Gabapentinoids for chemotherapy-induced peripheral neuropathy: systematic review and meta-analysis

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ABSTRACT

Introduction Chemotherapy-induced peripheral neuropathy (CIPN) affects patients' quality of life and treatment effectiveness. Gabapentinoids, like gabapentin and pregabalin, are often used for CIPN treatment, but their efficacy and safety remain uncertain. This study reviews and analyses randomised controlled trial data on this topic.

Materials/methods We searched PubMed, Embase and Cochrane CENTRAL until 29 August 2022 for studies on gabapentinoid use in CIPN. Meta-analysis was performed using RevMan V.5.4 and the Metafor package in R. Outcomes included pain scores, quality of life and adverse drug events.

Results For the prevention setting, our meta-analysis shows that pregabalin did not significantly improve average pain (standardised mean difference (SMD) −0.14, 95% CI −0.51 to 0.23; I^2=26% (95% CI 0% to >98%)) or quality of life (mean difference (MD) 2.5, 95% CI −4.67 to 9.67; p=0.49) in preventing CIPN compared with placebo. However, it showed a potential trend towards reducing the worst pain (SMD −0.28, 95% CI −0.57 to 0.01; I^2=0% (95% CI 0% to 98%; p=0.06)). For the treatment setting, some studies have shown a potential therapeutic effect of gabapentinoids. However, the results are not consistent between studies. Given the studies' heterogeneity, a meta-analysis in treatment setting was not performed.

Conclusion There is limited evidence to support the use of gabapentinoids in CIPN. In prevention setting, gabapentinoids do not significantly prevent CIPN. In treatment setting, studies have been inconsistent in their conclusions, lacking definitive benefits over placebo. More comprehensive and higher quality research is needed in the future.

PROSPERO registration number CRD42022361193.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Gabapentinoids are commonly used for the treatment or prevention of chemotherapy-induced peripheral neuropathy (CIPN) and even as a treatment for postherpetic neuralgia, but there is inconsistent evidence for their effectiveness in treating or preventing CIPN, and there is currently no comprehensive systematic review and meta-analysis.

WHAT THIS STUDY ADDS

For CIPN prevention, gabapentinoids show no significant benefits in reducing neuropathy among chemotherapy patients, with evidence being too weak to warrant their use without further study. Based on the current limited evidence, gabapentinoids seem to be beneficial in the treatment of CIPN, but more evidence is required to substantiate this.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

The use of gabapentinoids in CIPN requires more complete and comprehensive evidence to demonstrate their efficacy.

INTRODUCTION

One of the frequent side effects of chemotherapy for patients is chemotherapy-induced peripheral neuropathy (CIPN). The range of CIPN prevalence is between 30% and 55%.[1] Symptoms and signs of CIPN include sensory, motor and autonomic nerve dysfunction, such as pain, gait disturbance and constipation or diarrhoea.[2 3] Severe symptoms may lead to a deterioration in quality of life 6.5 months after completion of treatment.[4] Since the occurrence of CIPN may affect the patient's quality of life, and may interrupt their treatment plan, problems associated with CIPN are well known. Appropriate measures can be taken to improve the adverse effects of chemotherapy drugs,

but there is no specific prevention strategy or management that has been shown to be effective.[5–7]

A systematic review and meta-analysis published in 2022 revealed that the antidepressant duloxetine, which had been suggested to have some benefit in the prevention and treatment of CIPN, had a limited role.[8] Adjuvant analgesics, scrambler therapy, acupuncture and exercise might decrease CIPN symptoms in some randomised controlled trials (RCT) and meta-analysis.[9–11]

Gabapentin and pregabalin are classified pharmacologically as gabapentinoids. They are used primarily as epileptic seizure treatment, prevention of epileptic seizures or restless leg syndrome. Due to their possible pain relief mechanism, indications such as neuropathic pain and fibromyalgia are also off-label used. The gabapentinoids used in CIPN have also been mentioned in the literature. Vondracek *et al* addressed the decrease in pain score of CIPN with pregabalin despite the suboptimal study design.[12] Results from a pilot study did not show clinical benefits using pregabalin to prevent CIPN with paclitaxel adjuvant chemotherapy or oxaliplatin adjuvant chemotherapy.[13] Another RCT even ended early due to insufficient confidence in the interim analysis.[14]

