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Original Article

Comparative effectiveness of netupitant-palonosetron plus dexamethasone versus aprepitant-based regimens in mitigating chemotherapy-induced nausea and vomiting: a meta-analysis of randomized controlled trials

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Abstract

Background: Despite guidelines for managing chemotherapy-induced nausea and vomiting (CINV), there remains a need to clarify the optimal use of neurokinin-1 (NK_1) receptor antagonists. Comparing the effectiveness of NEPA (netupitant-palonosetron) plus dexamethasone with other NK1 antagonist-based regimens combined with a 5HT3 receptor antagonist and dexamethasone is crucial for informed decision-making and improving patient outcomes.

Methods: We conducted a systematic review of the literature to assess randomized controlled trials (RCTs) comparing the efficacy, safety, and cost-effectiveness of NEPA plus dexamethasone and other NK1 antagonist-based regimens combined with a 5HT3 receptor antagonist and dexamethasone. PubMed, Embase, and the Cochrane Library databases were systematically searched, with the latest update performed in December 2023. Data on patient demographics, chemotherapy regimen characteristics, and outcomes were extracted for meta-analysis using a random-effects model.

Results: Seven RCTs were analyzed. NEPA plus dexamethasone showed superior efficacy in achieving complete response in the overall (risk ratio [RR], 1.15; 95% CI, 1.02–1.30) and delayed phases (RR, 1.20; 95% CI, 1.03-1.41) of chemotherapy. It was more effective in controlling nausea (overall phase RR, 1.20; 95% CI, 1.05-1.36; delayed phase RR, 1.21; 95% CI, 1.05-1.40) and reducing rescue therapy use (overall phase RR, 1.45; 95% CI, 1.07-1.95; delayed phase RR, 1.75; 95% CI, 1.10-2.78). Adverse event rates were comparable (RR, 1.03; 95% CI, 0.96-1.10). Subgroup analysis indicated NEPA's particular efficacy in patients receiving moderately emetogenic chemotherapy (RR, 1.31; 95% CI, 1.07-1.60).

Conclusion: NEPA plus dexamethasone regimens exhibit superior efficacy in preventing CINV, supporting their preferential inclusion in prophylactic treatment protocols. Its effective symptom control, safety profile, and cost-effectiveness endorse NEPA-based regimens as a beneficial option in CINV management.

Key words: Chemotherapy-induced nausea and vomiting (CINV); Neurokinin-1 (NK_1) receptor antagonists; Netupitant-palonosetron (NEPA); Aprepitant; Meta-analysis.

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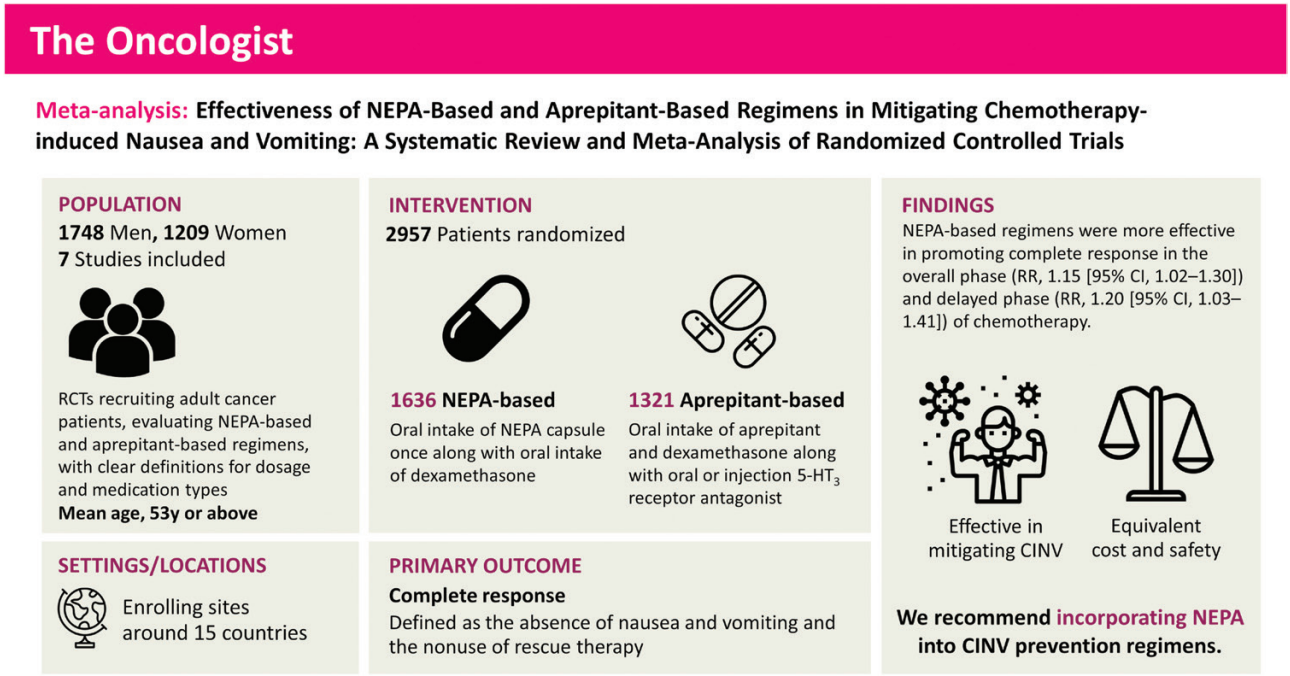
Graphical Abstract



Abbreviations: 5-HT_3: 5-hydroxytryptamine-3; CI: confidence interval; NK_1: neurokinin-1; HEC: highly emetogenic chemotherapy; MEC: moderately emetogenic chemotherapy; RCT: randomized control trial; NEPA: netupitant-palonosetron

Implications for Practice

Our findings demonstrate the superior efficacy of NEPA-based regimens over aprepitant-based regimens in managing CINV, particularly in the delayed and overall phases for patients undergoing moderately emetogenic chemotherapy (MEC), a distinction not addressed in current guidelines. Additionally, our cost-effectiveness analysis underscores NEPA's effectiveness in CINV management, while safety analysis indicates comparable safety profiles between NEPA and aprepitant groups. As the first systematic review and meta-analysis research focusing on the comparison of different NK_1 receptor antagonists, these findings highlight the necessity for further research to bolster existing evidence and inform clinical practice.

