Pharmacology and Clinical Pharmacy Research
Volume 7 No. 2 August 2022
ISSN:2527-7322 | e-ISSN: 2614-0020
doi: 10.15.416/pcpr.v4i3.37936

The Efficacy and Safety of Adding Olanzapine to Triple Drugs Regimen to Prevent Chemotherapy-induced Nausea and Vomiting: A systematic Review and Meta-analysis of RCTs

Sharanabasayyaswamy B. Hiremath[1*] and Srinivas L. Devendrappa[2]

[1]Department of Pharmacology, Kodagu Institute of Medical Sciences, Madikeri, Karnataka - India
[2]Department of Pharmacology, JJM Medical College, Davangere, Karnataka - India

Abstract

Chemotherapy-induced nausea and vomiting (CINV) is a complication of highly emetogenic chemotherapy (HEC) agents. The present meta-analysis was conducted to quantify and analyze the efficacy and safety of adding olanzapine to a Neurokinin Receptor Antagonist (NKRA) based triple-drug regimen in preventing HEC-induced CINV. Electronic database searches in PUBMED and Cochrane library was conducted using MeSH search terms "olanzapine" and "chemotherapy-induced nausea and vomiting." Randomized or cross-over trials comparing the efficacy of "olanzapine + NKRA based triple-drug regimen" vs. "placebo + NKRA based triple-drug regimen" in patients of age > 18 years with any malignancy receiving HEC were considered under inclusion criteria. Complete Response (CR) for the delayed (25–120 h) phase of CINV in patients receiving HEC agents was the primary outcome measure analyzed. Outcome measures were estimated by calculating the Risk Difference (RD) values and their 95% Confidence Intervals (CI). The Mantel-Haenszel method and both fixed and random effect models were used in the analysis by Revman 5.4.1 software. An additional 14% (RD: 0.14, 95% CI: 0.09 to 0.19) of patients treated with olanzapine + triple-drug regimen had a statistically significant higher CR in the delayed phase when compared to placebo + NKRA-based triple-drug regimen. Adding olanzapine at 10mg to the triple-drug regimen significantly improves delayed phase CR rates by 16% and delayed phase 'no significant nausea' rates by 30%. Results need to be interpreted cautiously in the background of variations in responses and limited trials included in our analysis.

Keywords: Olanzapine, chemotherapy-induced nausea vomiting, meta-analysis

Corresponding Author: Sharanabasayyaswamy Hiremath. Department of Pharmacology, Kodagu Institute of Medical Sciences, Madikeri, Karnataka - India. Email: dr.sharan83@yahoo.com
Received: 22 January 2022 **Revised**: 7 July 2022 **Published:** 31 August 2022

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a frequently encountered complication of highly emetogenic chemotherapy (HEC) agents.[1] It may lead to malnutrition, non-compliance with chemotherapy and low quality of life.[1] A standard triple-drug regimen consisting of dexamethasone (Dex), 5-HT3 receptor antagonists (5-HT3 RA), and Neurokinin-1 receptor antagonists (NKRA) is recommended by various international associations for the prevention or treatment of HEC-induced CINV.[1-4] However, the above triple-drug regimen's efficacy in preventing nausea, especially delayed phase nausea, is incomplete and subjected to individual variations.[4,5]

NKRA-based regimens were found to be most effective in preventing CINV, but their efficacy in preventing delayed nausea is comparatively low.[4] To overcome this disadvantage and as a cheaper alternative to NKRAs, olanzapine was tested and found to be equally efficacious in relieving vomiting and superior in relieving delayed phase nausea.[6-9] In addition, olanzapinewas also tested as an add-on to the NKRA based triple-drug regimen and was found to provide additional benefits in relieving nausea, especially delayed phase nausea.[10-15]

Though adding olanzapine to the triple-drug regimen provided additional benefit in relieving delayed phase nausea, it is inconsistent and has shown wide variation.[10-15] Understanding the reasons for the lack of consistency in the efficacy of olanzapine is the major motivation for conducting this meta-analysis and systematic review. The major challenge in the treatment of CINV is that, in the absence of treatment with any antiemetic agent, around 90% of patients receiving HEC present with CINV.[10] With the recommended NKRA based triple-drug regimen, this ratio reduces to around 50% for vomiting and 70% for nausea.[1,11]

There is no clarity on the overall quantity of additional benefits achieved by adding olanzapine to the NKRA-based triple- drug regimen. Further, it needs to be clarified whether adding olanzapine at 5 mg is equally efficacious and less sedative than at 10 mg in the triple-drug regimen. Hence, the present meta-analysis was conducted to quantify and analyze the efficacy and safety of adding olanzapine to the NKRA-based triple-drug regimen to prevent HEC-induced CINV. This systemic review would significantly enhance the understanding of the role of olanzapine as an add-on drug to the NKRA based triple-drug regimen.