In a study using gabapentin to lower the incidence of CIPN, a successful prevention outcome was also discovered. The difference in nerve conduction velocity between the gabapentin group and the placebo group was statistically lower (17.7% vs 61.0%).[15] However, gabapentin showed a negative effect compared with the placebo group in a prospective randomised trial and was not supported in reducing neurotoxicity in an observational prospective study.[16 17]

Due to the discrepancy in research results and their limited sample size, there is no specific role in the American Society of Clinical Oncology (ASCO) guidelines,[18] except that gabapentinoids used as an alternative agent were only seen in the 2020 joint European Society for Medical Oncology (ESMO)/European Oncology Nursing Society (EONS)/European Association of Neuro-Oncology (EANO) guidelines.[19]

Two review articles published in 2014 and 2011 shared similar perspectives on the lack of evidence of the efficacy of gabapentinoids in CIPN, but opinions on safety were the opposite. The possible side effects of gabapentinoids were a concern in the study by Pachman *et al*[20], but it appears to be a minor issue in the article by Piccolo and Kolesar.[3] Due to conflicting recommendations and inadequate evidence, a more comprehensive and updated systematic review is needed to represent the safety and efficacy of gabapentinoids in CIPN.

The objective of our research was to perform a meta-analysis on the results of all RCTs and other pertinent studies to determine the overall safety and effectiveness of gabapentinoids for the prevention and treatment of CIPN in order to offer comprehensive and groundbreaking advice.

MATERIALS/METHODS

Study protocol

This study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines.[21] We registered this meta-analysis on PROSPERO (CRD42022361193).

Literature search

Two authors (TWC, F-YY) searched PubMed, Cochrane, Embase and ClinicalTrials.gov from the inception until September 2022. We set the terms ('chemotherapy', 'peripheral neuropathy', 'chemotherapy-induced peripheral neuropathy' and 'gabapentin OR pregabalin') for the MeSH terms and free text search, without language restrictions. The search strategy is described in online supplemental appendix 1. References to relevant studies were also checked to identify potential literature to include. If there was a conflict between search results, senior authors were consulted to make the final decision.

Study selection

A format of Participant (P), Intervention (I), Comparison (C), Outcome (O) and Study (S) was defined for the study selection. PICOS includes P: patients with cancer; I: gabapentin or pregabalin; C: placebo or any other drug; O: efficacy and safety; S: RCT.

Eligibility criteria

We included:

- Studies that evaluated the efficacy and safety of gabapentin or pregabalin for the treatment or prevention of CIPN.
- RCT.
- Adult patients aged ≥18 who had cancer.
- Available in full text.

We excluded:

- Case report, case series, cohort studies, case–control study and quasirandomised and non-randomised trials.
- Conference posters, abstract only, protocol.
- Not available in full text.

Data extraction

Two authors (TWC, F-YY) independently extracted data from the included literature. The outcomes included the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) grade, pain score, neuropathy score, quality of life and adverse events. Additional information was also extracted, including the name of the first author, the country where the trial was conducted, the number of patients, the treatment protocol and other characteristics of the included studies.

Statistical analysis

RevMan V.5.4 software (Cochrane Collaboration, London, UK) was used for the meta-analysis of the