Introduction

Chemotherapy, a critical component of cancer treatment, often induces severe nausea and vomiting, extending beyond physical discomfort[1] and significantly impacting patients' emotional[2] and psychological well-being.[3] These adverse effects not only diminish quality of life but also contribute to nutritional deficits[4] and physical weakness, compromising patients' capacity to withstand cancer treatment.[5] Addressing chemotherapy-induced nausea and vomiting (CINV) is thus crucial for maintaining patients' physical health and resilience during cancer treatment.[6]

Current guidelines from leading oncology societies, including the American Society of Clinical Oncology,[7] the National Comprehensive Cancer Network,[8] the Multinational Association of Supportive Care in Cancer,[9] and the European Society of Medical Oncology,[10] offer strategies for CINV management. These guidelines commonly endorse specific medications combinations, although recommendations vary slightly based on the emetogenic potential of prescribed chemotherapy agents.[11] The recommended medications of neurokinin-1 (NK1) receptor antagonists, such as aprepitant, fosaprepitant, rolapitant, and netupitant-palonosetron; 5-hydroxytryptamine-3 (5-HT3) receptor antagonists, such as palonosetron, granisetron, and ondansetron; dexamethasone; and olanzapine.[7] Depending on the chemotherapy drugs used, there are recommendations for 2-drug, 3-drug, or 4-drug antiemetic regimens. However, explicit directives for selecting particular NK1 receptor antagonists tailored to individual patient requirements remain ambiguous, highlighting a gap in clinical guidance and underscoring the necessity for clarity in medication selection to aid healthcare providers in prescription decisions.

Netupitant-palonosetron (NEPA), the inaugural fixed-combination antiemetic, unites an NK_1 receptor antagonist (netupitant) with a potent 5-HT_3 receptor antagonist (palonosetron), combined with dexamethasone. Its formulation simplifies treatment regimens, potentially enhancing patient adherence and overall care quality. NEPA received U.S. Food and Drug Administration (FDA) approval in October 2014 for the prevention of both acute and delayed CINV. Subsequently, the European Medicines Agency (EMA) granted marketing authorization in May 2015, and it has been approved in several other regions, including Japan by the Pharmaceuticals and Medical Devices Agency (PMDA), Taiwan by the Taiwan Food and Drug Administration (TFDA), and China by the China National Medical Products Administration (NMPA). These approvals highlight the widespread acceptance of NEPA as a valuable treatment option for CINV. Furthermore,

the efficacy and safety of NEPA have been extensively discussed.[12-15] Nevertheless, a comprehensive analysis comparing the effectiveness of NEPA with that of other NK1 receptor antagonists, such as aprepitant, is lacking in the literature.

In response to this gap, we conducted a systematic review and meta-analysis to compare the efficacy of NEPA-based and aprepitant-based regimens in mitigating CINV among patients with cancer, with a particular focus on evidence garnered from randomized controlled trials (RCTs).

Materials and methods

Selection criteria

We conducted a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Trials that met the following criteria were included: (1) having an RCT design; (2) investigating the efficacy of an NEPA- or aprepitant-based regimen in preventing CINV; and (3) having clear definitions for dosage, types of medications, and outcomes. Trials were excluded if they met the following criteria: (1) having unclear reporting of dosage or types of medications, (2) having an unclear or non-RCT study design, and (3) comparing medications other than NEPA and aprepitant. The study was registered with PROSPERO (number: CRD42024496795).

Search strategy and study selection

Studies were identified through computerized searches of the PubMed, Embase, and Cochrane Library databases. The following terms were used as medical subject headings and combined in a Boolean search format: CINV, NEPA, chemotherapy-induced nausea and vomiting, chemotherapy-induced emesis, chemotherapy-associated nausea and vomiting, Netupitant, Aprepitant, Netupitant and Aprepitant, NK_1 receptor antagonist, and Dual NK_1 receptor antagonist therapy. The "Similar Articles" section in PubMed was used to broaden the search. We reviewed all abstracts, studies, and citations retrieved after the last search in December 2023. We did not apply language restrictions in the search.

Data extraction

Two reviewers (W.-T.L. and T.-W.H.) independently extracted. Key data points extracted included patient demographics (age, gender, and cancer type), chemotherapy regimens (dose, duration, and emetogenic potential), and study outcomes (complete response, nausea control, rescue therapy use, and adverse events). Notable differences in patient populations and chemotherapy treatments were identified and analyzed to understand their impact on study results. The details recorded by the 2 reviewers were compared, and disagreements were discussed and resolved by a third expert.

Methodological quality appraisal

Two reviewers (W.-T.L. and T.-W.H.) independently appraised the methodological quality of each study on the basis of version 2 of the Cochrane risk-of-bias tool for randomized trials described in the *Cochrane Handbook for Systematic Reviews of Interventions*.[16] We considered the following risk-of-bias domains: risk of bias arising from the randomization process, risk of bias due to deviations from the intended interventions, risk of bias due to missing outcome data, risk of bias in outcome measurement, and risk of bias in result selection.

Outcome assessments

The effects of NEPA- and aprepitant-based regimens were evaluated through outcome assessments. The primary outcome was complete response. Other outcomes comprised nausea, emesis, rescue therapy use, and adverse events. Additionally, we conducted a subgroup analysis to evaluate medication efficacy according to the chemotherapy regimen (moderately emetogenic chemotherapy [MEC] vs highly emetogenic chemotherapy [HEC]) received.

Statistical analysis

We conducted statistical analyses using Review Manager (version 5.4; Cochrane Collaboration, Oxford, UK). The meta-analysis was conducted in accordance with the PRISMA guidelines.[17] Dichotomous outcomes were analyzed using weighted risk ratios. Moreover, the precision of the effect sizes is expressed as 95% CIs (CIs). Pooled estimates of risk ratios (RRs) were computed using the DerSimonian and Laird random-effects model[18]; data were pooled only for studies that exhibited adequate clinical and methodological similarity. Statistical heterogeneity was assessed using the I^2 test, with I^2 representing the proportion of the total outcome variability attributable to differences among the studies. If multiple dosages were tested in a study, the dosage consistent with that used in other studies was chosen for inclusion in the meta-analysis.

Results

Trial characteristics

Figure 1 shows the study selection flowchart. Our initial search yielded 1339 studies, of which 382 were removed as duplicates and 11 were excluded for other reasons. After title and abstract screening of the remaining 946 studies, 908 were excluded, leading to the review of full texts for 38 studies. Among these, 14 studies were excluded due to the lack of a clinical trial design, and 13 were excluded because their control groups did not meet our inclusion criteria. Additionally, 4 studies were excluded due to single-arm study design, post hoc analysis, crossover study design, or lacked relevance. Consequently, 7 RCTs were eligible for inclusion in our meta-analysis.[19--25]

Table 1 shows the characteristics and patient demographics of the included RCTs. These studies, published between 2014 and 2023, had sample sizes ranging from 196 to 829 participants, all of whom were adult cancer patients with an average age of 53 or older. In the NEPA group, all RCTs used a single-dose administration of NEPA (300 mg netupitant + 0.5 mg palonosetron), except the RCT by Hesketh et al,[21] which used 3 doses of netupitant. Therefore, we standardized the dose to 300 mg for the integrated analysis. In the aprepitant group, patients received aprepitant over 3 days, with slight variations in the type and dosage of 5-HT3 receptor antagonists and dexamethasone administration methods across studies.

