Olanzapine 5mg vs 10mg for the Prophylaxis of Chemotherapy-Induced Nausea and Vomiting – A Network Meta-Analysis

Ronald Chow (ronald.chow@yale.edu)
Yale University https://orcid.org/0000-0001-6195-8624
Rudolph M Navari
World Health Organization
Bryan Terry
Yale University
Carlo DeAngelis
University of Toronto
Elizabeth Prsic
Yale University

Research Article

Keywords: olanzapine, prophylaxis, chemotherapy-induced nausea and vomiting

Posted Date: May 3rd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-318837/v1

Abstract

Introduction: Olanzapine administered at a 10mg dosage for prophylaxis of chemotherapy-induced nausea and vomiting may be associated with fatigue, drowsiness and reduced general activity. Therefore, a 5mg dose may be preferred, to reduce the occurrence of adverse events. The aim of this study was to conduct a network meta-analysis, and report on the efficacy of olanzapine administered at 5mg, relative to when administered at 10 mg.

Methods: We used previously-published data from the systematic review by Chow *et al* which identified 17 adult trials which used 10mg doses, 3 which used 5mg doses, and 1 which used a mix of 5 and 10mg doses. A multivariate network meta-analysis using a restricted maximum likelihood model was used.

Results: The complete response rate in the acute phase is not statistically different, between 5mg and 10mg doses of olanzapine – RR 0.97, 95% CI: 0.83 – 1.13. Additionally, in the overall phase, 5mg olanzapine is similarly as efficacious as 10mg olanzapine – RR 0.95, 95% CI: 0.56 – 1.60. Evaluation of data demonstrated that there was inadequate information to compare the toxicities of the two doses.

Conclusion: Our analyses support individual published trials, and the rationale for future trials to compare 5mg to 10mg olanzapine regimens in head-to-head comparisons.

Introduction

Chemotherapy-induced nausea and vomiting (CINV) can be a significant and distressing adverse event for patients undergoing cytotoxic cancer treatment[1]. It can negatively impact quality of life for patients, and also place patients at increased risk of treatment nonadherence[2]. Furthermore, poorly controlled CINV increases the risk of CINV during subsequent treatment cycles and also the risk of developing anticipatory nausea[3]. It is therefore prudent to provide effective antiemetics to patients undergoing emetogenic therapies.

At the time of this writing in early 2021, clinical guidelines published by the American Society of Clinical Oncology (ASCO)[4] and National Comprehensive Cancer Network (NCCN) [5] recommend a four-drug prophylactic regimen for patients receiving highly emetogenic chemotherapy (HEC), for which olanzapine is one of the drugs. However, olanzapine administered at a 10mg dosage may be associated with fatigue, drowsiness and reduced general activity[6]. Therefore, despite all the evidence supporting 10mg doses (guideline recommendations, documented superiority of olanzapine in the latest systematic review and meta-analysis[7], as well as cost-effectiveness[8]), clinicians may still hesitate to prescribe olanzapine at 10mg doses. A 5mg dose may be preferred, to reduce the likelihood of of adverse events.

There is currently a paucity of data reporting on olanzapine administered at the 5mg dose. Only 3 studies by Hasimoto *et al*[9], Mizukami *et al*[10] and Rumyantsev *et al*[11] have compared 5mg to placebo, while Ishimoto *et al*[12] compared 5-mg to 10-mg and to placebo. In contrast, 17 studies have reported on

olanzapine in the 10mg setting. As a result, there are no recommendations with respect to olanzapine when administered at 5mg.

Fundamentally, the clinical question remains whether 5mg dosing yields equivalent efficacy as 10mg dosing. Through a network meta-analysis, an indirect comparison between olanzapine at 5mg and 10mg would provide further precision in effect estimate than that provided alone, by Ishimoto *et al*. The aim of this study was to conduct a network meta-analysis, and report on the efficacy of olanzapine administered at 5mg, relative to when administered at 10mg.

Methods

Study Eligibility Criteria and Endpoints

We used previously-published data from the systematic review by Chow *et al*[7] which identified 17 adult trials which used 10mg doses, 3 which used 5mg doses, and 1 which used a mix of 5 and 10mg doses. Of those studies, 15 reported exclusively on HEC patients, 3 reported exclusively on patients receiving moderately emetogenic chemotherapy (MEC), and 3 on a study sample comprising of both HEC and MEC patients. Some trials had risk of bias, due to concerns around lack of blinding. More detailed description of study selection and demographics is reported therein[7].

