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Review Article

Drugs for preventing postoperative nausea and vomiting in adults after general anaesthesia: an abridged Cochrane network meta-analysis‡§

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Summary

Postoperative nausea and vomiting is a common adverse effect of anaesthesia. Although dozens of different anti-emetics are available for clinical practice, there is currently no comparative ranking of efficacy and safety of these drugs to inform clinical practice. We performed a systematic review with network meta-analyses to compare, and rank in terms of efficacy and safety, single anti-emetic drugs and their combinations, including 5-hydroxytryptamine$_3$, dopamine-2 and neurokinin-1 receptor antagonists; corticosteroids; antihistamines; and anticholinergics used to prevent postoperative nausea and vomiting in adults after general anaesthesia. We systematically searched for placebo-controlled and head-to-head randomised controlled trials up to November 2017 (updated in April 2020). We assessed how trustworthy the evidence was using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) and Confidence In Network Meta-Analysis (CINeMA) approaches for vomiting within 24 h postoperatively, serious adverse events, any adverse event and drug class-specific side-effects. We included 585 trials (97,516 participants, 83% women) testing 44 single drugs and 51 drug combinations. The studies' overall risk of bias was assessed as low in only 27% of the studies. In 282 trials, 29 out of 36 drug combinations and 10 out of 28 single drugs lowered the risk of vomiting at least 20% compared with placebo. In the ranking of treatments, combinations of drugs were generally more effective than single drugs. Single neurokinin-1 receptor antagonists were as effective as other drug combinations. Out of the 10 effective single drugs, certainty of evidence was high for aprepitant, with risk ratio (95%CI) 0.26 (0.18–0.38); ramosetron, 0.44 (0.32–0.59); granisetron, 0.45 (0.38–0.54); dexamethasone, 0.51 (0.44–0.57); and ondansetron, 0.55 (0.51–0.60). It was moderate for fosaprepitant, 0.06 (0.02–0.21) and droperidol, 0.61 (0.54–0.69). Granisetron and amisulpride are likely to have little or no increase in any adverse event compared with placebo, while dimenhydrinate and scopolamine may increase the number of patients with any adverse event compared with placebo. So far, there is no convincing evidence that other single drugs effect the incidence of serious, or any, adverse events when compared with placebo. Among drug class specific side-effects, evidence for single drugs is mostly not convincing. There is convincing evidence regarding the prophylactic effect of at least seven single drugs for postoperative vomiting such that future studies

investigating these drugs will probably not change the estimated beneficial effect. However, there is still considerable lack of evidence regarding safety aspects that does warrant investigation.

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Introduction

Postoperative nausea and vomiting is a common adverse effect of anaesthesia and surgery, with an estimated incidence of 30% in the general surgical population and up to 80% in high-risk patients [1–5]. These outcomes are a major cause of patient dissatisfaction after surgery [6, 7] and lead to prolonged hospital stay and higher costs [8, 9]. Considering that nearly 3 million general anaesthetics are given annually in the UK alone [10], the public health impact of reducing postoperative nausea and vomiting (PONV) is substantial. Enhanced recovery programmes in surgical patients and the promotion of day case surgery both require and include adequate prophylaxis of PONV [11].

There are dozens of different anti-emetic drugs, mostly within the drug classes of 5-hydroxytryptamine$_3$ ($5HT_3$), dopamine-2 (D_2) and neurokinin-1 (NK_1) receptor antagonists, corticosteroids, antihistamines and anticholinergics [5, 12–14]. Varying adverse effects have been attributed to the six different substance classes, such as headache and constipation (5-HT_3 receptor antagonists); extrapyramidal symptoms, sedation, arrhythmia and QT prolongation (D_2 receptor antagonists); hyperglycaemia, immunosuppression and poor wound healing (corticosteroids); drowsiness, dry mouth and urinary difficulties (antihistamines); and dry mouth and visual disturbances (anticholinergics) [5, 13, 14]. There is currently limited evidence on adverse effects arising from NK_1 receptor antagonists. However, increased dizziness and headache have been described by individual studies [15].

Since the 1960s, a tremendous number of clinical studies investigating prophylactic measures for PONV have been published.

In 2015, Tricco et al. published a systematic review mainly limited to the comparison of the many serotonin receptor antagonist drugs for the prevention of PONV [16, 17]. The authors used a novel approach called network meta-analysis that allows comparisons of more than two interventions in a single, coherent analysis of all the relevant RCTs with both direct and indirect comparisons. For example, if three drugs (A, B, C) are compared in pairs in separate RCTs, drug B in A vs. B trials can be indirectly compared with drug C in A vs. C trials because of the common comparator drug A [18]. A network meta-analysis allows one to simultaneously estimate relative effectiveness for any pair of interventions forming an evidence network. The ranking of available anti-emetics with regard to their effectiveness for PONV prophylaxis, as well as adverse effects to provide best evidence for clinical practice, becomes possible.

Despite the continuing increase in the number of clinical trials on PONV, there is still no current evidence-based overview of all relevant substance classes, nor a clinically useful ranking of all anti-emetic drugs in terms of efficacy and safety. To maximise the benefit and avoid overtreatment [19] with adverse effects [20], a comprehensive systematic review is urgently needed. Therefore, this network meta-analysis – spanning all relevant drug classes – illuminates and ranks the differences in dose and effect of single and multiple drug interventions, which existing reviews do not address [16]. This review provides a complete evidence-base to inform guideline updates [4, 5].

Methods

This systematic review with network meta-analysis was registered in the Cochrane Database of Systematic Reviews and followed a published protocol [21].

