The efficacy of the 5-HT_3 receptor antagonists combined with droperidol for PONV prophylaxis is similar to their combination with dexamethasone. A meta-analysis of randomized controlled trials

[L'efficacité de la combinaison des antagonistes des récepteurs 5-HT_3 et du dropéridol ou de la dexaméthasone est similaire pour prévenir les NVPO. Une méta-analyse d'essais randomisés et contrôlés]

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Purpose: The aim of this quantitative systematic review is to compare the efficacy and side effects of combining one of the 5-HT_3 receptor antagonists (5-HT) with droperidol or dexamethasone for postoperative nausea and vomiting (PONV) prophylaxis.

Methods: We performed a systematic search (Medline, Embase, and the Cochrane Library) for randomized controlled trials that compared the antiemetic efficacy of combining one of the 5-HT with droperidol or dexamethasone *vs* 5-HT alone. Relevant endpoints were prevention of early (0 to 6 hr), and overall (0 to 24 hr) PONV, and side effects. The articles that could meet the inclusion criteria were scored for inclusion and methodological validity using the three-item, five-point, Oxford-scale. Relative risk and numbers needed-to-treat with 95% confidence intervals were calculated for each combination *vs* 5-HT alone. The two combinations were then indirectly compared. A random effects model was used.

Results: We considered 41 trials for analysis but subsequently excluded eight. Thirty-three trials with data from 3,447 patients were analyzed. Except for early nausea with the 5-HT plus droperidol, both combinations were significantly more effective than 5-HT in preventing early and overall PONV. There was no difference in antiemetic efficacy between the two combinations. The incidence of commonly reported side effects was also similar in the two combination groups.

Conclusion: We conclude that there is no statistically significant difference in antiemetic efficacy or side effects profile when one of the 5-HT is combined with either droperidol or dexamethasone and that both combination regimens are significantly more effective than 5-HT alone.

Objectif : *Notre revue systématique quantitative visait à comparer l'efficacité et les effets secondaires de la combinaison de l'un des antagonistes des récepteurs 5-HT_3 (5-HT) avec le dropéridol ou la dexaméthasone pour prévenir les nausées et vomissements postopératoires (NVPO).*

Méthode : *Nous avons réalisé une recherche systématique (Medline, Embase et Cochrane Library) des essais randomisés et contrôlés où on compare l'efficacité antiémétique de la combinaison de l'un des 5-HT avec le dropéridol ou la dexaméthasone vs le 5-HT employé seul. Les paramètres pertinents étaient la prévention des NVPO précoces (0 à 6 h) et globaux (0 à 24 h), et les effets secondaires. Les articles répondant aux critères d'inclusion ont été classés pour leur validité d'inclusion et de méthodologie grâce à l'échelle Oxford de trois éléments en cinq points. Le risque relatif et les nombres nécessaires à traiter selon un intervalle de confiance de 95 % ont été calculés pour chaque combinaison vs le 5-HT seul. Les deux combinaisons ont été ensuite comparées indirectement. Un modèle à effets aléatoires a été utilisé.*

Résultats : *Sur les 41 essais retenus pour l'analyse, huit ont été exclus et 33, comprenant les données sur 3 447 patients, ont donc été analysés. Mis à part les nausées précoces observées avec le 5-HT combiné au dropéridol, les deux combinaisons ont été significativement plus efficaces que le 5-HT seul pour prévenir les NVPO précoces et l'ensemble des NVPO. Les deux combinaisons ont présenté une efficacité antiémétique et des effets secondaires habituels similaires.*

Conclusion : *Il n'y a pas de différence statistiquement significative d'efficacité antiémétique ou d'effets secondaires quand on combine un 5-HT avec le dropéridol ou la dexaméthasone et les deux combinaisons sont significativement plus efficaces que le 5-HT seul.*

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THERE are at least four major receptor systems involved in the etiology of postoperative nausea and vomiting (PONV). The concept of combination antiemetic therapy was first introduced in 1988 by Parikh in chemotherapy induced vomiting.[1] Its success prompted similar research in the field of PONV. More than 40 randomized controlled trials have been published comparing the relative efficacy of combination *vs* single agent antiemetic prophylaxis. Most of these studies suggested that a better prophylaxis against PONV might be achieved by the use of two antiemetics acting at different receptors compared with monotherapy.[2–4]

The most frequently studied combinations have included a 5-HT_3 receptor antagonist with droperidol or dexamethasone. There is a paucity of data directly comparing the antiemetic efficacy of these two combination regimens. The aim of this quantitative systematic review was to compare the relative efficacy and side-effects profile of the combination of the 5-HT_3 receptor antagonists with droperidol *vs* their combination with dexamethasone.

