




Olanzapine combined with 5-hydroxytryptamine type 3 receptor antagonist (5-HT₃ RA) plus dexamethasone for prevention and treatment of chemotherapy-induced nausea and vomiting in high and moderate emetogenic chemotherapy: a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

We performed a pooled analysis to evaluate the efficacy and adverse events (AEs) of olanzapine combined with dexamethasone plus 5-hydroxytryptamine type 3 receptor antagonist (5-HT₃ RA) compared with 5-HT₃ RA plus dexamethasone for the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV) in high and moderate emetogenic chemotherapy based on randomised controlled trials (RCTs). PubMed, EMBASE, Web of Science, the Cochrane Library, China Biomedical Literature database (CBM), WanFang Database, China National Knowledge Infrastructure (CNKI), and Chinese Science and Technology Periodical Database (VIP) (from their inception to April 2019) were searched to capture relevant articles. Relative risk with 95% confidence intervals for CINV and AEs were all extracted or calculated. Eleven studies with 1107 cancer patients were involved in this review. The pooled RR of delayed CINV (RR 0.50, 95% CI 0.38 to 0.66; $p < 0.01$) were significantly decreased in the olanzapine group. The occurrence of insomnia was also statistically decreased, as was the rate of acute CINV (RR 0.60, 95% CI 0.48 to 0.75; $p < 0.01$). However, only the percentages of CINV III and CINV IV were significantly decreased in the acute and delayed phases. Subgroup analysis demonstrated that the efficacy was not statistically significantly different between 5 mg and 10 mg olanzapine. Olanzapine significantly decreased the occurrence of CINV III and IV and insomnia in high and moderately emetogenic chemotherapy. Compared with 10 mg per day, 5 mg oral olanzapine may be more appropriate for patients with cancer.

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is a common adverse effect (AE) in the treatment of cancer, which can significantly

impair the patient's quality of life, resulting in poor compliance and malnutrition.¹ The incidence of acute CINV (occurrence within 24 hours of administration of chemotherapy) was found to be 36% and for delayed CINV it was 59% (2–5 days after the administration of chemotherapy).² While 5-hydroxytryptamine type 3 receptor antagonist (5-HT₃ RA),³ dexamethasone, and neurokinin-1 receptor antagonist (NK-1 RA)⁴ have significantly decreased the incidence of CINV, 54.7% of patients still experience nausea when these agents are used.⁵

The US Food and Drug Administration (FDA) approved olanzapine as an anti-psychotic agent that blocks $\alpha 1$ adrenergic receptors, serotonin 5-HT_{2a}, 5-HT_{2c}, 5-HT₃, 5-HT₆ receptors, muscarinic receptors, dopamine D₁, D₂, D₃ receptors, and histamine H₁ receptors.⁵ Randomised controlled trials (RCTs)^{6–7} and meta-analyses^{8–10} have suggested that olanzapine is useful for patients with cancer who receive chemotherapy. The 2016 Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology (MASCC/ESMO) guidelines¹¹ recommend olanzapine combined with 5-HT₃ RA plus dexamethasone to prevent CINV, but the level of recommendation was graded low. The National Comprehensive Cancer Network (NCCN) guidelines for antiemesis (version

1.2019) also recommend olanzapine combined with a 5-HT₃ RA plus dexamethasone after NK-1 RA for high and moderate emetogenic chemotherapy; however, 5 mg per day was considered only when 10 mg per day caused serious sedation. RCTs^{12 13} demonstrated 5 mg oral olanzapine per day to be effective, and a randomised phase 2 dose-finding study¹⁴ even revealed that 5 mg had a higher complete control in delayed CINV compared with 10 mg (83.1% vs 77.6%). Meta-analysis¹⁵ also found that both 5 mg and 10 mg olanzapine exhibited similar efficacy. However, three (olanzapine, 5-HT₃ RA and dexamethasone) or four (olanzapine, 5-HT₃ RA, NK-1 RA and dexamethasone) drugs were used and the level of CINV was not reported. Therefore, we designed this review to evaluate the efficacy and AEs of olanzapine combined with 5-HT₃ RA plus dexamethasone compared with 5-HT₃ RA plus dexamethasone for the prevention and treatment of CINV in high and moderately emetogenic chemotherapy based on currently available studies.