The review reported on nine efficacy outcomes – complete response, no nausea, and no vomiting, each in the acute (0–24 hours post-chemotherapy), delayed (24–120 hours post-chemotherapy) and overall (0-120 hours post-chemotherapy) phases. Due to the paucity of endpoints in trials studying olanzapine at 5mg doses, the endpoints of interest in our network meta-analysis are (1) complete response in the acute phase, and (2) complete response in the overall phase.

Statistical Analyses

A multivariate network meta-analysis using a restricted maximum likelihood model was used, to compare olanzapine at 10mg, olanzapine at 5mg, and control, relative to each other. Risk ratios (RR) and accompanying 95% confidence intervals were calculated for each comparison. The threshold for statistical significance was set at $p < 0.05$.

To assess the primary underlying assumption used in network meta-analyses of consistency, we applied an inconsistency model[13]. A *p*-value of greater than 0.05 indicated no significant concern for inconsistency. All aforementioned analyses were conducted using Stata 16.1.

Results

Only one study directly compared the efficacy of olanzapine at 5mg relative to olanzapine at 10mg. Four studies compared 5mg olanzapine relative to control, and 18 compared 10mg olanzapine to control (Fig. 1). There was no significant concern for inconsistency and therefore model violation, for either endpoints.

Acute Phase

Ithimakin *et al* reported 5mg olanzapine regimens to yield similar complete response rates to 10mg olanzapine regimens – RR 1.00, 95% CI: 0.83–1.21. This network meta-analysis also reports that the complete response rate in the acute phase is not statistically different, between 5mg and 10mg doses of olanzapine – RR 0.97, 95% CI: 0.83–1.13 (Fig. 2).

Overall Phase

In the overall phase, Ithimakin *et al* also reported 5mg olanzapine to yield similar complete response rates relative to 10mg olanzapine – RR 0.86, 95% CI: 0.47–1.55. When estimated using network meta-analysis, 5mg olanzapine is similarly as efficacious as 10mg olanzapine – RR 0.95, 95% CI: 0.56–1.60 (Fig. 3).

Discussion

To our knowledge, this is the first network meta-analysis investigating olanzapine for the prophylaxis of chemotherapy-induced nausea and vomiting, and therefore the first to try to compare 5mg olanzapine to 10mg olanzapine regimens. Our findings suggest that 5mg olanzapine may be equally as efficacious as 10mg olanzapine in the prophylactic setting, and support the findings by Ithimakin *et al*[12].

While this network meta-analysis does give greater precision in the relative efficacy of 5mg olanzapine to 10mg olanzapine than the study of Ithimakin *et al* alone (a confidence interval width of 0.30 compared to 0.38 in the acute phase, and 1.04 relative to 1.08 for overall phase), it is important to note that there is still notable imprecision. In the 2021 meta-analysis by Chow *et al*[7], the confidence interval width for 10mg olanzapine relative to control is only 0.20 for acute phase and 0.39 in the overall phase. More studies reporting on 5mg olanzapine may help to increase the precision of this estimate.

With current statistical modeling intended to improve precision, 5mg olanzapine appears to be equally efficacious. In fact, in the overall phase, the network meta-analysis suggests that 5mg is more similar to 10mg than reported in Ithimakin *et al*, as noted by the RR point estimate closer to 1.0–0.95 in the network meta-analysis, compared to 0.86 as reported by Ithimakin *et al*. While we caution about using these results in clinical decision making, our results would support rationale for clinical trials studying 5mg olanzapine regimens in a head-to-head comparison with 10mg olanzapine regimens.

It is important to mention that this network meta-analysis did not compare the safety of 5mg to 10mg olanzapine. There seems to exist a greater paucity of safety data, relative to efficacy data; meta-analyzing any limited safety data at this time is uninformative in the best scenario, and misleading in the worst case scenario. Future head-to-head trials should not only report one efficacy, but also safety.

Under the premise that olanzapine administered at 5mg is equally as efficacious as 10mg, and that it is likely to yield fewer adverse events, 5mg could certainly be the preferred dosage. Its similar efficacy yet possibly better side effect profile would improve the benefit to risk ratio relative to non-olanzapine regimens, in terms of cost-effectiveness; the use of 5mg olanzapine regimens may be optimal[8]. This

optimistic outlook hopefully provides enthusiasm and motivation for future clinical trials on 5mg regimens. As per the international guidelines[4,5], olanzapine should be employed as the fourth agent in CINV prophylaxis for patient receiving highly emetogenic chemotherapy. If a 5mg dose has equal efficacy to a 10 mg dose with fewer side effects, it may be employed by more clinicians.