Methods

Inclusion and Exclusion Criteria

Randomized or cross-over trials comparing the efficacy of "olanzapine + NKRA based triple-drug regimen" vs. "placebo +NKRA based triple-drug regimen" in patients of age > 18 years with any malignancy receiving HEC were considered under inclusion criteria.

Trials testing orally administered olanzapine at any dose, and reporting data required for efficacy analysis, were the other inclusion criteria adapted for including in the efficacy assessment. No restriction was applied based on the phase and sample size used in the trials. No restrictions on language or year of publication were imposed. Trials publishing incomplete data required for statistical analysis or those published as abstracts were considered for exclusion. We didn't plan to contact the corresponding authors to access missing or other required data.

Source of Information and Literature Search

Electronic database search in PUBMED and Cochrane library was conducted using MeSH search terms "olanzapine" and "chemotherapy-induced nausea and vomiting." The limits applied for the search in PUBMED were

ISSN:2527-7322 | e-ISSN: 2614-0020
doi: 10.15.416/pcpr.v4i3.37936

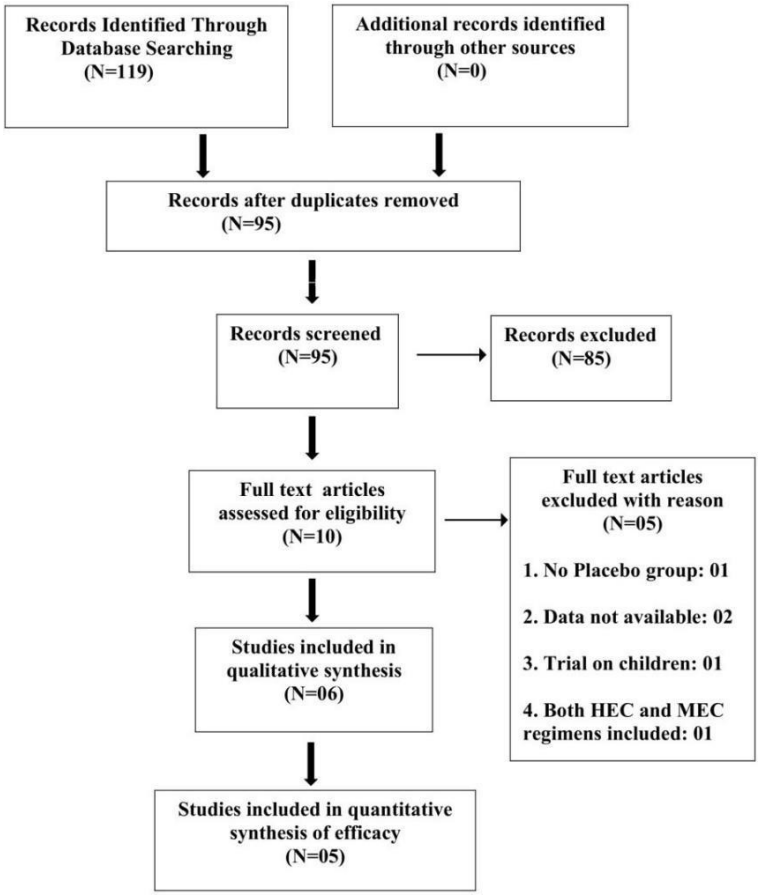

Figure 1. Literature Search Results and Study Attrition Diagram

"randomized controlled trial" and "humans," while the search was limited to "in trials" and "EMBASE" in the Cochrane library. We limited electronic database searches to articles published or available online until 2 5 t h January 2022, with no language restriction. An additional manual search of some of the reviews and relevant articles was also conducted to identify any missed trials by going through their references. Two authors were independently involved in conducting an electronic and manual database search.