We included RCTs that were reported as full-text journal publications or comprehensive study reports, published in any language. Retracted studies, and studies authored by Fujii et al. were not included [22, 23]. Studies were required to investigate adult participants undergoing any type of surgery with general anaesthesia; and compare single or multiple pharmacological intervention(s) with anti-emetic action belonging to one out of the six drug classes with each other, with no treatment, or with placebo. The current review includes the following 'interventions of direct interest' (decision set), listed here with the abbreviations used in the Tables and Figures:

1. 5-HT_3 receptor antagonists: dolasetron (dola), granisetron (gran), ondansetron (onda), palonosetron (palo), ramosetron (ramo) and tropisetron (trop)
2. D_2 receptor antagonists: amisulpride (amis), droperidol (drop), haloperidol (halo), metoclopramide (meto) and perphenazine (perp)
3. NK_1 receptor antagonists: aprepitant (apre), casopitant (caso), fosaprepitant (fosa) and rolapitant (rola)
4. Corticosteroids: dexamethasone (dexa) and methylprednisolone (meth)
5. Antihistamines (histamine-1 receptor antagonists): dimenhydrinate (dime), meclizine (mecl) and promethazine (prom)
6. Anticholinergics: scopolamine (scop)

Additionally, we included any other drug belonging to these drug classes in the network to increase the amount of available information in the analysis. All drugs had to be administered before or during anaesthesia with the aim of preventing PONV. Combinations of drugs represented a separate intervention of interest and therefore a separate node in the network meta-analysis. Different doses of drugs were combined into one node. Primary outcomes of the review were: vomiting within 24 h postoperatively; serious adverse events; and any adverse event, both within 7 days postoperatively. Secondary outcomes were: drug class-specific side-effects (e.g. headache, constipation, extrapyramidal symptoms, sedation, arrhythmia, QT prolongation, wound infection and visual disturbances); early and late vomiting; nausea; and 'complete response' (defined as no nausea, no vomiting and no rescue anti-emetic treatment for the first 24 h).

In November 2017, we searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, CINAHL, study registers (ClinicalTrials.gov, WHO ICTRP) and the reference lists of relevant systematic reviews for eligible trials. All included trials were checked for retractions against the Retraction Watch database (November 2018). The search was updated in April 2020. Details of the search strategy are provided in the full Cochrane review [21, 24].

The review team then independently, and in duplicate, assessed trials for inclusion and extracted data from eligible trials using Covidence (https://www.covidence.org). We assessed the study's risk of bias using the Cochrane 'risk of bias' assessment tool 1.0 and summarised the overall risk of bias for each study with reference to the judgements for the domains 'sequence generation', 'blinding of participant, personnel and outcome assessors' and 'incomplete outcome data'.

We assessed the distribution of potential effect modifiers across the studies contributing data to an outcome to check whether the transitivity assumption held true. For the effect modifiers 'risk of bias' and 'dose of intervention', we accepted differences in the distribution of these effect modifiers across treatment comparisons, and assessed their impact using sensitivity analysis and sub-group analysis, respectively.

Dichotomous outcome data in both pairwise meta-analyses and network meta-analyses were summarised as risk ratios (RR) (95%CI). Pairwise meta-analyses comparing single drugs of direct interest to placebo were performed using Review Manager 5.4 (The Nordic Cochrane Centre, Copenhagen, Denmark) and are presented in the full Cochrane review [24]. For network meta-analyses, we used a frequentist approach based on the graph-theoretical method by Rücker et al. [25]. We investigated network geometry and performed random-effects network meta-analysis using the R (R Development Core Team, Vienna, Austria) package netmeta version 1.0–1 [26, 27]. We included trials with zero events, using the constant continuity correction approach [28]. Multi-arm studies were included in the dataset as a series of two-arm comparisons with adjusted standard errors [25, 27, 29]. Results from network meta-analyses were presented as summary risk ratio for each possible pairing of treatments. Mixed treatment evidence was separated into direct and indirect evidence using the function netsplit of the R package netmeta.

We looked at comparative efficacies of the anti-emetic drugs, and expressed this using placebo as the reference comparator and presented the results in forest plots. Treatment effects in forest plots were ranked according to P scores using the function netrank of the R package netmeta [29]. P scores measure the extent of certainty that a

treatment is better than another treatment, averaged over all competing treatments [29].

Clinically meaningful effect sizes were pre-specified. For vomiting, effect estimates with the upper boundary of the RR 95%CI < 0.80 were declared beneficial. A lower boundary of the RR 95%CI > 1.25 was declared harmful. The range between 0.8 and 1.25 was termed the 'range of equivalence' (indicating no clinically-relevant difference from the comparator) [30]. For completeness, all drug and drug combinations were ranked against placebo as the reference standard. For serious adverse events, any adverse event and all class-specific side-effects, we defined the 'range of equivalence' more conservatively as an RR between 0.9 and 1.11.

We assessed heterogeneity of individual comparisons using the 95% prediction interval. We assumed heterogeneity if the 95% prediction interval and the 95%CI of the network meta-analysis treatment estimate differed with respect to the range of clinically-relevant effect sizes ('range of equivalence'). We assessed heterogeneity within studies comparing the same treatments, and inconsistency between studies comparing different sets of treatments of the whole network, using the *Q* statistic [31, 32] and the full random-effects design-by-treatment interaction model [31]. At a local level (regions of the network), we did a statistical evaluation of incoherence comparing direct and indirect evidence of comparisons using descriptive *Z*-tests and interpretation in terms of clinically-relevant effect sizes [33]. We investigated the effect modifier 'dose of the intervention' as potential source of heterogeneity and performed a network meta-analysis with sub-groups. We separated different doses of the same drug into 'low', 'recommended' and 'high' doses [21]. Dose recommendations are based on Gan et al. [5].

Publication bias was explored in standard pairwise meta-analysis of comparisons with 10 or more trials with contour-enhanced funnel plots, Rücker's arcsine test, and trim and fill sensitivity analyses using the R package meta version 4.9-7.