METHODS

This review was performed following the Cochrane Handbook for Systematic Reviews of Interventions. Moreover, we reported pooled results by the recommendations listed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) harms checklist¹⁶ statement (online supplementary data 1).

Search strategy

PubMed, Web of Science, the Cochrane Library, EMBASE, WanFang Database, China National Knowledge Infrastructure (CNKI), Chinese Science and Technology Periodical Database (VIP) and China Biomedical Literature database (CBM) (from corresponding inception to April 2019) were searched using the following terms: “olanzapine”, “chemotherapy-induced nausea and vomiting”, “CINV”, “emesis”, “nausea”. The search strategy for PubMed is documented in online supplementary data 2. Language or date restrictions were not imposed. The bibliographies of relevant trials and reviews were also browsed. Two researchers (LH and CX) conducted this part independently, and any inconsistency was solved by consulting a third researcher (HM).

Study inclusion

Two reviewers (J-GZ and LH) independently screened the studies based on inclusion and exclusion criteria. Any inconsistency was resolved by the third investigator (HM). Eligible studies had to meet the following criteria: (1) population—cancer patients who had received high and moderately emetogenic chemotherapy classified by MASCC/ESMO guidelines¹¹; (2) intervention—olanzapine combined with 5-HT₃ RA plus dexamethasone for the prevention and treatment of CINV; (3) comparison—dexamethasone plus 5-HT₃ RA for the prevention and treatment of CINV; (4) outcome—primary endpoint: the percentage delay of CINV; secondary endpoint: AEs; (5) study type—only RCTs were considered.

Exclusion criterion

Exclusion criteria were: (1) patients with no solid tumours; (2) use of other antiemetic drugs (ie, NK-1 RA); (3) letters to the editor or meeting abstracts.

Data extraction

Two researchers (S-HJ and CX) evaluated the eligibility of all identified studies by checking abstracts and titles fitting the inclusion and exclusion criteria, and full-text were carefully checked. Data involved authors, country, population, publication year, drug dosage and duration, the percentage of acute and delayed CINV, and AEs. All divergences about eligibility assessment and data extraction were resolved by consulting a third senior investigator (HM).

Assessment of methodologic quality

The methodologic quality was appraised using the Cochrane Collaboration's Risk Bias assessment tool for assessing the risk of bias¹⁷ by two researchers (J-GZ and CX), and RevMan (version 5.3) was used in this part. Seven domains (blinding of outcome assessment, blinding of participants and personnel, selective reporting, allocation concealment, random-sequence generation, incomplete outcome data, and other bias) were assessed for each study, and all of them were labelled as “high risk”, “unclear risk” or “low risk”.

Statistical analysis

The dichotomous outcomes were estimated using relative risk (RR) with 95% confidence intervals (95% CI). I^2 statistic and p value were used to estimate the level of heterogeneity of involved studies.¹⁸ We considered heterogeneity substantial if $I^2 \geq 50\%$ or $p < 0.10$.¹⁹ A fixed model was used when $I^2 < 50\%$ or $p > 0.10$; if significant heterogeneity was conducted, a random model was used. If noticeable differences were found in clinical characteristics and methodology, regardless of I^2 statistic or p value, a belief of qualitative analysis was conducted. An approximate standard error of the log rate ratio is given by SE of ln rate ratio = $\sqrt{\frac{1}{E_E} + \frac{1}{E_C}}$. A correction of 0.5 might be added to each count in the case of zero events (section 9.4.8 of the Cochrane Handbook version 5.1.0). Subgroup analysis of olanzapine dosage (5 mg vs 10 mg) was also conducted. Begg, Egger regression^{20 21} and LFK index²² (using MetaXL, www.epigear.com) were used to detect potential publication bias. All analyses used R (version 3.3.0) and the *Meta* package.

RESULTS

Literature research and characteristics of studies

As shown in online supplementary data 3, a total of 787 studies of olanzapine for the prevention and treatment CINV were identified, and 11 articles^{12 13 23–31} were evaluated in our review according to the set criteria.