Study Selection and Data Collection Process
Both authors independently went through the standard article selection and data collection process, capturing all the required data in a previously designed data extraction sheet. The screening process for eligible articles was conducted by going through the titles and abstracts of all articles retrieved from the literature search. Potential articles selected by this method were then screened in their complete text form for the availability of required data on population, intervention, comparator, and outcome (PICO) apart from trial design and other parameters to assess their eligibility for inclusion as per preset eligibility criteria.

Trials meeting all eligibility criteria were selected. Data on baseline demographic and clinical data, study characteristic data, intervention data, and data required for the estimation of outcome measures were collected by both authors individually. The number of patients achieving complete response (CR, defined as no vomiting and no rescue therapy),

Table 1. Baseline Demographic and Clinical Features (1)

	Clemons 2020		Yeo 2020		Hoshimato 2019	
	Olanzapine	Placebo	Olanzapine	Placebo	Olanzapine	Placebo
Sample size	113	105	60	60	355	351
Age (Yrs)	50 (23-74)	52 (23-88)	54.4 (36-71)	55.5 (32-71)	65 (22-75)	66 (30-75)
Weight (Kg)	78 (39-127)	77 (36-138)	57.3 (41.6-82.7)	58.9 (44.5-100.4)	NA	NA
M:F ratio (%)	0:100	0:100	0:100	0:100	67:33	67:33
Study design	R, DB, PC, MC, Ph2		R, UB, PC, SC, Ph2		R, DB, PC, MC, Ph3	
Country of origin	Canada		Hong Kong		Japan	
Cancer type:	Breast		Breast		Head & neck (8%) Lung (51%) Esophageal (22%) Gastric (5.5%) Gynecologic (10%) Other (4%)	
HEC drugs/ regimen:	DC FEC TCH		DC		Cisplatin regimens	
Antiemetic regimen:	A: 125mg PO,OD day1, 80mg OD days 2-3, O: 8mg PO, BID day 1, De: 12mg IV day 0 4mg PO,BID,days 2-3 Ol:5mg PO,OD,days1-4 Pl: PO,OD, days1-4		A: 125mg PO,OD day 0 80 mg OD days 2-3, O: 8 mg PO, OD day 0, 8mg, PO,OD, day 1, De: 12mg IV day 0 4mg PO,BID,days2-3 Ol:10mg PO,OD,days1-5		A: 125mg PO,OD,day1/ F: 150mg IV,OD,day1 A: 80 mg OD days 2-3 P: 8 mg PO, OD day 1, De: 12mg IV/PO, day 0 8mg PO/IV,days2-4/ 16mg PO/IV,days3-4 Ol:2.5mg PO, BD, days1-4	
Risk of Bias:						
1. RSG	LR		LR		LR	
2. AC	UR		HR		LR	
3. BPP	LR		HR		LR	
4. BOA	LR		HR		LR	
5. IOD	LR		LR		LR	
6. SR	LR		LR		LR	

M:F: Male:Female, R: randomized, DB: double blind, PC: placebo controlled, MC:multi center, SC: single center, Ph: Phase, D: doxorubicin, C: cyclophosphamide, F:5-fluorouracil, E:epirubicin, H:trastuzumab, T:docetaxel, A: Aprepitant, F: Fosaprepitant, O: Ondensetron, P: Palanosetron, De: Dexamethasone, Ol: Olanzapine, Pl: Placebo, RSG: Random Sequence Generation, AC: Allocation Concealment, BPP: Blinding of Participants and Personnel, BOA: Blinding of Outcome Assessment, IOD: Incomplete Outcome Data, SR: Selective Reporting, UR: Unclear Risk, HR: High Risk, LR: Low Risk, N/A: Not Available.
Values in median and range

Table 1. Baseline Demographic and Clinical Features (2)