Methods

The study was performed in accordance with the QUORUM statement for conducting systematic reviews.[5] We did a systematic search for full reports of randomized, controlled trials that compared prophylaxis with one of the currently used 5-HT_3 receptor antagonists (ondansetron, granisetron, tropisetron or dolasetron) when combined with either droperidol or dexamethasone *vs* the 5-HT_3 receptor antagonist alone. Relevant trials had to report the main endpoints; namely the incidence of nausea and vomiting in all study groups. The databases of Medline, Embase and the Cochrane Library were searched without language restriction. Furthermore, the reference lists of retrieved reports and review articles were screened. Data from abstracts, letters, retrospective studies and unpublished data were not considered. Keywords used in the search were "ondansetron;" "granisetron;" "tropisetron;" "dolasetron;" "droperidol;" "dexamethasone;" "nausea;" "vomiting;" or "emesis;" or "retching;" "anesthesia" or "anaesthesia;" "postoperative." Both medical subject headings and text words were used. The date of the last computer search was April 2003.

The articles that could meet the inclusion criteria were scored for inclusion and methodological validity using the three-item, five-point, Oxford-scale.[6] Reports that were described as randomized were given one point, with an additional point if the method of randomization was described and adequate. One point was assigned if the trials were described as double-blind, with a further point when the method of blinding was described and considered adequate. Finally, reports that described the number of and reasons for dropouts were given one additional point. Thus, the minimum score of an included randomized controlled trial was 2; the maximum score was 5.

Two of the authors (A.H. and T.G.) extracted the following data from each study independently from each other: patient demographics, type of surgery, dose of antiemetics, time of administration, study endpoints and reported adverse events. The extracted data were cross-checked for validity. If the data were not corresponding, they were reassessed from the original literature and by discussion between the two authors. Since some studies used different observation times postoperatively, the cumulative incidences of PONV were extracted for two separate time intervals: the incidence within the first six hours postoperatively (i.e., 0 to 6 hr) was called early PONV, and the incidence within 24 hr after surgery (i.e., 0 to 24 hr) was called overall PONV. When several events were reported at different times, we analyzed the cumulative values nearest to the sixth and 24 postoperative hours. Two different PONV events, nausea and vomiting including retching, both early and overall were extracted and treated separately. We did not consider nausea scores, number of, or time of first vomiting episodes. This methodology was adapted from previously published meta-analyses on PONV.[3,7] First, we performed an analysis of all the studies combined. Then, we repeated the analysis after excluding the studies published by the Japanese group (Fujii *et al.*) except for the side effects analysis, since, in the remaining trials, side effects were reported in only one study in the droperidol group and four studies in the dexamethasone group. We performed this subgroup analysis because the serial publication of antiemetic trials by Fujii and colleagues has been criticized in the literature.[8–10] Some authors warned that including data from these studies might significantly alter the overall results in meta-analyses.[11]

The data entry and all statistical calculations were performed using the computer software review manager (RevMan) version 4.2 provided by the Cochrane Collaboration.[12] A random-effect model was applied to calculate relative risks (RR) and numbers needed-to-treat (NNT) with 95% confidence intervals (CI). For each comparison, a test of heterogeneity was performed for the included studies.

In this analysis, we compared the two combination regimens *vs* each other, but not *vs* placebo. First, we calculated the RR with corresponding 95% CI for all

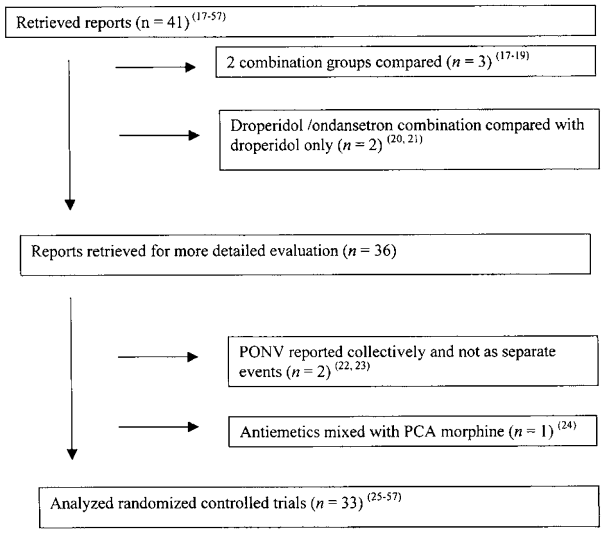

FIGURE 1 Flow chart of retrieved and analyzed reports (number of reports)[reference].

