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Walker, R orcid.org/0000-0003-2765-7363, Dias, S orcid.org/0000-0002-2172-0221 and Phillips, R S orcid.org/0000-0002-4938-9673 (2024) Antiemetic medications for preventing chemotherapy-induced nausea and vomiting in children:a systematic review and Bayesian network meta-analysis. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 747. ISSN 1433-7339

https://doi.org/10.1007/s00520-024-08939-9

Supportive Care in Cancer (2024) 32:747
https://doi.org/10.1007/s00520-024-08939-9

REVIEW

Antiemetic medications for preventing chemotherapy-induced nausea and vomiting in children: a systematic review and Bayesian network meta-analysis

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Received: 17 July 2024 / Accepted: 10 October 2024

Abstract

Purpose Children continue to experience chemotherapy-induced nausea and vomiting (CINV), despite effective antiemetic medications. Recommendations in clinical practice guidelines are underpinned by narrative syntheses and meta-analyses that compare only two treatments. This means not all antiemetics have been compared to one another, and estimates remain imprecise. We apply network meta-analysis (NMA) to overcome these limitations by comparing multiple treatments simultaneously.

Methods A systematic review identified and critically appraised RCTs comparing antiemetics recommended and licensed for the prevention of CINV in children. Bayesian NMA compared and ranked antiemetic effectiveness for the outcomes complete (CR) and partial response (PR) in the acute, delayed, and overall phases, nausea, and decreased food intake. Antiemetics given with and without dexamethasone were compared in separate networks as their underlying populations differed.

Results Sixteen RCTs (3115 patients receiving moderately (MEC) or highly emetogenic chemotherapy (HEC)) were included. When given with dexamethasone, NK1 antagonists with ondansetron ranked highest for CR and PR in the acute and overall phases, PR in the delayed phase, and decreased food intake. Post hoc analysis shows further a benefit of adding olanzapine to regimens of aprepitant and ondansetron. Ondansetron ranked lower than palonosetron, for CR in the delayed and overall phases, and ondansetron was less effective than palonosetron for nausea prevention. Rankings for other regimens, including those given without dexamethasone, were uncertain or inconsistent across outcomes.

Conclusions Our findings serve to support the current recommendations of olanzapine (when given with aprepitant and ondansetron) and NK1 antagonists' regimens receiving HEC, but note that evidence of a significant difference in relative benefit, between patients receiving MEC and HEC, does not yet exist. Recommendations for palonosetron as the preferred 5HT3 antagonists may be extended, particularly, to those who are at high risk of nausea.

Keywords Antiemetics · Nausea and vomiting · Children · Evidence synthesis

Introduction

Nausea and vomiting are common side effects of chemotherapy that continue to be a problem for children and young people undergoing treatment for cancer. The impacts of uncontrolled nausea and vomiting include dehydration, electrolyte imbalance, weight loss, anorexia, weakness, and increased susceptibility to infection [1, 2], as well as decreased mental performance [3] and distress. In particular, nausea is commonly identified by patients as being a distressing aspect of chemotherapy treatment [1].

Chemotherapy-induced nausea and vomiting (CINV) can occur prior to chemotherapy administration (anticipatory CINV), during or within 24 h of chemotherapy administration (acute CINV) and after chemotherapy administration (delayed CINV) (often defined as 1 to 5 days after the last chemotherapy administration). As anticipatory CINV may be a conditioned response to previous CINV experienced in the acute and delayed phases, adequately controlling these from the first chemotherapy administration could prevent subsequent anticipatory CINV [4].

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Published online: 27 October 2024

The current clinical practice guidelines of the Paediatric Oncology Group of Ontario (POGO) [5–7], Multinational Association of Supportive Care in Cancer (MASCC) [8], Children's Cancer and Leukaemia Group (CCLG) [9] (underpinned by Patel et al. 2017 [7]), and the American Society of Clinical Oncology(ASCO) guidelines [10, 11] recommend different combinations of antiemetic medications depending on the emetogenicity (the potential to cause vomiting in the absence of prophylaxis) of the chemotherapy being received (Table 1).

Recommendations are informed by systematic reviews and evidence syntheses [2, 5–7, 9–13] that have identified and combined evidence from randomised clinical trials (RCTs) using either narrative synthesis or conventional meta-analysis. Narrative synthesis is a textual approach to analysing relationships within and between studies and therefore cannot provide a statistical summary of relative treatment effect when multiple studies assess the same treatments. Meta-analysis does produce statistical summary estimates for treatments that have been compared directly in clinical trials but combines evidence of the relative treatment effect (and associated uncertainty) of two interventions meaning not all treatments can be compared to every other. For antiemetic use within children undergoing chemotherapy, this means that the overall picture of which antiemetics are most effective remains incomplete [2, 13], including knowledge of optimal dosing and scheduling of antiemetics [2, 5, 13]. Formal comparison of antiemetic efficacy in children is even more lacking for less well-reported outcomes, such as nausea [2, 13], despite this outcome being identified as being more distressing to patients [1].

The existing evidence syntheses that combine evidence of antiemetic use in children are also limited by the size of underlying clinical trials. RCTs comparing antiemetics in children and young people are also often small (< 50 participants), owing to challenges in recruiting to these supportive care trials [14–16]. Fewer trial participants ultimately mean less information (i.e. less power) to estimate treatment effects; and therefore, some existing estimates of treatment effect are imprecise, i.e. not estimated with sufficient certainty.