	Navari 2016		Clemons 2018	
	Olanzapine	Placebo	Olanzapine	Placebo
Sample size	192	188	51	50
Age (Yrs)	58 (29-86)	56 (28-89)	54 (22-72)	56 (22-74)
M: F ratio	27.6:72.4	27.7:72.3	57:43	62:38
Race:				
White	89.6	91	53	58
Black	4.7	4.8	41	38
Other	5.8	4.2	04	00
Study design:	R,DB,PC,MC,Ph3		R,DB,PC,MC,Ph3	
Country of origin:	USA		USA	
Cancer type:	Breast, Lung, and other		Hematological malignancies	
HEC regimen:	Cisplatin regimens DCy regimens		7+3/ICE regimen and ± Total body irradiation (TBI)	
Antiemetic regimen:	1) 5-HT3 antagonist day1: O: 8mg, PO/IV or P: 0.25mg,IV or G: 1mg,IV/2mg,PO 2) De:12mg,PO,day1 8mg,PO,days2-4 3) NKRA: F: 150mg,day1 A: 125mg,PO, day1 80mg.PO, days2-3 Ol:10mg,PO,day1-4 Pl: PO,day1-4		O:8-16mg,PO/IV,days1-4 D:8-20mg, PO days1-4 F:150mg,IV,day1 For patients receiving (TBI) O:8mg,PO,day0 De:4mg,PO,day0 Ol:10mg, PO,day1-4 Pl:PO, day1-4	
Risk of Bias:				
1. RSG	LR		LR	
2. AC	UR		UR	
3. BPP	LR		UR	
4. BOA	LR		UR	
5. IOD	LR		LR	
6. SR	LR		LR	

M:F: Male:Female, R: randomized, DB: double blind, PC: placebo controlled, MC:multi center, SC: single center, Ph: Phase, D: doxorubicin, C: cyclophosphamide, F:5-fluorouracil, E:epirubicin, H:trastuzumab, T:docetaxel, A: Aprepitant, F: Fosaprepitant, O: Ondensetron, P: Palanosetron, De: Dexamethasone, Ol: Olanzapine, Pl: Placebo, RSG: Random Sequence Generation, AC: Allocation Concealment, BPP: Blinding of Participants and Personnel, BOA: Blinding of Outcome Assessment, IOD: Incomplete Outcome Data, SR: Selective Reporting, UR: Unclear Risk, HR: High Risk, LR: Low Risk, N/A: Not Available. Values in median and range

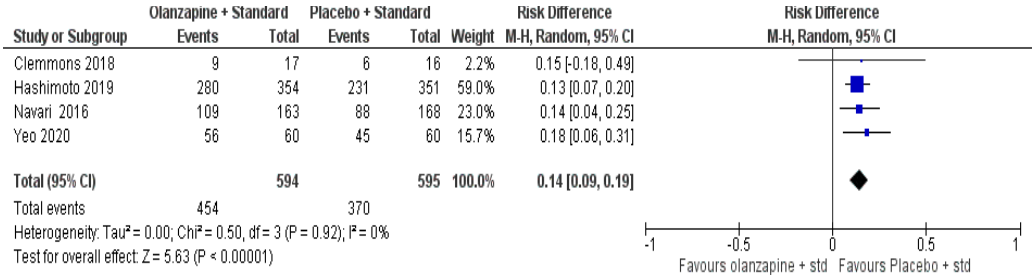

Figure 2. Forest Plot showing Risk Difference in Delayed Phase CR

no significant nausea (defined as 25mm on 100 mm visual analog scale (VAS)/another equivalent scale), and no nausea (defined as 0mm on 100 mm visual analog scale (VAS)/ another equivalent scale) in the acute (0-24h), delayed (25-120h), and overall (0-120h) phases of chemotherapy were the data extracted to compare efficacy. In addition, each group's various adverse drug reactions (ADRs) were extracted for safety evaluation. The authors did not seek the data from unpublished trials. Differences in opinions between the authors on the trial selection and data extraction were resolved after achieving consensus, and the final data extraction sheet was prepared.

Risk of Bias Assessment

Assessment of the risk of bias within the individual trials was independently done by two authors using the Cochrane Collaboration tool.[16] Discrepancies in allocating the level of bias in individual trials were resolved after the authors reached an agreement. Publication bias was analyzed by the funnel plot method.

Summary Measurement

CR for the delayed (25-120h) phase of CINV in patients receiving HEC agents was the primary outcome measure analyzed, while CR for acute (0-24h) and overall (0-120h) phases, the number of patients with "no significant nausea" and "no nausea" in all three phases of CINV in patients receiving HEC agents, and incidences of various ADRs were the secondary outcome measures analyzed.