All involved studies were published from 2009 to 2018; 1107 patients with cancer were included in this review,

with 561 patients in the olanzapine group and 546 patients in the control group, respectively. Except for Mukhopadhyay *et al.*,²³ all studies were from China. All patients with solid tumours received high or moderated emetogenic chemotherapy. Olanzapine combined with 5-HT3 RA plus dexamethasone was compared with 5-HT3 RA plus dexamethasone for the prevention and treatment of CINV. Two different olanzapine dosages were used in the intervention group: six studies^{23–25 28 30 31} used 10 mg oral once a day, and four studies^{12 13 26 29} used 5 mg oral once a day; Meng *et al.*²⁷ used 2.5 mg oral twice a day. Six studies^{12 13 25–28} reported CINV according to the WHO classification standards for gastrointestinal reactions of anticancer drugs: CINV I (nausea without vomiting), CINV II (vomiting 1–2 times a day, does not affect eating), CINV III (nausea and vomiting 3–5 times daily, affects eating, needed to treat), and CINV IV (uncontrollable nausea and vomiting, more than five times) were reported in the articles. Only Wang *et al.*,²⁸ Guo and Lin¹³ and Meng *et al.*²⁷ used National Cancer Institute Common Terminology Criteria for Adverse Events (NCICTCAE) 4.0 to evaluate the AEs; the others did not provide the

definition of all related AEs. The main characteristics of the involved studies are presented in [table 1](#).

Assessing risk of methodologic quality

The detail of the risk-of-bias assessment is summarised in online supplementary data 4. Except for Sandip *et al.*,²³ all studies were open-label randomised studies and assessed as high risk in allocation concealment. Four studies^{12 23 24 31} reported the detail of the randomised method, and the low risk was designated. Incomplete outcome data and selective reporting for all studies were assessed as low risk. For all studies the overall methodologic quality was accepted.

Efficacy of olanzapine for prevention and treatment of delayed CINV

As shown in [figure 1](#), 11 RCTs (1107 cancer patients) reported delayed CINV, and significant heterogeneity ($I^2=68\%$, $p<0.1$) was conducted. Therefore, a random model was used. There was a significantly lower rate of delayed CINV (RR 0.50, 95% CI 0.38 to 0.66; $p<0.01$) when olanzapine was added to 5-HT3 RA and dexamethasone.

Table 1 Main characteristics of the included studies

Studies	Year	Sample size	Intervention	Comparison
Zhao	2018	54	OLA 10 mg oral once daily d1–5, granisetron 3 mg iv once daily d1–3 DEX 10 mg iv once daily d1–3	Granisetron 3 mg iv once daily d1–3 DEX 10 mg iv once daily d1–3
He	2018	101	OLA 5 mg oral once daily d1–7, tropisetron 5 mg iv once daily d1–7 DEX 10 mg iv once daily d1–7	Tropisetron 5 mg iv once daily d1–7 DEX 10 mg iv once daily d1–7
Guo	2018	60	OLA 5 mg oral, tropisetron 5 mg iv, DEX 10 mg iv	Tropisetron 5 mg iv, DEX 10 mg iv
Tian	2017	100	OLA 10 mg oral once daily d1–2, tropisetron 5 mg once daily d1–2 DEX 10 mg oral once daily d1–2	Tropisetron 5 mg once daily d1–2 DEX 10 mg oral once daily d1–2
Liu	2017	117	OLA 5 mg oral once daily d1–4, tropisetron 5 mg iv once daily d1 DEX 5 mg iv once daily d1	Tropisetron 5 mg iv once daily d1 DEX 5 mg iv once daily d1
Sandip	2017	100	OLA 10 mg oral once daily d1–5, palonosetron 0.25 mg iv once daily d1, DEX 8 mg or 16 mg iv once daily d1, DEX 8 mg oral once or twice daily d2–5	Palonosetron 0.25 mg iv once daily d1, DEX 8 mg or 16 mg iv once daily d1, DEX 8 mg oral once or twice daily d2–5
Wang	2016	60	OLA 10 mg oral once daily d1–4, granisetron 5 mg iv, DEX 5 mg iv	Granisetron 5 mg iv, DEX 5 mg iv
Meng	2016	120	OLA 2.5 mg oral twice daily d1–5, granisetron 5 mg iv, DEX 5 mg iv	Granisetron 5 mg iv, DEX 5 mg iv
Li	2015	80	OLA 5 mg oral once daily, tropisetron 5 mg once daily, DEX 10 mg oral once daily	Tropisetron 5 mg iv once daily DEX 5 mg iv once daily
Chen	2015	86	OLA 10 mg oral once daily d1–5, tropisetron 5 mg iv once daily d1–5, DEX 10 mg iv once daily d1–5	Tropisetron 5 mg iv once daily d1–5, DEX 10 mg iv once daily d1–5
Tian	2009	229	OLA 10 mg oral once daily d1–5, azasetron 5 mg iv once daily d1–5, DEX 10 mg iv once daily d1–5	Azasetron 5 mg iv once daily d1–5, DEX 10 mg iv once daily d1–5

