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# Drugs for preventing postoperative nausea and vomiting in adults after general anesthesia: An abridged Cochrane network meta-analysis

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## Abstract

**Objective:** In this abridged version of the recently published Cochrane review on antiemetic drugs, we summarize its most important findings and discuss the challenges and the time needed to prepare what is now the largest Cochrane review with network meta-analysis in terms of the number of included studies and pages in its full printed form.

**Methods:** We conducted a systematic review with network meta-analyses to compare and rank single antiemetic drugs and their combinations belonging to $5HT_3$-, $D_2$-, $NK_1$-receptor antagonists, corticosteroids, antihistamines, and anticholinergics used to prevent postoperative nausea and vomiting in adults after general anesthesia.

**Results:** 585 studies (97 516 participants) testing 44 single drugs and 51 drug combinations were included. The studies' overall risk of bias was assessed as low in only 27% of the studies. In 282 studies, 29 out of 36 drug combinations and 10 out of 28 single drugs lowered the risk of vomiting at least 20% compared to placebo. In the ranking of treatments, combinations of drugs were generally more effective than single drugs. Single $NK_1$ receptor antagonists were as effective as other drug combinations. Of the 10 effective single drugs, certainty of evidence was high for aprepitant, ramosetron, granisetron, dexamethasone, and ondansetron, while moderate for fosaprepitant and droperidol. For serious adverse events (SAEs), any adverse event (AE), and drug-class specific side effects evidence for intervention effects was mostly not convincing.

**Conclusions:** There is high or moderate evidence for at least seven single drugs preventing postoperative vomiting. However, there is still considerable lack of evidence regarding safety aspects that does warrant investigation.

KEYWORDS
antiemetics, network meta-analysis, postoperative nausea and vomiting, systematic review, vomiting

## 1 | INTRODUCTION

Postoperative nausea and vomiting is a common adverse effect of anesthesia and surgery with an estimated incidence of 30% in the general surgical population and as high as 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 the nearly three million general anesthetics given annually in the United Kingdom alone,[10] the public health impact of reducing postoperative nausea and vomiting is substantial. Enhanced recovery programmes in surgical patients and the promotion of day case surgery include adequate prophylaxis of postoperative nausea and vomiting.[11]

There are a great number of different antiemetic drugs mostly within the drug classes of $5HT_3$-, $D_2$-, $NK_1$-receptor antagonists, corticosteroids, antihistamines, and anticholinergics with various mechanisms of action and side effects.[5,12–14] Varying adverse effects have been attributed to the six different substance classes, such as headache, constipation, arrhythmia, and QT prolongation (5-$HT_3$ receptor antagonists); extrapyramidal symptoms, sedation, arrhythmia, and QT prolongation ($D_2$ receptor antagonists); hyperglycemia, immunosuppression, and poor wound healing (corticosteroids); drowsiness, dry mouth, and urinary tract difficulties (antihistamines); 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 were described by individual studies.[15]

Since the 1960s, a tremendous number of clinical studies investigating prophylactic measures for postoperative nausea and vomiting have been published. In 2006, Carlisle and Stevenson performed a systematic review assessing available drugs with antiemetic action for prevention of postoperative nausea and vomiting in adults and children, including more than 700 randomized controlled trials (RCTs) with over 100 000 participants.[16] This review contained a large number of direct comparisons in pairwise meta-analyses of drug versus drug or drug versus placebo. However, a comparative ranking of all available drugs could not be provided. In 2015, Tricco and colleagues published a large systematic review with network meta-analysis, which was limited to the comparison of the many serotonin receptor antagonist drugs for the prevention of postoperative nausea and vomiting.[17,18]

Despite the continuing increase in the number of clinical trials and systematic reviews on postoperative nausea and vomiting, there is still no current evidence-based overview of all relevant substance classes and a lack of a clinically useful ranking of all antiemetic drugs in terms of efficacy and safety. To maximize 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 multidrug interventions, which existing reviews do not address.[16,17] This review provides a complete evidence-base to inform guideline updates.[4,5] In this abridged version, we summarize the review's most important findings and discuss challenges and the time needed to prepare what is now the largest Cochrane review with network meta-analysis in terms of the number of included studies (585) and pages in its full printed form (> 2200).[21]

## 2 | METHODS

This is an abridged version of the Cochrane review "Drugs for preventing postoperative nausea and vomiting in adults after general anesthesia: a network meta-analysis."[21] This review was registered in PROSPERO (CRD42017083360) and followed a published protocol.[22]

### 2.1 | Eligibility criteria

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 and colleagues were not included in the review.[23,24] Studies were required to investigate adult participants undergoing any type of surgery with general anesthesia; and compare single or multiple pharmacological intervention(s) with antiemetic action belonging to one of the six drug classes versus each other, versus no treatment, or versus placebo. The current review includes the following "interventions of direct interest" (decision set):