Subgroup Analysis

Subgroup analysis of two different doses of olanzapine (5mg and 10mg) was planned. Subgroup analysis excluding trials with significant variation in baseline demographic or clinical features was scheduled as a part of sensitivity analysis. Qualitative analysis by including trials adopting both HEC and Moderately Emetogenic Chemotherapy (MEC) regimens was also designed under subgroup analysis.

Synthesis of Results and Statistical Analysis

All the outcome measures were estimated by calculating the Risk Difference (RD) values and their 95% Confidence Intervals (CI). The Mantel-Haenszel method and both fixed and random effect models were used in the analysis by Revman 5.4.1 software. The sensitivity of the results was analyzed by assessing the results of the subgroup analyses and also by comparing the results of the fixed effect model and the random effect model. Heterogeneity between the studies was analyzed by using the Cochrane Q test for heterogeneity and the I^2 test. A chi-square test with a P value of 0.10 and an I^2 test value of > 50% was considered an indicator of significant heterogeneity.

Results and Discussion

Figure 1 shows the data search results and the attrition diagram with the number of articles excluded and reasons for exclusion. Many of the articles were published as abstracts, and only five trials were eligible and included in

Table 2. Results of Sub-group Analysis

Outcome measure & Subgroup	Complete response (Standard treatment)	No significant nausea (Standard treatment)
HEC, All studies:		
Acute:	0.14[0.03, 0.26], N=4, n=1221[h]	0.10[0.04, 0.16], N=4, n=1587
Delayed:	0.14[0.09, 0.19], N=4, n=1189	0.18[0.10, 0.25], N=4, n=1587[h]
Overall:	0.18[0.13, 0.23], N=4, n=1190	0.17[0.13, 0.22], N=4, n=1587
HEC, 10mg studies:		
Acute:	0.20[0.13, 0.28], N=3, n=516	0.19[0.08, 0.30], N=2, n=153
Delayed:	0.16[0.08, 0.24], N=3, n=484	0.30[0.18, 0.42], N=2, n=153
Overall:	0.24[0.15, 0.32], N=3, n=485	0.27[0.14, 0.40], N=2, n=153
HEC, 5mg studies:		
Acute:	0.06[0.02, 0.10], N=1, n=705	0.08[0.03, 0.13], N=2, n=1434[h]
Delayed:	0.13[0.07, 0.20], N=1, n=705	0.14[0.09, 0.18], N=2, n=1434
Overall:	0.14[0.08, 0.21], N=1, n=705	0.16[0.11, 0.20], N=2, n=1434
HEC& MEC studies:		
Acute:	0.14[0.05, 0.23], N=5, n=1333[h]	1.17[1.06, 1.29], N=5, n=1699[h]
Delayed:	0.17[0.11, 0.22], N=5, n=1301	0.22[0.13, 0.31], N=5, n=1699[h]
Overall:	0.22[0.15, 0.28], N=5, n=1302	0.21[0.14, 0.29], N=5, n=1699[h]

HEC: Highly emetogenic chemotherapy; MEC: Moderately emetogenic chemotherapy. h: evidence of heterogeneity present; All values are Risk Difference and their 95% Confidence intervals.

the quantitative synthesis of meta-analysis.[10-14] One of these trials (Clemons et al., 2018) used both HEC and Moderately Emetogenic Chemotherapy (MEC) agents, and only the data of HEC regimens were included in the qualitative synthesis.[13]

A similar trial including both HEC and MEC regimens was excluded due to a lack of data on HEC regimen receiving patients.[15] However, these two trials were included in the subgroup qualitative synthesis of analyzing the efficacy of olanzapine + triple drugs regimen in patients receiving either HEC or MEC regimens. Data on CR rates were not available from one of the five eligible trials (Clemons et al., 2020); while data on common ADRs of olanzapine were available only from three of the five trials (Clemons et al., 2020, Yeo et al., 2020 and Hoshimato et al. 2019).[10-12]

Characters of Included Studies

Table 1 shows the baseline demographic and clinical characteristics of patients included in individual trials. One of the five trials b y Clemons et al., 2018 differed significantly in terms of malignancy type and anticancer drug regimen employed.[13]

Significant quantities of improvements in other secondary and subgroup outcome measure were also evident in olanzapine groups as shown in Table 2. Quantities of reduction in rates of 'no nausea' were significantly high in olanzapine groups in delayed phase (RD: 0.13, 95% CI: 0.06, 0.19) and overall phase (RD: 0.12, 95% CI: 0.07, 0.18) but not in acute phase (RD:0.17, 95% CI:-0.08, 0.41) . There was no sufficient data to compare 10 mg vs 5 mg olanzapine with regard to the outcome measure 'no nausea'.