d, day(s); DEX, dexamethasone; iv, intravenously; OLA, olanzapine.

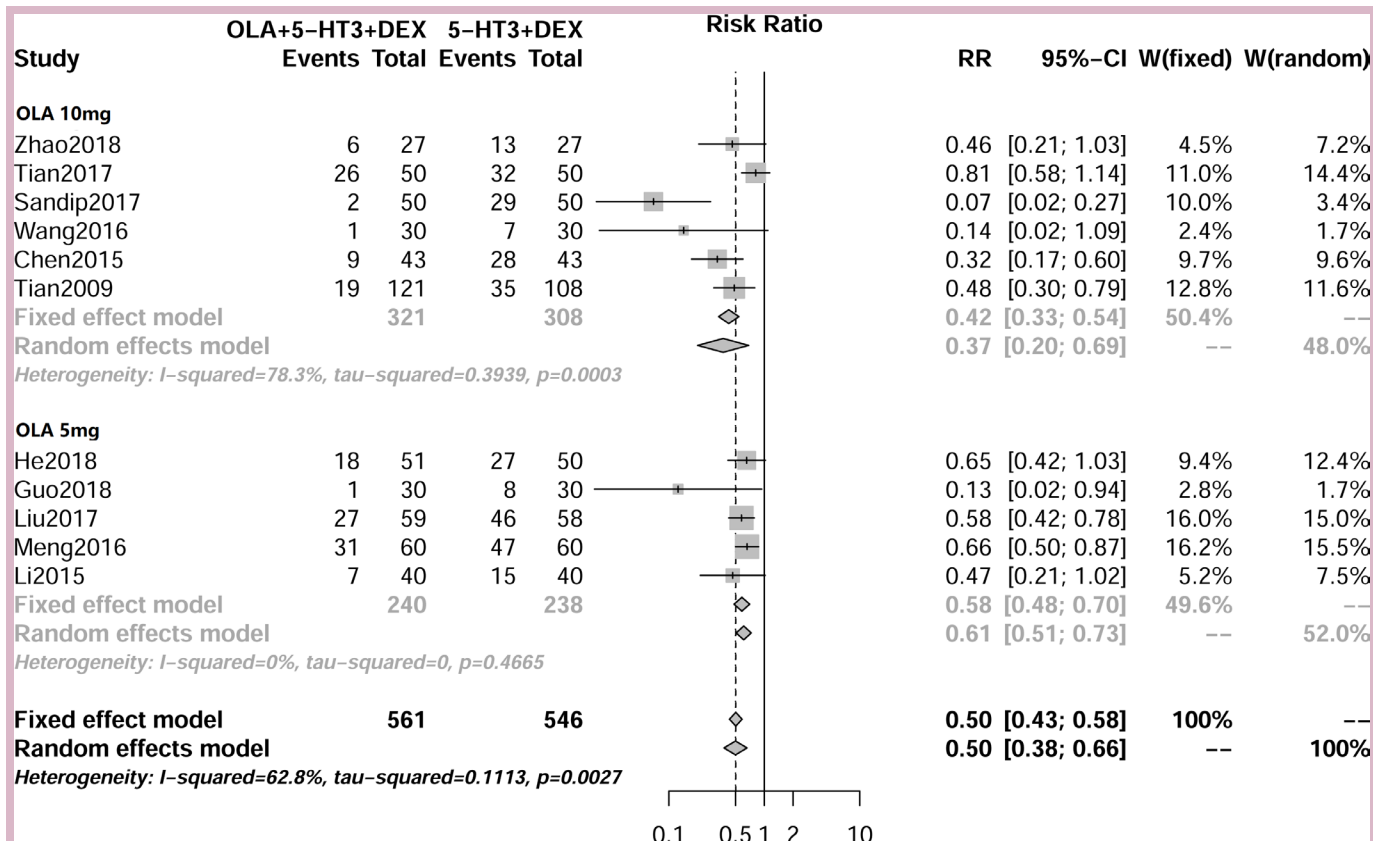


Figure 1 Result of the meta-analysis of the relative risk of delayed chemotherapy-induced nausea and vomiting. DEX, dexamethasone; 5-HT3 RA, 5-hydroxytryptamine type 3 receptor antagonist; OLA, olanzapine.