Of the included RCTs, 3 focused on patients undergoing moderately emetogenic chemotherapy (MEC) regimens,[22--24] and 3 involved highly emetogenic chemotherapy (HEC) regimens.[19,21,25] The study by Gralla et al[20] included 75.7% of patients undergoing MEC, with the remainder receiving HEC. Four studies[19,21,22,25] primarily included patients with lung cancer, while the others focused on breast,[23] gastric,[24] or lymph node cancers.[20]

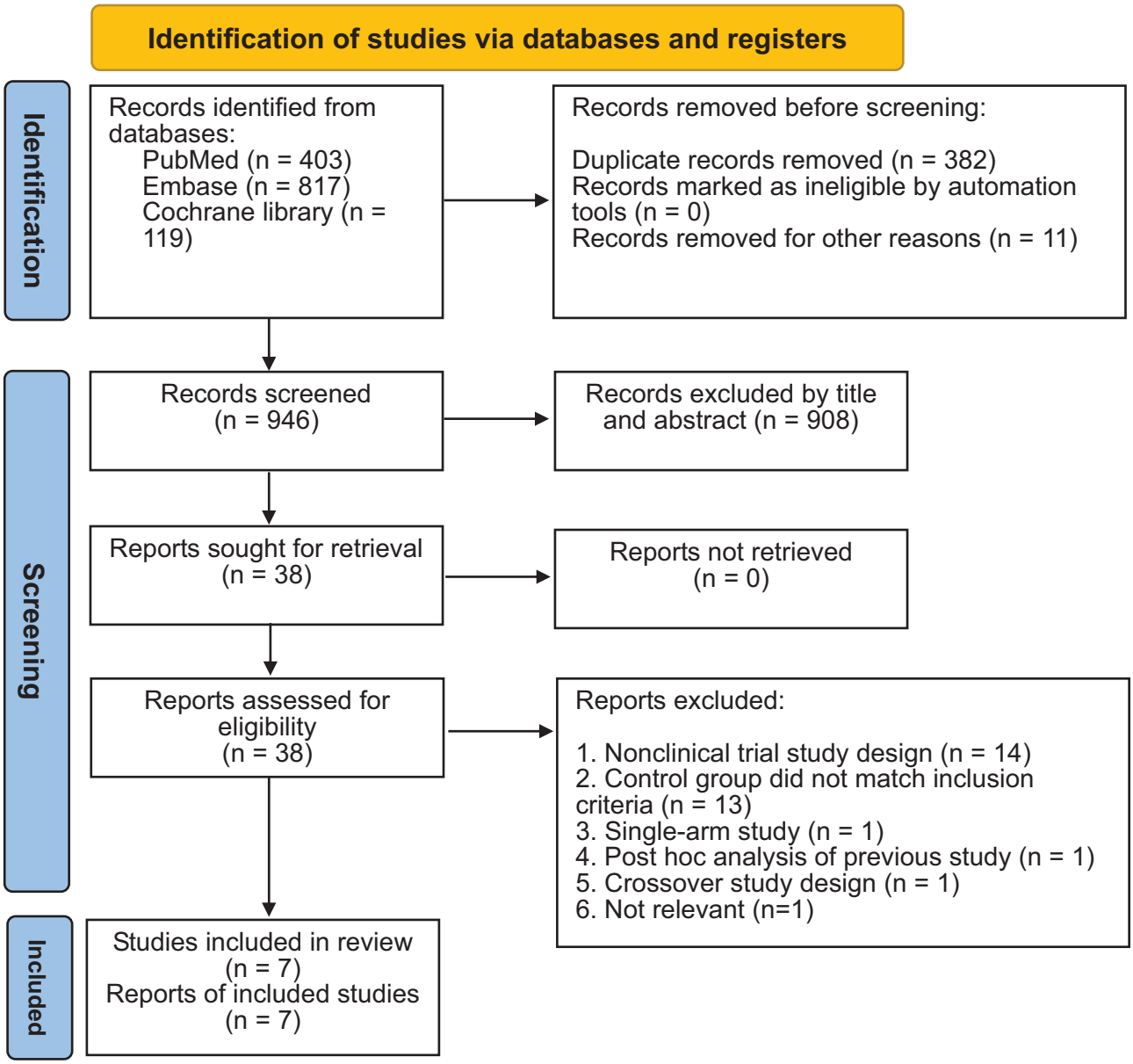


Figure 1. Flowchart of study selection.

The methodological quality of the included RCTs is presented in Table 2. Of the included RCTs, 4[19--21,25] demonstrated a low risk of bias in the randomization process. However, the remaining 3 RCTs[22--24] raised concerns about bias arising from insufficient information on concealment and participant allocation. Specifically, 2 of these RCTs[23,24] raised concerns about outcome measurement due to an unclear explanation of the procedure for blinding participants and assessors.

Overall, 4 RCTs[19--21,25] had a low overall risk of bias, whereas the remaining 3 RCTs[22--24] raised concerns of potential bias.

Complete response

Complete response, defined as the absence of nausea and vomiting and the nonuse of rescue therapy, was assessed in the 7 RCTs.[19--25] The term "complete response," which is used to describe the absence of both vomiting and the need for rescue medication within a specific time frame, was consistently adopted across all 7 included studies. This aligns with the guidelines from major oncology organizations, such as the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN), which recommend using "complete response" as an endpoint for evaluating antiemetic treatments. All RCTs evaluated complete response within 120 hours after chemotherapy (referred to as the overall phase). Additionally, 6 of the included RCTs evaluated complete response within 24 hours after chemotherapy (referred to as the acute phase).[19--21,23--25] Five RCTs evaluated complete response between 25- and 120 hours after chemotherapy (referred to as the delayed phase).[19--21,23,25] To provide a clearer visualization of the statistical results, we generated a forest plot illustrating the number of patients who did not achieve complete response. Compared with aprepitant, NEPA was significantly more effective in engendering complete response in the overall phase (RR, 1.15; 95% CI, 1.02--1.30) and delayed phase (RR, 1.20; 95% CI, 1.03--1.41); however, the effectiveness of NEPA and aprepitant did not differ significantly in the acute phase (RR, 1.09; 95% CI, 0.79--1.51; Figure 2).

Table 1. Characteristics of included studies.