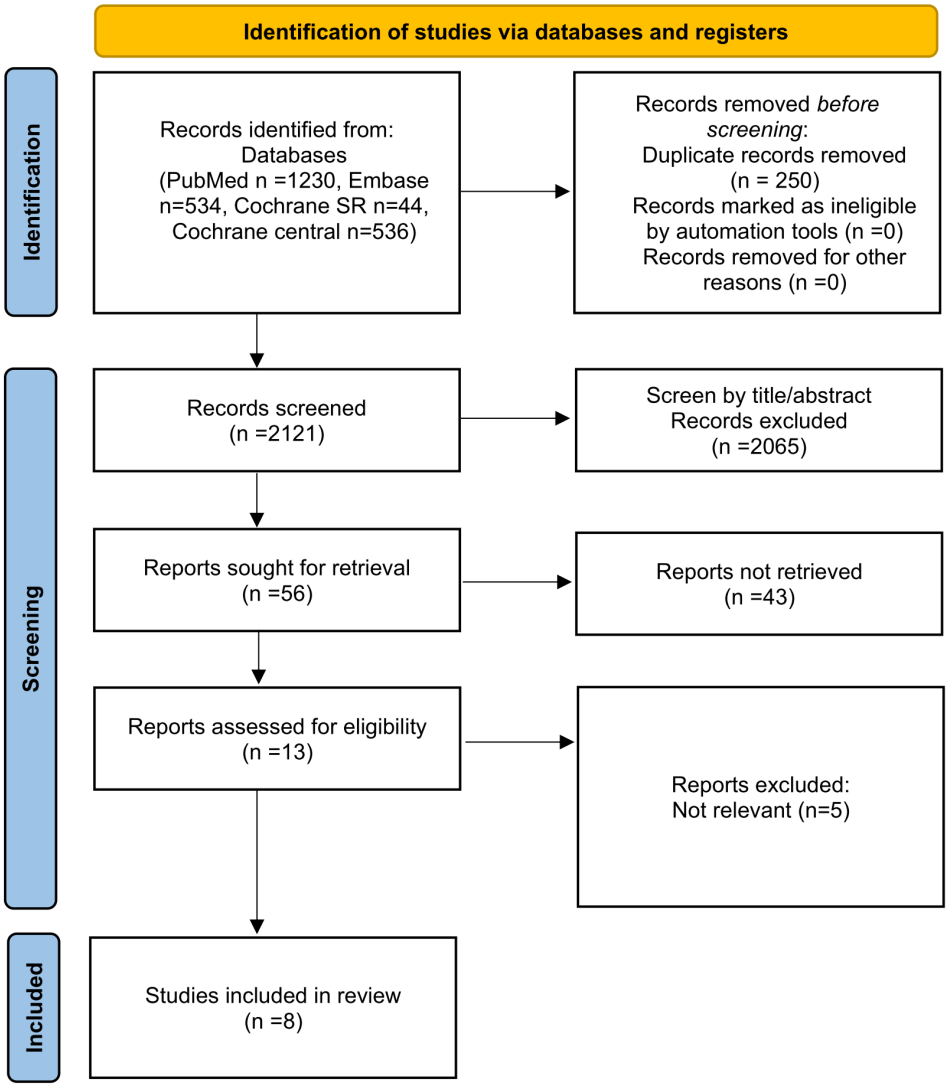

Figure 1. Study selection using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Figure 1 Study selection using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

data. Data included χ^2 test for heterogeneity and using I^2 for quantitative (test level 50%). Additionally, we use the Metafor package in R language to calculate the CI for heterogeneity.[22 23] If the results of the analysis indicated $p>0.05$ and $I^2\leq 50\%$, the heterogeneity is not significant. If the analysis results indicate $p<0.05$, the $I^2\geq 50\%$, indicating significant heterogeneity. When data are measured in inconsistent measurement units or different measurement scales, standardised mean difference (SMD) values were used instead of mean difference (MD), and the effect is expressed as a 95% CI. If ≥10 studies were included in a meta-analysis, funnel plots were used to detect asymmetric publication bias.

Quality assessment

To evaluate the quality of the included RCTs, we used the risk of bias (RoB) tool. The following is the Cochrane Collaboration's tool for evaluating the risk of bias in randomised trials[24]: allocation concealment, participant and staff blinding, outcome assessment, blinding, incomplete outcome data, selective reporting and other sources of bias are all examples of bias. Two authors (TWC, F-YY) independently assessed the quality of RCT. In case of conflict, the final decision will be made by a third author (C-HH). The RoB graphs were generated using RevMan V.5.4 software.