Network meta-analysis (NMA) may help to overcome the limitations discussed, by extending pairwise meta-analysis to coherently synthesise evidence on three or more treatments. NMA methods hold two main advantages in the context of children's research where evidence is sparse. Firstly, NMA facilitates the comparison of each treatment with every other and can estimate relative effects of treatments not compared directly in clinical trials by incorporating 'indirect evidence' provided by observed comparisons. Secondly, as some estimates may be informed by both direct and indirect evidence, NMA methods can increase the precision of treatment effect

Table 1 Antiemetic medications currently recommended for children and young people in the clinical practice guidelines of Paediatric Oncology Group of Ontario (POGO) [5–7], Multinational Association of Supportive Care in Cancer (MASCC) [12] and Children's Cancer and Leukaemia Group (CCLG) [9] and American Society of Clinical Oncology (ASCO) guidelines [10, 11]

Highly emetogenic chemotherapy (HEC)	Moderately emetogenic chemotherapy (MEC)	Low emetogenic chemotherapy (LEC)
An NK1 antagonist + a 5HT3 receptor antagonist + dexamethasone for prevention of acute CINV [5, 7–11] (olanzapine* may also be considered [5]) An NK1 antagonist + a 5HT3 receptor antagonist [5, 8] + dexamethasone for prevention of delayed CINV [5, 9]	A 5HT3 receptor antagonist + dexamethasone for prevention of A 5HT3 receptor antagonist for prevention of acute CINV [5, 9–11] Dexamethasone for prevention of delayed CINV [5]	9, 10]** No routine prophylaxis for prevention of delayed CINV [5]

Emetogenicity of chemotherapy is often categorised into 'low' causing a 10–30%, 'moderate' causing a 30–90%, and 'high' causing over a 90% incidence of emesis in the absence of prophylaxis [4]. Recommended NK1 antagonists: aprepitant or fosaprepitant. Recommended 5HT3 receptor antagonists: palonosetron, ondansetron, granisetron, or tropisetron

*The use of olanzapine would be off-label as this medicine is not yet indicated for use in the treatment of CINV in children and young people [10]

** [10] recommends ondansetron and granisetron as 5HT3 receptor antagonists

estimates, over and above that which would be produced by a meta-analysis considering direct evidence alone [17].

This research applies Bayesian network meta-analysis to synthesise evidence of effectiveness (and harms) and produce rankings of recommended antiemetics medications [5–7, 9, 12] in children and young people (age 0–18) undergoing chemotherapy treatment.

Methods

A systematic review and Bayesian NMA were conducted to identify and critically appraise published and unpublished clinical trials assessing antiemetic medications currently recommended and licensed (in European countries and/or the USA) [5–7, 9, 12], for the prevention of CINV in children and young people, and to synthesise their evidence on treatment effectiveness.

This research was prospectively registered in PROSPERO with the ID number CRD42022337928 and addresses the first research question within this protocol. *The remaining planned research detailed in the PROSPERO record involving the inclusion of adult data to potentially improve the certainty of estimates in children and facilitate predictions of the efficacy of olanzapine in children is underway and will be published in subsequent papers.*

This research is reported in accordance with the PRISMA NMA Checklist [18] (Supplementary file 1—eTable 1).

Study identification and selection

A search strategy was developed with an information specialist to identify clinical trials comparing antiemetic medications currently recommended and licensed to prevent CINV in children and young people (see Supplementary file 2 - Study identification for details). Time and resource did not allow for all articles to be double-screened. Instead, records identified were double-screened at the title and abstract stage (by RW and CW), in batches of 100 records, until an agreement level of > 90% was met (i.e. until authors made the same decision on the inclusion or exclusion of at least 90/100 records), and the remaining records were then single-screened. Full papers were obtained for potentially relevant records, and their eligibility was assessed by one reviewer (either RW or CW). Where there was uncertainty about inclusion decision, a third team member was consulted (SD or RSP).

Data collection and analysis

Baseline characteristic and outcome data (Supplementary file 4- Data extracted from primary studies) for each study arm were extracted by two reviewers (RW and CW) using a standardised form and checked for accuracy by a second reviewer (either RW, CW, or SS). WebPlotDigitizer Version 4.6 [19] was used to extract data that was only reported graphically.

The Cochrane tool RoB 2 tool [20] was used to assess the risk of bias of included studies. Where the study conduct was likely to have made the study results unreliable, these results were excluded from analysis. An example of this would be if patients received an alternative antiemetic agent after the acute phase when they did not respond to the regimen in which they were initially randomised, delayed-phase study results would not be included in our analyses.

Where sufficient data was available, a Bayesian network meta-analysis was conducted. Fixed effect and random effects models were compared (further details on these models including BUGS code used for fitting and model comparison statistics are reported in Supplementary file 5—Model comparison and BUGS code).

Binary outcomes were analysed using risk ratios (RRs) and 95% credible intervals (CrIs). The analyses were conducted on an intention-to-treat basis where all participants randomised to an intervention were included. Complete and delayed-phase outcomes were analysed as defined in the primary studies.

The analyses were implemented in OpenBUGS version 3.2.3, using code adapted [17, 21]. A Bayesian Markov chain Monte Carlo method was used with a burn-in period of 10,000 interactions. As data for some outcomes were particularly sparse, models were run for 100,000 interactions to ensure convergence. Networks were checked for loops, in which consistency between direct and indirect evidence could be evaluated.

N.B The antiemetic olanzapine was not included in the main analyses as this medication does not yet hold a licence (in European countries and/or the USA) for the prevention of CINV in children. However, as a recently published guideline, [5] *recommends its use in children for this indication, and the off-label use of the medication will likely increase; our analyses for the main outcomes complete response in the acute and delayed phases, and the patient-important outcome of nausea have been updated post-hoc to include olanzapine, the results of which are reported in the Supplementary file 11.*

Patient and family involvement

Children who either previously or currently had cancer along with their families were invited to a morning meeting held alongside Candlelighters, a non-profit organisation based in Leeds, England, who provide support to children with cancer and their families in the local community. The findings of the project and their interpretation