Rating of the certainty of evidence contributing to network estimates was based on the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group (https://www.gradeworkinggroup.org) and was assessed using an alternative system developed by Salanti et al. (termed CINeMA, Confidence in Network Meta-Analysis [34, 35]). The assessment of the certainty of evidence was restricted to primary outcomes and substance class-specific side-effects, and to the single drugs of direct interest (decision set). The body of the network meta-analysis evidence was assessed by two independent authors and reflects within-study risk of bias (study limitations), across-studies bias (publication bias), indirectness, imprecision, heterogeneity (variability between studies within each comparison) and incoherence (variability between direct and indirect evidence). The GRADE assessment resulted in one of four levels of certainty ('very low', 'low', 'moderate' or 'high'), which express our confidence in the estimate of effect [36]. For example, a 'high' GRADE rating asserts that further research with new RCTs is unlikely to change the magnitude of effect while a 'very low' GRADE rating indicates that the magnitude and even direction of effect is uncertain.

Results

Searching identified 21,016 records; 1762 were reviewed in full text, and 732 records reporting 585 studies were eligible for inclusion (Fig. 1). References to the included studies are available in online Supporting Information, Appendix S1). Awaiting classification in a future update of the review are 340 studies including 39 trials identified in the search update, all with insufficient information.

The 585 included RCTs, comprising 97,516 randomised participants, were mostly of small size with a median (IQR [range]) number of 100 (70–160 [20–5199]) participants, published between 1965 and 2017 (with 71% from 2000 onwards), and primarily conducted in Asia (51%), Europe (25%) and North America (16%). The overall population's mean (SD) age was 42.0 (12.5) years. Most participants were women (83%), of ASA physical status 1 and 2 (70%), who received peri-operative opioids (88%) and underwent gynaecological (32%) or gastrointestinal surgery (19%) under general anaesthesia using volatile anaesthetics (88%). In this review, 44 single drugs (21 interventions of direct interest and 23 additional interventions to supplement the analysis) and 51 drug combinations were included. Most studies investigated only single drugs (72%) and included an inactive control arm (66%). The three most investigated single drugs in this review were ondansetron (246 studies), dexamethasone (120 studies) and droperidol (97 studies). Almost all studies (89%) reported at least one efficacy outcome (vomiting, nausea or 'complete response') relevant for this review. However, only 56% reported at least one relevant safety outcome.

Altogether, 157 studies (27%) were assessed as overall low risk of bias, 101 studies (17%) as overall high risk of bias, and 327 studies (56%) as overall unclear risk of bias. About half of all studies were rated as low risk of bias for random sequence generation, blinding of participants and personnel, and outcome assessors. Incomplete reporting of

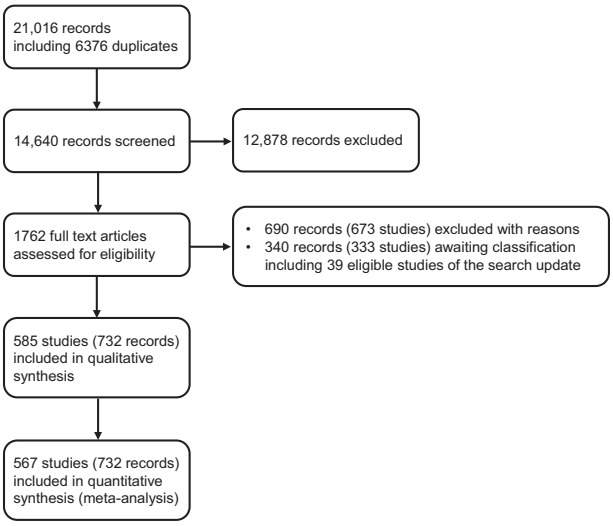

Figure 1 Systematic review flow diagram.

outcome data was assessed as low risk in 90% of the studies (Fig. 2). Only 12% and 2% of all studies were assessed as low risk of bias for allocation concealment and selective outcome reporting, respectively.

The direction and magnitude of network effect estimates, together with the level of evidence certainty is graphically summarised for GRADE-relevant outcomes and drugs of direct interest (decision set) compared with placebo in Fig. 3. Details on current evidence for all outcomes are provided in a Summary of Findings table for the most effective single drugs with moderate or high certainty evidence regarding vomiting (see online Supporting Information, Appendix S2).

Vomiting within 24 h postoperatively

Figure 4 shows the network of eligible comparisons for vomiting, including 282 RCTs with 50,812 participants and 65 interventions (36 drug combinations, 28 single drugs and placebo). Ondansetron (77 studies), dexamethasone (43 studies) and droperidol (41 studies), all compared with placebo, were the most common comparisons.

Figure 5 shows the network meta-analysis results with ranking of all interventions compared with placebo for vomiting. This ranking showed that combinations of drugs were generally more effective than single drugs in preventing vomiting. The NK_1 receptor antagonists were the most effective drug class and single NK_1 receptor antagonists (fosaprepitant, casopitant, aprepitant) were as effective as most of the drug combinations. Of all single drugs, fosaprepitant, casopitant, aprepitant, ramosetron, granisetron, dexamethasone, tropisetron, ondansetron, dolasetron and droperidol were more effective than placebo and ranked 1st, 2nd, 3rd, 5th, 6th, 8th, 9th, 13th, 14th and 20th, respectively. Treatment effects of all single drugs, expressed as RR (95%CI) compared with placebo ranged between 0.06 (0.02–0.21) for fosaprepitant and 1.08 (0.54–2.15) for buspirone. Of the drug combinations, 29 out of 36 were more effective than placebo. Treatment effects as RR (95%CI) ranged between 0.01 (0.00–0.19) for aprepitant-palonosetron and 1.04 (0.17–6.45) for metoclopramide-promethazine.