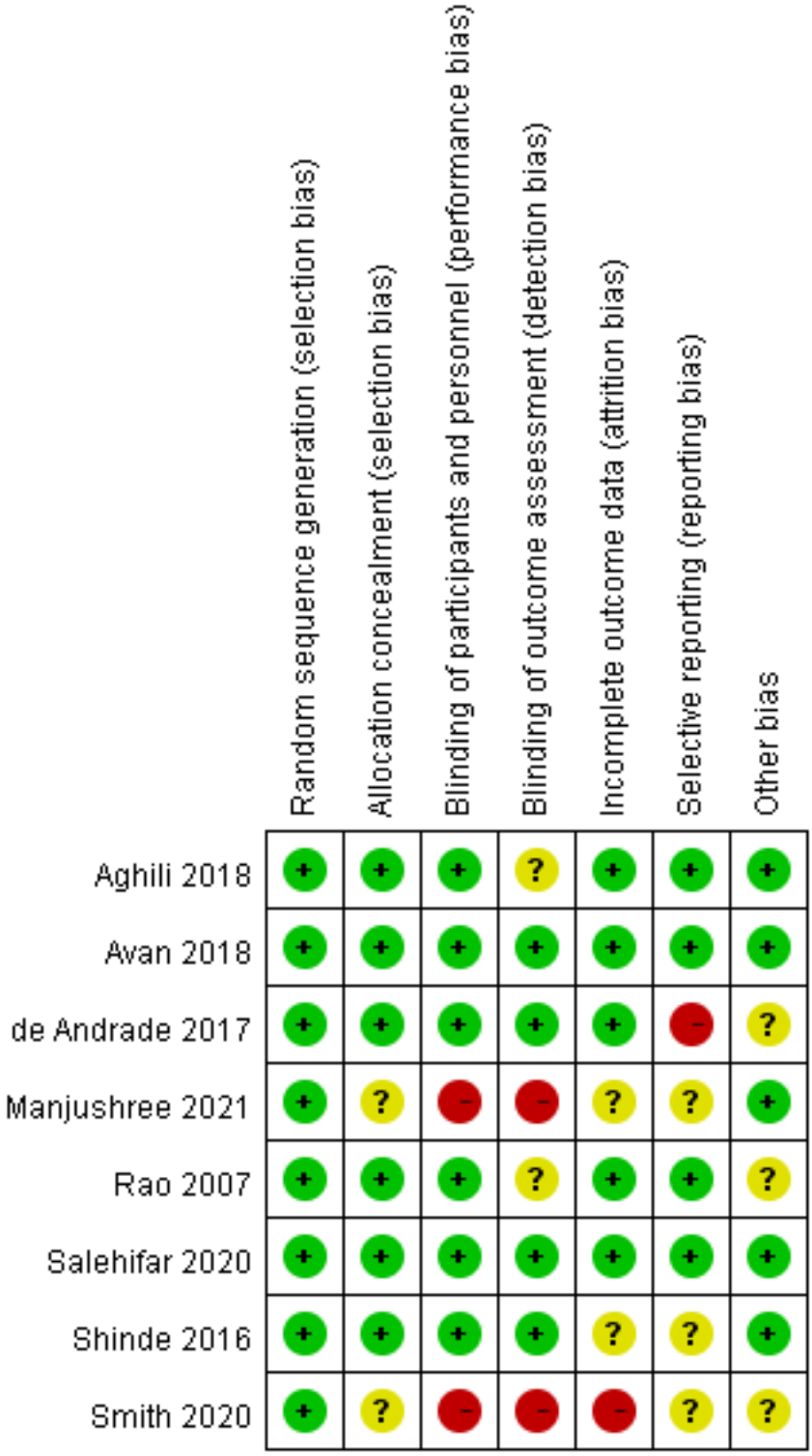

Figure 2 The risk of bias assessment results of the eight included trials.

RESULTS

Search results

A total of 2344 applicable publications were identified by the initial electronic search. After reviewing the titles, abstracts and deduplicate, nine references were identified as studies probably eligible for inclusion. Finally, eight studies met the inclusion criteria after full-text review (figure 1). A total of 631 participants were involved in the trial, of whom 428 were female and 203 were male.

Study characteristics

The majority of studies found that patients were between 50 and 55 years old on average. There