included studies comparing the combination of a 5-HT_3 receptor antagonist with droperidol *vs* 5-HT_3 receptor antagonists alone. Second, we performed a similar analysis of studies that compared the combination of a 5-HT_3 receptor antagonist with dexamethasone *vs* 5-HT_3 receptor antagonists alone. We analyzed estimates of efficacy of studies with an early event rate less than 55% and an overall event rate less than 75% in the 5-HT_3 receptor antagonists alone group, which served as a control group in this analysis. A significant difference between the two combinations was assumed if the 95% CI of the pooled RR from the above two comparisons (5-HT_3 + droperidol *vs* 5-HT_3 and 5-HT_3 + dexamethasone *vs* 5-HT_3) did not overlap. This approach has been recommended[13] and used in previously published meta-analysis on PONV.[7,11,14] More recently, the validity of meta-analysis using indirect comparisons has been established.[15]

When comparing each combination *vs* monotherapy, a RR < 1 means superiority of the combination *vs* 5-HT_3 receptor antagonists alone. The difference between the two groups is judged statistically significant when the 95% CI of the RR does not include the value of 1. As an estimate of the clinical relevance of a treatment effect, we also calculated the NNT with the corresponding 95% CI. In this analysis, the NNT is a

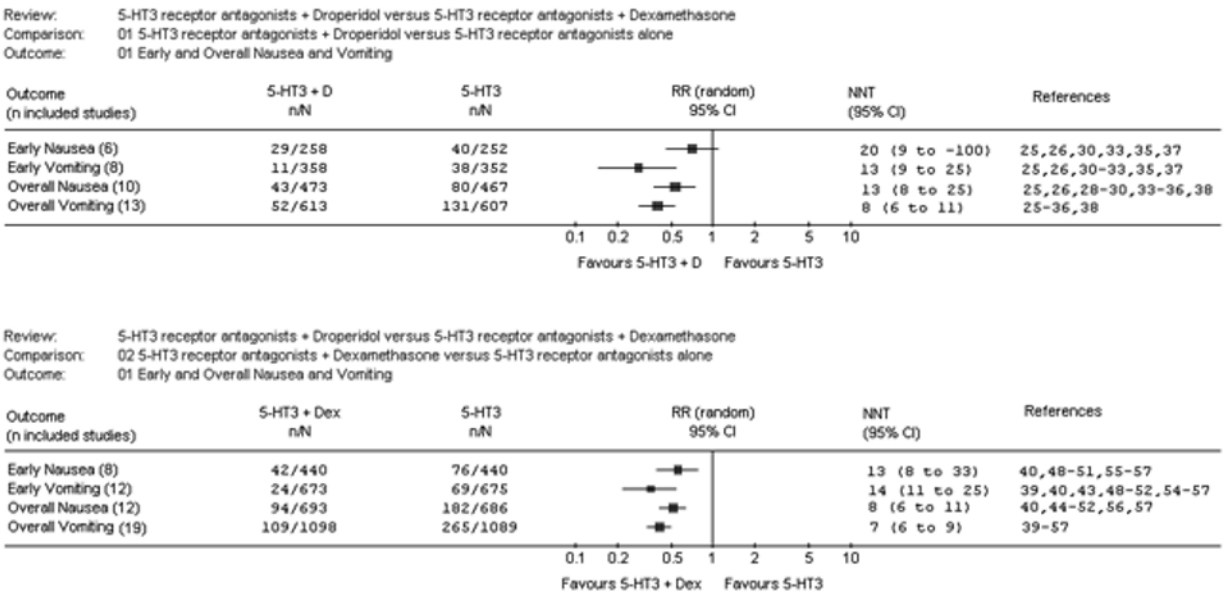

FIGURE 2 Forrest plot summarizing the pooled results of the comparison between the 5-HT_3 receptor antagonists (5-HT_3) *vs* the combination of 5-HT_3 receptor antagonists with droperidol (5-HT_3 + D) and the combination of 5-HT_3 receptor antagonists with dexamethasone (5-HT_3 + Dex) for the prevention of early (0 to 6 hr) and overall (0 to 24 hr) nausea and vomiting. The central square of each horizontal line represents the relative risk (RR) of the pooled results for each comparison. The lines demonstrate the range of the 95% confidence interval (95% CI). N = sample size; *n* = number with early or overall nausea or vomiting; NNT = number-needed-to-treat.

measure of how many patients must be treated with a combination of a 5-HT_3 receptor antagonist with droperidol or dexamethasone, to prevent one patient from having PONV who otherwise would have had PONV if treated with a 5-HT_3 receptor antagonist alone. The NNT is calculated as the inverse of the absolute risk reduction.