There was major heterogeneity within studies comparing the same treatments and inconsistency between studies comparing different sets of treatments ($p < 0.0001$). However, all inconsistency could be explained by the different treatment sub-sets. Sub-group analysis showed that recommended and high doses of granisetron, dexamethasone, tropisetron, ondansetron and droperidol were similarly effective, but both more effective than low doses. For other single drugs, there were no dose effects detectable. The most commonly used doses, routes and administration time-points of single drugs of direct interest for vomiting are summarised in Table 1.

We found high certainty evidence of clinical efficacy compared with placebo for aprepitant, ramosetron, granisetron, dexamethasone and ondansetron; and moderate certainty evidence for fosaprepitant and droperidol (Fig. 3, online Supporting Information, Appendix S2). Other single drugs of direct interest compared with placebo were either: clinically effective with very low or low certainty evidence (casopitant, tropisetron, dolasetron); minimally effective with moderate certainty evidence (amisulpride, promethazine); or minimally effective with very low or low certainty evidence

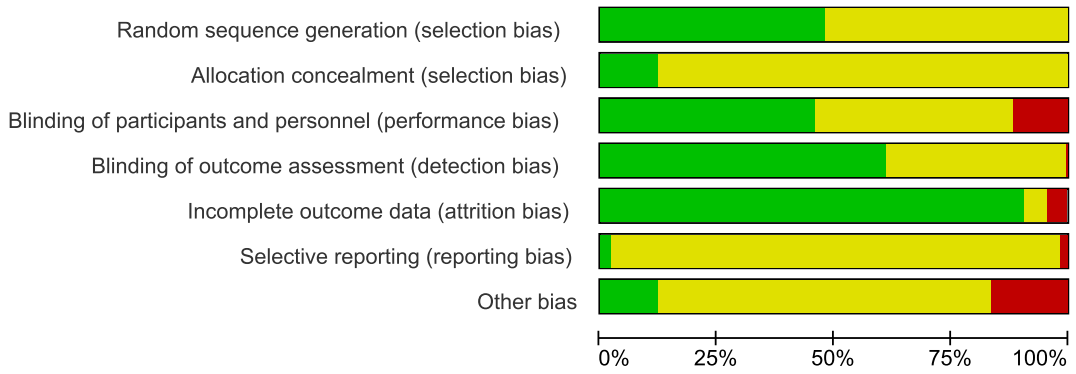

Figure 2 Risk of bias: review authors' judgements about each risk of bias item presented as percentages across all included studies. Green, low risk of bias; yellow, unclear risk of bias; red, high risk of bias.

Drugs	Outcomes										
	Vomiting 0 to 24h	SAE	Any AE	Headache	Constipation	Extrapyramidal symptoms	Sedation	Arrhythmia	QT prolongation	Wound infection	Visual disturbances
5-HT$_3$ antagonists											
Dolasetron	low	low	very low	low	NA	low	low	low	NA	NA	NA
Granisetron	high*	very low	moderate	very low	very low	very low	very low	very low	NA	NA	NA
Ondansetron	high*	very low	low	moderate	very low	very low	moderate*	very low	low	very low	low
Palonosetron	low	very low	low	very low	very low	very low	very low	NA	very low	NA	NA
Ramosetron	high	very low	very low	low	very low	very low	low	low	very low	NA	NA
Tropisetron	low*	very low	low	low	very low	very low	low	very low	very low	low	very low
D$_2$ receptor antagonists											
Amisulpride	moderate	low	moderate	low	very low	low	low	NA	NA	NA	NA
Droperidol	moderate*	low	low	moderate	NA	low	low	very low	low	NA	very low
Haloperidol	low	NA	NA	low	NA	low	very low	very low	low	NA	NA
Metoclopramide	very low	NA	low	very low	low	low	very low	very low	NA	very low	low
Perphenazine	NA	NA	NA	NA	NA	very low	very low	NA	NA	NA	NA
NK$_1$ receptor antagonists											
Aprepitant	high	very low	very low	low	very low	NA	very low	NA	very low	NA	NA
Casopitant	low	very low	very low	very low	very low	NA	NA	NA	NA	NA	NA
Fosaprepitant	moderate	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Rolapitant	very low	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Corticosteroids											
Dexamethasone	high*	very low	low	low	low	low	high	low	very low	very low	low
Methylprednisolone	NA	NA	NA	NA	NA	NA	low	very low	NA	very low	very low
Antihistamines											
Dimenhydrinate	very low	NA	low	very low	NA	NA	moderate	NA	NA	NA	NA
Meclizine	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Promethazine	moderate	NA	NA	very low	NA	NA	very low	NA	NA	NA	NA
Anticholinergics											
Scopolamine	low	very low	low	very low	NA	NA	very low	NA	NA	NA	low

Figure 3 Direction of network effect estimates (colour) of single drugs of direct interest compared with placebo with certainty levels of evidence (high, moderate, low, very low) for primary outcomes and side-effects. Colour code: important benefit (green), uncertain benefit (light green), no important effect (yellow), uncertain minimal (or no) effect (light yellow), uncertain harm (orange), important harm (red), no studies available (NA).

(palonosetron, haloperidol, metoclopramide, rolapitant, dimenhydrinate and scopolamine) (Fig. 3).

Serious adverse events

Twenty-eight RCTs were included in the network meta-analysis for serious adverse events, with 10,766 participants and 22 interventions (13 single drugs, 8 drug combinations and placebo) (Fig. 6a). Out of the 21 active interventions, none showed an important benefit or harm regarding serious adverse events compared with placebo, but all effect estimates showed a high level of uncertainty with wide 95%CIs (Fig. 6b). Treatment effects, expressed as RR (95%CI) of all interventions compared with placebo ranged between 0.31 (0.10–1.00) for dolasetron and 3.64 (0.57–23.11) for casopitant. The certainty of evidence for interventions of direct interest compared with placebo ranged from very low to low (Fig. 3, online Supporting Information, Appendix S2). No studies reporting serious adverse events were available for fosaprepitant.