1. 5-$HT_3$ receptor antagonists: for example, dolasetron (dola), granisetron (gran), ondansetron (onda), palonosetron (palo), ramosetron (ramo), and tropisetron (trop).
2. $D_2$ receptor antagonists: for example, amisulpride (amis), droperidol (drop), haloperidol (halo), metoclopramide (meto), and perphenazine (perp).
3. $NK_1$ receptor antagonists: for example, aprepitant (apre), casopitant (caso), fosaprepitant (fosa), and rolapitant (rola).
4. Corticosteroids: for example, dexamethasone (dexa) and methylprednisolone (meth).
5. Antihistamines (Histamine 1 receptor antagonists): for example, 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 anesthesia to prevent postoperative nausea and vomiting. 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 hours postoperatively, serious adverse events (SAEs) and any adverse event (any AE) both within seven days postoperatively. Secondary outcomes were drug class-specific side effects (eg, headache, constipation, extrapyramidal symptoms, sedation, arrhythmia, QT prolongation, wound infection, and visual disturbances), early and late vomiting, nausea, and complete response (CR, no nausea and no vomiting and no rescue antiemetic treatment for the first 24 hours).

## 2.2 | Information sources and search strategy

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 have been 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]

## 2.3 | Study selection and risk of bias assessment

The review team 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 summarized the overall risk of bias for each study by reference to the judgments of the domains "sequence generation," "blinding of participant, personnel, and outcome assessors," and "incomplete outcome data."

## 2.4 | Data synthesis and analysis

We visually assessed the distribution of potential effect modifiers (eg, risk of bias, dose of intervention, funding) across the studies contributing data to an outcome to check whether the transitivity assumption holds. 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 subgroup analysis, respectively. Due to the quantity of data and the lack of information for the effect modifier "funding source" in many studies, an objective and reliable assessment of the distribution of this effect modifier within all comparisons was not possible.

Dichotomous outcome data in both pairwise meta-analyses and network meta-analyses were summarized as risk ratios (RR) with 95% confidence intervals (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.[21] 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] Multiarm studies were included in the data set as a series of two-arm comparisons with adjusted standard errors.[25,27,29] Results from network meta-analyses were presented as summary RR 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 between the antiemetic 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]

As described elsewhere, clinically meaningful effect sizes were prespecified.[21] For vomiting, effect estimates with the upper boundary of the RR 95% CI less than 0.80 were declared beneficial (important benefit). A lower boundary of the RR 95% CI larger than 1.25 was declared harmful (important harm). The range between 0.8 and 1.25 was termed the "range of equivalence" (indicating no clinically relevant difference from the comparator).[30] The relative position of the point estimates indicated the direction of the effect as "benefit," "no or minimal effect," or "harm." The extent of the 95% CI indicated the certainty of the estimated effect as "important" or as "associated with uncertainty." For completeness, all drug and drug combinations were ranked against placebo as the reference standard. For safety outcomes such as SAEs, any AE, and all class-specific side effects, we defined the "range of equivalence" more conservatively as RR ranging from 0.9 to 1.11.

We assessed heterogeneity in individual pairwise comparisons and in comparisons of the network using the 95% prediction interval (PI). We assumed heterogeneity if the 95% PI and the 95% CI of the pairwise or the network meta-analysis treatment estimate differ with respect to the range of clinically relevant effect sizes ("range of equivalence").

Inconsistency is synonymous to incoherence and is the statistical manifestation of intransitivity that occurs when the direct and indirect estimates in a network of treatments do not agree. At a global level, we assessed heterogeneity and inconsistency of the whole network by decomposing the Q-statistic into variation of the effect estimates within designs (heterogeneity) and between designs (inconsistency).[31,32] A design is each combination of treatments within a study in a network meta-analysis (eg, for treatments A, B, and C, possible designs are A:B, A:C, B:C, and A:B:C). In addition, we used the full random-effects design-by-treatment interaction model to assess whether all interventions behave similarly in all comparisons.[31]. At a local level (regions of the network), we did a statistical evaluation of inconsistency 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 subgroups. We separated different doses of the same drug into low, recommended, and high doses.[22] 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.

## 2.5 | Assessment of the certainty of evidence

The rating of the certainty of evidence contributing to network estimates was based on the principles of the 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 reviewers 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, high), which express our confidence in the estimate of effect.[36]

# 3 | RESULTS

## 3.1 | Study selection

A detailed PRISMA study flow diagram is reported in Ref. (21). A total of 21 016 records were identified by the search, 1762 were reviewed in full text, and 732 records belonging to 585 studies were eligible for inclusion (references to included studies are available in Supporting Information 1). Note that, 673 articles (690 records) were excluded and reasons for exclusion are reported in Ref. (21). Awaiting classification at a future updating of the review are 340 study records including 39 trials identified in the search update, all with insufficient information.