Olanzapine can also be used for palliation of other symptoms such as anxiety, insomnia, delirium, and cachexia[14]. The benefit of using a lower dose could lessen the potential for toxicity, such as extrapyramidal symptoms and serotonin syndrome, all while having the potential to improve a multitude of symptoms frequently seen in patients undergoing chemotherapy. In the setting of CINV, the antiemetic action of olanzapine, compounded with the weight gain side effect, can help cancer patients slow weight loss[15,16].

There are limitations to this study. Due to the nature of systematic review and meta-analysis methodology that underlies the analyzed data, the validity of these conclusions are only as valid as the included studies; any risk of biases at the individual study level is not overcome by meta-analysis design. As well, as previously mentioned, there is a paucity of data. While a network meta-analysis may afford greater precision, it is ultimately limited to the number of published head-to-head trials.

In conclusion, 5mg olanzapine prophylactic regimens may be as efficacious as 10mg olanzapine regimens. Our analyses support individual published trials, and supports rationale for future trials to compare 5mg to 10mg olanzapine regimens in head-to-head comparisons.

Declarations

Funding: N/A

Conflicts of Interest: None

Ethics Approval: N/A

Consent to Participate: N/A

Consent to Publication: N/A

Availability of Data and Material: N/A

Code Availability: N/A

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

References

1. Cohen L, de Moor CA, Eisenberg P, Ming EE, Hu H. Chemotherapy-induced nausea and vomiting: incidence and impact on patient quality of life at community oncology settings. *Support Care Cancer* 2007; **15**(5): 497-503.
2. Osoba D, Zee B, Warr D, Latreille J, Kaizer L, Pater J. Effect of postchemotherapy nausea and vomiting on health-related quality of life. The Quality of Life and Symptom Control Committees of the National Cancer Institute of Canada Clinical Trials Group. *Support Care Cancer* 1997; **5**(4): 307-13.
3. Ahrari S, Chow R, Goodall S, DeAngelis C. Anticipatory nausea: current landscape and future directions. *Ann Palliat Med* 2017; **6**(1): 1-2.
4. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol* 2017; **35**(28): 3240-61.
5. Berger MJ, Ettinger DS, Aston J, et al. NCCN Guidelines Insights: Antiemesis, Version 2.2017.
6. Chow R, Chiu L, Navari R, et al. Efficacy and safety of olanzapine for the prophylaxis of chemotherapy-induced nausea and vomiting (CINV) as reported in phase I and II studies: a systematic review. *Support Care Cancer* 2016; **24**(2): 1001-8.
7. Chow R, Herrstedt J, Aapro M, 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. *Support Care Cancer* 2021.
8. Chow R, Chiu L, Herrstedt J, et al. Cost-effectiveness analysis of olanzapine-containing antiemetic therapy for the prophylaxis of chemotherapy-induced nausea and vomiting (CINV) in highly emetogenic chemotherapy (HEC) patients. *Support Care Cancer* 2021.
9. Hashimoto H, Abe M, Tokuyama O, 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. *Lancet Oncol* 2020; **21**(2): 242-9.
10. Mizukami N, Yamauchi M, Koike K, 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. *J Pain Symptom Manage* 2014; **47**(3): 542-50.
11. Rumyantsev A, Glazkova E, Nasyrova R, et al. Olanzapine (OLN) versus aprepitant (APR) in patients receiving high-emetogenic chemotherapy: final results of randomized phase II trial. *J Clin Oncol* 2019; **37**: 11504.
12. Ithimakin S, Theeratrakul P, Laocharoenkiat A, et al. Randomized, double-blind, placebo-controlled study of aprepitant versus two dosages of olanzapine with ondansetron plus dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving high-emetogenic chemotherapy. *Support Care Cancer* 2020.
13. White IR, Barrett JK, Jackson D, Higgins JP. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Synth Methods* 2012; **3**(2): 111-25.
14. Maglione M, Maher AR, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Rockville: Agency for Healthcare Research and Quality; 2011.

15. Naing A, Dalal S, Abdelrahim M, et al. Olanzapine for cachexia in patients with advanced cancer: an exploratory study of effects on weight and metabolic cytokines. *Support Care Cancer* 2015; **23**(9): 2649-54.
16. Nasrallah H. A review of the effect of atypical antipsychotics on weight. *Psychoneuroendocrinology* 2003; **28 Suppl 1**: 83-96.