Adverse events

Sixty-one RCTs were included in the network meta-analysis for any adverse event, with 19,423 participants and 27 interventions (15 single drugs, 11 drug combinations and placebo) (Fig. 7a). Scopolamine and dimenhydrinate showed significant harm compared with placebo. All other effect estimates showed no or little (beneficial) effect or were of high uncertainty (imprecise 95%CI). Treatment effects, as RR (95%CI), of all interventions compared with placebo ranged between 0.09 (0.01–1.55) for betamethasone and 5.70 (1.36–23.93) for dimenhydrinate (Fig. 7b). The certainty of evidence for interventions of direct interest ranged from very low to moderate (Fig. 3, online Supporting Information, Appendix S2). There is

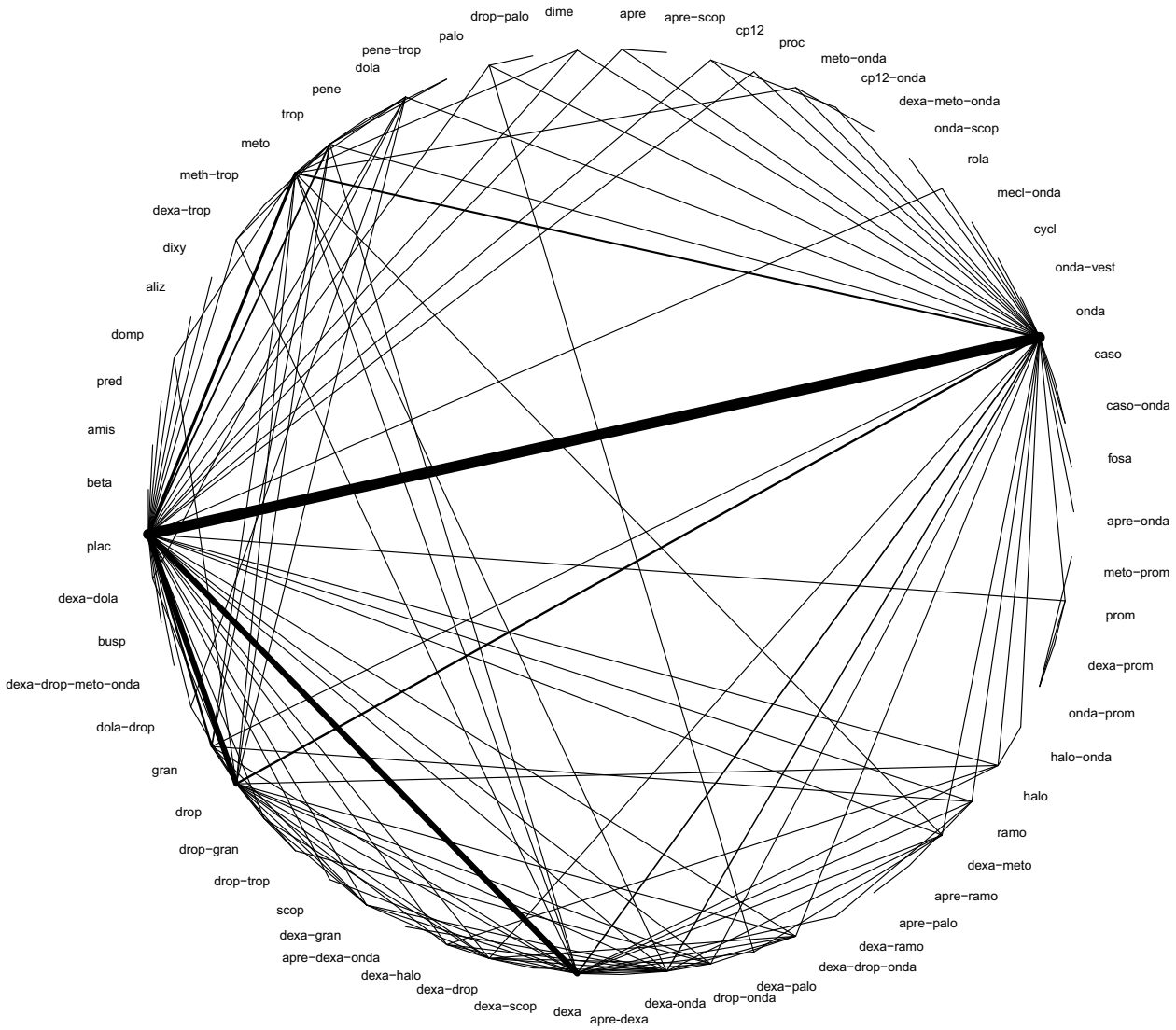

Figure 4 Network geometry of eligible comparisons for postoperative vomiting within 24 h after surgery. The thickness of the edges is proportional to the number of included studies comparing two treatments. Abbreviations for treatments are listed in the Methods.

moderate certainty evidence, as RR (95%CI) that granisetron 0.92 (0.80–1.05) and amisulpride, 0.97 (0.90–1.06) have little or no effect on any adverse event. No studies reporting any adverse event were available for fosaprepitant.