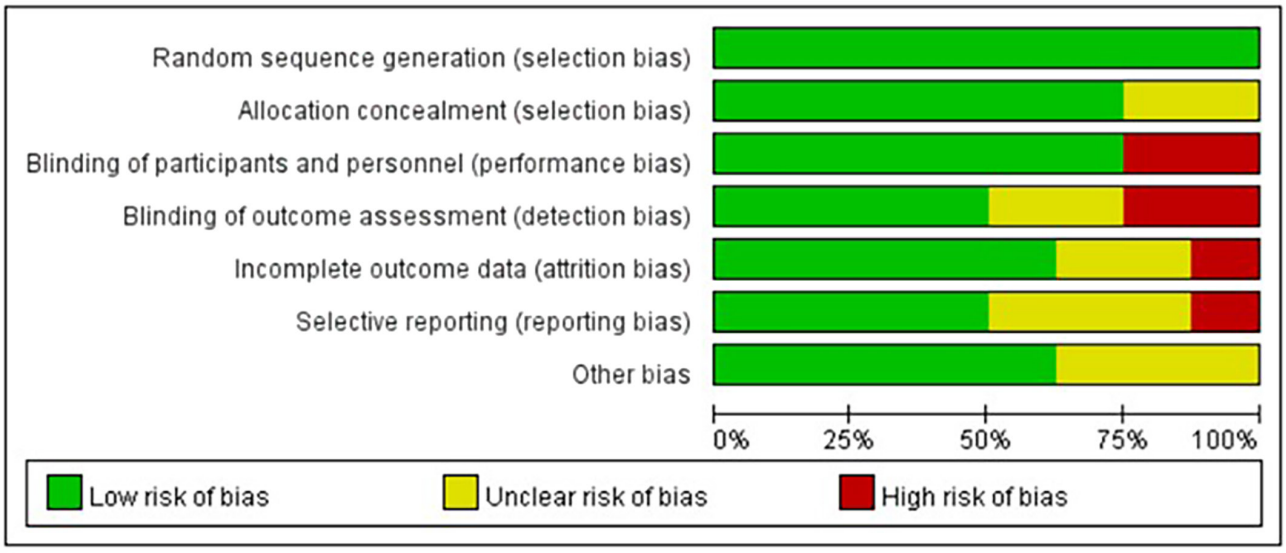

Figure 3 The risk of bias assessment graph in the study included.

were five studies on breast cancer, one on head and neck cancer and one on colorectal cancer. The other studies included one on breast cancer (36.50%), one on ovarian cancer (19.04%), one on multiple myeloma (11.11%), one on lung cancer (7.93%), one on oesophageal cancer (4.76%), one on cervix cancer (1.58%) and one on other cancer (19.04%). Types of chemotherapy included oxaliplatin-based regimen, taxane-based regimen and doxorubicin in most of the studies. Both gabapentin and pregabalin were used to treat CIPN, and the average follow-up time was 12.5 weeks. Online supplemental table 1 displays the characteristics of the studies. The results of the research are shown in online supplemental table 2.

Four of the included articles were used to prevent CIPN side effects, including Aghili *et al* ([15]) (Iran), de Andrade *et al* ([25]) (Brazil), Shinde *et al* ([13]) (USA) and Smith *et al* ([26]) (USA). Four articles were used for the treatment of CIPN, including Salehifar *et al* ([27]) (Iran), Manjushree *et al* ([28]) (India), Avan *et al* ([29]) (Iran) and Rao *et al* ([30]) (USA).

Quality assessment

For each included study, two review authors (TWC, F-YY) independently assessed methodological quality and risk of bias for eight RCTs contributing results on our primary outcomes using the RoB 1.0 tool. We assessed the following seven domains. For more details on each assessment, see figure 2; see figure 3 for the 'Risk of bias table'.

Allocation

Two studies did not report on the concealment method of allocation. Therefore, we have classified the risk of selection bias for these studies as 'unclear'.[26 28] We assessed the risk of selection bias for the remaining studies as low.

Blinding

For six studies, participants and study staff, including those who delivered the intervention, were effectively blinded to allocation.[13 15 25 27 29 30] The results of the review on the other two articles regarding performance bias indicate a high risk[26 28]; blinding of outcome assessors was adequately described in four studies.[13 25 27 29] In the remaining four studies, the method for blinding of outcome assessors was not described or was described insufficiently.

Incomplete outcome data

Intention-to-treat analysis was used in five trials that were able to follow all patients enrolled throughout the study period.[15 25 27 29 30] Whether there was loss to follow-up was not determined in two trials.[13 28] A study did not characterise any information on drop-outs and was judged to be at high risk of bias.[26]

Selective reporting

We judged three studies to have an unclear risk of reporting bias because the study authors did not notify the prior protocol or clinical trial registration information.[13 26 28] One study did not fully report all predefined outcomes; therefore, we classified the risk of reporting bias for these studies as 'high'.[25] We considered the remaining four studies to have a low risk of bias in this domain.[15 27 29 30]

Other bias

Three studies did not provide enough data to evaluate other possible financial sources of help and financial support,[25 26 30] there are no declared conflicts of interest in five studies.[15 26–29]

Publication bias

We were unable to evaluate publication bias in this review.[13 15 25–30] Only eight studies were included.