## 3.2 | Characteristics of included studies

The 585 included RCTs comprising 97 516 randomized 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 onward), and primarily conducted in Asia (51%), Europe (25%), and North America (16%). The overall population's mean age was 42 years (12.5). Most participants were women (83%), of American Society of Anaesthesiologists (ASA) physical status I and II (70%), received perioperative opioids (88%), and underwent gynaecological (32%), or gastrointestinal surgery (19%) under general anesthesia using volatile anesthetics (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, CR) relevant for this review. However, only 56% reported at least one relevant safety outcome.

## 3.3 | Risk of bias

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

## 3.4 | Outcomes

### 3.4.1 | Vomiting within 24 hours postoperatively

Figure 1 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 to placebo, were the most common comparisons.

Figure 2 shows the network meta-analysis' results with ranking of all interventions compared to 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. Treatment effects of all single drugs compared to placebo ranged between RR 0.06 (0.02 to 0.21) for fosaprepitant and RR 1.08 (0.54 to 2.15) for buspirone. Of the drug combinations, 29 out of 36 drug combinations were more effective than placebo. Treatment effects ranged between RR 0.01 (0.00 to 0.19) for aprepitant-palonosetron and RR 1.04 (0.17 to 6.45) for metoclopramide-promethazine.

There was large 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 subsets. Subgroup analysis showed that recommended and high doses of granisetron, dexamethasone, tropisetron, ondansetron, and droperidol were similarly effective, but 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 summarized in the full Cochrane review.[21]

For interventions of the decision set, we found high certainty evidence of a clinical important effect compared to placebo for aprepitant,