In order to assess whether there is a difference in treatment effect between adult and pediatric studies, and between Fujii and non-Fujii studies, we performed a test of interaction as described by Altman and Bland.[16]

Results

We considered 41 trials for analysis[17–57] but subsequently excluded eight (Figure 1).

Thirty-three randomized controlled trials with data from 3,447 patients were analyzed. Twenty-three trials were in adults, and eight were in children. The included studies with the dose regimens, time of administration of antiemetic agents, and the Oxford score of each included study, are shown in the Appendix (available as additional material at www.cja-jca.org).

A summary of the pooled results of comparing the combination of 5-HT_3 receptor antagonists with droperidol or dexamethasone *vs* 5-HT_3 receptor antagonists is presented in Figure 2. Detailed results are shown in Figures 3 to 7 (available as Additional Material at www.cja-jca.org).

Except for early nausea with 5-HT_3 receptor antagonists + droperidol, both combinations provided significantly better prophylaxis compared to 5-HT_3 receptor antagonists alone. Since the 95% CI of the RR from comparing the two combination regimens *vs* 5-HT_3 receptor antagonists alone is overlapping, we can conclude that there are no statistically significant differences in antiemetic efficacy between the two combinations.

Also, analysis of adult and pediatric data separately did not show a significant difference in antiemetic efficacy between the two combination regimens (data not presented). A test of interaction did not indicate a difference in treatment effect between adult and pediatric studies ($P = 0.2$ and $P = 0.8$ for early and overall vomiting respectively in the droperidol + 5-HT_3 receptor antagonists group, $P = 0.3$ and $P = 0.9$ for early and overall vomiting respectively in the dexamethasone + 5-HT_3 receptor antagonists group).

We then re-analyzed the data after excluding Fujii's articles (16 out of the total 33 articles). This did not alter the conclusion regarding the comparison between the two combinations (Table I). When the combinations were compared to 5-HT_3 receptor antagonists alone, however, the statistical significance was lost for all comparisons in the droperidol group and for early nausea in the dexamethasone group.

A test of interaction between Fujii and non-Fujii studies revealed a significant difference in treatment effect ($P < 0.01$) for overall vomiting in both groups (5-HT_3 receptor antagonists + droperidol *vs* 5-HT_3 receptor antagonists alone and 5-HT_3 receptor antagonists + dexamethasone *vs* 5-HT_3 receptor antagonists alone). For early and overall nausea, and for early vomiting in both groups, there was no evidence to support a different treatment effect between Fujii and non-Fuji articles.

Side effects were reported in seven studies involving the combination with droperidol and in 13 studies involving the combination with dexamethasone. The most commonly reported side effects were dizziness, headache and drowsiness. The incidence of adverse events was not different between the combination groups and 5-HT_3 receptor antagonists alone group. Since the 95% CI of the RR from comparing both combination regimens *vs* 5-HT_3 receptor antagonists alone is overlapping, we can also conclude that there is no statistically significant difference between the two combination groups in the incidence of adverse events (Table II).

Discussion

In this meta-analysis, we found no statistically significant difference in the incidence of early or overall PONV when a 5-HT_3 receptor antagonist was combined with either droperidol or dexamethasone. Both combination regimens provided significantly better PONV prophylaxis compared with 5-HT_3 receptor antagonists alone.

We decided to compare the combination of 5-HT_3 receptor antagonists with droperidol *vs* their combination with dexamethasone since they were the most commonly studied combinations. Furthermore, following the Food and Drug Administration black box warning on droperidol, it became important to find alternatives to this widely used cost-effective agent.

