



Do we still need to study palonosetron for chemotherapy-induced nausea and vomiting? A cumulative meta-analysis



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ARTICLE INFO

Keywords:

Chemotherapy-induced nausea and vomiting
Efficacy
Safety
Palonosetron
Antiemetic

ABSTRACT

Introduction: The aim is to conduct an updated systematic review comparing palonosetron to other 5-HT₃RA for the prophylaxis of CINV, assess for publication biases, and determine whether further RCTs are required, that could potentially lead to a different meta-conclusion.

Methods: Random-effects analysis model was used to generate odds ratio (OR), risk differences (RD) and accompanying 95% confidence intervals (CI). Funnel plots to assess for biases and cumulative meta-analyses to assess effect size over time were generated.

Results: 4145 patients were randomized to palonosetron and 4911 received other 5-HT₃RA. In the majority of efficacy endpoints, the meta-conclusion has not changed over time - recent clinical trials simply narrow CIs the meta-conclusion. Safety profile boasts a stable conclusion over time. No publication biases exist.

Conclusion: Considering the vast amount of resources needed to conduct RCTs, resources should be dedicated to other prophylactic treatments/settings which have not been as well explored.

1. Introduction

Many antiemetics have been designed to target pathways involved in chemotherapy-induced nausea and vomiting (CINV), a debilitating adverse event of chemotherapy that can decrease the quality of life of patients (Chiu et al., 2016; Chow et al., 2016). Disrupting the CINV pathway where serotonin released from enterochromaffin cells binds to 5-hydroxytryptamine type 3 (5-HT₃) receptors on vagal afferents is accomplished by using 5-HT₃ receptor antagonists (5-HT₃RA) such as ondansetron, granisetron and palonosetron (Navari and Aapro, 2016; Saito et al., 2009). Aprepitant, netupitant and rolapitant are neurokinin-1 (NK₁) receptor antagonists designed to block the pathway where substance P initiates impulses to the medulla and induces CINV by binding to NK₁ receptors (Diemunsch and Grelot, 2000; Aapro et al., 2014; Chow et al., 2018a).

Palonosetron has been extensively compared to other 5-HT₃RA with respect to its efficacy and safety (Eisenberg et al., 2003; Gralla et al., 2003; Aapro et al., 2006; Chen et al., 2007; Li et al., 2009; Yu

et al., 2009; Ghosh and Dey, 2010; Kaushal et al., 2010; Dong et al., 2011). The most recent systematic review in 2018 (Chow et al., 2018b) incorporated the results of 24 randomized-controlled trials (RCTs), which served as an update to the original 2014 meta-analysis by Popovic et al. which initially included 16 RCTs (Popovic et al., 2014). The latest publication found that palonosetron was clinically superior in only 1 of 19 endpoints and approached clinical superiority in another 2 endpoints, a change from the results previously found in 2014 when 3 endpoints were reported to be clinically superior and 6 approached clinical superiority (Chow et al., 2018b). The results support the latest clinical guidelines published by the Multinational Association of Supportive Care in Cancer (MASCC) and the European Society for Medical Oncology (ESMO) in 2016 (Roila et al., 2016), American Society of Clinical Oncology (ASCO) in 2017 (Hesketh et al., 2017), and National Comprehensive Cancer Network (NCCN) in 2017 (Berger et al., 2017) for not recommending palonosetron as the preferred 5-HT₃RA for all CINV therapies.

As with all systematic reviews, there exists the limitation of

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<https://doi.org/10.1016/j.critrevonc.2019.07.017>

Received 23 January 2019; Received in revised form 14 July 2019; Accepted 18 July 2019

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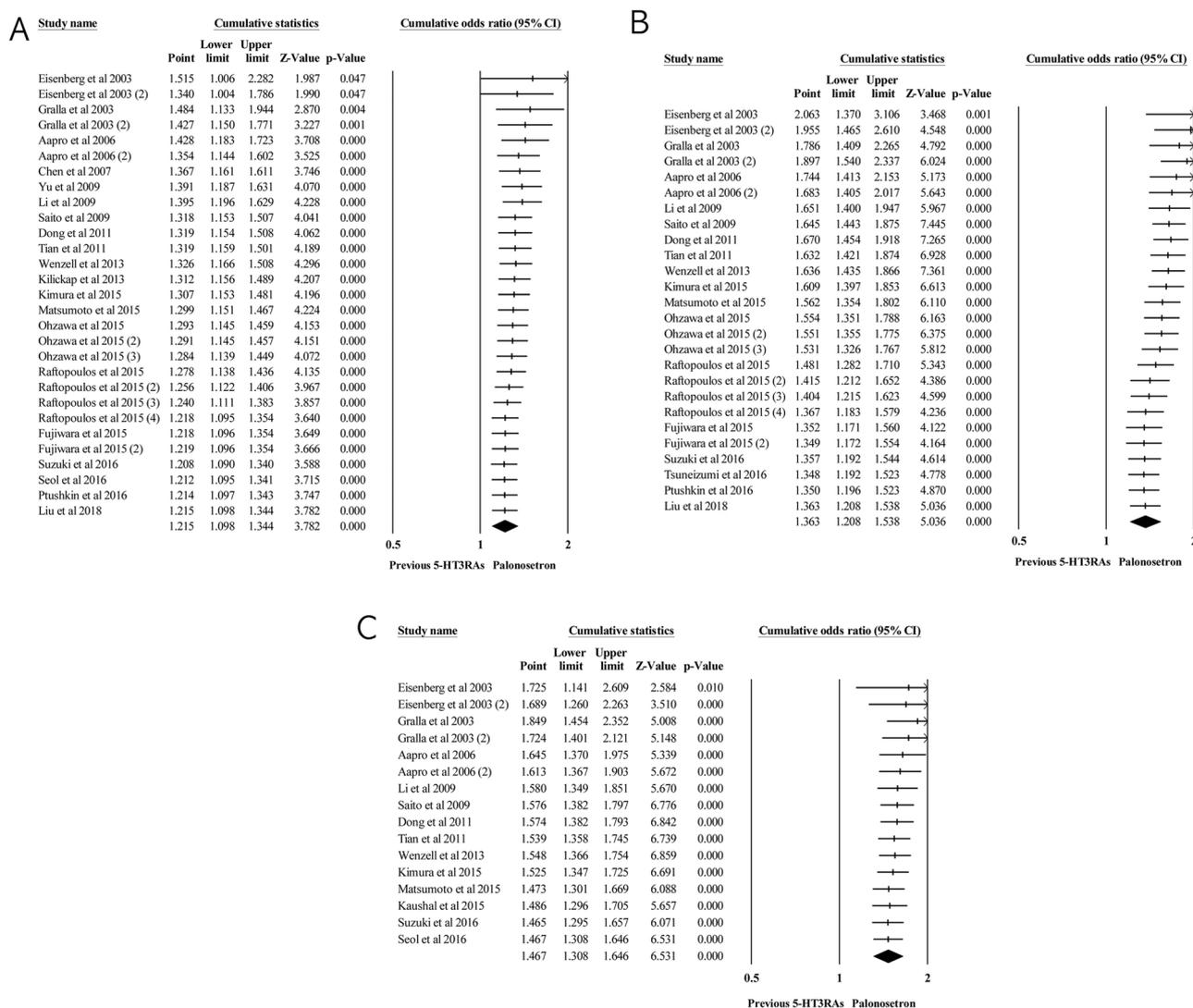


Fig. 1. Efficacy of palonosetron compared with other 5-HT₃RAs in the prophylaxis of chemotherapy-induced nausea and vomiting over time – complete response. a. Acute Phase, b. Delayed Phase, c. Overall Phase.

publication bias, which was not assessed in the prior systematic reviews (Chow et al., 2018b; Popovic et al., 2014). Additionally, RCTs are commonly repeated following meta-analyses, which spurs more meta-analyses and produces a vicious cycle/positive feedback loop. For instance, following the 2014 review (Popovic et al., 2014), an additional 8 studies were published in addition to the preexisting 16 trials. As of the latest meta-analyses (Chow et al., 2018b), there are already 24 RCTs, which randomized approximately 9000+ total patients to palonosetron or other 5-HT₃RAs. Given that palonosetron has already been extensively studied, and that significant resources are required to conduct RCTs, it is important to elucidate whether further studies are still required.

The primary aim of this study is to conduct a comprehensive meta-analysis to determine whether further trials could potentially lead to different conclusions in future meta-analyses. A secondary aim was to assess for publication biases.

2. Methods

The literature search was extended to August 2018 from the final search date of the prior meta-analysis by our group in 2017 and data extraction completed as per methodology previously reported by Chow et al. (2018b). To recap briefly, a literature search was conducted with

the search limited to clinical trials and English-language publications. Studies were screened by titles and abstracts, and then by full-texts, to determine whether RCTs compared palonosetron to other 5-HT₃RAs with respect to any of the following efficacy endpoints:

- 1 Complete response (CR) – no emesis and no use of rescue antiemetics
- 2 Complete control (CC) – no emesis, no rescue medication and no more than mild nausea
- 3 No episodes of nausea
- 4 No emetic episodes
- 5 No use of rescue medication

Safety endpoints of constipation, diarrhea, dizziness and headache were also recorded. Extracted endpoints, where possible, were recorded in the acute (0–24 hours post-chemotherapy), delayed (24–120 hours) or overall phases (0–120 hours).