Author (Year)	Inclusion criteria	Chemotherapy regimen	Cancer type	Number of patients (% male)	Age, year, mean ± SD	Intervention
Chang [2020]	Adult patients with cancer who received HEC regimens	Gemcitabine (27.9%), pemetrexed (20.1%), docetaxel (18.9%), etoposide (15.4%), and other regimens	Lung (72.4%) and other types	N: 339 (69) A: 328 (70)	N: 54.4[a] A: 54.9[a]	N: Oral intake of NEPA capsule once along with a 4-day course of dexamethasone starting from the day of chemotherapy A: Oral intake of aprepitant for 3 days, dexamethasone for 4 days, along with granisetron injection once starting from the day of chemotherapy
Gralla [2014]	Adult patients with cancer who received HEC and MEC regimens	Carboplatin (45.9%), cisplatin (23.1%), oxaliplatin (16.0%), and other regimens	Lymph nodes (30.1%), lung (13.8%), liver (12.1%), and other types	N: 308 (50) A: 104 (51)	N: 57.0[b] A: 58.5[b]	N: Oral intake of NEPA capsule once along with a 4-day course of dexamethasone starting from the day of chemotherapy A: Oral intake of aprepitant for 3 days, dexamethasone for 1 or 4 days, along with oral palonosetron once starting from the day of chemotherapy
Hesketh [2014]	Adult patients with cancer who received cisplatin-based regimens	Cisplatin-based regimens	Lung/respiratory (26.0%), head and neck (21.9%), ovarian (18.2%), and other types	N: 135 (57) A: 134 (56)	N: 53.0[b] A: 55.5[b]	N: Oral intake of NEPA capsule once along with a 4-day course of dexamethasone starting from the day of chemotherapy A: Oral intake of aprepitant for 3 days, dexamethasone for 4 days, along with ondansetron injection once starting from the day of chemotherapy
Jordan [2016]	Adult patients with cancer who received carboplatin-based regimens	Carboplatin-based regimens	Lung/respiratory (51.5%), gynecological (26.5%), head and neck (10.2%), and other types	N: 145 (54) A: 51 (53)	N: 57 ± 10 A: 58 ± 11	N: Oral intake of NEPA capsule once along with dexamethasone A: Oral intake of aprepitant for 3 days, along with oral palonosetron and dexamethasone once starting from the day of chemotherapy
Zelek [2021]	Adult patients with cancer who received MEC regimens	Cyclophosphamide (44.0%), epirubicin (38.1%), oxaliplatin (30.8%), carboplatin (22.3%), and other regimens	Breast (43.7%), gastric (18.5%), lung (8.3%), and other types	N: 187 (36) A: 186 (28)	N: 62 ± 12 A: 59 ± 12	N: Oral intake of NEPA capsule once along with a 4-day course of dexamethasone starting from the day of chemotherapy A: Oral intake of aprepitant for 3 days, dexamethasone for 4 days, along with ondansetron injection once starting from the day of chemotherapy
Zelek [2023]	Adult patients with cancer who received MEC regimens	Oxaliplatin (53.6%), carboplatin (38.4%), irinotecan (16.1%), and other regimens	Gastric (33.2%), colorectal (17.1%), lung/respiratory (14.7%), and other types	N: 109 (60) A: 102 (47)	N: 65.6 ± 10.6 A: 63.4 ± 10.1	N: Oral intake of NEPA capsule once along with a 4-day course of dexamethasone starting from the day of chemotherapy A: Oral intake of aprepitant for 3 days, dexamethasone for 4 days, along with ondansetron injection once starting from the day of chemotherapy
Zhang [2018]	Adult patients with cancer who received cisplatin-based regimens	Cisplatin-based regimens	Lung (58.3%), head and neck (6.6%), and other types	N: 413 (71) A: 416 (71)	N: 54.6 ± 9.6 A: 54.5 ± 10.2	N: Oral intake of NEPA capsule once along with a 4-day course of dexamethasone starting from the day of chemotherapy A: Oral intake of aprepitant for 3 days, dexamethasone for 4 days, along with granisetron injection once starting from the day of chemotherapy

[a]Reported as means rather than means ± SDs.
[b]Reported as medians rather than means ± SDs.
Abbreviations: A = aprepitant group; N = NEPA (netupitant-palonosetron) group; = HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; RCT = randomized controlled trial.

Table 2. Assessment of methodological quality of included trials.

Author [year]	Randomizing process	Deviation from the intended treatment	Missing outcome data	Measurement of outcome	Selection of the reported result	Overall risk
Chang [2020]	Low	Low	Low	Low	Low	Low
Gralla [2014]	Low	Low	Low	Low	Low	Low
Hesketh [2014]	Low	Low	Low	Low	Low	Low
Jordan [2016]	Some concerns	Low	Low	Low	Low	Some concerns
Zelek [2021]	Some concerns	Low	Low	Some concerns	Low	Some concerns
Zelek [2023]	Some concerns	Low	Low	Some concerns	Low	Some concerns
Zhang [2018]	Low	Low	Low	Low	Low	Low

