lotal	Events	Total	weight	M-H, Random, 95% Cl	M–H, Random, 95% Cl
3.2.1 Aduits Tan et al, 2009	112	121	73	108	38.4%	1 27 11 10 1 50	+
Fanietiai, 2009 Shumwayietiai, 2015	112 6	121	73	108	38.4% 1.4%	1.37 [1.19, 1.58] 1.20 [0.57, 2.53]	
Wang et al, 2015	40	42	34	42	28.9%	1.18 [1.00, 1.38]	
Yeo et al, 2020	56	60	46	60	31.3%	1.22 [1.04, 1.42]	
Subtotal (95% CI)	20	232			100.0%	1.26 [1.16, 1.38]	
Total events	214		158				
Heterogeneity: Tau ² = 0 Test for overall effect: 2	0.00; Chi ²			(P = 0	.50); I ² =	0%	
3.2.2 HEC							
Tan et al, 2009	44	56	26	46	12.9%	1.39 [1.04, 1.85]	_
Shumway et al, 2015	6	9	5	9	1.9%		
Wang et al, 2015	40	42	34	42	40.9%	1.18 [1.00, 1.38]	
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				
Heterogeneity: Tau ² = Test for overall effect: 2				(P = 0	.76); I ² =	0%	
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				
Heterogeneity: Not app							
Test for overall effect: 2	Z = 1.95 ((P = O)	05)				
3.2.4 Olanzapine 10m	g						
Tan et al, 2009	112	121	73	108	38.4%	1.37 [1.19, 1.58]	
Shumway et al, 2015	6	9	5	9	1.4%	1.20 [0.57, 2.53]	
Wang et al, 2015	40	42	34	42	28.9%	1.18 [1.00, 1.38]	
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		-		
Heterogeneity: Tau ² =				(P = 0)	.50); I ² =	0%	
Test for overall effect: 2	Z = 5.24 ((P < 0.1	00001)				
3.2.5 Double-Blind Pl	acebo-Co	ontroll	ed Desig	In			
Yeo et al, 2020	56	60	46		100.0%	1.22 [1.04, 1.42]	
Subtotal (95% CI)		60		60	100.0%	1.22 [1.04, 1.42]	◆
Total events	56		46				
Heterogeneity. Not app							
Test for overall effect: 2	Z = 2.49 ((P = 0.	01)				
3.2.6 Open Controlled	l Design	(Contr	ol Arm =	All An	tiemetic	s, 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	46.6%	1.18 [1.00, 1.38]	
Subtotal (95% CI)		163		150	100.0%	1.28 [1.09, 1.49]	◆
Total events	152		107		-		
Heterogeneity: $Tau^2 = 1$. (P = 0	.15); I ² =	52%	
Test for overall effect: 2	2 = 3.10 ((P = 0.	002)				
3.2.7 Open Controlled	l Design	(Contr	ol Arm =	Antier	netics No	ot In Olanzapine Arm)	
Shumway et al, 2015	6	9	5	9	100.0%	1.20 [0.57, 2.53]	
Subtotal (95% CI)		9			100.0%	1.20 [0.57, 2.53]	
Total events	6		5				
Heterogeneity: Not app	licable						
Test for overall effect: 2	Z = 0.48 ((P = O)	63)				
							0.1 0.2 0.5 1 2 5 10
							Favours Control Favours Olanzapine
Fig 3 (continued)							•

Fig. 3 (continued)

	Olanzap		Contr			Risk Ratio	Risk Ratio
Study or Subgroup 3.3.1 Adults	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Fan et al, 2009	102	121	73	108	69.7%		
Shumway et al. 2015	4	9	2	9	1.1%	1.25 [1.07, 1.45] 2.00 [0.48, 8.31]	
eon 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	21		100.0%	1.32 [1.13, 1.54]	•
Fotal events	167		113				•
Heterogeneity: Tau ² = Test for overall effect:				(P = 0	.36); I ² =	7%	
3.3.2 HEC							
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		7		
Heterogeneity: Tau ² = Fest for overall effect:				(P = 0	.62); I² =	0%	
3.3.3 MEC							<u> _</u>
Tan et al, 2009	58	65	47	62	87.0%	1.18 [1.00, 1.39]	
leon et al, 2019 Subsect (25% CD	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	<i>с</i> р с	0.42.12	~~~	
Heterogeneity: Tau² = Test for overall effect:				(r = 0	.84); F =	V26	
3.3.4 Olanzapine 10n	ng						
Tan et al, 2009	102	121	73	108	69.7%	1.25 [1.07, 1.45]	
5humway et al, 2015	4	9	2	9	1.1%	2.00 [0.48, 8.31]	
leon 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)	4.67	219		202	100.0%	1.32 [1.13, 1.54]	◆
Total events Heterogeneity: Tau² =	167		113 at 7	/n o	261.12	70/	
Test for overall effect:				(r = 0	.50), 1" =	7.76	
3.3.5 Double-Blind P	lacebo-Co	ntrolle	d Desig	n			
leon 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: Tau ² = Test for overall effect:				(P = 0	.24); I² =	27%	
3.3.6 Open Controlle	d Design (Contro	I Arm =	All An	tiemetic	s, Except Olanzapine)	
Tan et al, 2009	102	121	73		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 app Test for overall effect:		P = 0.0	04)				
3.3.7 Open Controlle	d Design (Contro	I Arm =	Antier	netics No	ot In Olanzapine Arm)	
5 5 humway 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 app							
	7 = 0.05 / 1	P = 0.3	41				
Test for overall effect:	2 = 0.95 (i	I - V.S					I
Test for overall effect:	2 = 0.95 (i	- 0.5	.,				

Fig. 3 (continued)

	Olanzapine		Control			Risk Ratio	Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl					
4.1							_					
Nakagaki et al, 2017	10	22	5	40	100.0%	3.64 [1.42, 9.30]						
Subtotal (95% CI)		22		40	100.0%	3.64 [1.42, 9.30]						
Total events	10		5									
Heterogeneity: Not applicable Test for overall effect: Z = 2.69 (P = 0.007)												
4.2												
Navari and Gray, 2009	21	32	19	68	100.0%	2.35 [1.49, 3.71]						
Subtotal (95% CI)		32		68	100.0%	2.35 [1.49, 3.71]	•					
Total events Heterogeneity: Not app	21 Vachla		19									
Test for overall effect: Z		= 0.00	02)									
4.3												
Navari et al, 2013	38	56	12	52	100.0%	2.94 [1.73, 4.99]						
Subtotal (95% CI)		56		52	100.0%	2.94 [1.73, 4.99]	-					
Total events	38		12									
Heterogeneity: Not applicable Test for overall effect: Z = 4.00 (P < 0.0001)												
4.4												
Navari et al, 2013	39	56	16	52	100.0%	2.26 [1.45, 3.52]						
Subtotal (95% CI)		56		52	100.0%	2.26 [1.45, 3.52]	-					
Total events	39		16									
Heterogeneity: Not appl		- 0.00	202				0.1 0.2 0.5 1 2 5 10					
Test for overall effect: Z	= 3.02 (P	= 0.00	U3)				Favours Control Favours Olanzapine					

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 metaanalyzed for the efficacy endpoints of complete response; there was much less statistical power relative to metaanalyses looking at HEC patients alone. Furthermore, even for the efficacy endpoints of complete response, these metaanalysis 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 5mg 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-olanzapinecontaining regimens. Studies comparing 5-mg doses to 10mg 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 metaanalysis 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.

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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.

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