Six articles (table 2) reported delayed CINV. CINV III (RR 0.27, 95% CI 0.14 to 0.52; $p < 0.01$) and CINV IV (RR 0.16, 95% CI 0.04 to 0.60; $p < 0.01$) were significantly decreased in the olanzapine group. Subgroup analysis (table 3) showed that there was no statistical difference between 5 mg and 10 mg olanzapine for delayed CINV.

AEs of olanzapine used for prevention and treatment of CINV

There were seven AEs (dizziness, constipation, somnolence, anorexia, fatigue, insomnia, thirst) included in

this systematic review for quantitative analysis. Anorexia and thirst were found to be heterogeneous. Therefore, a random model was used. For the rest of the AEs no significant heterogeneity was detected, and a fixed model was therefore used in this review. As shown in table 4, except for insomnia, the RR is 0.12 (95% CI 0.06 to 0.26; $p < 0.01$). Taking all AEs together, no statistically significant difference was found between the two groups. The results of subgroup analysis were as follows:

Table 2 Results of the meta-analysis of the relative risk of the level of acute and delayed chemotherapy-induced nausea and vomiting (CINV)

CINV	No. of studies	No. of patients	Mode	RR and 95% CI	Heterogeneity		P value for RR
					P value	I ² (%)	
Acute CINV	10	502/488	Fixed	0.60 (0.48 to 0.75)	0.90	0.0	<0.01
Acute CINV I	6	254/253	Fixed	1.19 (0.76 to 1.87)	0.43	0.0	0.44
Acute CINV II	6	254/253	Fixed	0.66 (0.38 to 1.17)	0.99	0.0	0.16
Acute CINV III	6	254/253	Fixed	0.26 (0.13 to 0.54)	0.64	0.00	<0.01
Acute CINV IV	3	151/150	Fixed	0.17 (0.04 to 0.73)	0.63	0.0	0.02
Delayed CINV	11	561/546	Random	0.50 (0.38 to 0.66)	<0.01	62.8	<0.01
Delayed CINV I	6	254/253	Random	0.79 (0.43 to 1.45)	0.09	47.8	0.44
Delayed CINV II	6	254/253	Fixed	0.61 (0.35 to 1.05)	0.88	0.0	0.07
Delayed CINV III	6	254/253	Fixed	0.27 (0.14 to 0.52)	0.99	0.0	<0.01
Delayed CINV IV	5	211/210	Fixed	0.16 (0.04 to 0.60)	0.91	0.0	<0.01

Table 3 Results of subgroup analysis about dose of olanzapine

Olanzapine dose	No. of studies	No. of patients	Mode	RR and 95% CI	Heterogeneity		P value for two groups
					P value	I ² (%)	
Acute CINV							
10 mg	6	321/308	Fixed	0.65 (0.45 to 0.95)	0.95	0.0	0.53
5 mg	4	181/180	Fixed	0.56 (0.43 to 0.74)	0.45	0.0	
Delayed CINV							
10 mg	6	321/308	Random	0.37 (0.20 to 0.69)	0.00	78.3	0.13
5 mg	5	240/238	Fixed	0.58 (0.48 to 0.70)	0.47	0.0	

CINV, chemotherapy-induced nausea and vomiting.

Dizziness

Five studies reported the occurrence of dizziness. Since no significant heterogeneity ($I^2=0.0\%$, $p=0.97$) was conducted, a fixed model was used. As shown in [table 4](#), no significant difference was found between the two groups (RR 1.14, 95% CI 0.66 to 1.98; $p=0.65$). The subgroup analysis revealed that no statistically significant difference was observed between the 10 mg and 5 mg olanzapine doses ([table 3](#)).

