Supplementary

## Appendix 1 Study proposal

Olanzapine for antiemetic prophylaxis for chemotherapy induced nausea and vomiting—do we still need to study its effectiveness? A cumulative meta-analysis

### Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a common side-effect related to cancer treatment that has a detrimental effect on quality of life and may lead to dose reductions and/or noncompliance with treatment (27,28). Since the 1970s, many antiemetics have been designed to target pathways involved in CINV. In 2014, olanzapine, an atypical antipsychotic agent, was incorporated into the National Comprehensive Cancer Network (NCCN) antiemetic guidelines, as phase 2 studies of olanzapine, in combination with a 5-HT3-receptor antagonist and dexamethasone, found the agent to be effective at controlling both acute and delayed chemotherapy-induced emesis in patients who are being treated with highly or moderately emetogenic drugs (27).

Since then, olanzapine-containing antiemetic regimens have been compared extensively to other antiemetics regimens without olanzapine, with respect to efficacy and safety, including several systematic reviews and meta-analysis by our group and others (10,29-33). As with all systematic reviews, there exists the possibility of publication bias, which was not assessed in the prior systematic reviews. In addition, consistent with the volume of literature on this topic, multiple new RCTs have been conducted in more recent years, spurring more meta-analyses that may not change the overall conclusions on the efficacy of olanzapine in the CINV setting.

Given the significant resources required to conduct further RCTs, and the robust literature that now exists on olanzapine in the CINV setting, it is important to elucidate whether further studies are needed. The effect of the latest RCTs on the literature's summary statistics can be understood using a cumulative meta-analysis. This statistical technique computes the summary effect size each time a study is published, and subsequently compares the new to the previous effect size. Such comparisons facilitate an appreciation of scenarios in which the summary effect sizes shifts in point estimate and narrows in CI. When a CI is relatively narrow and little adjustments in effect size are noted with the inclusion of new studies, one may postulate that future studies will have little impact on the literature's summary statistic and, therefore, future studies are not needed.

The primary aim of this study is to conduct a cumulative meta-analysis on the efficacy of olanzapine on chemotherapy-induced nausea and emesis to determine whether further trials could lead to different conclusions in future meta-analyses. A secondary aim was to assess for publication biases.

### Methods

We will conduct a secondary data analysis of the previously-published systematic review and meta-analysis published in 2016 (10). That review has been cited by the 2017 American Society of Clinical Oncology's antiemetic guideline to support their new recommendation of olanzapine for the prophylaxis of CINV for patients receiving highly-emetogenic chemotherapy (11). The methodology for study eligibility and data extraction was previously described (10). Briefly, ten RCTs were included, and the meta-analysis reported olanzapine to be more efficacious than other standard antiemetics for both the prophylaxis and rescue of CINV, with respect to the endpoints of nausea control and emesis control.

A Mantel-Haenszel random-effects analysis model will be used to compute cumulative RR and accompanying 95% CIs. Funnel plots will be generated to qualitatively assess for publication bias. All analyses will be conducted using Comprehensive Meta-Analysis (Version 3) by Biostat.

### References

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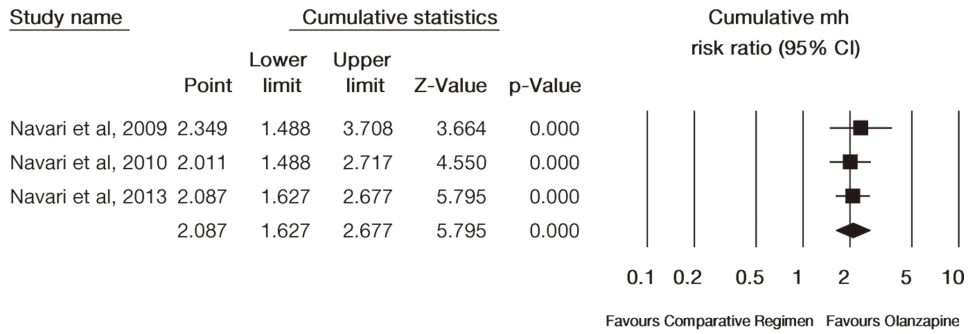


**Figure S1** Cumulative efficacy of olanzapine for the rescue of breakthrough chemotherapy-induced emesis.

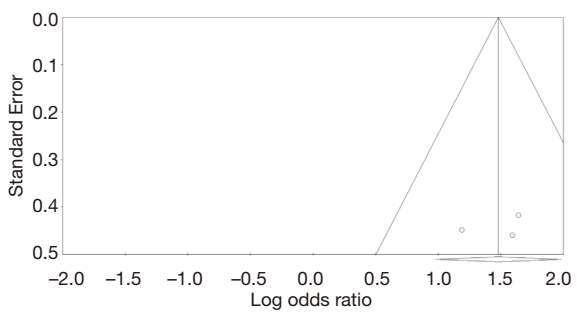


**Figure S2** Assessment of publication bias for studies reporting on the efficacy of olanzapine for the rescue of breakthrough chemotherapy-induced emesis.


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