In our analysis, we included the four 5-HT_3 receptor antagonists (ondansetron, granisetron, dolasetron and tropisetron) within one group. This was done under the presumption that there are no major differences in antiemetic efficacy between the four 5-HT_3 receptor antagonists when used alone or in combination with droperidol or dexamethasone. Several studies have shown similar efficacy of different 5-HT_3 receptor antagonists.[58–64] More recently, a panel of experts agreed that there is no evidence of any difference in the efficacy of the 5-HT_3 receptor antagonists in the pro-

TABLE I Results of the subgroup analysis after excluding Fujii's articles. Early and overall PONV with 5-HT$_3$ receptor antagonists + droperidol (5-HT$_3$ + D) and 5-HT$_3$ receptor antagonists + dexamethasone (5-HT$_3$ + Dex) *vs* 5-HT$_3$ receptor antagonists alone

Droperidol group	*Trials (N)*	*N patients 5-HT$_3$ + D*	*N patients 5-HT$_3$*	*N (%) Event 5-HT$_3$ + D*	*N (%) Event 5-HT$_3$*	*NNT (95% CI)*	*RR (95% CI)*	*References*
Early nausea	3	108	102	27 (25)	30 (29.4)	20 (6.3– -17)	0.84 (0.56, 1.26)	25, 26, 37
Early vomiting	3	108	102	5 (4.6)	10 (9.8)	20 (8.3– -50)	0.47 (0.17, 1.30)	25, 26, 37
Overall nausea	5	213	207	36 (16.9)	53 (25.6)	11 (5– -100)	0.56 (0.29, 1.09)	25, 26, 28, 36, 38
Overall vomiting	6	253	247	43 (17.0)	57 (23.1)	20 (7.1– -33)	0.74 (0.41, 1.34)	25–28, 36, 38
Dexamethasone group	*Trials (N)*	*N patients 5-HT$_3$ + Dex*	*N patients 5-HT$_3$*	*N (%) Event 5-HT$_3$ + Dex*	*N (%) Event 5-HT$_3$*	*NNT (95% CI)*	*RR (95% CI)*	*References*
Early nausea	4	230	230	43 (18.7)	52 (22.6)	25 (8– -20)	0.81 (0.43, 1.54)	40, 55–57
Early vomiting	6	353	355	15 (4.2)	37 (10.4)	25 (13–∞)	0.45 (0.26, 0.77)	39, 40, 43, 55–57
Overall nausea	5	356	349	80 (22.5)	131 (37.5)	7 (5–13)	0.60 (0.22, 0.78)	40, 44, 45, 56, 57
Overall vomiting	10	681	672	97 (14.2)	196 (29.2)	7 (5–11)	0.49 (0.38, 0.64)	39–45, 55–57

PONV = postoperative nausea and vomiting; NNT = number needed-to-treat; CI = confidence interval; RR = relative risk.

TABLE II Side effects of the combination of 5-HT$_3$ receptor antagonists with droperidol (5-HT$_3$ + D) or dexamethasone (5-HT$_3$ + Dex) *vs* 5-HT$_3$ receptor antagonists alone

Droperidol group	*Trials (N)*	*N patients 5-HT$_3$ + D*	*N patients 5-HT$_3$*	*N (%) event 5-HT$_3$ + D*	*N (%) event 5-HT$_3$*	*NNH (95% CI)*	*RR (95% CI)*	*References*
Dizziness	4	210	210	8 (3.8)	8 (3.8)	∞ (25– -33)	1.01 (0.38, 2.68)	29, 30, 34, 35
Headache	7	325	325	33 (10.2)	33 (10.2)	∞ (25– -25)	1 (0.63, 1.58)	25, 29–32, 34, 35
Drowsiness	5	250	250	17 (6.8)	14 (5.6)	-100 (50– -20)	1.21 (0.61, 2.38)	30–32, 34, 35
Dexamethasone group	*Trials (N)*	*N patients 5-HT$_3$ + Dex*	*N patients 5-HT$_3$*	*N (%) event 5-HT$_3$ + Dex*	*N (%) event 5-HT$_3$*	*NNH (95% CI)*	*RR (95% CI)*	*References*
Dizziness	12	696	703	77 (11.1)	72 (10.2)	100 (33– -50)	0.92 (0.68, 1.25)	44–54, 57
Headache	13	698	691	94 (13.5)	104 (15.1)	100 (25– -50)	0.90 (0.70, 1.15)	40, 44–54, 57
Drowsiness	53	303	302	5 (7.6)	21 (6.4)	-100 (50– -20)	1.19 (0.68, 2.07)	45–47, 53, 54

Data from all studies combined. NNH = number needed-to-harm; RR = relative risk; CI = confidence interval.