The number of events and the total number of patients randomized to each arm, per study, were computed (Chow et al., 2018b). Statistical analyses were conducted using Review Manager (RevMan 5.3) by Cochrane IMS and Comprehensive Meta-Analysis (Version 3) by Biostat. Previously published forest plots that required inclusion of new studies were produced by RevMan 5.3. Funnel plots to assess for publication

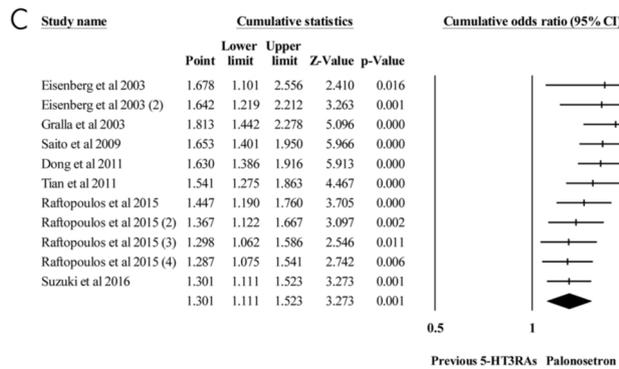
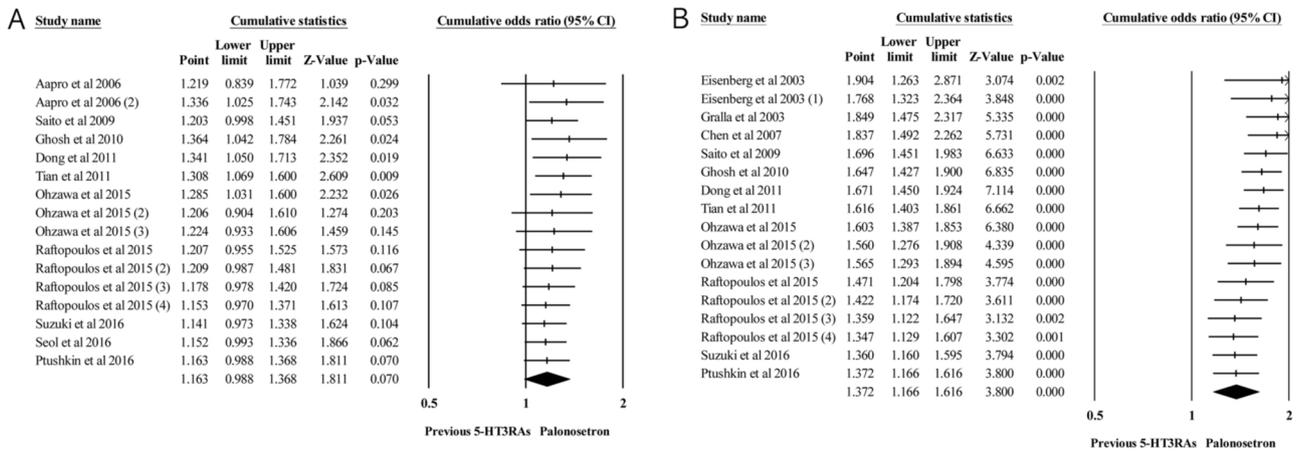


Fig. 2. Efficacy of palonosetron compared with other 5-HT₃RAs in the prophylaxis of chemotherapy-induced nausea and vomiting over time – complete control. a. Acute Phase, b. Delayed Phase, c. Overall Phase.

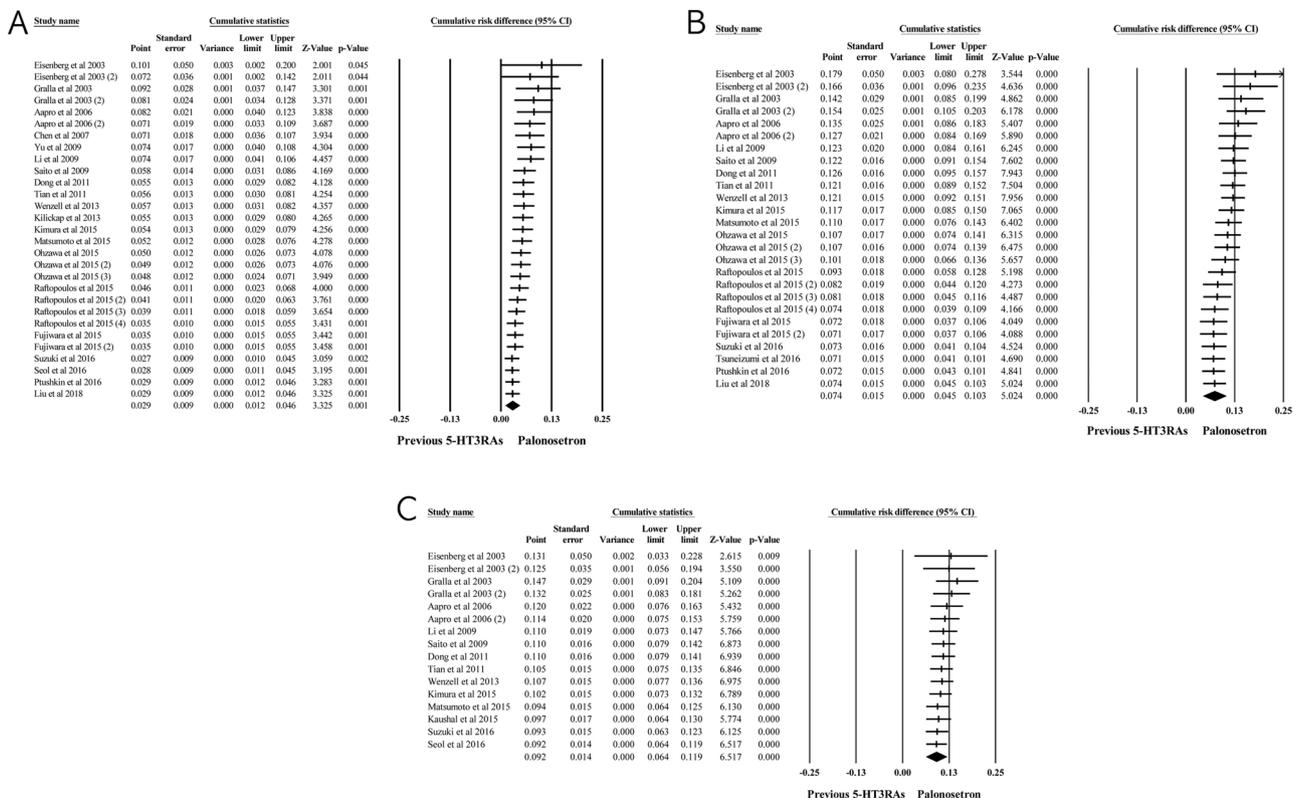


Fig. 3. Absolute risk difference between palonosetron versus other 5-HT₃RAs intervention arms over time – complete response. a. Acute Phase, b. Delayed Phase, c. Overall Phase.

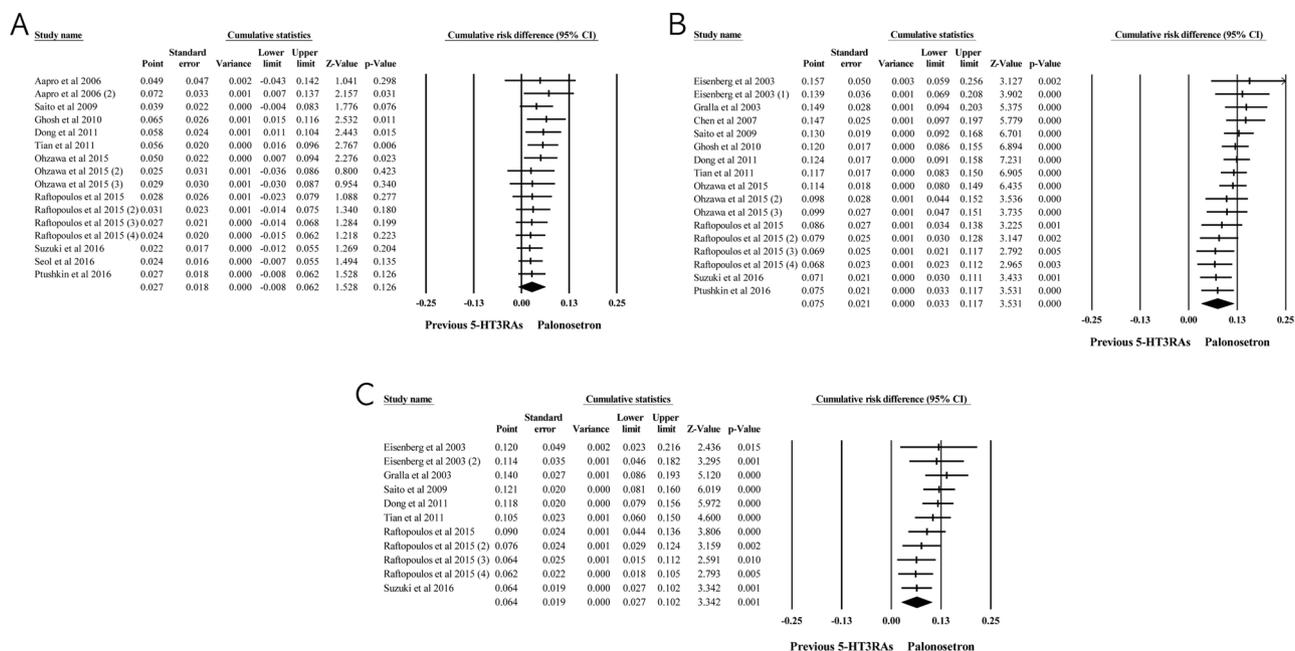


Fig. 4. Absolute risk difference between palonosetron versus other 5-HT₃RAs intervention arms over time – complete control. a. Acute Phase, b. Delayed Phase, c. Overall Phase.

bias via visual inspection and cumulative meta-analyses to assess odds ratio and risk difference over time were generated by Comprehensive Meta-Analysis. In all cases, a random-effects analysis model was used to generate odds ratio (OR), risk difference (RD) and accompanying 95% confidence intervals (CI). As with the prior meta-analyses, studies with more than 2 study arms had numerous ORs computed to compare palonosetron with other 5-HT₃RAs. RDs were compared to the 10% threshold as set by MASCC/ESMO for consideration of whether statistical significance translates to clinical significance and requires consideration of adjusting guidelines (Roila et al., 2016).

3. Results

3.1. Updated meta-analysis

Since the publication of the last review that included 24 studies (Chow et al., 2018a; Eisenberg et al., 2003; Gralla et al., 2003; Aapro et al., 2006; Chen et al., 2007; Li et al., 2009; Yu et al., 2009; Ghosh and Dey, 2010; Kaushal et al., 2010; Dong et al., 2011; Tian et al., 2011; Huang et al., 2013; Kilickap et al., 2013; Wenzell et al., 2013; Raftopoulos et al., 2014; Fujiwara et al., 2015; Kaushal et al., 2015; Kimura et al., 2015; Matsumoto et al., 2015; Ohzawa et al., 2015; Ptushkin et al., 2016; Seol et al., 2016; Suzuki et al., 2016; Tsuneizumi et al., 2016), 1 paper by Liu et al. has been published (Liu et al., 2018) [Appendix 1]. In the study, 50 patients were randomized to palonosetron and 50 patients randomized to tropisetron, resulting in a cumulative total reported in the literature of 4145 patients randomized to palonosetron and 4911 receiving other 5-HT₃RAs for the prophylaxis of CINV. Liu et al. reported on complete response in both the acute and delayed phase, and nausea in the overall phase. The updated OR analyses (analyses of statistical significance) are displayed in Appendices 2–4; updated RD analyses (analyses of clinical significance) did not lead to a change in the number of clinically significant endpoints compared to the prior review.