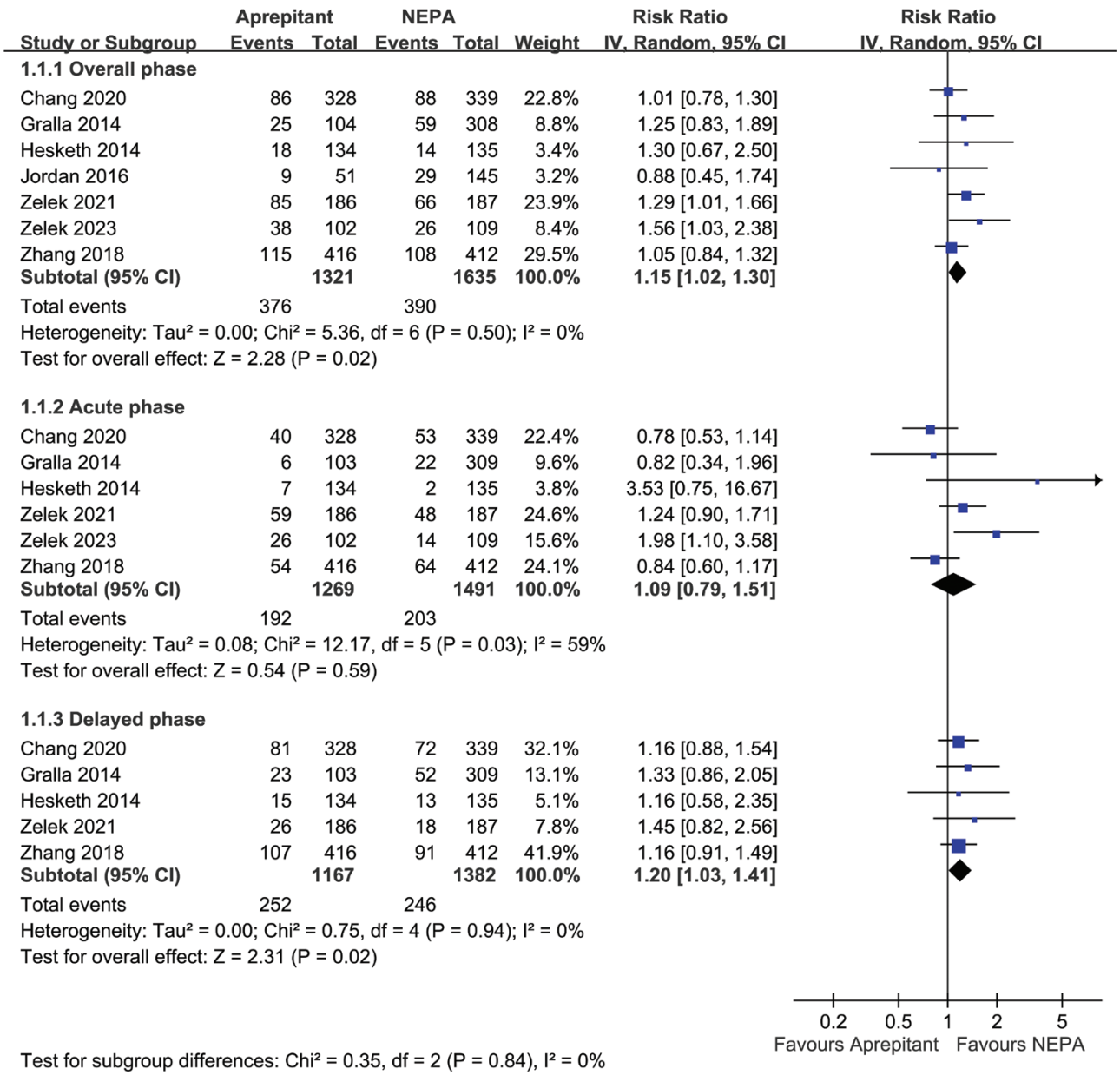


Figure 2. Forest plot comparing NEPA and aprepitant. Outcome: Complete response.

Nausea

Nausea was assessed in 6 RCTs.[19--21,23--25] Of these 6 RCTs, 5[19--21,23,25] provided data for the overall, acute, and delayed phases, whereas one[24] provided only data for the acute phase. Compared with aprepitant, NEPA was significantly more effective in managing nausea in the overall phase (RR, 1.20; 95% CI, 1.05--1.36) and delayed phase (RR, 1.21; 95% CI, 1.05--1.40); nevertheless, the effectiveness of NEPA and aprepitant did not differ significantly in the acute phase (RR, 1.23; 95% CI, 0.91--1.67; Figure 3).

Emesis

Emesis was assessed in 5 RCTs.[19,21,23--25] Of these 5 RCTs, 4[19,21,23,25] provided data for the overall, acute, and delayed phases, whereas one[24] disclosed only data for the acute phase. Compared with aprepitant, NEPA showed a trend toward being more effective in managing emesis in the delayed phase (RR, 1.16; 95% CI, 0.97--1.39); however, the effectiveness of NEPA and aprepitant did not differ significantly in the overall phase (RR, 1.07; 95% CI, 0.92-1.24) or the acute phase (RR, 1.00; 95% CI, 0.77--1.30; Figure 4).

Rescue therapy

Rescue therapy use was assessed in 2 RCTs,[23,25] both of which disclosed data for the overall, acute, and delayed phases. Compared with aprepitant, NEPA was significantly more effective in reducing the use of rescue therapy in the overall phase (RR, 1.45; 95% CI, 1.07--1.95) and delayed phase (RR, 1.75; 95% CI, 1.10--2.78); nevertheless, the effectiveness of NEPA and aprepitant did not differ significantly in the acute phase (RR, 1.25; 95% CI, 0.81--1.93; Supplementary Supplementary Figure S1).

Adverse events

The occurrence of adverse events was assessed in 5 RCTs.[19--21,23,25] All 5 RCTs reported no significant differences in the incidence of adverse events (RR, 1.03; 95% CI, 0.96--1.10) between the NEPA and aprepitant groups. Moreover, 3 RCTs[20,21,23] reported treatment-related adverse events, with no significant difference observed (RR, 0.99; 95% CI, 0.58--1.69) between the NEPA and aprepitant groups. We also analyzed the most commonly reported adverse events, including constipation, headaches, and hiccups. Our results indicated a trend toward a higher occurrence of constipation in the NEPA