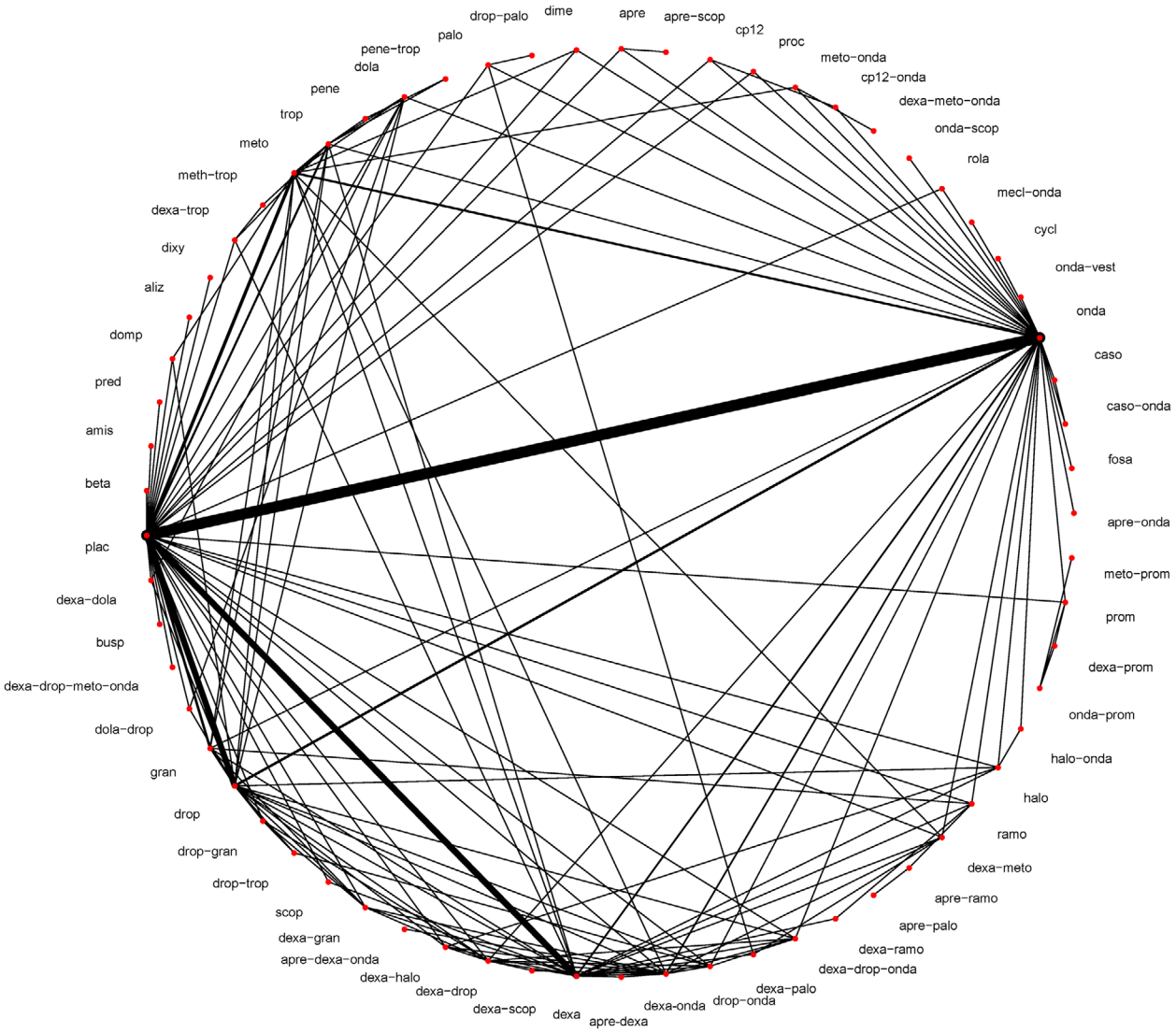


**FIGURE 1** Network geometry of eligible comparisons for postoperative vomiting within 24 hours after surgery. The thickness of the edges is proportional to the number of included studies comparing two treatments. Abbreviations for treatments are listed in the Methods

ramosetron, granisetron, dexamethasone, and ondansetron; and moderate certainty evidence for fosaprepitant and droperidol (Supporting Information 2). Other single drugs of direct interest compared to placebo were either clinically effective with very low or low certainty evidence (casopitant, tropisetron, dolasetron), or minimally effective with moderate certainty evidence (amisulpride, promethazine), or minimally effective with very low or low certainty evidence (palonosetron, haloperidol, metoclopramide, rolapitant, dimenhydrinate, and scopolamine) (Supporting Information 2). No studies reporting vomiting were available for perphenazine, methylprednisolone, and meclizine.

### 3.4.2 | Serious adverse events (SAEs)

Twenty-eight RCTs were included in the network meta-analysis for SAEs with 10 766 participants and 22 interventions (13 single drugs, 8 drug combinations, and placebo) (Supporting Information 3). None of the 21 active interventions showed an important benefit or harm regarding SAEs compared with placebo, but all effect estimates showed a high level of uncertainty with wide 95% CIs. Treatment effects of all interventions compared to placebo ranged between RR 0.31 (0.10 to 1.00) for dolasetron and 3.64 (0.57 to 23.11) for casopitant (Supporting Information 3). The certainty of evidence for interventions of the decision set compared to placebo ranged from very low to low (Supporting Information 3). No studies reporting SAEs were available for haloperidol, metoclopramide, perphenazine, fosaprepitant, rolapitant, methylprednisolone, dimenhydrinate, meclicine, and promethazine.

### 3.4.3 | Any adverse event (any AE)

Sixty-one RCTs were included in the network meta-analysis for any AE with 19 423 participants and 27 interventions (15 single drugs, 11 drug combinations, and placebo) (Supporting Information 4). Scopolamine