3.2. Complete response and complete control

Analysis of CR and CC reveal that, over time, palonosetron has been reported as having a decreasing degree of statistically superior efficacy

when compared to other 5-HT₃RAs [Figs. 1 and 2]. Lack of clinically significant difference, as assessed by cumulative risk difference and using the 10% threshold established by MASCC/ESMO, has been the meta-conclusion for CR and CC in the acute phase since the first clinical trials. With the publication of the latest trials from the year 2015 and onwards, palonosetron is now not believed to be clinically significantly superior to other agents in CR and CC, in the delayed and overall phase, even if the recent meta-analysis reported that palonosetron seems to be more efficacious and safe than other 5-HT₃RAs – statistically superior in 10 of 19 endpoints [Figs. 3 and 4].

There is no obvious asymmetry in the funnel plot for CR and CC in all three phases, suggesting that no publication bias exists. [Figs. 5 and 6].

3.3. No emesis and No nausea

A statistically significant greater efficacy of palonosetron compared with other 5-HT₃RAs for emesis in all three phases has been documented since the first trial. Palonosetron's statistically superior efficacy to counter nausea in the acute phase has been the meta-conclusion since the second clinical trial published in 2009. With respect to the delayed and overall phases, the latest clinical trials from 2015 have shifted the meta-conclusion from favouring palonosetron to regarding palonosetron as having no significant difference in efficacy relative to other 5-HT₃RAs [Appendices 5–6].

Clinical superiority of palonosetron in preventing emesis in the delayed and overall phases, and nausea in all phases, has consistently been unclear, with cumulative 95% CIs of RD overlapping the 10%. The meta-conclusion since 2009 has been that palonosetron is not significantly clinically superior to other 5-HT₃RAs in treating emesis in the acute phase when one uses the 10% absolute difference criterion [Appendices 7–8]. No clear publication biases exist for this endpoint [Appendices 9–10].

3.4. No use of rescue medication

In the overall phase, studies by Kimura et al. and Raftopoulos et al. in 2015 have changed the meta-conclusion, suggesting palonosetron as having similar non-significant difference in statistical and clinical

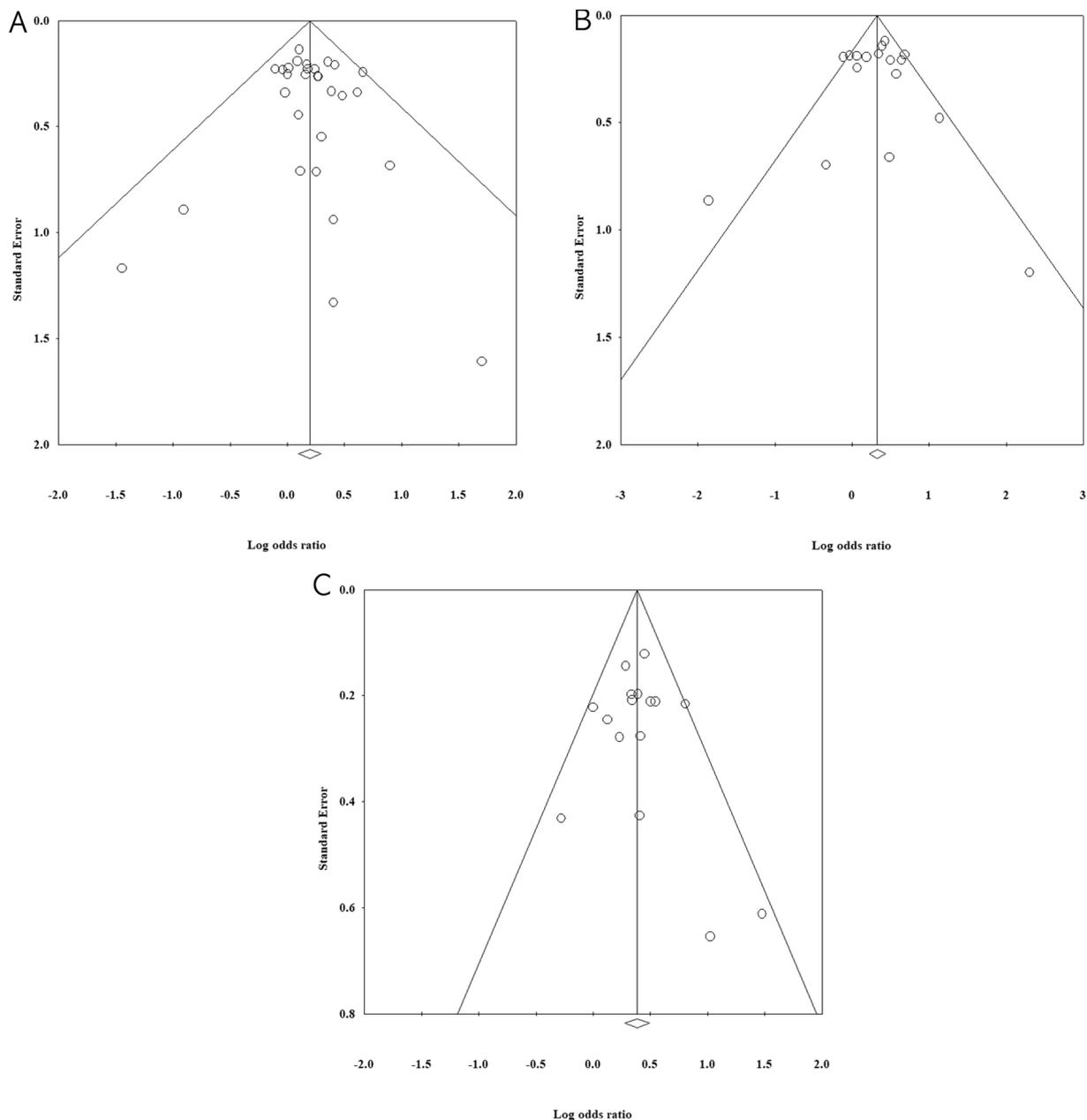


Fig. 5. Assessment of publication bias with respect to studies reporting about palonosetron compared to other 5-HT₃RAs for the endpoint of complete response. a. Acute Phase, b. Delayed Phase, c. Overall Phase.

efficacy to other 5-HT₃RAs [Appendix 11.3; Appendix 12.3]. Raftopoulos et al.’s study in 2015 also changed the meta-conclusion for the acute and delayed phases; these phases also have only 2–3 studies in total [Appendices 11.1–11.2; Appendices 12.1–12.2]. As with all other efficacy endpoints, no obvious publication biases existed [Appendix 13].

3.5. Safety endpoints

In general, meta-conclusions with regards to safety have remained the same over time – palonosetron is as safe as other 5-HT₃RAs, and in fact, statistically safer than others with respect to dizziness [Appendix 15]. Safety endpoints of constipation, dizziness and headache do not have any evidence of publication biases; the endpoint of diarrhea has more published literature documenting the superior statistical efficacy of palonosetron over previous 5-HT₃RAs [Appendix 16].

4. Discussion

This updated meta-analysis, with over 9050 randomized patients and hence the highest statistical power to-date, can help make an informed decision about whether further trials are needed to compare palonosetron to previous 5-HT₃RAs in the setting of acute and delayed CINV based on single-day emetogenic chemotherapy.

The publication of clinical trials over the last several years has changed the meta-conclusion in some efficacy endpoints such as CR and CC in both the delayed and overall phases (palonosetron, as of 2015, is statistically superior but no longer considered clinically superior), and preventing nausea in the delayed and overall phases (as of 2015, is no longer statistically superior). Change in the meta-conclusion was also noted for the endpoints of rescue medication, but only a few studies have reported on this endpoint and as such it is more likely for conclusions to change with introduction of new trials. In the majority of efficacy endpoints, the meta-conclusion has not changed over time,

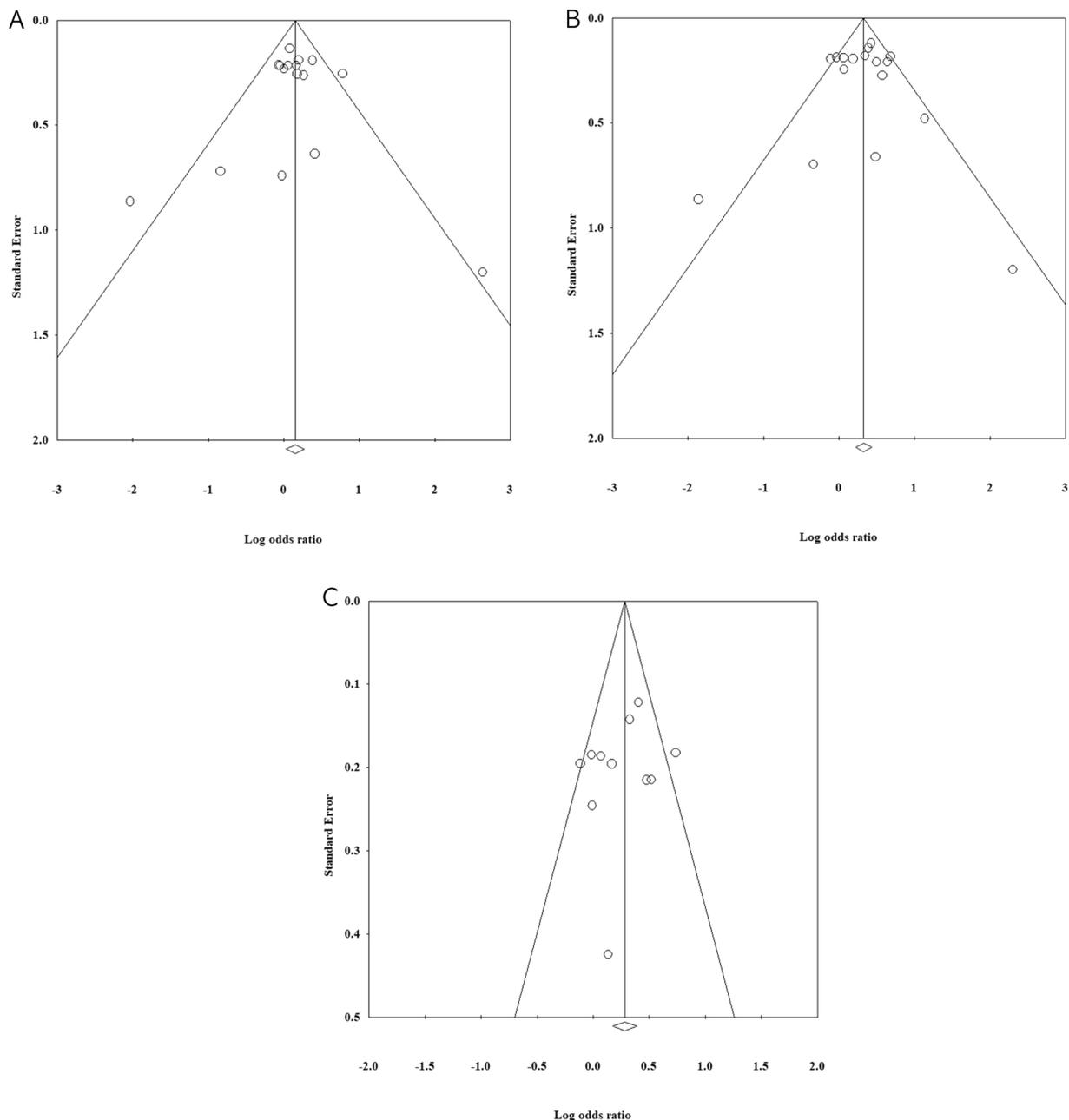


Fig. 6. Assessment of publication bias with respect to studies reporting about palonosetron compared to other 5-HT₃RAs for the endpoint of complete control. a. Acute Phase, b. Delayed Phase, c. Overall Phase.