Headache was the most studied adverse event, with 208 RCTs, and QT prolongation the rarest, with 18 RCTs. The full Cochrane review provides detailed results of all side-effects [24]. When analysing substance class-specific side-effects, network estimates of single drugs were mostly imprecise and showed a high level of uncertainty. We did find that droperidol reduced headache, dimenhydrinate increased sedation and scopolamine increased visual disturbances. In the ranking of interventions for specific outcomes, the class of 5-HT_3 receptor antagonists generally increased the risk of headache and D_2 receptor antagonists increased the risk of extrapyramidal symptoms more than other substance classes, respectively. The certainty of evidence mostly ranged from very low to low for single drugs of direct interest (Fig. 3), but there was moderate certainty evidence, as RR (95%CI) that ondansetron increases, 1.16 (1.06–1.28), and droperidol reduces, 0.76 (0.67–0.86), headache when compared with placebo. There was moderate certainty evidence, RR (95% CI), that dimenhydrinate increased, 7.66 (3.10–18.94) and ondansetron reduced, 0.87 (0.79–0.96) sedation and high certainty evidence that dexamethasone had no effect on sedation 1.00 (0.91–1.09), all compared with placebo. No

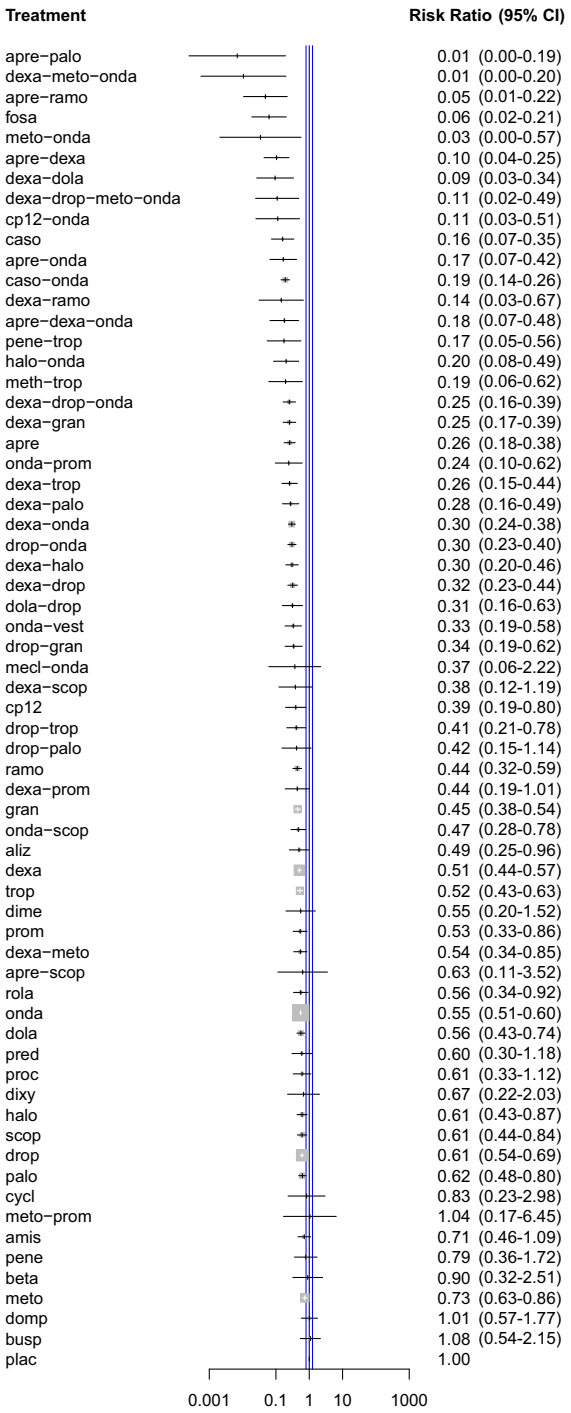

Figure 5 Forest plot of network meta-analysis of all trials for postoperative vomiting within 24 h after surgery. Single drugs and combinations were compared with placebo (reference compound). RR < 1 favours the intervention, RR > 1 favours placebo. The blue lines indicate the range of equivalence (RR = 0.8–1.25). Treatments were ranked based on P scores with most effective drug on the top. Abbreviations for treatments are listed in the Methods. RR, risk ratio.

studies assessed substance class-specific side-effects for fosaprepitant.

The network meta-analysis of nausea showed less benefit for the NK_1 antagonists, fosaprepitant and aprepitant, than for vomiting. Ramosetron, droperidol, granisetron, dexamethasone and ondansetron all showed similarly important benefit for nausea and their anti-nausea efficacy was comparable to their anti-emetic efficacy. For the composite outcome 'complete response' all seven drugs showed important benefit and ranked with decreasing order according to efficacy: ramosetron, granisetron, fosaprepitant, aprepitant, dexamethasone, droperidol and ondansetron. Details on nausea, complete response, early and late vomiting are provided in the full Cochrane review [24].

Discussion

This is the first network meta-analysis to compare all available anti-emetic drugs of relevant substance classes, assess the certainty of evidence, and produce a ranking of all drugs in terms of efficacy and safety. Using this novel approach, which allows for direct and indirect comparison and subsequent ranking of prophylactic anti-emetics, we found seven effective single drugs for the prevention of postoperative vomiting in this review. Five had high certainty evidence (aprepitant, ramosetron, granisetron, dexamethasone and ondansetron) and two moderate certainty evidence (fosaprepitant and droperidol). Therefore, four of the six substance classes ($5-HT_3$ antagonists, D_2 antagonists, NK_1-receptor antagonists and corticosteroids) with different mechanisms of action are represented by at least one drug that effectively prevents vomiting.

In absolute numbers, for every 1000 patients, of whom 300 would vomit after surgery if given placebo [5], 282 would benefit from fosaprepitant (the most effective drug among the seven single drugs with moderate/high evidence) and 18 would not. By giving droperidol (the least effective drug among the seven single drugs with moderate/high evidence), 117 patients would benefit and 183 would not. Aprepitant, ramosetron, granisetron, dexamethasone and ondansetron were located between fosaprepitant and droperidol in terms of their efficacy for the prevention of vomiting.

Compared with existing systematic reviews and recommendations, newer drugs such as fosaprepitant, aprepitant and ramosetron are worthy of recommendation in addition to the standard anti-emetics (ondansetron, dexamethasone, droperidol and granisetron) and should replace older, less effective substances such as metoclopramide and scopolamine [1].

Table 1 Most commonly used dosages, routes and administration time-points of single drugs of direct interest (primary outcome: vomiting).