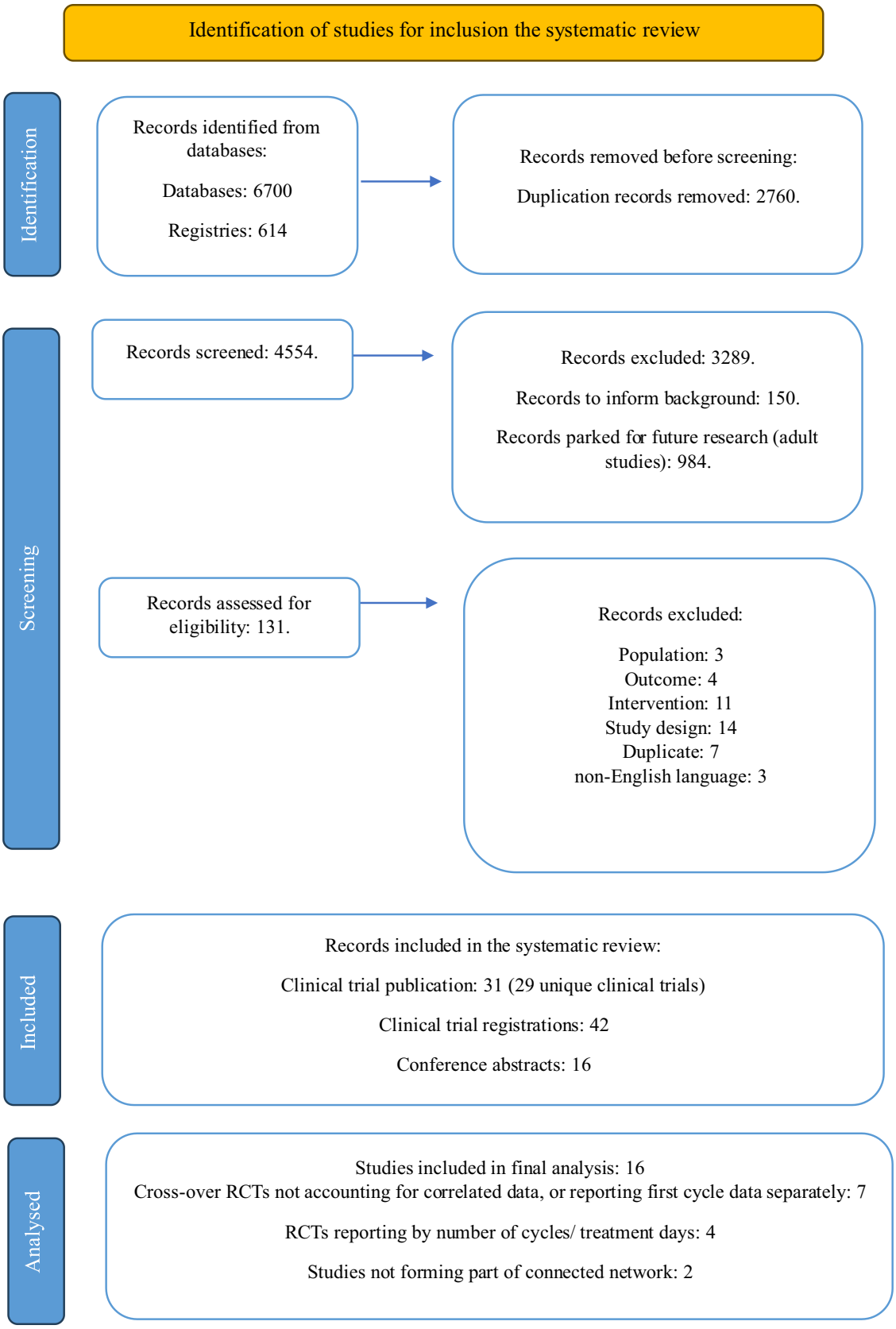

Fig. 1 PRISMA flow diagram, showing the number of records, identified, screened, and included in the review

were discussed, along with ideas about how children and families may use in practice and/or discuss the information with their clinicians.

Results

Thirty-one publications were identified for inclusion from 29 unique clinical trials (Fig. 1). In addition, 42 clinical trial registrations and 16 conference abstracts were identified (Fig. 1) and used to determine any missing and/or ongoing studies. Of the 29 unique clinical trials, 11 reported their outcomes in a way (as detailed in the PRISMA diagram, Fig. 1) that meant they could not be meaningfully combined with the other RCT data [22–32]. Two RCTs [33, 34] did not form part of the connected networks for any outcome. Sixteen RCTs with 3115 patients were included in the final analyses (Fig. 1). The results of their risk of bias assessment are reported in Supplementary file 8—Results of risk of bias assessment.

These patients were a diverse population, aged between 0 and 18, with a broad range of primary cancer diagnoses, and treated with a variety of different moderately and highly emetogenic chemotherapy. Study characteristics are summarised in Supplementary file 7—Table of characteristics.

Patients received one of the following antiemetic regimens:

- Aprepitant + ondansetron (with or without dexamethasone)
- Fosaprepitant + ondansetron (with or without dexamethasone)
- Ondansetron (with or without dexamethasone)
- Palonosetron (with or without dexamethasone)
- Granisetron (without dexamethasone)
- Metoclopramide (with dexamethasone)

Fig. 2 Complete response in the acute phase (0–24 h after chemotherapy administration): network diagram of interventions. The size of the nodes is proportionate to the number of participants assigned to the intervention. The thickness of the lines is proportionate to the number of randomised trials that studied the respective comparison. Abbreviations defined in the 'Abbreviations' section

Determining the network structures

The initial network structures attempted to maintain variations of dose, schedule, and route of administration as separate nodes in the network, but this produced highly disconnected networks. Clinical advice, empirical results from clinical trials [35–38], and a secondary analysis [39] were used to determine the appropriateness of grouping variations (see Supplementary file 6—Determining the structure of the networks, for further detail). The final network structures grouped different doses of ondansetron and dexamethasone, and maintained antiemetics given with and without dexamethasone, in separate networks.

Comparative efficacy of antiemetic regimens

Data were available to assess comparative efficacy for the outcomes of complete control (i.e. zero episodes) and partial control (one or two episodes) of vomiting in the acute, delayed, and overall phases, as well as nausea and the patient-identified outcome of decreased food intake. No other patient-important outcomes identified in this study (Supplementary material 3- Patient public involvement) were reported sufficiently to conduct an NMA.

Networks of antiemetic regimens given without dexamethasone, generally, compared a greater number of antiemetic regimens than networks of antiemetics with dexamethasone, but had less patients contributing to each comparison, making the estimates of treatment effect less certain.