with the most recent clinical trials simply narrowing the confidence interval and increasing the precision of the meta-conclusion. Also, when looking at some of the seemingly most straight-forward endpoints, such as no emesis and no nausea, and more complicated endpoints, such as CR and CC where additional criteria are required for patients to be defined as a successfully prophylaxis, more complex research methodology has not altered the course of meta-conclusions. Given the vast amount of resources required to conduct a clinical trial, and also that the most recent clinical trials affirm the same findings of previously published articles, one may question why substantial amounts of resources should still be committed to investigating the efficacy of an already-extensively studied prophylactic agent.

Although fewer studies report on the safety of palonosetron, safety endpoints were still highly powered, with anywhere from 1700 to over 4200 patients randomized per intervention arm. The meta-conclusion has remained consistent over time – palonosetron has a similar safety

profile to other 5-HT₃RAs – with most recent studies, again, simply increasing the precision of the conclusion. As such, further studies are not likely to yield a substantially different meta-conclusion.

The lack of publication biases, as noted from visual inspection of funnel plots, suggests that the existing literature provides an accurate and representative assessment of palonosetron. This, coupled with the aforementioned results that palonosetron’s meta-conclusion is relatively consistent over time, further emphasizes the comprehensive nature of the existing literature. Further trials with greater degree of rigor are not necessary, as the results of the existing palonosetron trials seem to lack publication biases.

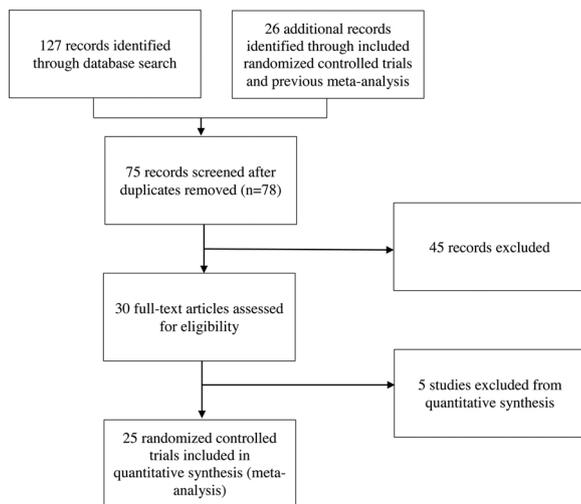
This review shares limitations with prior meta-analyses on this topic (Chow et al., 2018b; Popovic et al., 2014) – individual patient-level data was not extracted; differential outcomes between arms for the acute phase may have a carry-over phase on delayed phase results [37]. No statistical analyses were performed to accompany funnel plots, such

as Egger’s test or Begg’s test, and thus no quantitative assessment to assess publication biases was considered; however, visual inspection of funnel plots does not reveal any obvious asymmetry and hence these additional tests are unlikely to yield any different conclusions. Assessment of publication biases using funnel plots should also be interpreted with caution for endpoints that have only several studies reporting on it (i.e. the endpoint of no use of rescue medication).

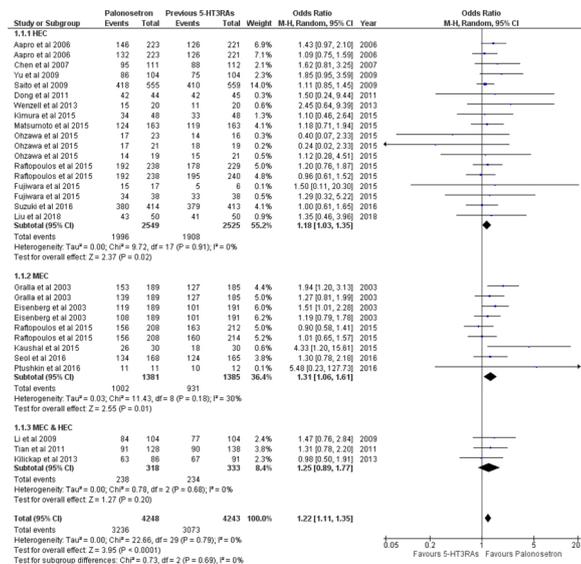
In conclusion, palonosetron has been extensively studied for prevention of single-day emetogenic chemotherapy, with 25 published

RCTs to date and over 9050 patients randomized to palonosetron or another 5-HT₃RAs. Analyses to assess the effect of the most recent RCTs reveal that these studies are confirming preexisting estimates and only refining the point estimate of palonosetron’s efficacy. Considering this trend and the vast amount of resources needed to conduct a RCT, CINV trial resources should be dedicated elsewhere to other prophylactic treatments that have not been as well explored. Today’s use of daily anticancer drugs and the use of chemotherapy given over several days are areas where studies are needed (Navari and Aapro, 2016).

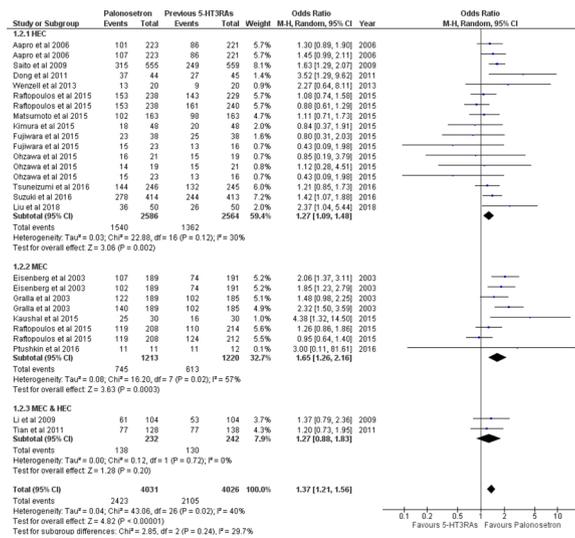
Appendix 1. PRISMA Flow Diagram



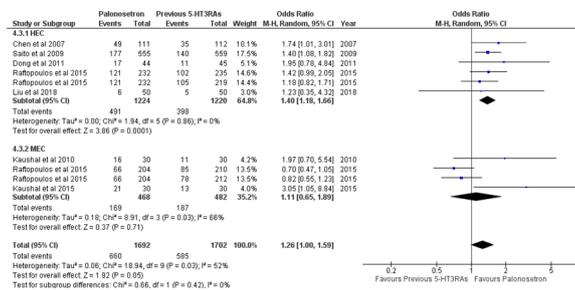
Appendix 2. Efficacy of palonosetron compared with other 5-HT₃RAs in the prophylaxis of chemotherapy-induced nausea and vomiting – complete response in the acute phase



Appendix 3. Efficacy of palonosetron compared with other 5-HT₃RAs in the prophylaxis of chemotherapy-induced nausea and vomiting – complete response in the delayed phase

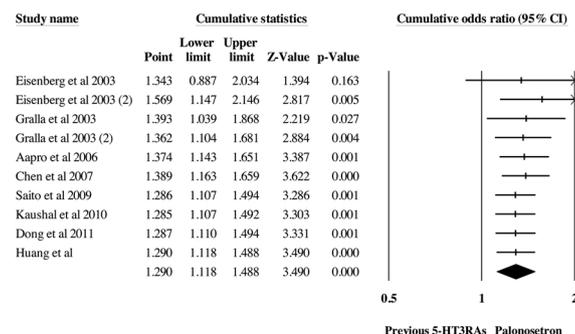


Appendix 4. Efficacy of palonosetron compared with other 5-HT₃RAs in the prophylaxis of chemotherapy-induced nausea and vomiting – no nausea in the overall phase

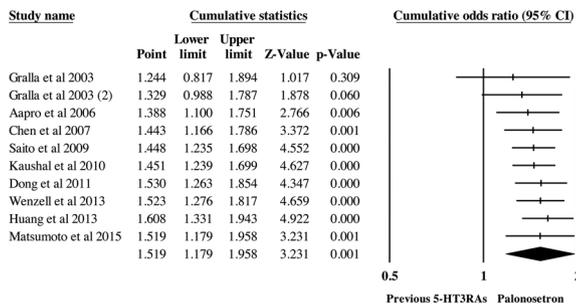


Appendix 5. Efficacy of palonosetron compared with other 5-HT₃RAs in the prophylaxis of chemotherapy-induced nausea and vomiting over time – no emesis. 5.1 Acute Phase 5.2 Delayed Phase 5.3 Overall Phase