Constipation

Seven studies reported on constipation and a fixed model was used ($I^2=0.0\%$, $p=0.25$). The rate of constipation was comparable (RR 1.13, 95% CI 0.87 to 1.46; $p=0.35$) between the two groups. No significant difference was detected by the subgroup analysis ([table 3](#)).

Anorexia

Two studies reported data on anorexia and significant heterogeneity ($I^2=68.1\%$, $p=0.08$) was found. Therefore, a random model was used. The RR of anorexia was 1.73 (95% CI 0.13 to 23.60; $p=0.68$). A subgroup analysis was not conducted.

Somnolence

Four studies reported data on somnolence and a fixed model ($I^2=0.0\%$, $p=0.61$) was used. No significant difference was found between the two groups (RR 1.20, 95% CI 0.63 to 2.77; $p=0.58$). Furthermore, subgroup analysis did

not detect a significant difference between the 10 mg and 5 mg olanzapine doses ([table 3](#)).

Fatigue

Four studies reported the occurrence of fatigue. Since no significant heterogeneity ($I^2=42.2\%$, $p=0.85$) was seen, a fixed model was used. As shown in [table 4](#), no significant difference was found between the groups (RR 0.94, 95% CI 0.61 to 1.43; $p=0.76$). All studies used 5 mg olanzapine per day and hence subgroup analysis was not conducted.

Insomnia

Two studies were included in this review and a fixed model was used ($I^2=0.0\%$, $p=0.45$). As shown in [table 4](#), the percentage of insomnia was significantly lower in the olanzapine group (RR 0.12, 95% CI 0.06 to 0.26; $p<0.01$). Because only two studies were involved, subgroup analysis was not conducted.

Thirst

Two studies were included and a random model was used ($I^2=50.5\%$, $p=0.16$). No significant difference was found (RR 1.24, 95% CI 0.65 to 2.12; $p=0.60$). Because only two studies were involved, subgroup analysis was not conducted.

Efficacy of olanzapine for prevention and treatment of acute CINV

As shown in [figure 2](#), 10 RCTs (990 cancer patients) provided data on acute CINV. Since no statistically

Table 4 Result of the meta-analysis of the relative risk of adverse events

Adverse events	No. of studies	No. of patients	Mode	RR and 95% CI	P value for RR	Heterogeneity	
						P value	I ² (%)
Dizziness	5	208/207	Fixed	1.14 (0.66 to 1.98)	0.65	0.97	0.0
Constipation	7	317/315	Fixed	1.13 (0.87 to 1.46)	0.35	0.55	0.0
Anorexia	2	101/100	Random	1.73 (0.13 to 23.60)	0.68	0.08	68.1
Somnolence	4	206/205	Fixed	1.20(0.63 to 2.27)	0.58	0.61	0.0
Fatigue	4	210/208	Fixed	0.94 (0.61 to 1.43)	0.76	0.85	42.2
Insomnia	2	90/90	Fixed	0.12 (0.06 to 0.26)	<0.01	0.45	0.0
Thirst	2	119/118	Random	1.24 (0.65 to 2.12)	0.60	0.16	50.5