Ranking positions across outcomes

Antiemetic regimens given with dexamethasone

Aprepitant 125 mg (day 1) 80 mg (day 2–3) + ondansetron (multiple doses (MD)) + dexamethasone (MD) had a high

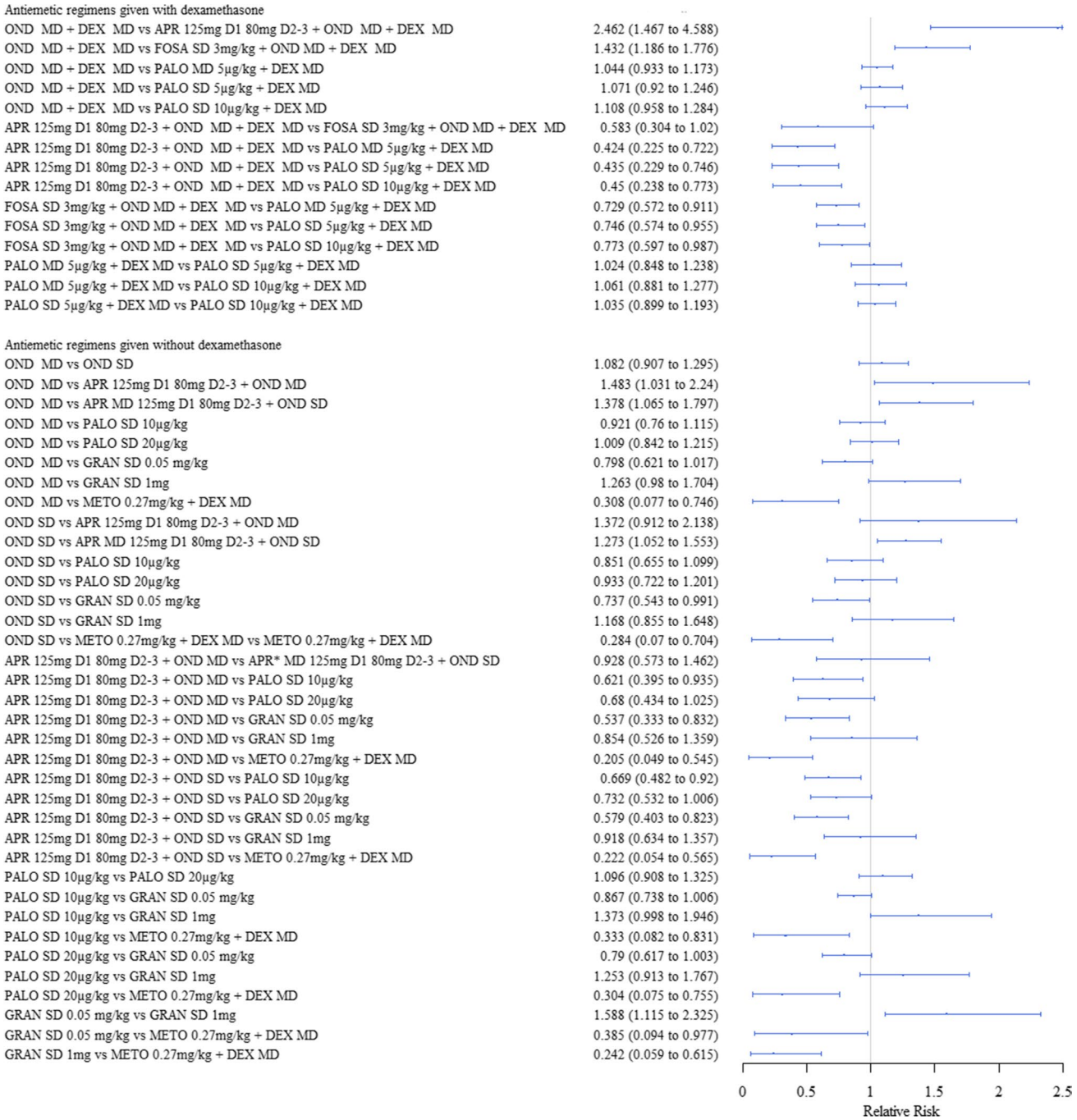

Fig. 3 Forest plot: relative risks (95% credible interval) of antiemetic regimens for the outcome of complete response in the acute phase. Preferred models: fixed effects. Values above 1 favour the second named intervention. N.B Clinical advice to this project suggests granisetron 1 mg is an unusually high dose; and therefore, results should be interpreted with caution

probability (i.e. > 75%) of being ranked most effective for complete response in the acute and overall phases, partial response in the acute, delayed, and overall phases, and decreased food intake (any phase). Fosaprepitant 3 mg/kg (single dose (SD)) + ondansetron (MD) + dexamethasone (MD) had a high probability of being ranked the second most effective treatment, across the outcomes of complete response in the acute phase and partial response in the acute and overall phases.

Ondansetron (MD) + dexamethasone (MD) had a high probability of being ranked the least effective, for the outcomes of complete response in the delayed and overall

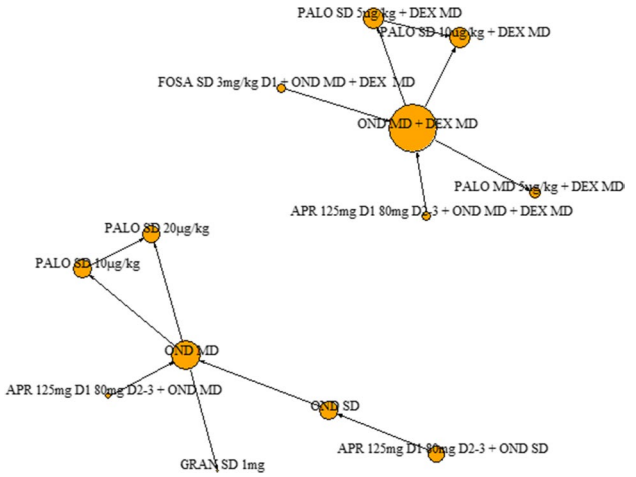

Fig. 4 Complete response in the delayed phase (24 h to 5–7 days after chemotherapy administration): network diagram of interventions. The size of the nodes is proportionate to the number of participants assigned to the intervention. The thickness of the lines is proportionate to the number of randomised trials that studied the respective comparison. Abbreviations defined in the 'Abbreviations' section

phases, where comparison was made with palonosetron regimens (5 µg/kg (SD and MD) and 10 µg/kg (MD)) and NK1 antagonist regimens, as well as partial response in the overall phase and food intake, where it ranked behind the NK1 antagonist regimens.