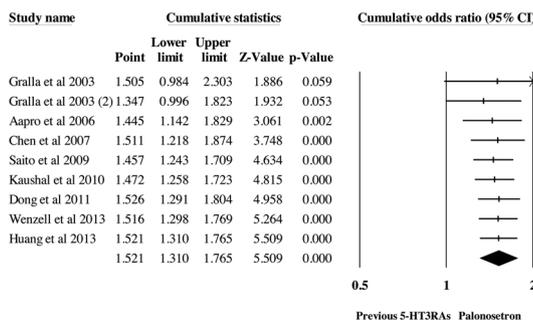
Appendix 5.1



Appendix 5.2

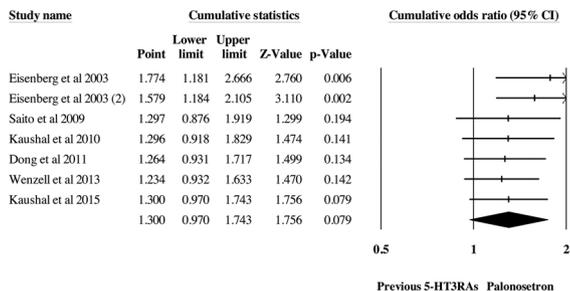


Appendix 5.3

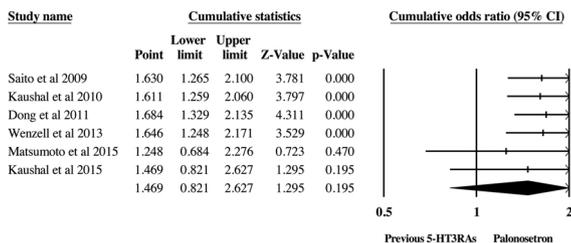


Appendix 6. Efficacy of palonosetron compared with other 5-HT₃RAs in the prophylaxis of chemotherapy-induced nausea and vomiting over time – no nausea. 6.1 Acute Phase 6.2 Delayed Phase 6.3 Overall Phase

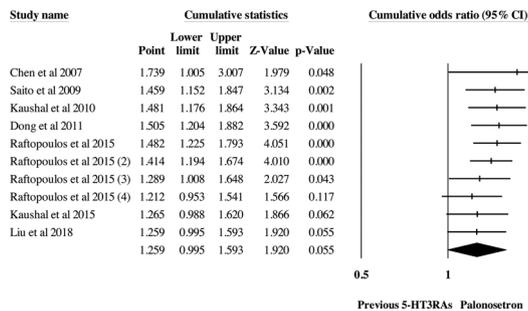
Appendix 6.1



Appendix 6.2

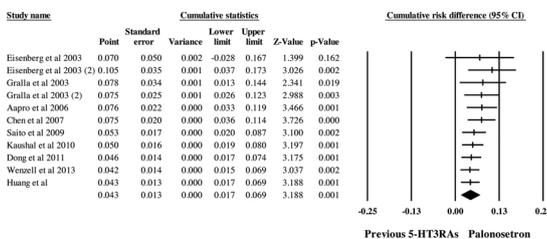


Appendix 6.3

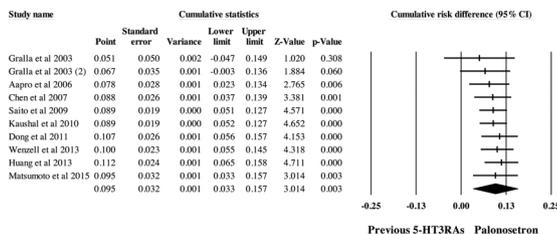


Appendix 7. Absolute risk difference between palonosetron versus other 5-HT₃RAs intervention arms over time – no emesis. 7.1 Acute Phase 7.2 Delayed Phase 7.3 Overall Phase

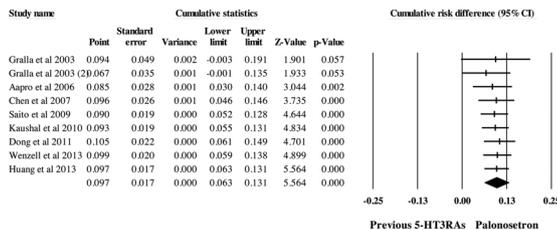
Appendix 7.1



Appendix 7.2

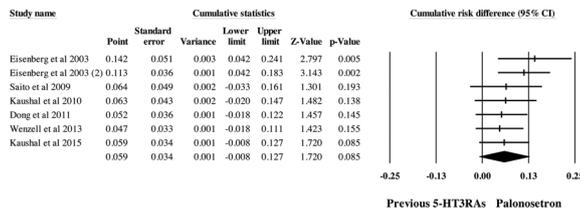


Appendix 7.3

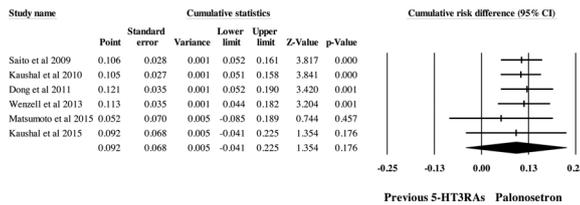


Appendix 8. Absolute risk difference between palonosetron versus other 5-HT₃RAs intervention arms over time – no nausea. 8.1 Acute Phase 8.2 Delayed Phase 8.3 Overall Phase

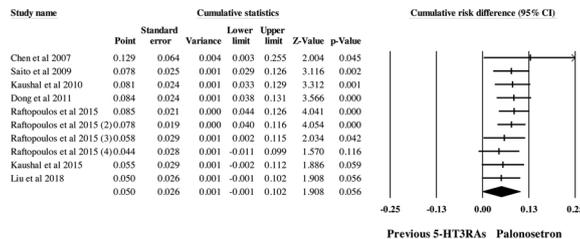
Appendix 8.1



Appendix 8.2

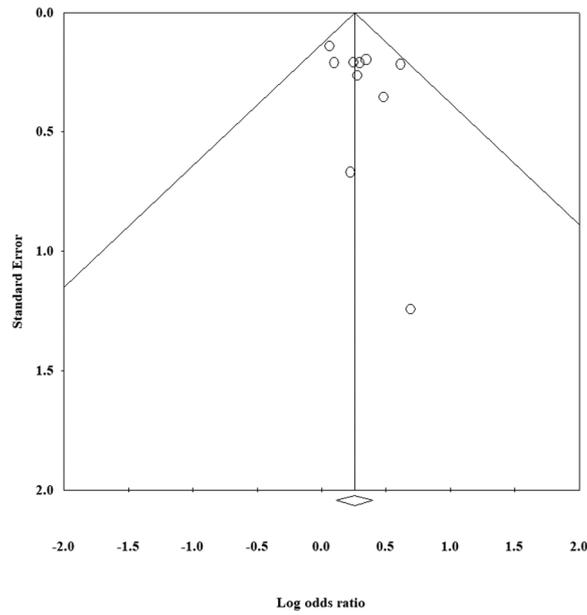


Appendix 8.3

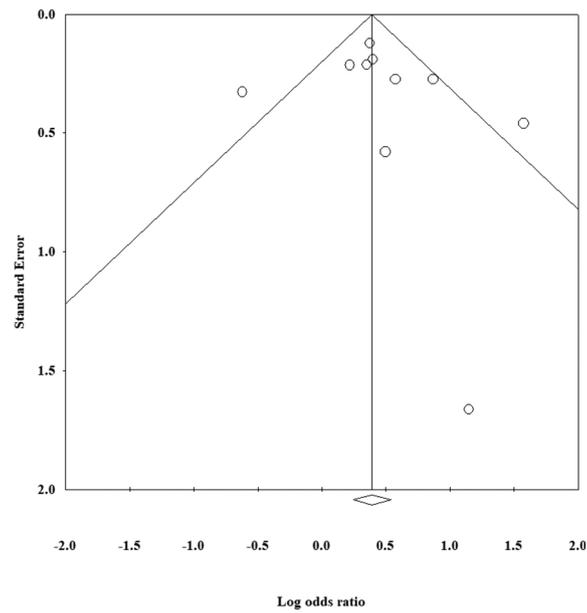


Appendix 9. Assessment of publication bias with respect to studies reporting about palonosetron compared to other 5-HT₃RAs for the endpoint of no emesis. 9.1 Acute Phase 9.2 Delayed Phase 9.3 Overall Phase

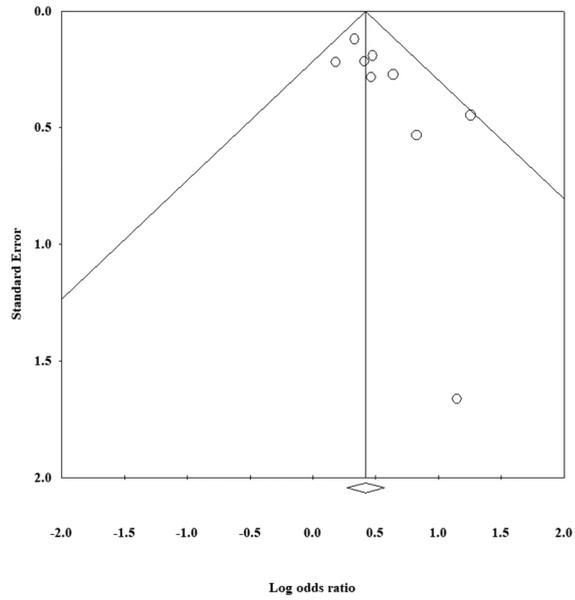
Appendix 9.1



Appendix 9.2

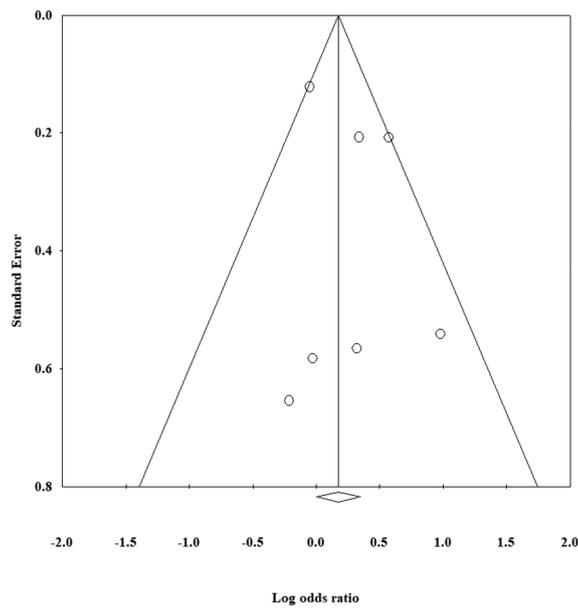


Appendix 9.3

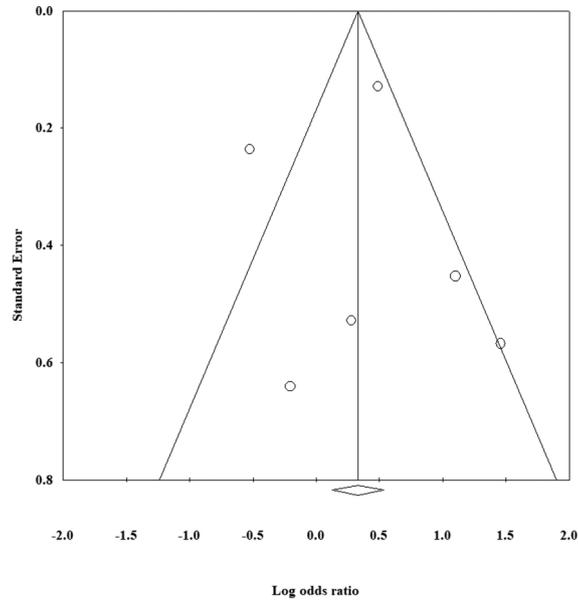


Appendix 10. Assessment of publication bias with respect to studies reporting about palonosetron compared to other 5-HT₃RAs for the endpoint of no nausea. 10.1 Acute Phase 10.2 Delayed Phase 10.3 Overall Phase