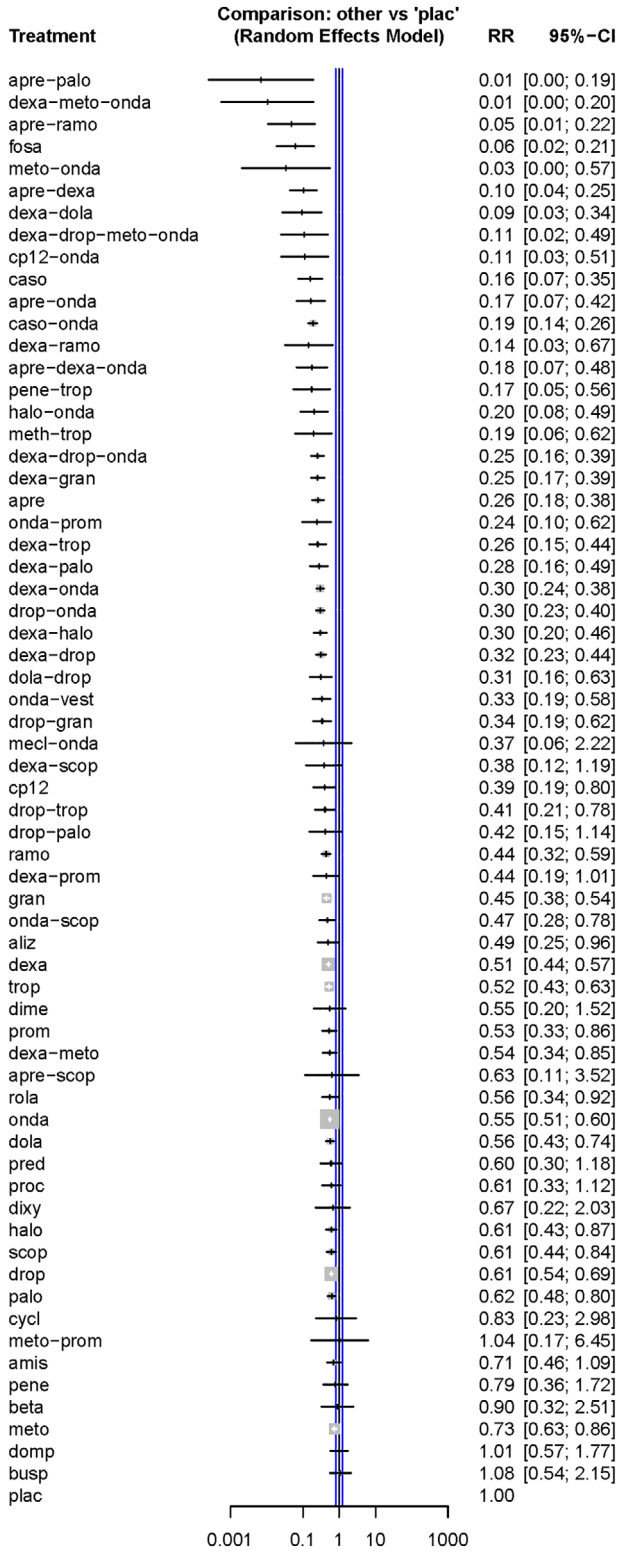


**FIGURE 2** Forest plot of network meta-analysis of all trials for postoperative vomiting within 24 hours after surgery. Single drugs and combinations were compared with placebo (reference compound). RR = risk ratio, 95% CI = 95% confidence interval. RR < 1 favors the intervention, RR > 1 favors placebo. The blue lines indicate the range of equivalence (RR = 0.8 to 1.25). Treatments were ranked based on *P* scores with most effective drug on the top. Abbreviations for treatments are listed in the Methods

and dimenhydrinate showed important harm compared to placebo. All other effect estimates showed no or little (beneficial) effect or were of high uncertainty (imprecise 95% CI). Treatment effects of all interventions compared to placebo ranged between RR 0.09 (0.01 to 1.55) for betamethasone and RR 5.70 (1.36 to 23.93) for dimenhydrinate (Supporting Information 3). The certainty of evidence for interventions of the decision set ranged from very low to moderate (Supporting Information 3). There is moderate certainty evidence that granisetron (RR 0.92, 0.80 to 1.05) and amisulpride (RR 0.97, 0.90 to 1.06) have little or no effect on any AE. No studies reporting any AE were available for haloperidol, perphenazine, fosaprepitant, rolapitant, methylprednisolone, meclicine, and promethazine.

## 3.5 | Substance class-specific side effects

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.[21] When analyzing substance class-specific side effects, network estimates of single drugs were mostly imprecise and showed a high level of uncertainty. However, we did find precise effect estimates for reduced headache by droperidol, increased sedation by dimenhydrinate, and increased visual disturbances by scopolamine, all compared to placebo. 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, but there was moderate certainty evidence that ondansetron increases (RR 1.16, 1.06 to 1.28) and droperidol reduces headache (RR 0.76, 0.67 to 0.86), both compared to placebo. We have moderate certainty evidence that dimenhydrinate increases (RR 7.66, 3.10 to 18.94) and ondansetron reduces sedation (RR 0.87, 0.79 to 0.96), and high certainty evidence that dexamethasone has no effect on sedation (RR 1.00, 0.91 to 1.09), all compared to placebo. No studies assessed any substance class-specific side effects for fosaprepitant and rolapitant.

## 3.6 | Nausea, complete response, early, and late vomiting

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 antinausea efficacy was comparable to their antiemetic efficacy. The seven drugs with moderate or high certainty evidence for a clinical important effect against vomiting showed also important benefit for the composite outcome "complete response" and ranked with decreasing order according to efficacy as: ramosetron, granisetron, fosaprepitant, aprepitant, dexamethasone, droperidol,

| 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 (color) 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. Color 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)

and ondansetron. Details on nausea, complete response, early and late vomiting are provided in the full Cochrane review.[21]

### 3.7 | Certainty of evidence

The direction and magnitude of network effect estimates, together with the level of evidence certainty is graphically summarized for primary outcomes and side effects of all drugs of direct interest (decision set) compared with placebo in Figure 3.

## 4 | DISCUSSION

This is the first network meta-analysis comparing all available antiemetic drugs of relevant substance classes with assessment of the certainty of evidence and producing a ranking of all drugs in terms of efficacy and safety. Using this approach that allows for direct and indirect comparison and subsequent ranking of antiemetic prophylaxes, we found seven effective single drugs for the prevention of postoperative vomiting in this review—five with high certainty evidence (aprepitant, ramosetron, granisetron, dexamethasone, and ondansetron) and two with moderate certainty evidence (fosaprepitant and droperidol). Therefore, four of the six substance classes (5-HT$_3$-, D$_2$-, NK$_1$-receptor antagonists, and corticosteroids) with different mechanisms of action are represented by at least one drug effectively preventing vomiting.