The remaining antiemetic regimens given with dexamethasone either lacked consistency across outcomes in their ranking position or did not have a high probability of being ranked in any position (i.e. the ranking positions were uncertain).

Antiemetic regimens given without dexamethasone

Metoclopramide had a high probability of being ranked the least effective treatment, for the outcomes of complete and partial response in the acute phase. All remaining antiemetic regimens given without dexamethasone either lacked consistency across outcomes in their ranking position or lacked certainty in their ranking positions.

Relative treatment effects by outcome

Here, we report the relative treatment effect estimates for each outcome in turn, highlighting where these are significant. Outcomes of complete response in the acute and delayed phases as well as nausea are reported below with their summary data (i.e. *N* experiencing and event/total number of participants) reported in Supplementary file 9- Summary data, and the remaining efficacy outcomes and side effects reported in Supplementary file 10- Additional outcomes.

Complete response in the acute phase

Sixteen clinical trials informed the analyses for the outcome of complete response in the acute phase, six of which gave antiemetic regimens with dexamethasone (1503 patients across six different antiemetic regimens) and ten which gave them without (1612 patients across nine different antiemetic regimens) (Fig. 2).

Of the regimens given with dexamethasone, those with NK1 antagonists increased the chances of having a complete response in the acute phase compared to all others. The different doses and schedules of palonosetron included in the analyses (SD or MD of 5 µg/kg + dexamethasone, and SD of 10 µg/kg + dexamethasone) had a similar efficacy to each other and showed no significant difference in efficacy when compared to ondansetron (Fig. 3).

Of the regimens given without dexamethasone, those with aprepitant increased the chances of having a complete response compared to every other antiemetic regimen, except for palonosetron 20 µg/kg (SD) and granisetron 1 mg. Metoclopramide 0.27 mg/kg decreased the chances of having a complete response compared to all other antiemetic regimens. The efficacy of palonosetron 10 µg/kg (SD) and 20 µg/kg (SD) showed no significant difference in efficacy to ondansetron (MD) or to one another (Fig. 3).

Complete response in the delayed phase

Eleven clinical trials informed the analyses for the outcome of complete response in the delayed phase, six of which gave antiemetic regimens with dexamethasone (1075 patients across six different antiemetic regimens) and seven which gave them without (1004 patients across seven different antiemetic regimens) (Fig. 4).

Of the regimens given with dexamethasone, fosaprepitant 3 mg/kg (SD) + ondansetron (MD) and palonosetron 10 µg/kg (SD) increased the chances of having a complete response compared to ondansetron (MD) and palonosetron 5 µg/kg (MD), whilst palonosetron 10 µg/kg (SD) also increased the chances of having a complete response compared to palonosetron 5 µg/kg (SD).

Of the regimens given without dexamethasone, granisetron 1 mg (SD) was shown to decrease the likelihood of having a complete response in the delayed phase compared to palonosetron 20 µg/kg (SD). Palonosetron 20 µg/kg (SD) may also increase the likelihood of having a complete response compared to ondansetron (MD) and palonosetron 10 µg/kg (SD), but these results were uncertain, i.e. credible intervals crossed the line of no effect. The one clinical trial comparing ondansetron (SD) to ondansetron (MD) [20] had all patients achieve a complete response in both arms; and therefore, a treatment effect estimate was not estimable for