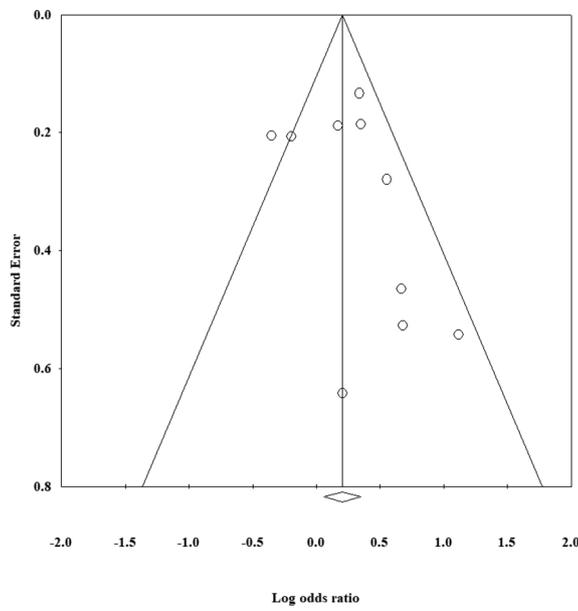
Appendix 10.1



Appendix 10.2

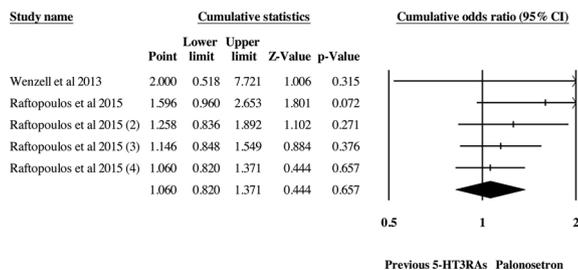


Appendix 10.3

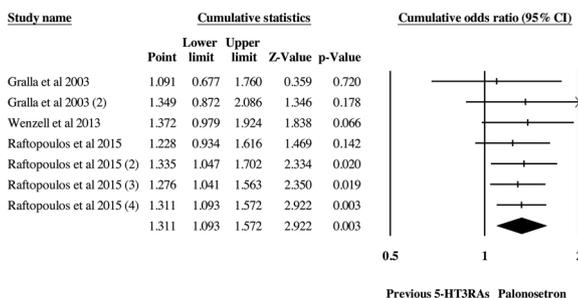


Appendix 11. Efficacy of palonosetron compared with other 5-HT₃RAs in the prophylaxis of chemotherapy-induced nausea and vomiting over time – no rescue medication. 11.1 Acute Phase 11.2 Delayed Phase 11.3 Overall Phase

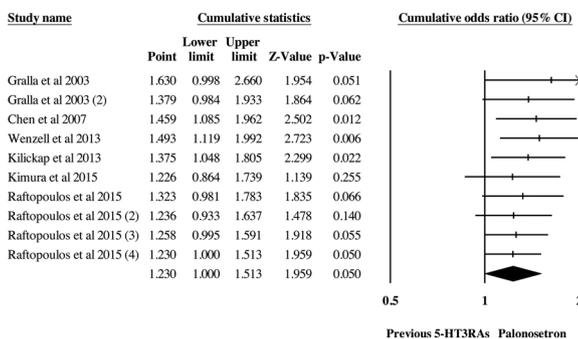
Appendix 11.1



Appendix 11.2

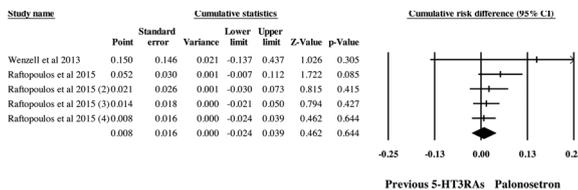


Appendix 11.3

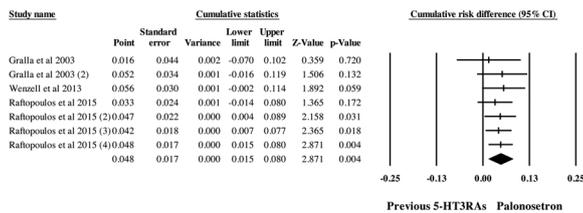


Appendix 12. Absolute risk difference between palonosetron versus other 5-HT₃RAs intervention arms over time – no rescue medication. 12.1 Acute Phase 12.2 Delayed Phase 12.3 Overall Phase

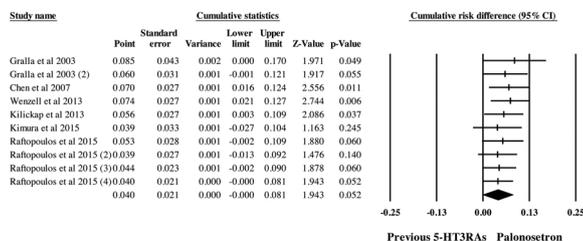
Appendix 12.1



Appendix 12.2

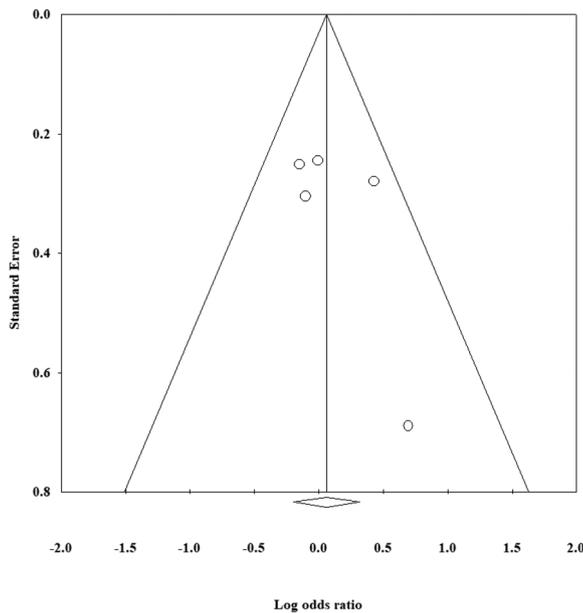


Appendix 12.3

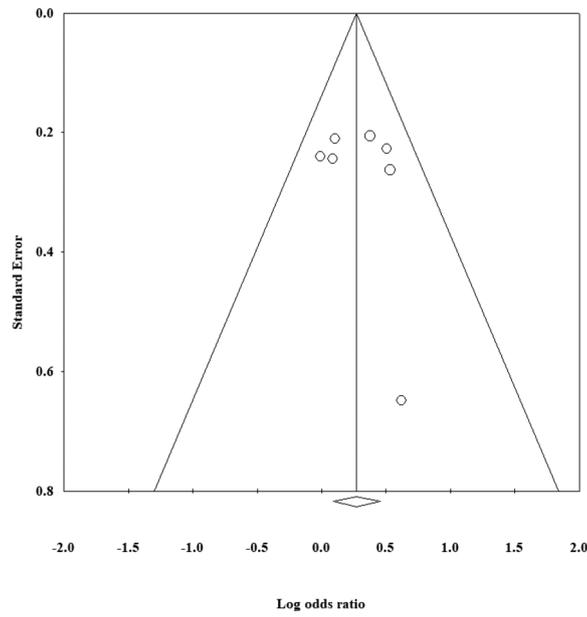


Appendix 13. Assessment of publication bias with respect to studies reporting about palonosetron compared to other 5-HT₃RAs for the endpoint of no rescue medication. 13.1 Acute Phase 13.2 Delayed Phase 13.3 Overall Phase

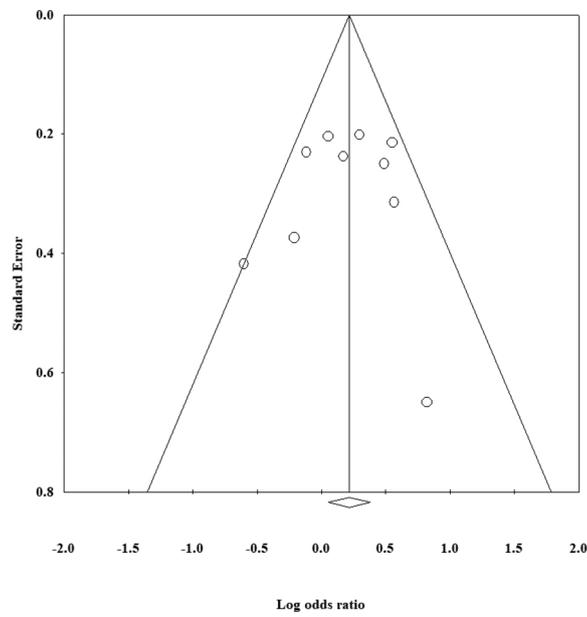
Appendix 13.1



Appendix 13.2

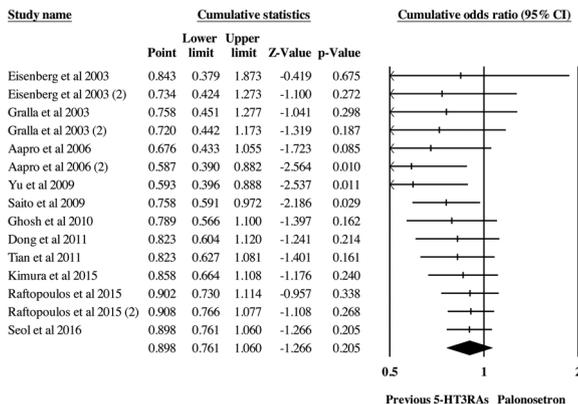


Appendix 13.3

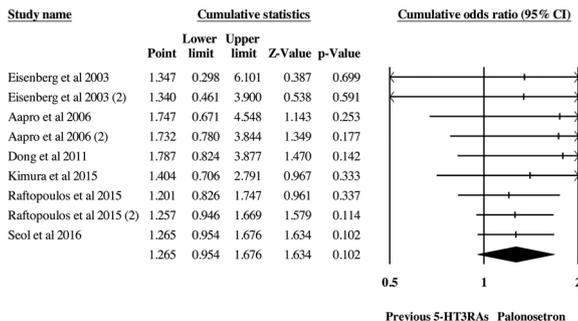


Appendix 14. Safety of palonosetron compared with other 5-HT₃RAs in the prophylaxis of chemotherapy-induced nausea and vomiting over time – treatment-related adverse events. 14.1 Constipation 14.2 Diarrhea 14.3 Dizziness 14.4 Headache