Adding olanzapine appeared to be safe as there were no statistically significant increase in incidences of common ADRs like fatigue and insomnia of grade ≤1 (RD: 0.02, 95% CI: -0.07, 0.10 and RD: -0.01, 95% CI: -0.03, 0.02 respectively) as well as of grades ≥2 (RD:-0.03, 95% CI: -0.08, 0.03 and RD: -0.02, 95% CI: -0.07, 0.03 respectively). However, there was significant increase in incidence of grade ≤1 sedation/somnolence (RD: 0.0, 95% CI: -0.04, 0.14) but not of grade ≥2 (RD: 0.03, 95% CI: -0.02, 0.08) in groups receiving olanzapine. We didn't get sufficient data from all trials to analyze incidences of other ADRs. The observed increase in the incidence of grade ≤1 sedation/somnolence was evident in trials testing 5mg olanzapine and we expect it to significant with 10mg olanzapine also.

As shown in Table 2, Adding olanzapine at 10mg achieved 20% higher rates of 'no significant nausea' compared to 5mg in the delayed phase. The rates of achieving higher CR and 'no significant nausea' were slightly higher when patients receiving MEC regimens were included in the analysis. The results of the study appeared robust since there was no major variation in effect measures analyzed by random and fixed effect models. There was no evidence of publication bias in any of the outcome measures analyzed. There was evidence of heterogeneity between the trials in a few of the outcome measures as shown in Table 2.

Results of our study support adding olanzapine to the NKRA based triple-drug regimen for providing additional benefits in terms of CR and delayed phase nausea relief. The quantity of increase in rates of delayed phase CR and "no significant nausea" by 16% and 30%, respectively, is encouraging. Though olanzapine at 5mg was equally efficacious as at 10mg concerning CR rates and less sedative in other trials, our study results support the use of 10 mg for providing additional relief from delayed phase nausea. However, since the number of trials testing 5 mg olanzapine trials is scarce, it needs to be interpreted cautiously.

There were no reports of the occurrence of sedation or somnolence in three of the five of our included trials testing 10mg of olanzapine.[11,13,14] It supports preferring 10mg olanzapine over 5 mg about concerns of sedation as a safety parameter. The lack of sufficient data on ADRs adds to the inconclusiveness of our analysis of the safety profile of olanzapine. Olanzapine-based triple-drug regimens are equally efficacious as NKRA-based triple-drug regimens in reduced CR rate and are superior to delayed phase nausea. [17–20] With a triple-drug regimen, the incidence of delayed nausea would be reduced to around 70% from 90%.[1,10,11]

An additional reduction in rates of delayed nausea by about 30% after adding 10mg of olanzapine as a fourth drug would further reduce their incidence to around 40%. However, as shown in Table 3, these quantitative benefits are inconsistent across all trials comparing the olanzapine + NKRA-based triple-drug regimen.[10-15] There are also variations in the quantity of benefits between NKRA and olanzapine-based triple-drug regimen groups.[17–20]

Some trials comparing olanzapine vs. NKRA-based triple-drug regimens have achieved identical or higher rates than olanzapine + NKRA-based triple-drug regimens.[10–15,17–20] There are wide variations in the reduction rates in both CR and delayed phase nausea. Decoding the reasons for these variations in efficacy is difficult due to multiple genetic and non-genetic factors.[5] Nonetheless, publication bias and other biases must be ruled out for these variations. In this background, it is difficult to accurately quantify the benefits of

adding olanzapine to the triple-drug regimen.