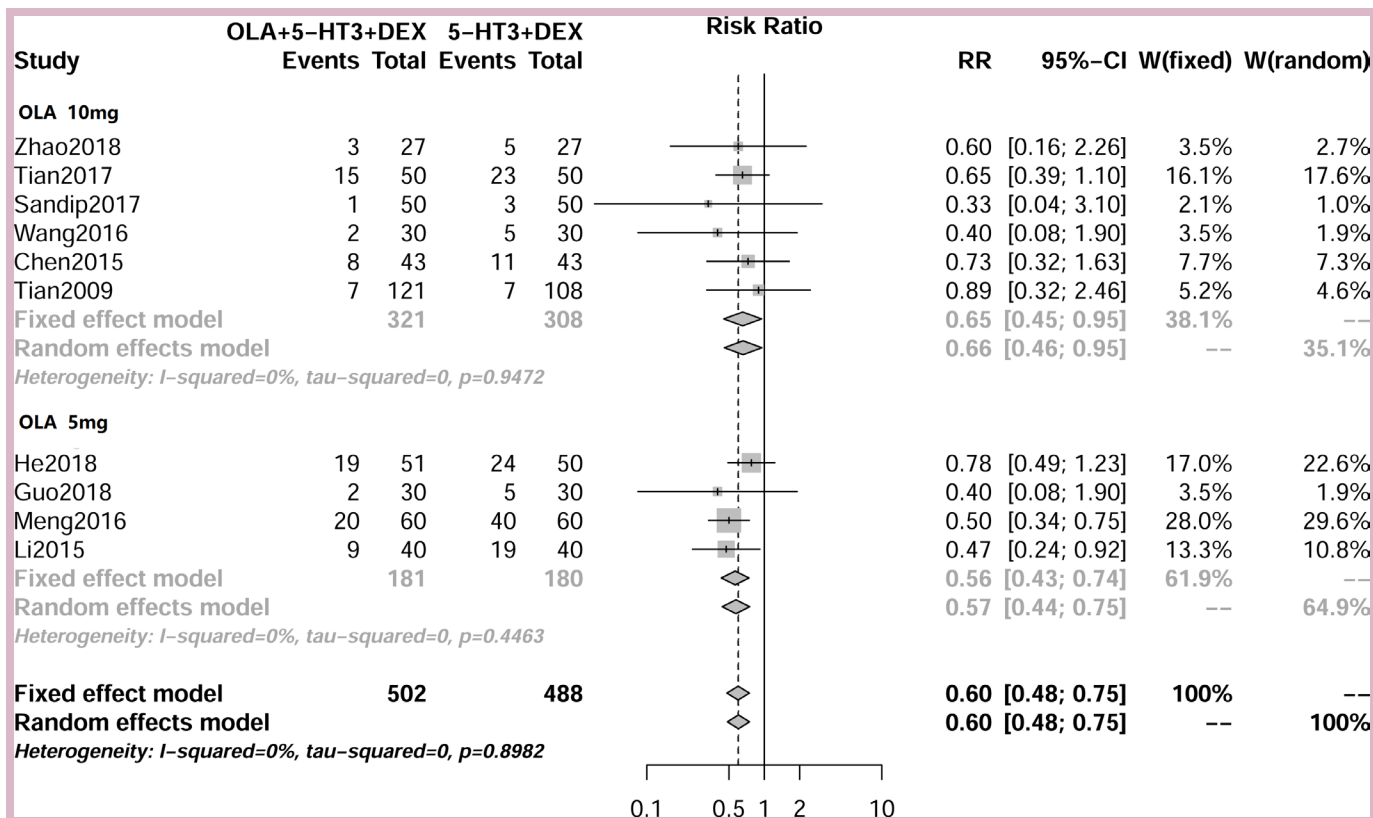


Figure 2 Result of the meta-analysis of the relative risk of acute chemotherapy-induced nausea and vomiting. DEX, dexamethasone; 5-HT3 RA, 5-hydroxytryptamine type 3 receptor antagonist; OLA, olanzapine.

significant difference was found, a fixed model was used. The overall pooled RR of acute CINV was 0.60 (95% CI 0.48 to 0.75; $p < 0.01$). Six articles (table 2) reported the level of acute CINV, while only CINV III (RR 0.26, 95% CI 0.13 to 0.54; $p < 0.01$) and CINV IV (RR 0.17, 95% CI 0.04 to 0.73; $p = 0.02$) revealed a statistically significant difference. Subgroup analysis (table 3) showed that there was no statistically significant difference between the 5 mg and 10 mg doses of olanzapine for acute CINV.

Publication bias

The publication bias of our meta-analysis was assessed using Begg, Egger regression and LFK index. Evidence of publication bias was found from the use of these statistical tests (Begg's test, $p = 0.02$, Egger's test, $p < 0.01$, LFK = -4.90).

DISCUSSION

Eleven studies with 1107 cancer patients were involved in this review. The key finding is that olanzapine combined with 5-HT3 RA plus dexamethasone is more effective and induces less insomnia compared with 5-HT3 RA plus dexamethasone for the prevention and treatment of CINV in high and moderately emetogenic chemotherapy. It has to be noted that, compared with 10 mg per day, 5 mg oral olanzapine may be more appropriate for cancer patients.