Compared to existing systematic reviews and recommendations, newer drugs such as fosaprepitant, aprepitant, and ramosetron are worthy to be recommended in addition to the standard antiemetics (ondansetron, dexamethasone, droperidol, and granisetron) and should replace older, less effective substances such as metoclopramide and scopolamine.[1,16] 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 to six different substance classes. Twenty-one of the 44 drugs were of direct interest (decision set), all of which except meclizine were listed in the newest consensus guidelines for the management of postoperative nausea and vomiting.[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 that assesses how trustworthy current evidence of antiemetic drugs is in terms of efficacy and safety based on GRADE. Certainty of evidence of effect estimates can greatly vary across comparisons within a network. In making inferences regarding the choice of an intervention, recognizing 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 for vomiting. However, there is still uncertainty about the evidence that makes these drugs today less reliable than others do.

Prophylaxis of postoperative nausea and vomiting has a large impact on patient care in high-risk populations. However, in a general surgical population of low to moderate risk (ie, about 30% of patients experiencing vomiting[5]), most patients will not benefit from routinely administered prophylactic antiemetics, 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 SAEs, any AE, and substance class-specific side effects. Moreover, the ranking of drugs for all safety outcomes is unreliable due to excessive uncertainty in the relative effects. In contrast to the large number of studies (89%) reporting relevant efficacy outcomes for this review, just over half of all studies (56%) reported at least one relevant safety outcome. Thus, relevant safety outcomes were highly underrepresented in the included studies. Furthermore, we could not exclude a certain risk of bias, as side effects may be prone to selective outcome reporting and may have been reported more frequently when the findings were generally positive.

This review is currently the largest Cochrane Review with network meta-analysis in terms of the number of included studies, with 585, and longest with the full printed version running to more than 2200 pages. Production of the review took two years starting with the literature search in November 2017 and ending with submission of the completed review in December 2019, followed by eight months of editorial processing before publication in October 2020.

The effort spent to develop the protocol played an important role in ensuring the straightforward production of the review with a focus on the feasibility of the immense workload involved.[22] During protocol development, a multidisciplinary team of authors including methodologists, statisticians, and experienced clinicians defined a specific and narrow review question in terms of the PICO criteria, study designs, and publication types. For example, we restricted the population to adults undergoing surgery with general anesthesia and excluded children and regional anesthetic procedures. This reduced the number of potentially eligible trials, but limited applicability to the defined patient population with restricted external validity (generalizability) for other types of patient.

We decided to include only RCTs published in full text and excluded conference abstracts to speed up the literature search and screening. Although this may mean that some potentially relevant data were not included, our analyses on publication bias did not suggest that potentially missing studies would alter the conclusions.[21]

At the protocol stage, we defined the interventions of interest (decision set) for current practice. We limited our reporting of findings and assessment of the certainty of evidence to these interventions compared to placebo. Consequently, the review does not include an assessment of the certainty of evidence for all drug combinations and all active comparisons. As this review includes so many studies (585 RCTs) and interventions (44 single drugs and 51 drug combinations) and several different outcomes, grading the certainty of evidence for all possible combinations of interventions would be difficult in a reasonable time frame and challenging to present in an accessible and comprehensive manner. As an example, for vomiting within 24 hours, the 65 different treatments meant that 2080 pairwise combinations of treatments were possible and would have required 2080 evaluations of the certainty of evidence. This would be almost unmanageable and would yield an overload of information for readers.

To produce the review, we recruited four medical students, three worked full-time in literature screening and risk of bias assessment, and one produced Excel spreadsheets for analysis and contributed as the second reviewer in grading the evidence. All students were trained by the Cochrane Interactive Learning Modules (https://training.cochrane.org/interactivelearning) and directly by the review's first author.

We used Covidence (https://www.covidence.org/) for literature screening and data extraction, allowing the whole review team to work simultaneously from anywhere and providing optimal management of the screening and extraction process. It took eight months for two independent review authors to screen the literature, extract data, and assess risk of bias. All conflicts were resolved by the review's first author. One particular challenge in the identification of individual studies was duplicate publications of trials in different journals and multiple listings in trial registries with different leads authors, which also complicated the data synthesis. This highlights the need for uniform trial identification in order to identify redundant and duplicate publications, which, per se, are not worrisome if they can be tracked in a transparent manner. By making the dataset fully and freely available,[21] we welcome perusal by outside researchers to identify mistakes in the data, our analysis or our interpretation. Study details reported in the "Characteristics of included studies" table and the risk of bias assessment were imported from Covidence into RevMan. Excel spreadsheets for further analysis including study characteristics, intervention details, and outcome data of all 585 included studies were prepared manually over two months, including double-checking.