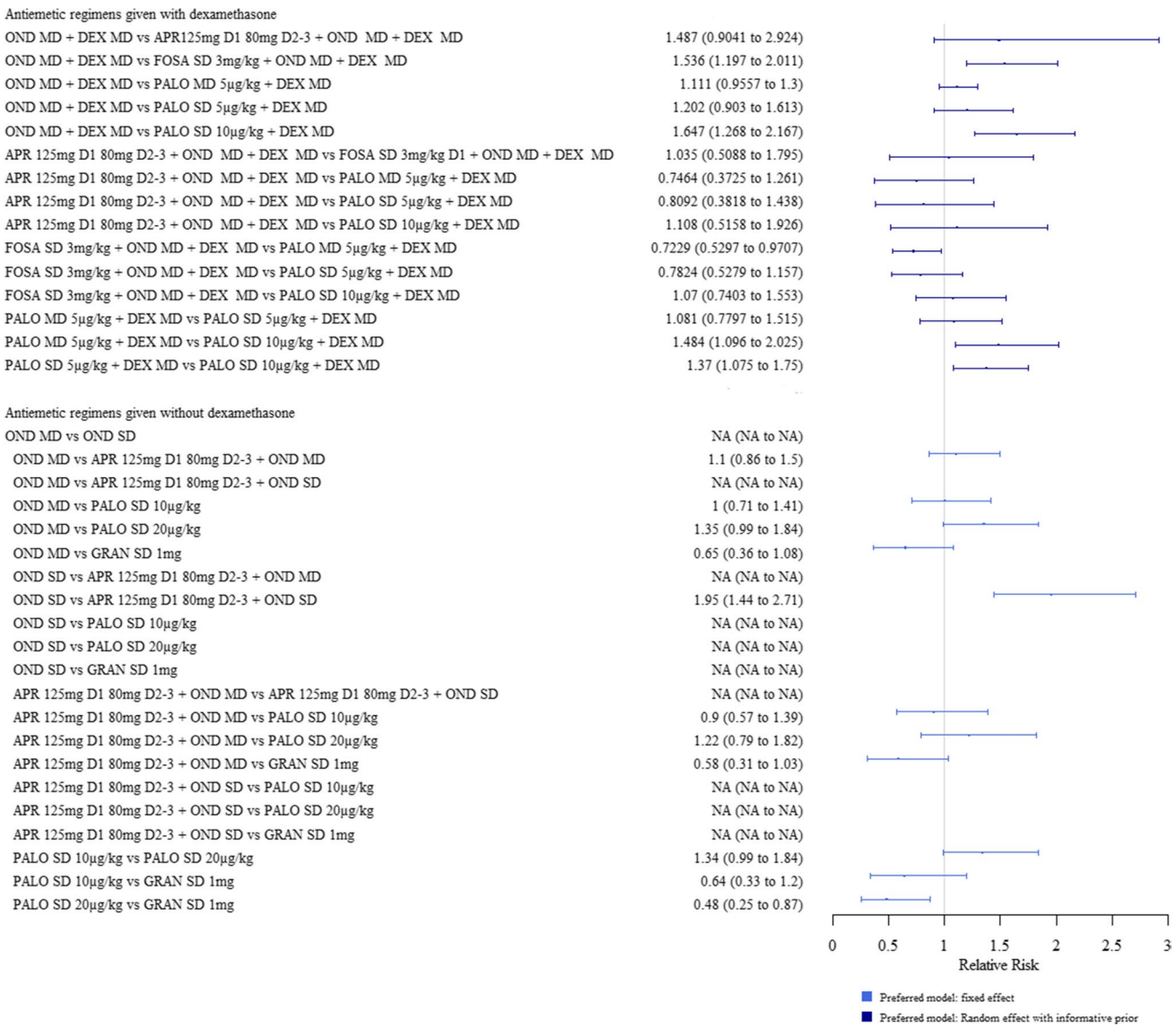

Fig. 5 Forest plot: relative risks (95% credible interval) of antiemetic regimens given with dexamethasone and those given without for the outcome of complete response in the delayed phase. Values greater than 1 favour the second named intervention. Where there are no results for certain models, the treatment effect for that comparison was not estimable (i.e. had a very wide credible interval). N.B Clinical advice to this project suggests granisetron 1 mg is an unusually high dose; and therefore, results should be interpreted with caution

this comparison, or for those [40] which are linked to the main network via this comparison (Fig. 5).

Nausea (overall phase)

Eight clinical trials informed the analyses for the outcome of nausea, four of which gave antiemetic regimens with dexamethasone (615 patients across four different antiemetic regimens) and four which gave them without (903 patients across seven different antiemetic regimens) (Fig. 6).

This showed that palonosetron 5 µg/kg (SD) + dexamethasone decreased the risk of experiencing nausea compared to ondansetron (MD) + dexamethasone (MD). The palonosetron 5 µg/kg (SD) + dexamethasone and the palonosetron 10 µg/kg (SD) + dexamethasone had a similar efficacy to each other (Fig. 7).

For antiemetics given without dexamethasone, there was no evidence of difference between any antiemetic regimen in the analysis (Fig. 7).

Patient and family interpretation

Children/young people and their families involved in this project talked about the trade-off between taking more antiemetics (i.e. the triplet regimens) that may better prevent

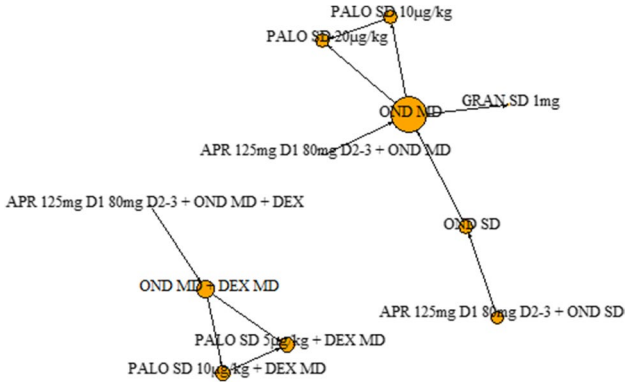

Fig. 6 Network diagram for the outcome of nausea (any phase). Network diagram of interventions. The size of the nodes is proportionate to the number of participants assigned to the intervention. The thickness of the lines is proportionate to the number of randomised trials that studied the respective comparison. Abbreviations defined in the 'Abbreviations' section

them from feeling or being sick, and the side effects of antiemetics such as constipation that can exacerbate side effects of other treatments/chemotherapy. Children and young people spoke of the difficulties of managing these trade-offs and that they would sometimes need to modify the number/type of antiemetic medications taken each day, to mitigate against other side effects depending on how bad these side effects were on any given day. One young person also raised the difficulties of taking multiple oral medications when already feeling sick, and that intravenous formulations may be preferable.

Discussion

Bayesian network meta-analysis has allowed for comparison of a greater number of antiemetics compared to what has previously been done, as well as comparisons of different doses and schedules of antiemetics. Whilst some estimates of treatment effect remain imprecise for some comparisons, particularly for antiemetic regimens given without dexamethasone, there is some evidence on which antiemetics are most effective.

Overall regimens with NK1 antagonists were ranked most efficacious, across the greatest number of outcomes, compared to other antiemetics regimens in those analyses. This is broadly supportive of current recommendations [5, 7–9] of aprepitant or fosaprepitant combined with 5HT3 antagonists and dexamethasone for patients receiving HEC. However, the evidence of effectiveness comes from mixed populations of patients receiving both HEC and MEC, and there does not yet exist evidence that patients receiving HEC gain greater relative benefit from the addition of aprepitant to ondansetron and dexamethasone. It, therefore, appears recommendations in clinical practice guidelines are targeting the most effective treatments for those patients with a higher baseline risk of CINV and, given that aprepitant and fosaprepitant remain expensive in comparison to ondansetron [41], likely incorporate an element of cost consideration, without formally assessing cost-effectiveness.