CINV III and CINV IV greatly reduce the quality of life of patients, and medical treatment is needed. Six studies included in our review reported the level of CINV, and

the rates of CINV III and CINV IV were significantly less in the olanzapine groups. Olanzapine was still found to be effective when aprepitant failed to control CINV in patients receiving highly emetogenic chemotherapy.³² One can conclude that olanzapine is an excellent alternative for the prophylaxis of CINV. The percentage of acute and delayed CINV in the olanzapine group was lower compared with the study of Rudolph *et al*⁵ (acute CINV: 17.1% vs 26.2%; delayed CINV: 26.2% vs 57.6%). Possible reasons may be: (1) our review involved high and moderately emetogenic chemotherapy, and Rudolph *et al* only included high emetogenic chemotherapy; (2) compared with Rudolph *et al*, the time periods of 5-HT3 RA and dexamethasone application were longer (4–5 days vs 1 day). This calls for more studies in the future.

Two different olanzapine dosages were used in this review, and subgroup analysis shows that both doses (10 mg and 5 mg olanzapine) provided comparably significant improvement in acute and delayed CINV. The phase 2 trial by Yanai *et al*¹⁴ found that 5 mg of olanzapine had a higher complete control in delayed CINV compared with 10 mg (83.1% vs 77.6%). Because olanzapine may lead to central nervous system depression, especially in elderly and debilitated patients,³³ 5 mg per day of olanzapine should be more suitable for cancer patients.

Polled analysis was conducted with seven AEs (dizziness, constipation, somnolence, anorexia, fatigue, insomnia, thirst) in this systematic review, and the incidence of

insomnia (RR 0.12, 95% CI 0.06 to 0.26; $p < 0.01$) was found to be significantly lower in the olanzapine groups. Insomnia is the most common AE of dexamethasone³⁴ and olanzapine is an atypical antipsychotic agent that may cause drowsiness.³⁵ The patients with cancer had lower insomnia when olanzapine was combined with NK-1 RA and dexamethasone. At the same time, olanzapine did not increase the incidence of somnolence, while no studies reported the severity and duration of AEs. Our current RCT about olanzapine combined with tropisetron and dexamethasone for the prevention and treatment of nausea and vomiting induced by chemotherapy of patients with lung cancer (NCT03571126) concentrates on the level of AEs, and the aforementioned concern may be resolved. Subgroup analysis showed that there is no significant difference between 5 mg and 10 mg doses of olanzapine in regard to dizziness, constipation and somnolence. Therefore, 5 mg may be more appropriate. A previous phase 3 trial⁵ found that there were no serious adverse events related to olanzapine, and no patient discontinued olanzapine because of toxic effects. Therefore olanzapine can be regarded as being safe to use in the control of CINV.

For the first time, we analysed the level of CINV that is most important for patients and doctors. The result showed that CINV III and CINV IV were significantly decreased when olanzapine was used. This review is less biased compared with previous studies^{9 10 15 36} because the intervention measure is more consistent in all involved articles. Furthermore, we analysed the efficacy and AEs of olanzapine combined with 5-HT₃ RA plus dexamethasone compared with 5-HT₃ RA plus dexamethasone. Finally, our review involves the largest sample numbers (1107 cancer patients) based on RCTs; therefore a higher level of evidence may be expected. Nevertheless, our review also has limitations. Not all included studies reported the whole range of AEs and the grade of AEs was not reported. The above mentioned ongoing RCT conducted by our team will report relevant data about that in the future. Also, different types and dosages of 5-HT₃ RA were used in this review, and the efficacy and AEs were not all comparable between the different types of 5-HT₃ RA³⁷; therefore potential bias may exist. Finally, the period of use of the antiemetic drugs and the use of dexamethasone were not all consistent, which could affect the results to some degree.

In conclusion, olanzapine significantly decreases the occurrence of CINV III and CINV IV and insomnia in high and moderately emetogenic chemotherapy. Compared with 10 mg per day, 5 mg olanzapine orally may be more appropriate for cancer patients. Nevertheless, there is still uncertainty about the severity and duration of AEs.

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Contributors LH and J-GZ contributed equally to this work as first authors. LH and CX conducted the "search strategy", J-GZ and LH screened the studies, S-HJ and CX extracted the data, J-GZ and CX assessed the methodologic quality, and any inconsistencies were resolved by consulting with HM.

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