phylaxis of PONV.[65] We did not consider the variation in the doses used since these were almost similar in the different studies (Appendix, available as Additional Material at www.cja-jca.org). Ondansetron 4 mg was used in all adult studies. The dose of granisetron was 3 mg or 40 μg·kg^{-1} in all adult studies (n = 11), except for two studies where 1 mg and 20 μg·kg^{-1} were used. A study by Wilson and colleagues demonstrated no difference in efficacy between 1 mg and 3 mg single *iv* doses of granisetron.[66] Dolasetron 12.5 mg *iv* was used in two studies and 50 mg *po* in two studies. The similar efficacy of the two regimens has been reported previously.[67] In adults, the dose of dexamethasone was 8 mg in 12 studies, 5 mg in one study, 4 mg in two studies and 20 mg in one study. In a meta-analysis, Henzi *et al.* could not establish a dose-response relationship for dexamethasone.[3] Three studies in adults used 2.5 mg of droperidol, one study 10 μg·kg^{-1} and six studies 1.25 mg (20 μg·kg^{-1} in two studies). These doses were shown previously to have the best efficacy for the prevention of PONV.[68]

In contrast to the large number of trials comparing combination antiemetics *vs* monotherapy, there is a paucity of data on the comparison between different antiemetic combinations. To date, there has been only one recent small study that compared the combination of ondansetron with droperidol *vs* its combination with dexamethasone and reported no difference in antiemetic efficacy between both groups.[69] This study, however, was not adequately powered to detect a difference between the two groups (30 patients per group). Even if we assume a baseline risk of 30% with

one combination, 74 patients would be needed per group to have an 80% power to detect a 35% reduction in the incidence of PONV, at a significance level of 0.05. In order to increase power, we included all the studies comparing the combination of 5-HT_3 receptor antagonists with droperidol or dexamethasone *vs* 5-HT_3 receptor antagonists alone, and then performed an indirect comparison between the two combinations. We decided to compare the two combinations *vs* 5-HT_3 receptor antagonists alone rather than *vs* placebo, because a placebo group was used in only nine of the included trials. Furthermore, the similar efficacy of the different 5-HT_3 receptor antagonists has been previously established.[65]

Control event rate restriction (restricting the analysis to a predefined event rate in the control group) has previously been described and used in several meta-analyses in the PONV literature.[3,7,14] Although restricting data to a certain range introduces a bias that may confound the apparent accuracy of the overall estimate, it has been shown that this bias is not large.[70,71] In this analysis, the 5-HT_3 receptor antagonists group constituted the control group. We therefore applied an upper boundary restriction of the control event rate to the 5-HT_3 receptor antagonists alone group (< 55% for early events and < 75% for overall events). However we used a slightly lower upper boundary restriction than previously described (60% and 80% for early and overall events respectively)[3,7,14] and did not restrict low event rates since, in this analysis, the control group patients are receiving an antiemetic intervention. This truncation process maintained a uniform control event rate in the droperidol and dexamethasone groups. All the included data were highly homogenous, except for one occasion (overall vomiting in the droperidol group) when heterogeneity was due to one trial with a lower event rate in the single agent group compared to the combination group. Excluding this trial eliminated the heterogeneity, without significantly altering the overall result or conclusion.

Due to concerns about altering the results of meta-analysis by including the studies published by Fujii and colleagues,[11] we decided to perform a sub-analysis after excluding the publications by this group. We also performed a test of interaction to assess whether there is a difference in treatment effect between Fujii and non-Fujii papers. The significant difference in treatment effect for overall vomiting supports the need to perform this subgroup analysis. In this meta-analysis, however, excluding Fujii's studies did not alter the conclusion regarding the indirect comparison between the two combination regimens.

The NNT in this analysis ranged from 8.3 to 20 in the 5-HT_3 receptor antagonists + droperidol group and from 7.7 to 20 in the 5-HT_3 receptor antagonists + dexamethasone group. While this may seem outside the clinically relevant range for many comparisons, it is important to remember that the NNT is highly dependent on the baseline risk of an event. A smaller NNT will result from a certain reduction in the incidence of PONV if the baseline risk is higher. In this analysis, the combinations are compared to 5-HT_3 receptor antagonists rather than placebo; hence the baseline risk is originally lower. This also emphasizes that the use of a combination of two antiemetics should only be reserved for patients at high risk for PONV.

In conclusion, we found that the combination of 5-HT_3 receptor antagonists with droperidol or with dexamethasone was significantly more effective than 5-HT_3 receptor antagonists alone. The indirect comparison between the two combination regimens did not show a statistically significant difference in the incidence of early or overall PONV, or in the incidence of reported side effects.

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