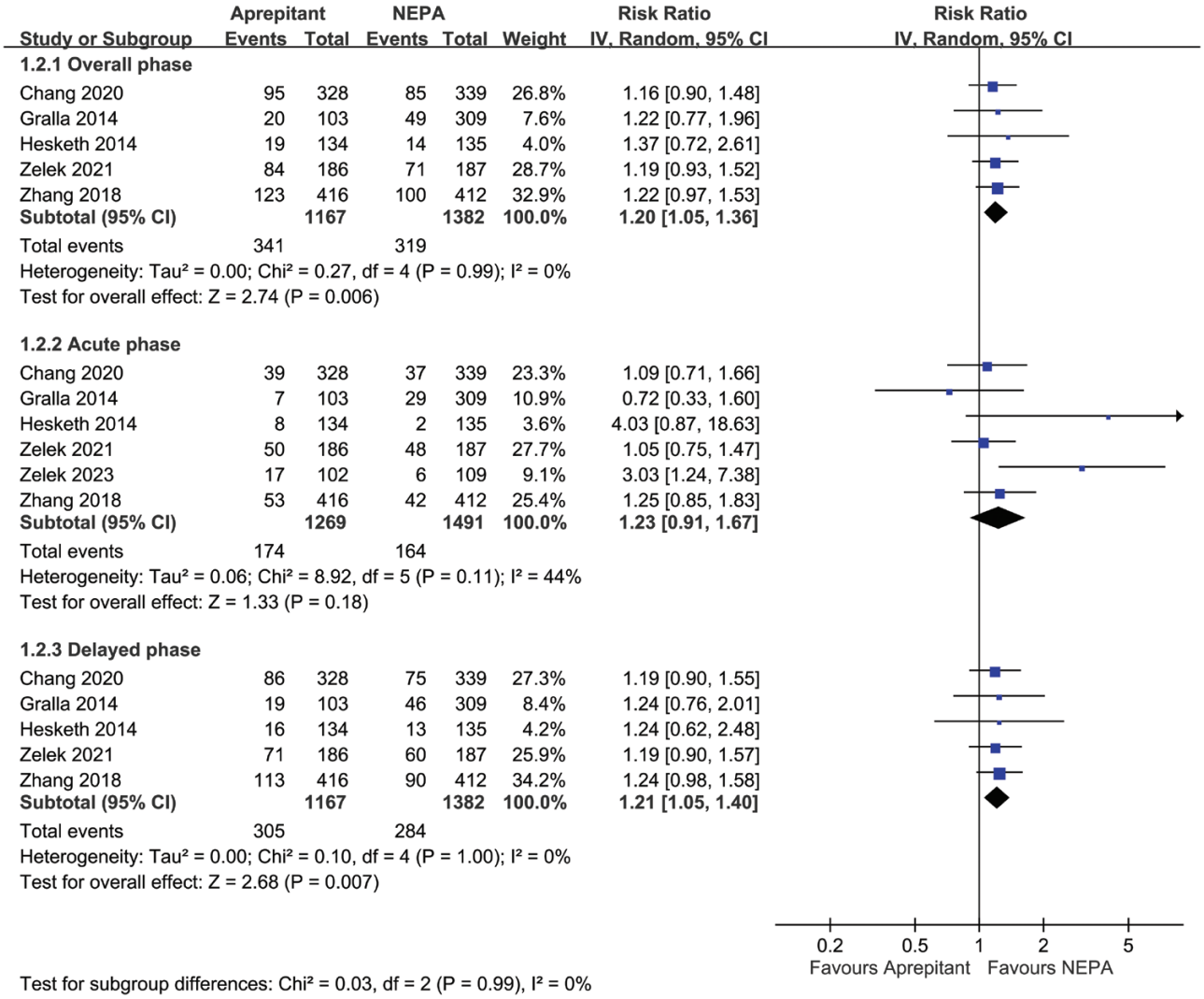


Figure 3. Forest plot comparing NEPA and aprepitant. Outcome: Nausea.

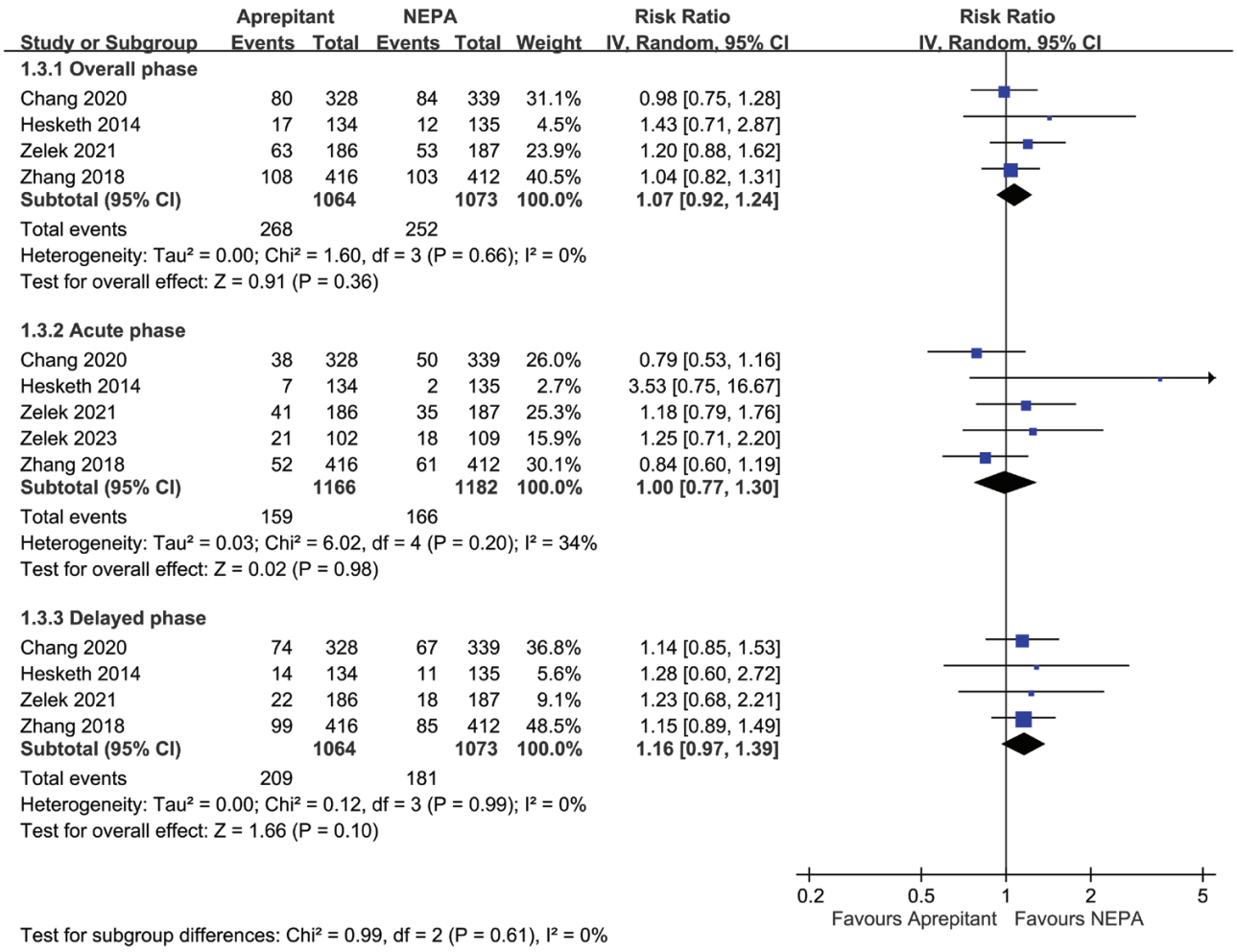


Figure 4. Forest plot comparing NEPA and aprepitant. Outcome: Emesis.

group (RR, 0.77; 95% CI, 0.54--1.10). However, no significant differences were observed in the occurrence of headaches (RR, 1.73; 95% CI, 0.35--8.49) or hiccups (RR, 0.30; 95% CI, 0.05--1.89) between the 2 groups (Supplementary Supplementary Figure S2).

Complete response from subgroup analysis

We conducted a subgroup analysis of complete response for the 6 RCTs that exclusively applied either MEC or HEC regimens.[19,21--25] This analysis was stratified by phase. In the overall phase, RCTs applying HEC regimens[19,21,25] revealed no difference between the NEPA and aprepitant groups (RR, 1.05; 95% CI, 0.89--1.24); however, in RCTs employing MEC regimens,[22--24] the NEPA group was significantly more likely to achieve complete response (RR, 1.31; 95% CI, 1.07--1.60). In the acute phase, RCTs employing HEC regimens[19,21,25] revealed no significant difference between the NEPA and aprepitant groups (RR, 0.88; 95% CI, 0.60--1.28); nevertheless, in studies applying MEC regimens,[23,24] the NEPA group was more likely to achieve complete response (RR, 1.46; 95% CI, 0.94-2.28). Finally, in the delayed phase, RCTs employing HEC regimens[19,21,25] revealed no significant difference between the NEPA and aprepitant groups (RR, 1.10; 95% CI, 0.93--1.30). The only study in this phase, conducted by Zelek et al[23] using MEC regimens, observed no significant difference between the NEPA and aprepitant groups (RR, 1.16; 95% CI, 0.91--1.49; Figure 5).