Drug	Doses*	Dose category	Route	Timing
Amisulpride	5–10 mg	rec	i.v	At induction of anaesthesia
Aprepitant	40 mg	rec	p.o.	Before surgery
Casopitant	150 mg	rec	p.o.	Before surgery
Dexamethasone†	4–5 mg	rec	i.v.	At induction of anaesthesia
Dimenhydrinate	< 1 mg.kg^{-1}	low	i.v./i.m	At induction of anaesthesia/before surgery
Dolasetron	12.5 mg	rec	i.v.	End of surgery
Droperidol	0.625–1.25 mg	rec	i.v.	At induction of anaesthesia
Fosaprepitant	150 mg	N/A	i.v.	At induction of anaesthesia
Granisetron	0.35–3 mg	rec	i.v.	All time-points
Haloperidol	0.5 to < 2 mg	rec	i.v.	At induction of anaesthesia
Metoclopramide	25–50 mg	low	i.v.	At induction of anaesthesia
Ondansetron (i.v.)	4 mg	rec	i.v.	At induction of anaesthesia
Ondansetron (p.o.)	8 mg	rec	p.o.	Before surgery
Palonosetron	0.075 mg	rec	i.v.	At induction of anaesthesia
Promethazine‡	< 6.25 mg	low	i.v.	At induction of anaesthesia
Ramosetron (i.v.)	0.3 mg	rec	i.v.	End of surgery
Rolapitant	70–200 mg	rec	p.o.	Before surgery
Scopolamine	1.5 mg	N/A	t.d.	Before surgery
Tropisetron (i.v.)†	2 mg	rec	i.v.	At induction of anaesthesia

N/A, not applicable; i.v., intravenous; i.m., intramuscular; p.o., per oral; t.d., transdermal; rec, recommended.
*Most commonly used in included studies.
†Most of the studies investigated high doses, but recommended were also effective.
‡Not used in any of the included studies with the recommended dose.

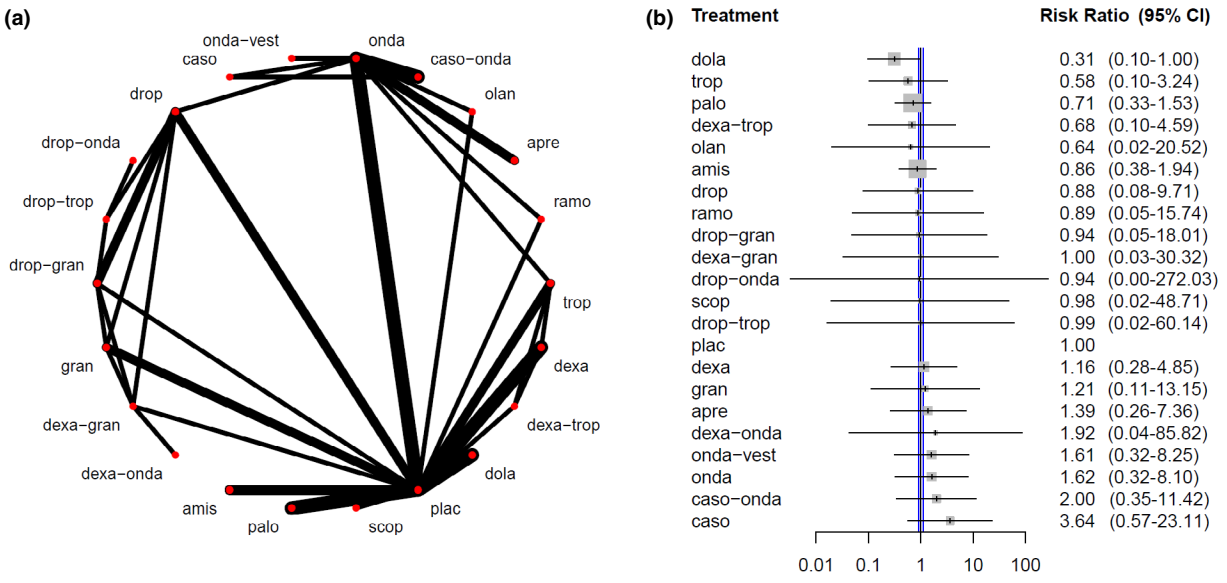

Figure 6 Network geometry of eligible comparisons (a) and forest plot (b) for serious adverse events. RR < 1 favours the intervention, RR > 1 favours placebo. The blue lines indicate the range of equivalence (RR = 0.9–1.11). Treatments were ranked based on P scores with safest drug on the top. Abbreviations for treatments are listed in the Methods. RR, risk ratio.