There is evidence that ondansetron may be less effective than palonosetron (when these 5HT3 antagonists are given with dexamethasone) for controlling delayed-phase CINV and nausea (the latter of which to our knowledge is new evidence). The most recent POGO guidelines informed by both children's and adult evidence [5] recommend palonosetron in the acute phase as the preferred 5HT3 antagonists in patients at high risk of delayed-phase CINV; however, this recommendation was based solely on adult evidence. Here, we provide evidence supporting this recommendation in children. The recommendation of palonosetron as the favoured 5HT3 antagonist could also be extended, particularly to those with a higher baseline risk of nausea, e.g. those who have experienced significant nausea in previous chemotherapy cycles, as these patients are likely to have the largest absolute risk reduction.

This research has also allowed for the comparison of different doses and schedules of palonosetron. Where similarities in treatment effect were demonstrated, i.e. for outcomes of nausea and complete response in the acute phase, the results suggest that either the 5 µg/kg dose or 10 µg/kg dose may be used, and that no significant benefit is lost from giving the 5 µg/kg dose once before chemotherapy, compared to giving one dose before chemotherapy and additional doses afterwards. For prevention of delayed-phase CINV, the more effective palonosetron dose of 10 µg/kg may be recommended, particularly for those patients with a higher risk of this outcome, e.g. those who have experienced delayed-phase CINV in previous chemotherapy cycles. To note, this evidence comes from patients who received a single dose of palonosetron before chemotherapy. We do not have evidence for or against the use of the manufacturer's recommended dose of 20 µg/kg from our analyses, due to the sparsity of evidence in the network of antiemetic regimens given without dexamethasone.

Finally, post hoc analysis shows that the addition of olanzapine, to aprepitant, ondansetron, and dexamethasone, is beneficial for a complete response in both the acute and delayed phases, evidence supporting its recommendation in the most recent POGO guidelines [5]. However, importantly, benefits were less, when olanzapine was given with just ondansetron and dexamethasone, and so the quadruplet therapy is likely the preferred option for high-risk patients. Existing research also indicates olanzapine may be a cost-effective option when added to regimens of aprepitant, dexamethasone, and ondansetron [42].

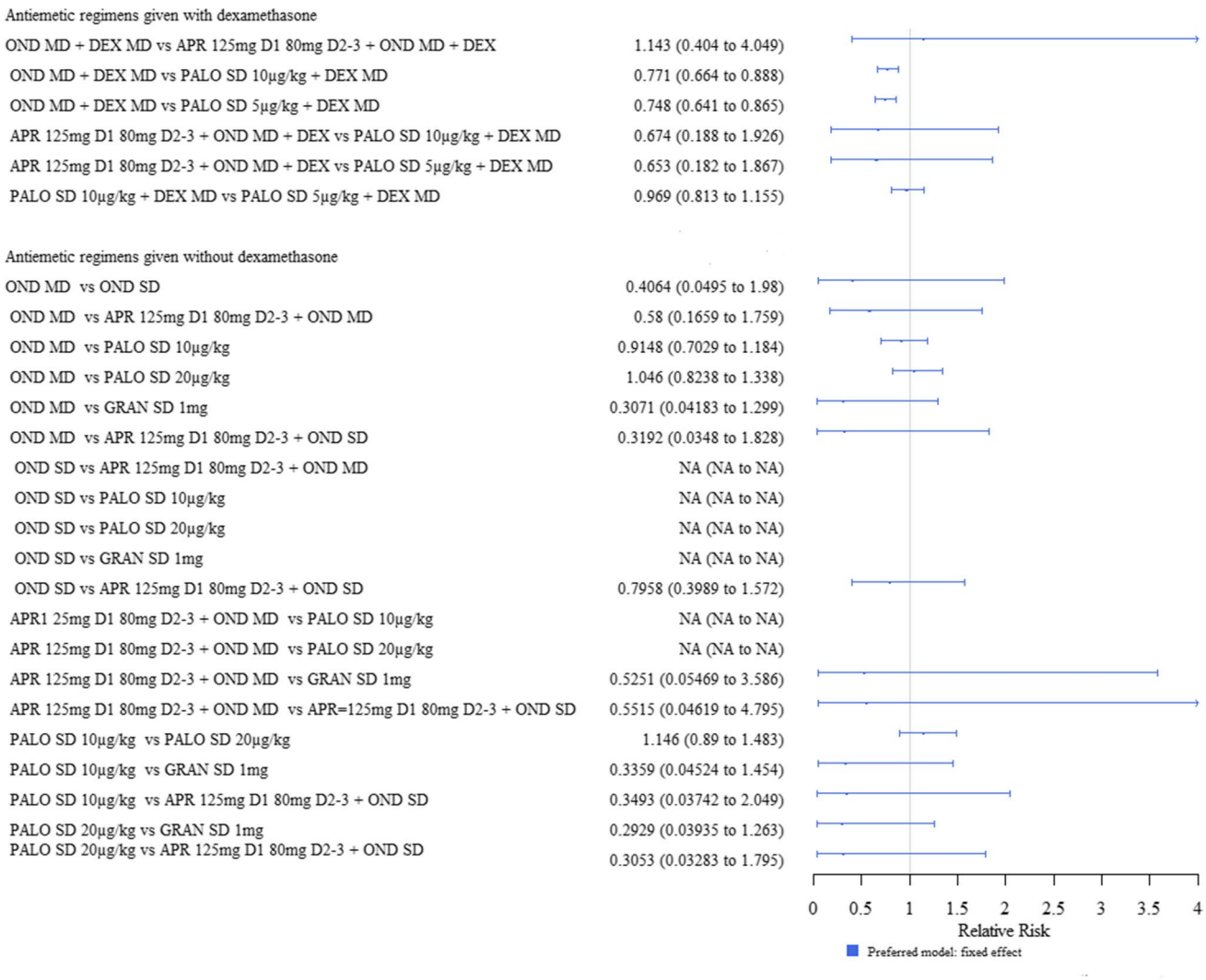

Fig. 7 Forest plot: relative risks (95% credible interval) of antiemetic regimens given with dexamethasone and those given without for the outcome of nausea (any phase). Values less than 1 favour the second named intervention. Where there are no results for certain models, the treatment effect for that comparison was not estimable (i.e. had a very wide credible interval). N.B Clinical advice to this project suggests granisetron 1 mg is an unusually high dose; and therefore, results should be interpreted with caution

Decisions about which 5HT3 antagonists to prescribe and/or whether to prescribe doublet, triplet, or quadruplet regimens prior to and during the first cycle of chemotherapy will consider not only the clinical benefits (i.e. a reduction in CINV and related outcomes such as poor nutritional status, infection-related adverse events, and anticipatory CINV in subsequent cycles), but also the possible risks (e.g. side effects of antiemetics and potential drug interactions), as well as cost considerations (both of the antiemetic themselves and the additional medications and/or treatments that would be required if CINV is poorly controlled).