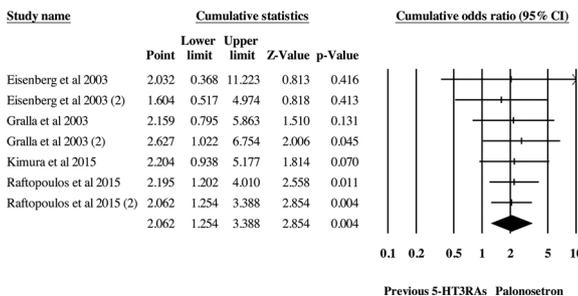
Appendix 14.1



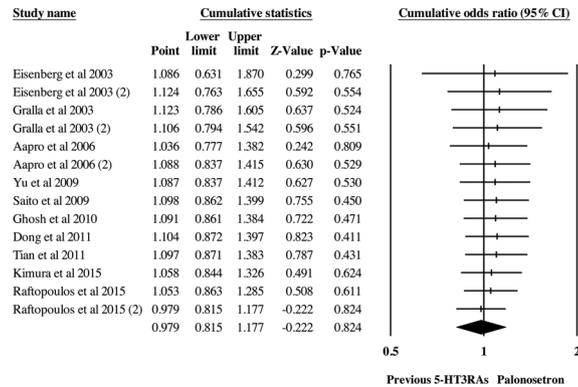
Appendix 14.2



Appendix 14.3

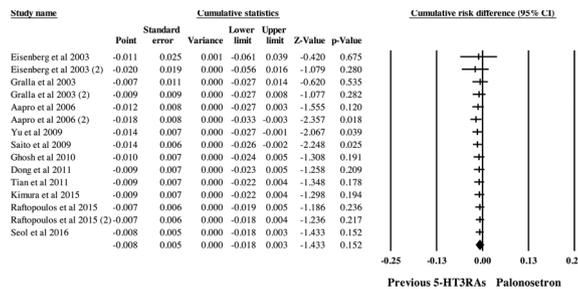


Appendix 14.4

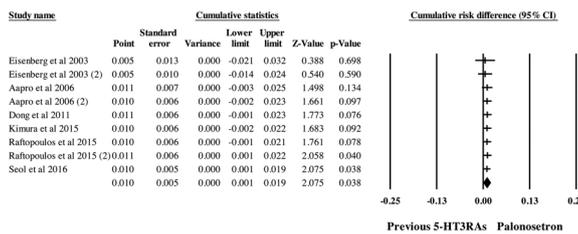


Appendix 15. Absolute risk difference between palonosetron versus other 5-HT₃RAs intervention arms over time – safety endpoints. 15.1 Constipation 15.2 Diarrhea 15.3 Dizziness 15.4 Headache

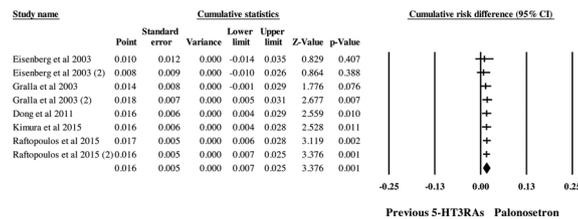
Appendix 15.1



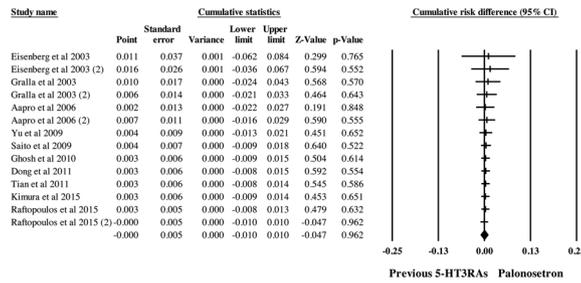
Appendix 15.2



Appendix 15.3

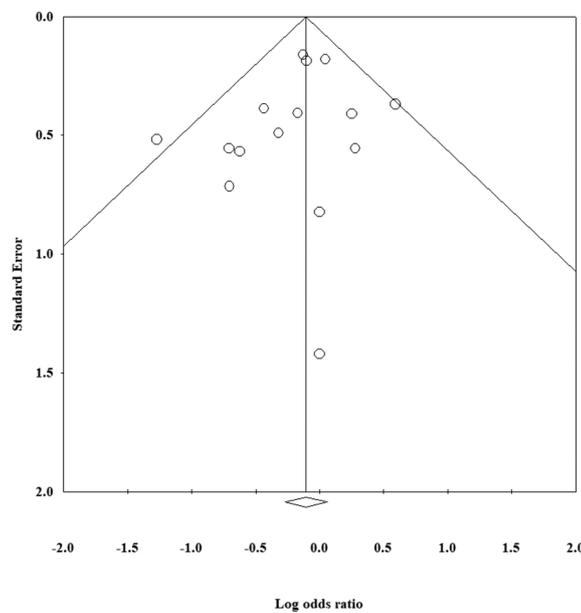


Appendix 15.4

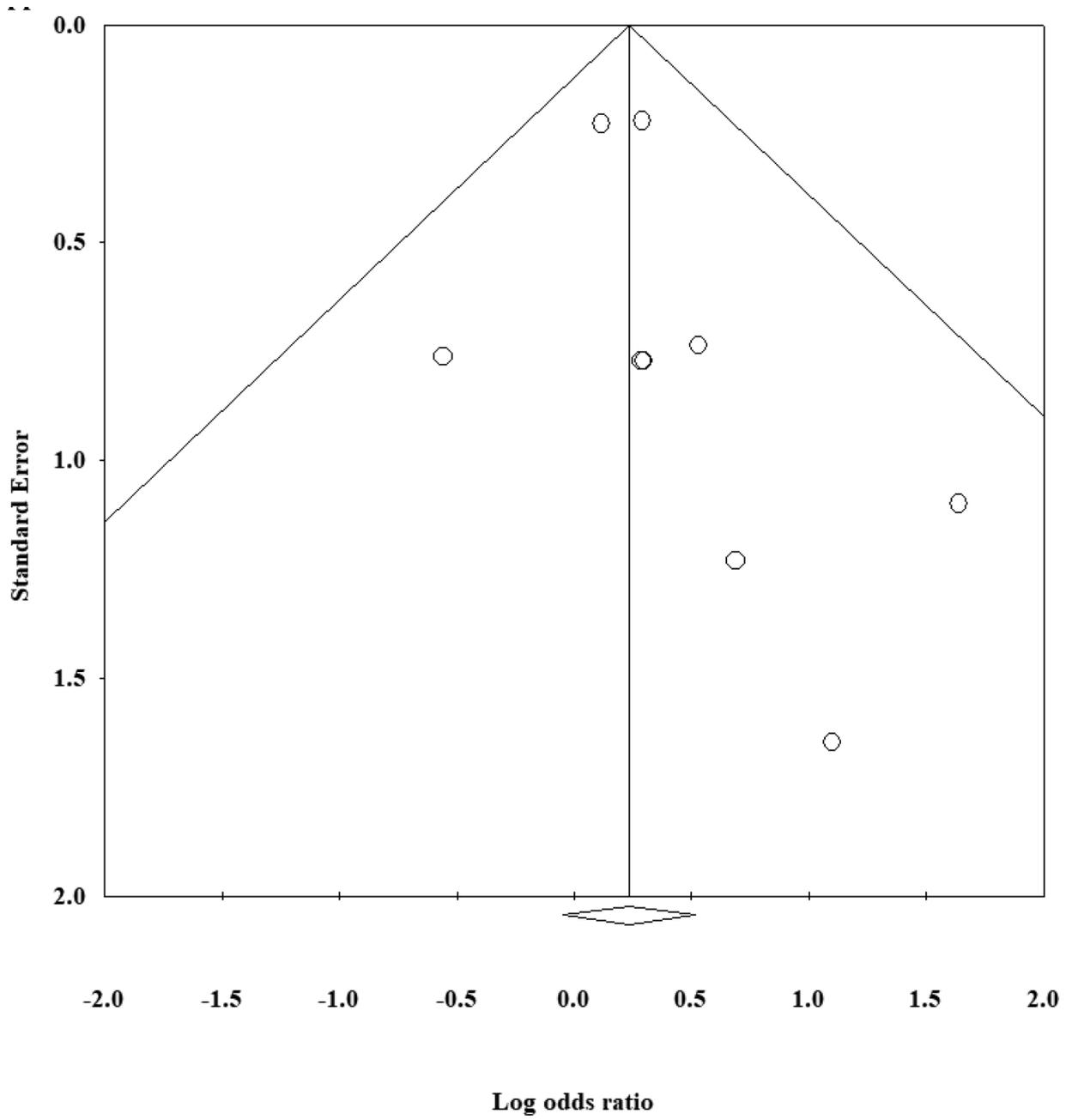


Appendix 16. Assessment of publication bias with respect to studies reporting about palonosetron compared to other 5-HT₃RAs for safety endpoints. 16.1 Constipation 16.2 Diarrhea 16.3 Dizziness 16.4 Headache