Discussion

Our systematic review and meta-analysis provide a comprehensive comparison of NEPA- and aprepitant-based regimens in managing CINV. The findings demonstrate that NEPA-based regimens exhibit superior efficacy in preventing CINV, particularly in the delayed and overall phases of chemotherapy. This superiority is consistent across various patient demographics and chemotherapy regimens, highlighting NEPA's robust effectiveness.

Understanding the mechanisms through which these medications act on symptoms is crucial for comparing the effectiveness of NEPA-based and aprepitant-based chemotherapy regimens. Chemosensitive receptors detect emetic agents such as dopamine, 5-HT, and substance P in the bloodstream.[26] These signals are transmitted through the vagal nerve afferents from the gastrointestinal tract to the emetic center in the brainstem, specifically involving key components like the area postrema.[27] Consequently, various medications targeting these emetic agents have been widely used in clinical settings. Notably, in vitro studies have demonstrated the synergistic relationship between netupitant and palonosetron.[28,29] Netupitant induces a dose-dependent inhibition of substance P responses, whereas palonosetron prevents crosstalk between the 5-HT_3 and NK_1 receptor pathways without binding directly to the NK_1 receptor.[30] Thus, the combined use of these medications results in an enhanced inhibition of substance P responses.

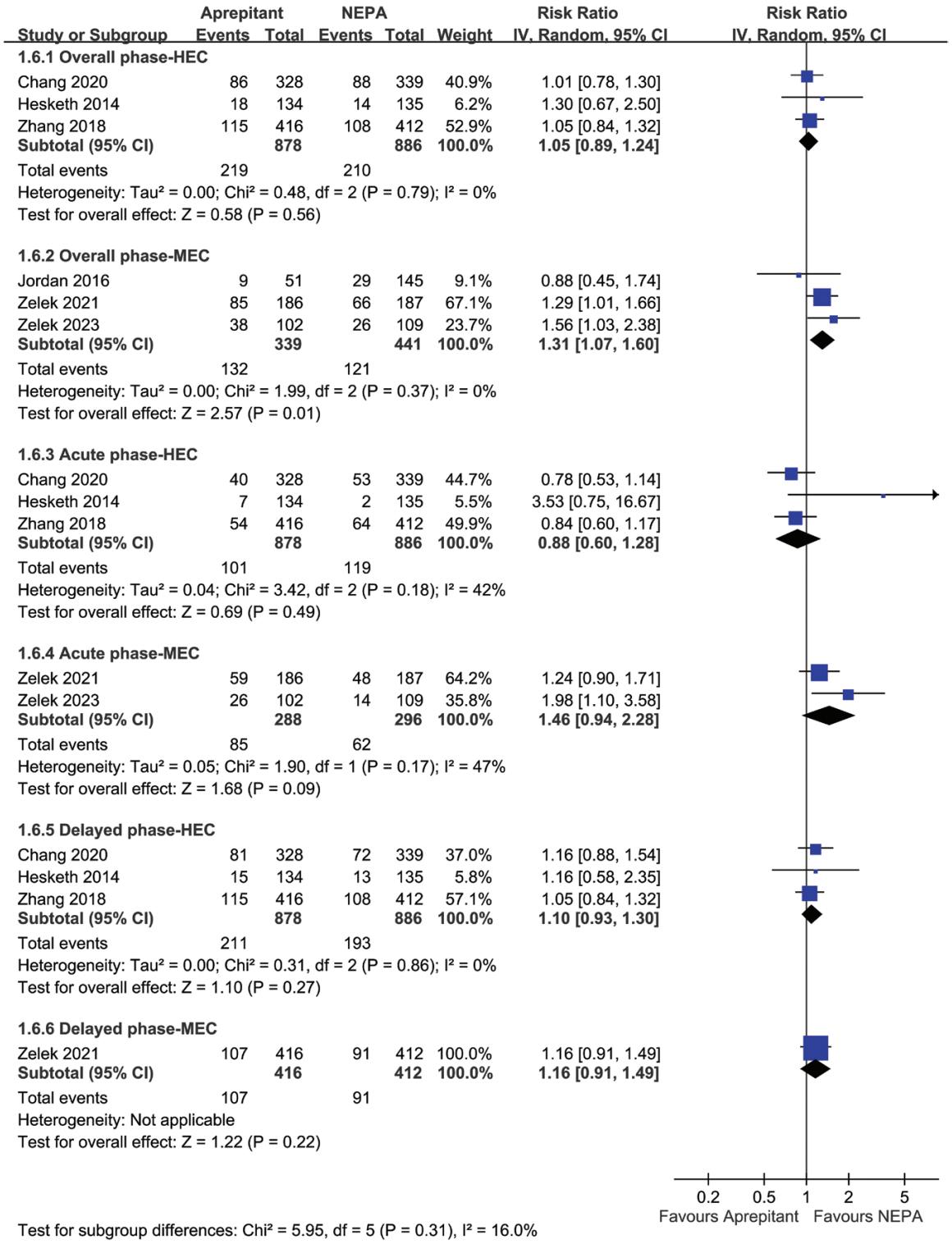


Figure 5. Forest plot comparing NEPA and aprepitant. Outcome: Complete response from subgroup analysis.

Netupitant is distinct from other NK1 receptor antagonists due to its unique pharmacokinetics and combination formulation. Unlike aprepitant, fosaprepitant, and rolapitant, netupitant is typically combined with palonosetron to form NEPA, enhancing protection against both acute and delayed phases of CINV. Netupitant has a long half-life, providing sustained NK1 receptor blockade and contributing to its high potency in preventing CINV.[14,21] The fixed-dose combination of NEPA simplifies the dosing regimen to a single oral capsule, improving patient adherence compared to multi-dose regimens.[15,21] This combination is in line with guideline recommendations and offers a simple, convenient option for prophylaxis against acute and delayed CINV in patients receiving highly or moderately emetogenic chemotherapy.

Our findings are consistent with existing guidelines,[11] which recommend considering a triple antiemetic regimen

involving NK_1 receptor antagonists for patients undergoing MEC or HEC. Our study revealed that NEPA is often superior to aprepitant-based regimens in patients undergoing MEC. Building on a previous study[31] that demonstrated the superiority of aprepitant over control medications (those not using NK_1 receptor antagonists) in managing CINV symptoms in the delayed and overall phases, our study indicates that NEPA appears to be more effective than aprepitant-based regimens in these phases. These insight is not yet reflected in existing guidelines.

Biologically, it is rational to observe better performance in MEC compared to HEC because the intensity of the emetogenic challenge in HEC might overwhelm the protective effects of the antiemetic agents, despite their potency. MEC regimens generally induce a lower incidence of nausea and vomiting compared to HEC regimens, meaning that antiemetic agents might exhibit higher efficacy in MEC settings simply because the emetic challenge is less severe. NEPA's pharmacokinetic profile, which includes a long half-life for netupitant, ensures sustained receptor blockade, providing prolonged protection against CINV. This might be particularly advantageous in MEC, where prolonged but less intense antiemetic coverage is beneficial. This aligns with clinical observations where multidrug antiemetic regimens are often required to manage HEC, while dual or even single-agent regimens can be effective in MEC.