Our out-of objective meta-analysis result of three trials comparing olanzapine vs. NKRA-based triple-drug regimen head-to-head, show no significant difference between the comparison groups.This was evident in the outcome measuresof CR and 'no nausea' in all three phases of CINV. However, this contradicts the evidence that NKRAs' efficacy in preventing delayed phase nausea, even in patients receiving MEC, is insignificant; while olanzapine is better than NKRAs in providing relief from delayed phase nausea.[8,21]

Compared to previously conducted meta-analysis studies, there are variations in the estimated benefits of our study, which included more trials than they did. A network meta-analysis estimates significant improvements in delayed phase 'no nausea' rates in olanzapine based triple-drug regimens compared to NKRA based triple-drug regimens (Odds ratio OR: 3.07, 95% CI; 2.09, 4.52).[8]

Direct pairwise meta-analysis results of our study estimate a lesser quantity of reduction between these pairs concerning delayed phase 'no nausea' (OR: 1.73, 95% CI: 1.22, 2.44) and 'no significant nausea' (OR: 2.29, 95% CI: 1.14, 3.64). Similar is the scenario of variation and inconsistency in the rates of CR achieved. A network meta-analysis including two trials and patients receiving either an HEC or MEC regimen estimates insignificant benefits in overall phase CR rates (odds ratio: 4.53, 95% CI: 0.69, 29.68).[9] But our study estimates significant improvements in general phase CR rates in patients receiving either HEC or MEC regimens (OR: 2.43, 95% CI: 1.88, 3.15).

These variations could be due to our efforts to avoid heterogeneity by adopting stringent inclusion criteria, especially the inclusion of only those patients receiving HEC regimens. This opinion of ours is supported by a meta-analysis analyzing the efficacy of olanzapine in various settings and subgroups.[7] Considering the differences in efficacy and results of subgroupanalysis, results of only those trials testing 10mg olanzapine in patients receiving only HEC perhaps should be considered as actual effects of olanzapine.

Conclusion

Adding olanzapine to the NKRA based triple-drug regimen significantly improves rates of delayed phase CR and "no significant nausea." Olanzapine at 10mg is better than 5mg in enhancing rates of delayed phase 'no significant nausea.' Sedation is expected to become more common as olanzapine is added to the NKRA based triple-drug regimen. Results need to be interpreted cautiously in the background of variations in responses and limited trials included in our analysis. The major strength of our study is the inclusion of patients receiving only HEC regimens. Major limitations are the lack of sufficient data for analyzing the efficacy of 5mg olanzapine and safety outcome measures.

Acknowledgments

None

Funding

None

Conflict of Interest

None

References

1. Zhou JG, Huang L, Jin SH, Xu C, Frey B, Ma H, et al. Olanzapine combined with 5-hydroxytryptamine type 3 receptor antagonist (5-HT3 RA) plus dexamethasone for prevention and treatment of chemotherapy-induced