Figures

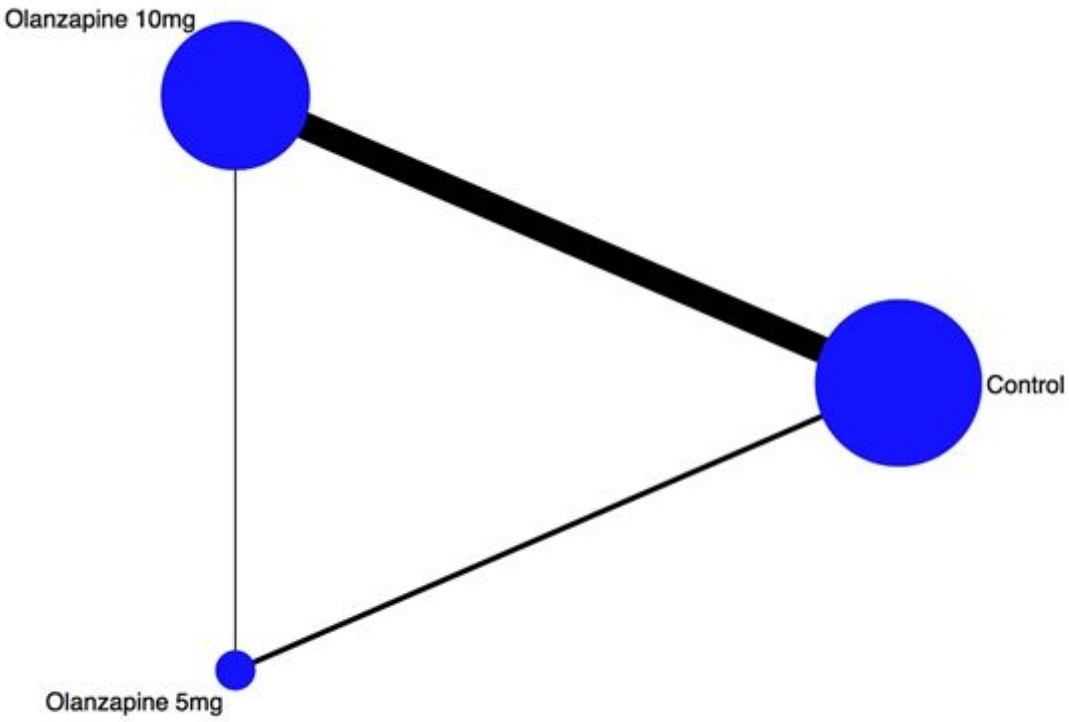

Figure 1

Network Diagram of Existing Randomized Controlled Trials

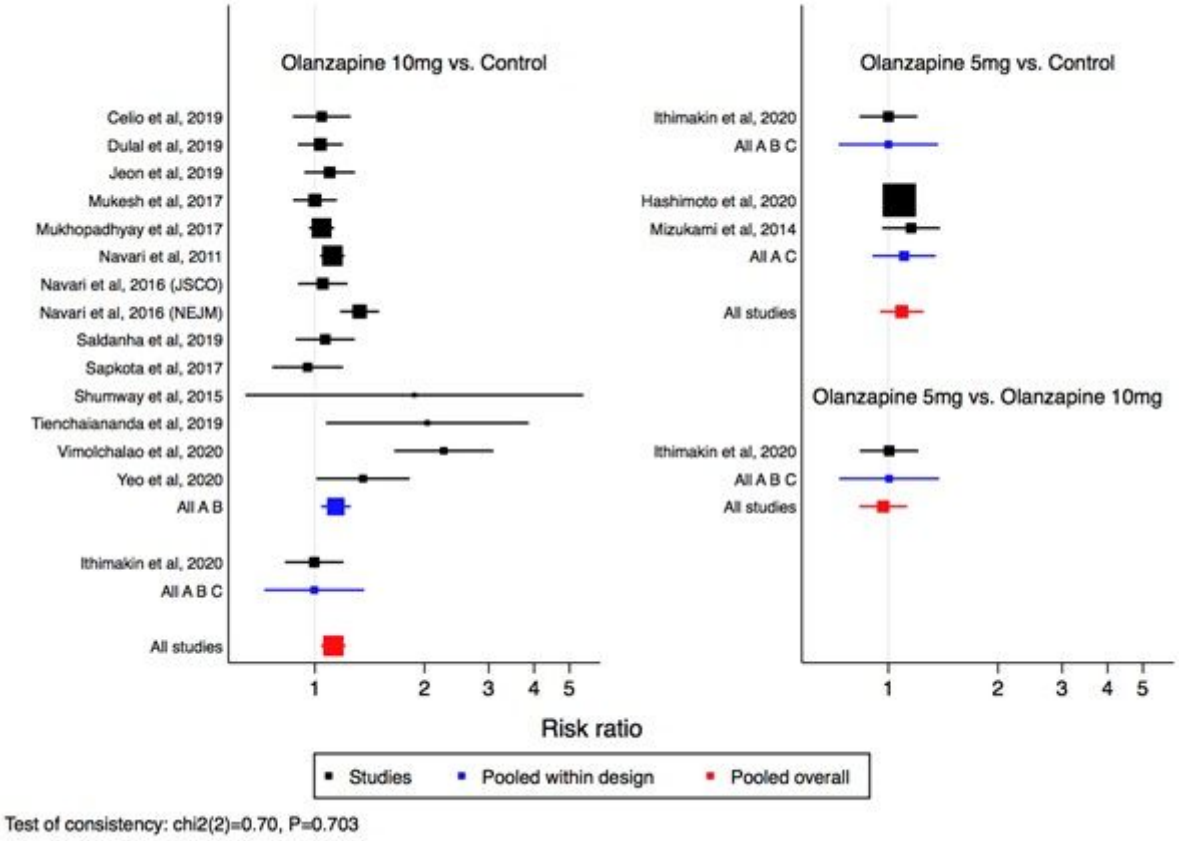

Figure 2