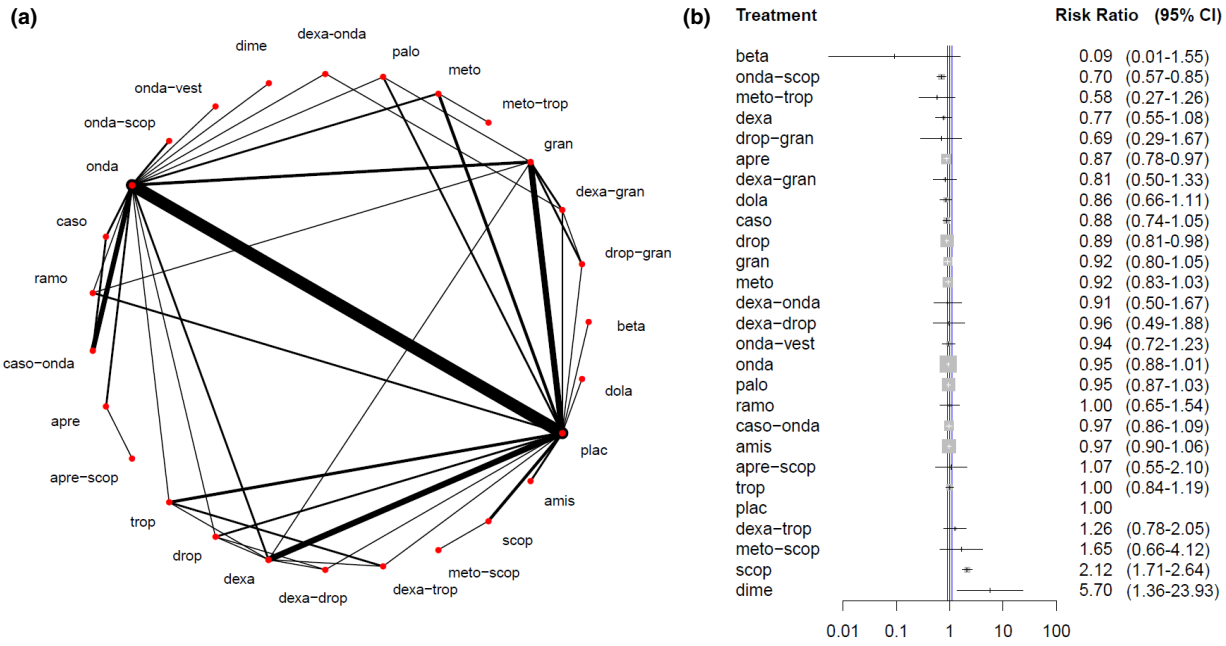

Figure 7 Network geometry of eligible comparisons (a) and forest plot (b) for any adverse event. RR < 1 favours the intervention, RR > 1 favours placebo. The blue lines indicate the range of equivalence (RR = 0.9–1.11). Treatments were ranked based on P scores with safest drug on the top. Abbreviations for treatments are listed in the Methods. RR, risk ratio.

Our network meta-analysis on prevention of vomiting showed that recommended and high doses of granisetron, dexamethasone, ondansetron and droperidol were similarly effective, but more effective than low doses. With available RCTs, there was no dose-response effect detectable for aprepitant and ramosetron, which are both used as recommended by Gan et al. [5]. Fosaprepitant, for which no dose recommendations have been made so far [4, 5], has been used in doses of 150 mg.

In the ranking of interventions, combinations of drugs were generally more effective than the corresponding single drugs in preventing vomiting. This concept that a combination therapy using different classes of drugs is more effective than single therapy was originally demonstrated including dexamethasone, droperidol and ondansetron [37]. In this review, we found that NK_1 receptor antagonists were the most effective drug class for prevention of vomiting and these single drugs have comparable efficacy to most of the drug combinations.

This review compared 44 single drugs belonging with six different substance classes. Twenty-one of the 44 drugs were of direct interest, all of which except meclizine were listed in the newest consensus guidelines for the management of PONV [4]. The additional 23 drugs not of direct interest were investigated in only 7% of all included studies reflecting the lack of importance of these drugs in clinical practice.

This is the first review to assess how trustworthy the current evidence of anti-emetic drugs is in terms of efficacy and safety, based on the GRADE approach. Certainty of evidence of effect estimates can greatly vary across comparisons within a network. In making inferences regarding the choice of an intervention, recognising the certainty of each comparison is far more valuable than ranking efficacy alone [38]. In this context, casopitant, dolasetron and tropisetron are as effective as, for example, aprepitant or ondansetron when considering the ranking of drugs against vomiting. However, there is still uncertainty about the evidence that makes these drugs less reliable today than others.

Prophylaxis of PONV has a large impact on patient care in high-risk populations. However, in a general surgical population of low to moderate risk (i.e. about 30% of patients experiencing vomiting [5]), most patients will not benefit from routinely administered prophylactic anti-emetics, because about 70% do not suffer from vomiting. In this scenario, it is important to understand the risk of side-effects for a risk-benefit assessment. For most of the single drugs of direct interest, we found only very low to low certainty evidence for safety outcomes such as occurrence

of serious, or any, adverse events and substance class-specific side-effects. The ranking of drugs for all safety outcomes is unreliable due to excessive uncertainty in the relative effects. To increase the chances of detecting even rare side-effects (e.g. QT prolongation, arrhythmia or extrapyramidal symptoms) non-randomised cohort studies, and systematic reviews including such studies in addition to RCTs, will be useful in future.

According to the newest version of a guideline on the management of PONV [4], multimodal prophylaxis should be considered for patients with medium or high risk. Most of the studies included in this review were conducted in patients at medium to high risk of nausea and vomiting, that is, healthy women receiving inhalational anaesthesia and peri-operative opioids. To what extent patients with more severe disease, or those in other clinical settings derive benefit or harm from anti-emetic prophylaxis is not answered by this review.

We performed a comprehensive literature search. However, we decided to exclude all trials published as conference abstracts, to enhance feasibility of the workload. Although there is the possibility that a certain amount of potentially relevant data were not included, our analyses on reporting bias did not suggest that potentially missing studies alter the conclusion of the results [24]. Several studies had duplicate publication in different journals and were listed in trial registries under different first authors; this complicated the process of data synthesis. By making the dataset fully and freely available [24], we welcome perusal by outside researchers to identify mistakes in our dataset, our analysis or our interpretation.

In conclusion, there is little need for further efficacy studies as there is moderate to high certainty evidence that there are seven single drugs with relevant benefit for prevention of vomiting. However, studies are still needed investigating potential side-effects of these drugs and considering patient populations with comorbidities (e.g. individuals with diabetes and heart disease). This network meta-analysis represent the most comprehensive, currently available evidence base to guide clinical practice and guideline development regarding anti-emetic prophylaxis for postoperative vomiting.

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Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. List of references of included studies of the Cochrane review [24].

Appendix S2. Estimates of effects and certainty of the evidence of antiemetic drugs for prevention of postoperative nausea and vomiting in adults after general anaesthesia.