Network meta-analysis was performed using the netmeta package in the R environment.[26] Confidence in the network meta-analysis estimates was evaluated using the CINeMA (https://cinema.ispm.unibe.ch/) methodological framework, which simplifies this complex evaluation process.[39] Summary of findings tables were prepared according to the format developed by Yepes-Nuñez and colleagues.[40] Data analysis, grading of the evidence, and interpretation took 8 months, including group meetings and discussions and then writing and agreeing the draft of the review, including several hundred pages of supplementary files, took an additional six months before we were ready to submit it.

Our study has some limitations as noted above, mainly due to our attempts to cope with the immense workload. These include the lack of potentially relevant data (exclusion of conference abstracts), limited external validity (narrow PICO question), and lack of grading of the certainty of evidence for all interventions and comparisons (excluding anything outside the decision set). However, these constraints were necessary when the review was launched, in order to ensure completion in a reasonable time frame.

In conclusion, this network meta-analysis represents the largest and most comprehensive, currently available evidence base to guide clinical practice and guideline development regarding antiemetic prophylaxis for postoperative vomiting. 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 or systematic reviews including nonrandomized studies of interventions are still needed to gather evidence on potential side effects of these drugs.

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## CONFLICT OF INTEREST

SW, MSS, DR, GR, NLP, TS, PM have no competing interests declared.

PKi, LHJE, and PKr have financial relationships with Baxter GmbH Germany (PKi), Air Liquide Medical GmbH Germany (PKi), TEVA Ratiopharm GmbH (LHJE, PKi, PKr), Fresenius Kabi GmbH Germany (LHJE, PKr), Pajunk (PKr) that might have an interest in the submitted work in the previous three years; they have no other relationships or activities that could appear to have influenced the submitted work.

LHJE and PKr were involved in the conduct of studies related to the current review. They did not assess the relevant studies for inclusion or exclusion and were not allowed to extract data and critically appraise the quality of the relevant studies.

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## REFERENCES

1. UpToDate. Postoperative nausea and vomiting. Available at https://www.uptodate.com/contents/postoperative-nausea-and-vomiting (accessed July 24/2020).
2. Apfel CC, Kranke P, Katz MH, et al. Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design. *Br J Anaesth*. 2002;88:659-668.
3. Apfel CC, Laara E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. *Anesthesiology*. 1999;91:693-700.
4. Gan TJ, Belani KG, Bergese S, et al. Fourth consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. 2020;131:411-448.
5. Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. 2014;118:85-113.
6. Gan T, Sloan F, Dear Gde L, El-Moalem HE, Lubarsky DA. How much are patients willing to pay to avoid postoperative nausea and vomiting? *Anesth Analg*. 2001;92:393-400.
7. Myles PS, Williams DL, Hendrata M, Anderson H, Weeks AM. Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10,811 patients. *Br J Anaesth*. 2000;84:6-10.
8. Dorman RB, Miller CJ, Leslie DB, et al. Risk for hospital readmission following bariatric surgery. *Plos One*. 2012;7:e32506.
9. Parra-Sanchez I, Abdallah R, You J, et al. A time-motion economic analysis of postoperative nausea and vomiting in ambulatory surgery. *Canad J Anaesth*. 2012;59:366-375.
10. Cook TM, Woodall N, Frerk C. Fourth National Audit P. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 1: anaesthesia. *Br J Anaesth*. 2011;106:617-631.
11. Nicholson A, Lowe MC, Parker J, Lewis SR, Alderson P, Smith AF. Systematic review and meta-analysis of enhanced recovery programmes in surgical patients. *Br J Surg*. 2014;101:172-188.
12. Gan TJ, Meyer TA, Apfel CC, et al. Society for ambulatory anesthesia guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. 2007;105:1615-1628.table of contents.
13. Horn CC, Wallisch WJ, Homanics GE, Williams JP. Pathophysiological and neurochemical mechanisms of postoperative nausea and vomiting. *Euro J Pharmacol*. 2014;722:55-66.
14. Wiesmann T, Kranke P, Eberhart L. Postoperative nausea and vomiting—a narrative review of pathophysiology, pharmacotherapy and clinical management strategies. *Expert Opin Pharmacother*. 2015;16:1069-1077.
15. Diemunsch P, Joshi GP, Brichant JF. Neurokinin-1 receptor antagonists in the prevention of postoperative nausea and vomiting. *Br J Anaesth*. 2009;103:7-13.
16. Carlisle J, Stevenson CA. Drugs for preventing postoperative nausea and vomiting. *Cochrane Database of Systematic Reviews*. 2006;Issue 3. Art. No.: CD004125. https://doi.org/10.1002/14651858.CD004125.pub2 (accessed May 11/2021).
17. Tricco AC, Soobiah C, Blondal E, et al. Comparative efficacy of serotonin (5-HT3) receptor antagonists in patients undergoing surgery: a systematic review and network meta-analysis. *BMC Med [Electr Resour]*. 2015;13:136.
18. Tricco AC, Soobiah C, Blondal E, et al. Comparative safety of serotonin (5-HT3) receptor antagonists in patients undergoing surgery: a systematic review and network meta-analysis. *BMC Med [Electr Resour]*. 2015;13:142.
19. Malhotra A, Maughan D, Ansell J, et al. Choosing wisely in the UK: the Academy of Medical Royal Colleges' initiative to reduce the harms of too much medicine. *BMJ (Clin Res Ed.)*. 2015;350:h2308.
20. Polderman JA, Farhang-Razi V, Van Dieren S, et al. Adverse side effects of dexamethasone in surgical patients. *Cochr Datab System Rev (Online)*. 2018;11:CD011940.
21. Weibel S, Rücker G, Eberhart LH, et al. Drugs for preventing postoperative nausea and vomiting in adults after general anaesthesia: a network meta-analysis. *Cochr Datab System Rev (Online)*. 2020;10:CD012859.
22. Weibel S, Jelting Y, Pace N, et al. Drugs for preventing postoperative nausea and vomiting in adults after general anaesthesia: a network meta-analysis. *Cochr Datab System Rev (Online)*. 2017;11:CD012859.
23. Tramer MR. The Fujii story: a chronicle of naive disbelief. *Euro J Anaesthesiol*. 2013;30:195-198.
24. Kranke P, Apfel CC, Roewer N, Fujii Y, et al. Reported data on granisetron and postoperative nausea and vomiting by Fujii et al. are incredibly nice! *Anesth Analg*. 2000;90:1004-1007.
25. Rücker G. Network meta-analysis, electrical networks and graph theory. *Res Synth Methods*. 2012;3:312-324.
26. Rücker G, Krahn U, König J, Efthimiou O, Schwarzer G. netmeta: network meta-analysis using frequentist methods. R package version 1.0-1. 2020. https://CRAN.R-project.org/package=netmeta
27. Rücker, G, Schwarzer, G. Reduce dimension or reduce weights? Comparing two approaches to multi-arm studies in network meta-analysis. *Stat Med*. 2014;33:4353-4369.