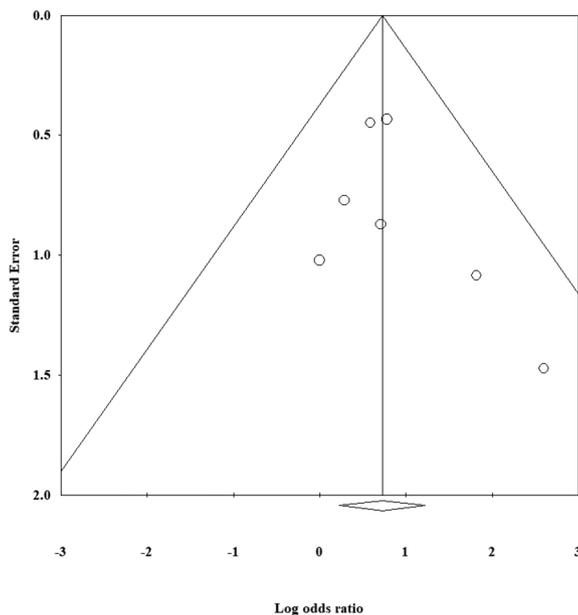
Appendix 16.1



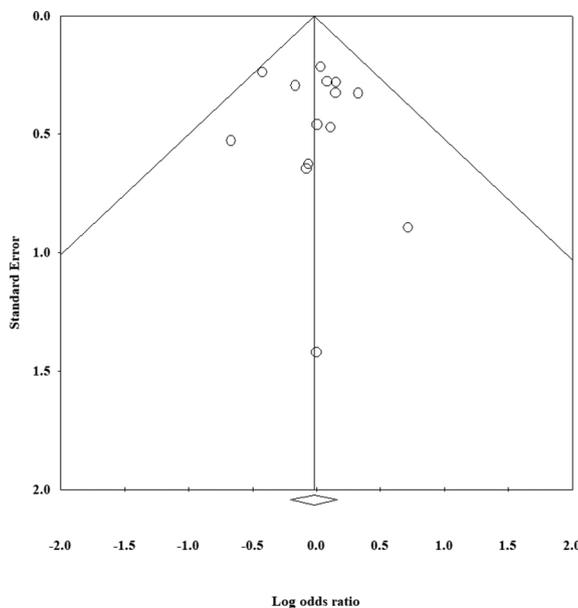
Appendix 16.2



Appendix 16.3



Appendix 16.4



References

Chiu, L., Chow, R., Popovic, M., et al., 2016. Efficacy of olanzapine for the prophylaxis and rescue of chemotherapy-induced nausea and vomiting (CINV): a systematic review and meta-analysis. *Support Care Cancer* 24, 2381–2392.

Chow, R., Chiu, L., Navari, R.M., et al., 2016. 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* 24, 1001–1008.

Navari, R.M., Aapro, M., 2016. Antiemetic prophylaxis for chemotherapy-induced nausea and vomiting. *NEJM* 374, 1356–1367.

Saito, M., Aogi, K., Sekine, I., et al., 2009. Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy : a double-blind, double-dummy, randomized, comparative phase III trial. *Lancet Oncol.* 10, 115–124.

Diemunsch, P., Grelot, L., 2000. Potential of substance P antagonists as anti-emetics. *Drugs* 60, 533–546.

Aapro, M., Rugo, H., Rossi, G., et al., 2014. A randomized phase III study evaluating the efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy. *Ann. Oncol.* 25, 1328–1333.

Chow, R., Tsao, M., Chiu, L., et al., 2018a. Efficacy of the combination of neurokinin-1 receptor antagonist, palonosetron and dexamethasone compared to others for the prophylaxis of chemotherapy-induced nausea and vomiting: a systematic review and meta-analysis of randomized controlled trials. *Ann. Palliat. Med.* 7 (2), 221–223.

Eisenberg, P., Figueroa-Vadillo, J., Zamora, R., et al., 2003. Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel 5-HT₃ receptor antagonist. *Cancer* 98 (11), 2473–2482.

Gralla, R., Lichinitser, M., Van der Vegt, S., et al., 2003. Palonosetron improves

- prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. *Ann. Oncol.* 14, 1570–1577.
- Aapro, M.S., Grunberg, S.M., Manikhas, G.M., et al., 2006. A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. *Ann. Oncol.* 17, 1441–1449.
- Chen, Y.X., Qin, S.K., Cheng, Y., et al., 2007. A multicenter, double-blind randomized control clinical trial of palonosetron hydrochloride injection to prevent chemotherapy-induced nausea and vomiting. *Chin. Clin. Oncol.* 12, 161–165.
- Li, Z.Q., Xu, J.M., Liu, D.Q., et al., 2009. Phase II trial of hydrochloride in the prevention of moderately to severely emetogenic chemotherapy induced nausea and vomiting. *Chin. Clin. Oncol.* 14, 487–490.
- Yu, Z., Liu, W., Wang, L., et al., 2009. The efficacy and safety of palonosetron compared with granisetron in preventing highly emetogenic chemotherapy-induced vomiting in the Chinese cancer patients: a phase II, multi-center, randomized, double-blind, parallel, comparative clinical trial. *Support Care Cancer* 17, 99–102.
- Ghosh, S., Dey, S., 2010. Comparing different antiemetic regimens for chemotherapy induced nausea and vomiting. *Int. J. Collab. Res. Int. Med. Pub. Health* 2 (5), 142–156.
- Kaushal, J., Gupta, M.C., Kaushal, V., et al., 2010.) clinical evaluation of two antiemetic combinations palonosetron dexamethasone versus ondansetron dexamethasone in chemotherapy of head and neck cancer. *Singap. Med. J.* 51 (11), 871–875.
- Dong, X., Huang, J., Cao, R., Liu, L., 2011. Palonosetron for prevention of acute and delayed nausea and vomiting in non-small-cell lung carcinoma patients. *Med. Only* 28, 1425–1429.
- Chow, R., Warr, D.G., Navari, R.M., et al., 2018b. Should palonosetron be a preferred 5-HT₃ receptor antagonist for chemotherapy-induced nausea and vomiting? An updated systematic review and meta-analysis. *Support Care Cancer* 26, 2519–2549.
- Popovic, M., Warr, D.G., DeAngelis, C., et al., 2014. Efficacy and safety of palonosetron for the prophylaxis of chemotherapy-induced nausea and vomiting (CINV): a systematic review and meta-analysis of randomized controlled trials. *Support Care Cancer* 22, 1685–1697.
- Roila, F., Molassiotis, A., Herrstedt, J., et al., 2016. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiation-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. *Ann. Oncol.* 27, v119–v133.
- Hesketh, P.J., Kris, M.G., Basch, E., et al., 2017. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline update. *J. Clin. Oncol.* 35 (28), 3240–3261.
- Berger, M.J., Ettinger, D.S., Aston, J., et al., 2017. NCCN guidelines insights: antiemesis, version 2.2017. *J. Natl. Compr. Cancer Netw.* 15, 883–893.
- Tian, W., Wang, Z., Zhou, J., et al., 2011. Randomized, double-blind, crossover study of palonosetron compared with granisetron for the prevention of chemotherapy-induced nausea and vomiting in a Chinese population. *Med. Oncol.* 28, 71–78.
- Huang, J., Wang, X.J., Yu, D., et al., 2013. The effect of palonosetron hydrochloride in the prevention of chemotherapy-induced moderate and severe nausea and vomiting. *Exp. Ther. Med.* 5, 1418–1426.
- Kilickap, S., Kacan, T., Akgul Babacan, N., 2013. The efficacy of palonosetron compared with granisetron in preventing chemotherapy-induced nausea and vomiting: a randomized study. *Eur. J. Cancer* 49, S272.
- Wenzell, C.M., Berger, M.J., Blazer, M.A., et al., 2013. Pilot study on the efficacy of an ondansetron- versus palonosetron-containing antiemetic regimen prior to highly emetogenic chemotherapy. *Support Care Cancer* 21 (10), 2845–2851.
- Raftopoulos, H., Boccia, R., Cooper, W., et al., 2014. Comparison of an extended-release formulation of granisetron (APF530) versus palonosetron for the prevention of chemotherapy-induced nausea and vomiting associated with moderately or highly emetogenic chemotherapy: results of a prospective, randomized, double-blind, non-inferiority phase 3 trial. *Support Care Cancer* 23, 723–732.
- Fujiwara, S., Terai, Y., Tsunetoh, S., et al., 2015. Palonosetron versus granisetron in combination with aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with gynecologic cancer. *J. Gynecol. Oncol.* 26 (4), 311–319.
- Kaushal, P., Atri, R., Soni, A., et al., 2015. Comparative evaluation of triplet antiemetic schedule versus doublet antiemetic schedule in chemotherapy-induced emesis in head and neck cancer. *ecancer* 9, 567.
- Kimura, H., Yamamoto, N., Shirai, T., et al., 2015. Efficacy of triplet regimen antiemetic therapy for chemotherapy-induced nausea and vomiting (CINV) in bone and soft tissue sarcoma patients receiving highly emetogenic chemotherapy, and an efficacy comparison of single-shot granisetron and consecutive-day granisetron for CINV in a randomized, single-blinded crossover study. *Cancer Med.* 4 (3), 333–341.
- Matsumoto, K., Takahashi, M., Sato, K., et al., 2015. Palonosetron or granisetron for prevention of CINV in patients with breast cancer receiving dexamethasone and fosaprepitant following anthracycline plus cyclophosphamide (AC) regimen. *J. Clin. Oncol.* 33.
- Ohzawa, H., Miki, A., Hozumi, Y., et al., 2015. Comparison between antiemetic effects of palonosetron and granisetron in breast cancer patients with anthracycline-based regimens. *Oncol. Lett.* 9, 119–124.
- Ptushkin, V., Sharkunov, N., Mayorova, S., et al., 2016. Randomised comparison of palonosetron and ondansetron both combined with dexamethasone in prevention of emesis in lymphoma patients receiving moderately emetogenic regimen bendamustine and rituximab. *Haematologica* 101 (489).
- Seol, Y.M., Kim, H.J., Choi, Y.J., et al., 2016. Transdermal granisetron versus palonosetron for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: a multicenter, randomized, open-label, cross-over, active-controlled, and phase IV study. *Support Care Cancer* 24 (2), 945–952.
- Suzuki, K., Yamanaka, T., Hashimoto, H., et al., 2016. Randomized, double-blind, phase III trial of palonosetron versus granisetron in the triplet regimen for preventing chemotherapy-induced nausea and vomiting after highly emetogenic chemotherapy: TRIPLE study. *Ann. Oncol.* 27, 1601–1606.
- Tsuneizumi, M., Saito, M., Ogata, H., et al., 2016. Trial of antiemetic triplet therapy comparing palonosetron and granisetron in breast cancer patients receiving AC chemotherapy: double blind randomized comparative phase III study. *Support Care Cancer* 24 (Suppl 1), S87.
- Liu, L., Guo, J., Fang, S., et al., 2018. Therapeutic effects of palonosetron plus tropisetron on chemotherapy-induced nausea and vomiting. *Int. J. Clin. Exp. Med.* 11 (4), 4108–4113.