However, among the articles we included, there were only 3 RCTs in both the MEC and HEC groups. More research is needed to support these results and hypotheses. Further studies should investigate the long-term outcomes and effectiveness of NEPA-based regimens across diverse patient populations and chemotherapy protocols to provide a more robust evidence base for clinical guidelines.

Regarding the safety of medications, caution is imperative. All of the included RCTs in our meta-analysis reported no significant difference in the incidence of adverse events between the NEPA and aprepitant groups. The most commonly reported adverse events varied across the RCTs and comprised constipation, headaches, and hiccups; the corresponding estimated incidence rates ranged from 50.0% to 68.6% in the NEPA group and 53.0% to 69.2% in the aprepitant group. However, the incidence of treatment-related adverse events was considerably lower in both groups, and most of these were of mild intensity. Among the included RCTs, those conducted by Chang et al[19] and Zhang et al[25] reported more severe adverse events in the aprepitant group; by contrast, the RCT conducted by Zelek et al[23] recorded a slightly higher incidence of serious adverse events in the NEPA group, but none of these events were considered treatment related. The most severe adverse events in the included RCTs included atrial fibrillation, hypotension, bundle branch block, and pancreatitis; the incidence of these events did not significantly differ between the NEPA and aprepitant groups. Despite slight variations across the RCTs, NEPA and aprepitant demonstrated comparable safety profiles.

The cost-effectiveness of a particular medication could substantially influence the decision to use the medication. Although none of the RCTs included in our meta-analysis addressed cost concerns regarding NEPA and other medications, previous studies have indicated the cost-effectiveness of these 2 medication groups. Navari et al[32] conducted a retrospective cohort study comprising over 15 000 adult patients with cancer and suggested that healthcare resource utilization and costs were lower for patients receiving NEPA than for those receiving fosaprepitant (the prodrug of aprepitant) plus palonosetron after cisplatin-based chemotherapy. Moreover, a study conducted in Spain[33] demonstrated that NEPA was more effective in controlling emesis than aprepitant plus ondansetron or palonosetron and was more cost-effective for patients with cancer undergoing HEC regimens. Botteman et al[34] conducted a randomized, double-blind, phase III clinical trial to analyze patient-level outcomes over a 5-day post-HEC period and indicated that NEPA is more cost-effective than an aprepitant-based regimen for preventing CINV. Furthermore, a study conducted in Italy[35] demonstrated that NEPA is more effective and less expensive than aprepitant plus ondansetron or palonosetron for patients with cancer undergoing HEC or MEC. According to the aforementioned studies, cost evaluations must account for both treatment and failure management costs. These studies have indicated that NEPA is a cost-effective choice for physicians and patients.

However, it is important to consider the potential impact of patent expirations on these evaluations. NEPA, like other medications, is subject to patent protections that can influence its cost-effectiveness. According to the U.S. Patent and Trademark Office, utility patents, including those for pharmaceuticals, typically expire 20 years from the filing date. However, extensions can be granted due to regulatory delays, such as those experienced during FDA approval processes. Any recent changes in patent status or market exclusivity could potentially affect the cost-effectiveness analysis.

In our study, all included articles used NEPA in combination with dexamethasone. According to previous studies, glucocorticoids may act through anti-inflammatory effects, interaction with neurotransmitters such as serotonin and receptor proteins like tachykinin NK_1 and NK_2, and by reducing pain and the concomitant use of opioids, which in turn reduces opioid-related nausea and vomiting.[36] However, in the age of immunotherapy, it is crucial to consider the potential deleterious effects of dexamethasone on the immune system. Janowitz et al[37] advocated for alternatives to high doses of dexamethasone due to its potential negative effects with immune checkpoint inhibitors and chemotherapy, recommending the lowest effective steroid dose tailored to the patient. Celio et al,[38] in a randomized controlled trial, found that dexamethasone-sparing on days 2-4, when combined with NEPA, can be equally effective in preventing CINV in high-emetic-risk settings, such as cisplatin-based chemotherapy. Several subsequent studies[39,40] also supported that a single dose of dexamethasone on day 1 is as effective as multiple-day dosing in achieving a complete response, without adversely affecting patient-reported daily food intake post-chemotherapy. These studies give hope to dexamethasone-sparing regimens; however, they predominantly used cisplatin as the chemotherapy agent. More research using different chemotherapy agents is needed to determine the suitability of dexamethasone-sparing regimens.

Our analyses revealed a low degree of heterogeneity among the included RCTs. Nevertheless, the RCTs exhibited some differences, which can be attributed to several factors, including differences in chemotherapy regimens, cancer types, medication doses, and administration times across trials. Moreover, the variability in baseline conditions of patients with cancer and the subjective nature of symptoms may have contributed to the observed differences.

The strengths of our meta-analysis lie in its comprehensive search for eligible studies, careful consideration of study quality,

and execution of rigorous analyses. Moreover, this is the first systematic review and meta-analysis to compare the efficacy, safety, and cost-effectiveness of NEPA and aprepitant-based regimens; hence, our results can serve as a reference in the formulation of care plans for patients with cancer. Nevertheless, this study has several limitations. First, some RCTs exhibited imbalances in patient numbers, potentially affecting the robustness of the evidence. Second, variations in baseline data among the RCTs introduced complexity in evaluating medication efficacy based on cancer type or treatment. Finally, because our evaluation and comparison focused solely on oral medications, the results may not be directly applicable to other administration routes, such as intravenous administration.

Conclusions

Effectively managing CINV is crucial for enhancing the physical and mental well-being of patients with cancer. Our study demonstrated that NEPA-based regimens are more effective than aprepitant-based regimens in managing CINV, particularly in the delayed and overall phases in patients undergoing MEC. Similarly, cost-effectiveness analysis results indicate NEPA to be effective in managing CINV, and safety analysis results reveal comparable safety levels between the NEPA and aprepitant groups. Therefore, we recommend incorporating NEPA into CINV prevention regimens to provide patients with a more effective means of alleviating symptoms without severe side effects.

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Author contributions

W.T.L. and T.W.H. devised and designed the study, W.T.L. and C.L.C. extracted the data, W.T.L., C.L.C., M.S.N.G., and T.W.H. analyzed and interpreted the data, and W.T.L., M.S.N.G., and T.W.H. drafted the manuscript. All authors contributed to the subsequent drafts and approved the final version of the manuscript.

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Conflicts of Interest

The authors have no conflicts of interest or financial ties to disclose. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. All authors have reviewed and approved the final manuscript and declare that they have no other competing interests.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary material

Supplementary material is available at *The Oncologist* online.

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