28. Sweeting, MJ, Sutton, AJ, Lambert, PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med*. 2004;23:1351-1375.
29. Rücker, G, Schwarzer, G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol [Electr Resour]*. 2015;15:58.
30. Nikolakopoulou, A, Higgins, JPT, Papakonstantinou, T, Chaimani, A, Del Giovane, C, Egger, M, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. *PLoS Med*. 2020;17(4):e1003082. https://doi.org/10.1371/journal.pmed.1003082
31. Higgins, JP, Jackson, D, Barrett, JK, Lu, G, Ades, AE, White, IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods*. 2012;3:98-110.
32. Krahn, U, Binder, H, Konig, J. A graphical tool for locating inconsistency in network meta-analyses. *BMC Med Res Methodol [Electr Resour]*. 2013;13:35.
33. Chaimani, A, Caldwell, DM, Li, T, Higgins, JPT, Salanti, G. (2019). Chapter 11: undertaking network meta-analyses. In: Higgins JPT, Thomas J, Chandler J, et al., eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019)*. Cochrane, Available from www.training.cochrane.org/handbook
34. Salanti, G, Del Giovane, C, Chaimani, A, Caldwell, DM, Higgins, JP. Evaluating the quality of evidence from a network meta-analysis. *Plos One* 2014;9:e99682.
35. Papakonstantinou, T, Nikolakopoulou, A, Rucker, G, et al. Estimating the contribution of studies in network meta-analysis: paths, flows and streams. *F1000Res*. 2018;7:610.
36. Balshem, H, Helfand, M, Schunemann, HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64:401-406.
37. Apfel, CC, Korttila, K, Abdalla, M, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *N Engl J Med*. 2004;350:2441-2451.
38. Puhan, MA, Schunemann, HJ, Murad, MH, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ (Clin Res Ed.)*. 2014;349:g5630.
39. Nikolakopoulou, A, Higgins, JPT, Papakonstantinou, T, et al. CINeMA: an approach for assessing confidence in the results of a network meta-analysis. *Plos Med*. 2020;17:e1003082.
40. Yepes-Nunez, JJ, Li, SA, Guyatt, G, et al. Development of the summary of findings table for network meta-analysis. *J Clin Epidemiol*. 2019;115:1-13.
41. Weibel S, Schaefer MS, Raj D, Rücker G, Pace NL, Schlesinger T, Meybohm P, Kienbaum P, Eberhart LHJ, Kranke P. Drugs for preventing postoperative nausea and vomiting in adults after general anaesthesia: an abridged Cochrane network meta-analysis. *Anaesthesia*. 2020 Nov 10. https://doi.org/10.1111/anae.15295. Epub ahead of print. PMID: 33170514.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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