In an ideal scenario, a formal cost-effectiveness analysis, considering all of these elements would be conducted, to determine whether using the more effective (but more expensive [43]) antiemetics, palonosetron and aprepitant, across patients receiving both HEC and MEC is a cost-effective option compared to ondansetron, and compared to each other. However, given the remaining uncertainty in treatment effects estimates, coupled with poor and inconsistent reporting of side effects in clinical trial publications, a meaningful analysis (like those demonstrating the cost-effectiveness of aprepitant regimens in patients receiving HEC [44]) would likely require individual patient data (IPD) (i.e. the 'raw' data from clinical trials).

Aggregate data suggests side effects may be more common, with regimens of multiple antiemetics. Given this, and the fact that patients and their families raised concerns about the number of antiemetics to be taken each day, and

their potential to cause and exacerbate side effects, future research may consider reducing the number of antiemetic medications per regimen (i.e. omitting those considered least effective) to establish whether this is possible without a significant reduction in efficacy. Consistent reporting of side effects also remains critical across RCTs of antiemetics, so that comparative safety can be better established. Further direction for future research is reported in Supplementary file 12.

Limitations of the analyses

The analyses conducted here are limited by treatment comparisons informed by few clinical trials and small clinical trials (< 50 patients). This has contributed to uncertain estimates of treatment effect and means there is little information about differences in treatment effect between studies (see Supplementary file 5—Model comparison and model specification for further detail). Studies included in the syntheses are heterogeneous by design, with differences in terms of the definition (i.e. length) of the acute phase across studies, and in some cases the definition of complete response (no vomiting vs no vomiting or use of rescue medication). The synthesised evidence is also from a heterogenous population, and the distributions of patient and treatment-related factors which could impact treatment effectiveness (e.g. age, length of chemotherapy block, and emetogenicity of chemotherapy for example) vary across studies; as such, caution is required when interpreting results. In particular, highly emetogenic chemotherapy and multi-day chemotherapy regimens may make antiemetics appear less effective.

Sparse and inconsistent reporting of patient/treatment-related factors meant that conducting separate analyses for different subgroups of patients was not possible. Of note, it was not possible to conduct separate analyses for patients receiving MEC vs HEC, as few studies reported subgroup analyses and not all studies reported the emetogenicity of chemotherapy, meaning these studies would not have been able to be included in the analyses. To ameliorate this limitation, we have kept antiemetic regimens given with and without dexamethasone in separate networks, as those receiving regimens given with dexamethasone predominantly received HEC and those receiving regimens given without dexamethasone predominantly received MEC (see Supplementary file 6 Determining the structure of the networks for further detail). These limitations are being further addressed using individual participant data in the second stage of this research project (see Supplementary file 12- Further directions for future research for further detail).

We have focused on clinical trials assessing antiemetics currently approved for use in children by the United States Food and Drug Administration or European Medicines Agency. Clinical trials included in the analyses are, therefore, predominantly undertaken in high- and middle-income countries, and a limited number of these trials report ethnicity data. Understanding how these medicines may function in low-income countries is potentially limited by the underrepresentation of different populations, but is also more complex, in that it will involve issues of cost and accessibility that have not been assessed as part of this project.

Conclusions

Regimens of olanzapine given with aprepitant, ondansetron, and dexamethasone are most effective for complete response outcomes, followed by NK1 antagonist given with ondansetron. Of the 5HT3 antagonists, palonosetron shows greatest promise. Recommendation for the use of these more effective regimens may remain and where applicable, extended, particularly to those at high risk of the outcomes which they prevent.

Abbreviations *APR*: Aprepitant; *OND*: Ondansetron; *PALO*: Palonosetron; *GRAN*: Granisetron; *FOSA*: Fosaprepitant; *DEX*: Dexamethasone; *METO*: Metoclopramide; *SD*: One dose given before chemotherapy; *MD*: Multiple doses, with one dose given before chemotherapy followed by subsequent doses after initial chemotherapy administration; *D1*: Day 1 of chemotherapy administration; *D2*: Days 2 and 3 following initial chemotherapy administration; *5HT3*: 5-Hydroxytryptamine; *NK1*: Neurokinin 1 receptor

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00520-024-08939-9.

Acknowledgements We would like to thank Connor Evans and Sahar Sherif for contributing to the systematic review elements of this projects, as well Helen Fulbright and Melissa Harden for contributing to the development of the search strategy.

Author contributions RW, BP, and SD were responsible for the design of the study. RW conducted the analysis with oversight from BP and SD. RW wrote the main manuscript text and prepared figures/tables. All authors critically reviewed the manuscript and approved the final version and are accountable for all aspects of the work.

Funding This study was funded by a National Institute of Health and Social Care Research (NIHR) doctoral fellowship grant held by Ruth Walker Grant ID: NIHR302291. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR, NHS, or the UK Department of Health and Social Care.

Data and code availability The extracted data used in our analyses is reported in the Supplementary file 9- Summary data, and the code used to conduct the analyses is provided in Supplementary file 5- Model comparison and model specification.

Declarations

Ethics approval This is a secondary analysis of published randomised control trial data. A research ethics committee at the University of York has confirmed no ethical approval is needed for this study.

Competing interests The authors declare no competing interests.

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