Network Meta-Analysis – Complete Response, Acute Phase

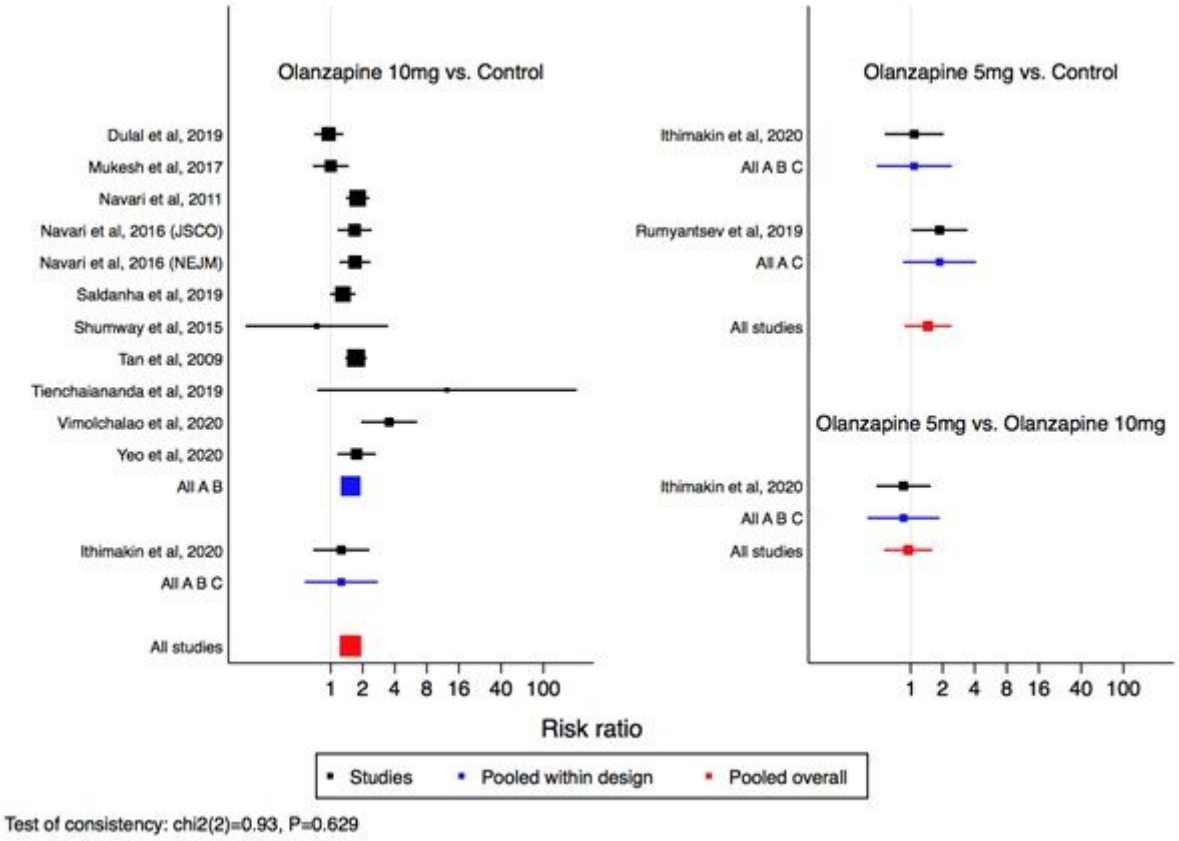

Figure 3

Network Meta-Analysis – Complete Response, Overall Phase