nausea and vomiting in high and moderate emetogenic chemotherapy: a systematic review and meta-analysis of randomised controlled trials. *ESMO Open.* 2020;5:e000621.
2. Herrstedt J, Roila F, Warr D, Celio L, Navari RM, Hesketh PJ, et al. 2016 Updated MASCC/ESMO consensus recommendations: preventing nausea and vomiting following high emetic risk chemotherapy. Supportive Care in Cancer. 2017;25:277-288.
3. Hesketh PJ, Kris MG, Basch E, Bohlke K, Barbour SY, Clark-Snow RA, Danso MA, Dennis K, Dupuis LL, Dusetzina SB, Eng C. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *Journal of Clinical Oncology*. 2017;35:3240-3261.
4. Shi Q, Li W, Li H, Le Q, Liu S, Zong S, et al. Prevention of cisplatin-based chemotherapy-induced delayed nausea and vomiting using triple antiemetic regimens: a mixed treatment comparison. *Oncotarget*. 2016;7:24402-24414.
5. Jin Y, Jin G, Zhao J, Jiang C, Zhao L, Jiang Y, et al. Clinical Observation of Gene Polymorphism of Olanzapine or Aprepitant in Prevention of CINV. *Pharmagenomics Personalized Medicine*. 2021;14:867-875.
6. Hiu L, Chow R, DeAngelis C, Lock M, Simone CB 2nd. Secondary and cumulative meta-analysis of olanzapine for antiemetic prophylaxis for chemotherapy-induced nausea and vomiting: do we still need to study its effectiveness?. *Annals of Palliative Medicine*. 2021;10:2540-2547.
7. Chow R, Herrstedt J, Aapro M, Chiu L, Lam H, Prsic E, et al. 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. *Supportive Care in Cancer.* 2021;29:3439-3459.
8. Zhang Z, Zhang Y, Chen G, Hong S, Yang Y, Fang W, et al. Olanzapine-based triple regimens versus neurokinin-1 receptor antagonist-based triple regimens in preventing chemotherapy-induced nausea and vomiting associated with highly emetogenic chemotherapy: A network meta-analysis. *The oncologist.* 2018;23:603-616.
9. Yokoe T, Hayashida T, Nagayama A, Nakashoji A, Maeda H, Seki T, et al. Effectiveness of antiemetic regimens for highly emetogenic chemotherapy-induced nausea and vomiting: a systematic review and network meta-analysis. *The oncologist.* 2019;24:e347-357.
10. Hashimoto H, Abe M, Tokuyama O, Mizutani H, Uchitomi Y, Yamaguchi T, et al. Olanzapine 5 mg plus standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting (J-FORCE): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology*. 2020;21:242-249.
11. Yeo W, Lau TK, Li L, Lai KT, Pang E, Cheung M, et al. A randomized study of olanzapine-containing versus standard antiemetic regimens for the prevention of chemotherapy-induced nausea and vomiting in Chinese breast cancer patients. *The Breast*. 2020;50:30-38.
12. Clemons M, Dranitsaris G, Sienkiewicz M, Sehdev S, Ng T, Robinson A, et al. A randomized trial of individualized versus standard of care antiemetic therapy for breast cancer patients at high risk for chemotherapy-induced nausea and vomiting. *The Breast.* 2020;54:278-285.
13. Clemmons AB, Orr J, Andrick B, Gandhi A, Sportes C, DeRemer D. Randomized, placebo-controlled, phase III trial of fosaprepitant, ondansetron, dexamethasone(FOND) versus FONDplus olanzapine (FOND-O) for the prevention

of chemotherapy-induced nausea and vomiting in patients with hematologic malignancies receiving highly emetogenic chemotherapy and hematopoietic cell transplantation regimens: the FOND-O trial. *Biology of Blood and Marrow Transplantation*. 2018;24:2065-2071.
14. Navari RM, Qin R, Ruddy KJ, Liu H, Powell SF, Bajaj M, et al. Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting. N Engl J Med. 2016;375:134-142.
15. Mizukami N, Yamauchi M, Koike K, Watanabe A, Ichihara K, Masumori N, et al. Olanzapine for the prevention of chemotherapy-induced nausea and vomiting in patients receiving highly or moderately emetogenic chemotherapy: a randomized, double-blind, placebo-controlled study. *Journal of pain and symptom management*. 2014;47:542-550.
16. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
17. Shumway N, Terrazzino S, Jones C. A randomized pilot study comparing olanzapine (Zyprexa) to aprepitant (Emend) for treatment of chemotherapy induced nausea and vomiting. *Journal of Pain Management*. 2015;8:233-241.
18. Navari RM, Gray SE, Kerr AC. Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. *The journal of supportive oncology*. 2011;9:188-195.
19. Pehalajani JK, Babu KG, Lokanatha D, Jacob LA, Babu MS, Lokesh KN, et al. A prospective phase III randomized study to evaluate the efficacy of olanzapine for prevention of nausea and vomiting in patients receiving highly emetogenic chemotherapy (HEC). *Annals of Oncology*. 2018;29:ix129.
20. Babu G, Saldanha SC, Kuntegowdanahalli Chinnagiriyappa L, Jacob LA, Mallekavu SB, Dasappa L, et al. The Efficacy, Safety, and Cost Benefit of Olanzapine versus Aprepitant in Highly Emetogenic Chemotherapy: A Pilot Study from South India. *Chemotherapy Research and Practice*. 2016;2016:3439707.
21. van der Vorst MJ, Neefjes EC, Konings IR, Verheul HM. Prophylactic treatment for delayed chemotherapy-induced nausea and vomiting after non-AC based moderately emetogenic chemotherapy: a systematic review of randomized controlled trials. *Support Care Cancer*. 2015;23:2499-2506.