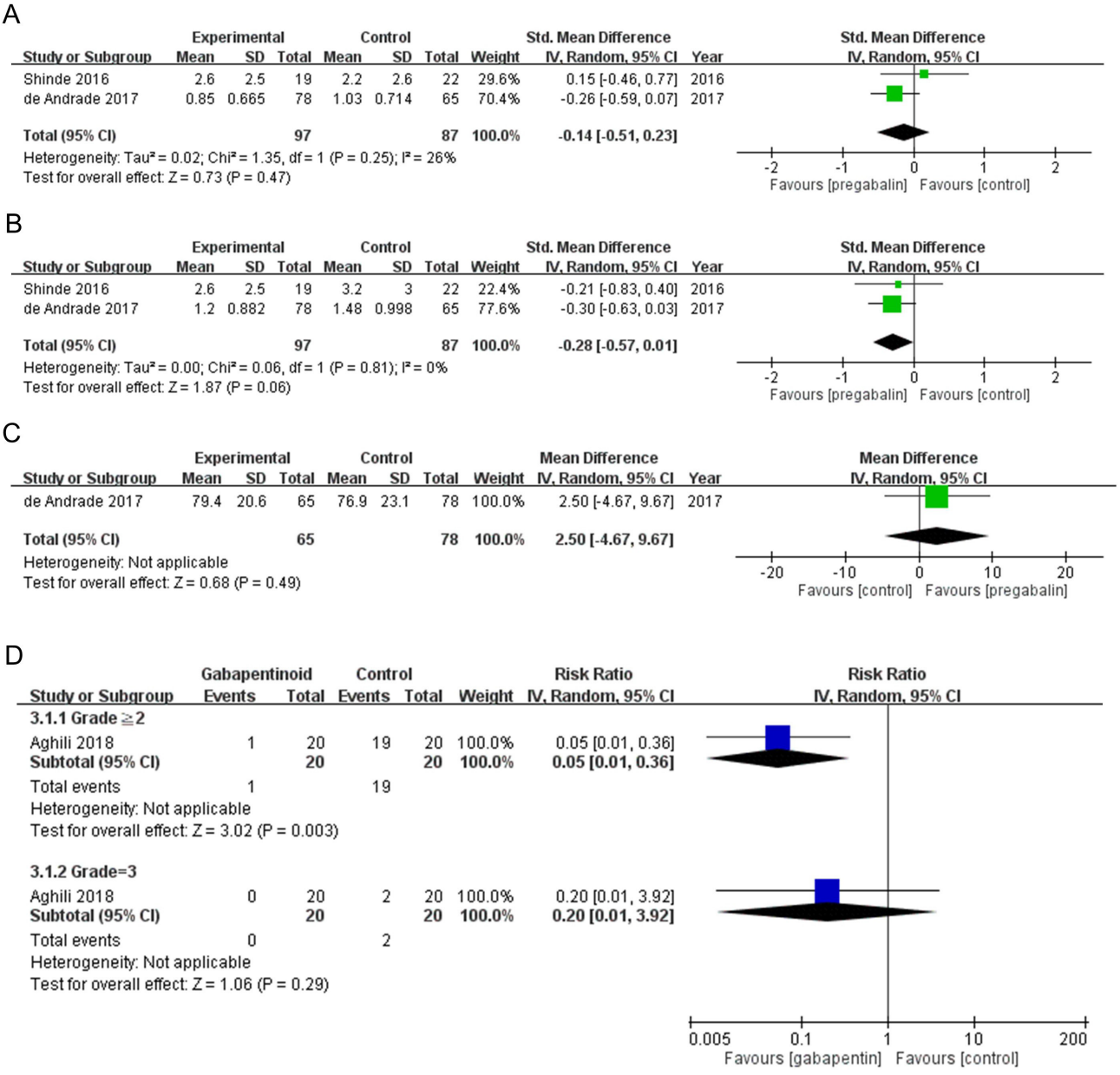

Figure 4 Gabapentinoids compared with placebo in the prevention setting. (A) Average pain. (B) Worst pain. (C) Quality of life. (D) Common Terminology Criteria for Adverse Events grades 2 and 3 or grade 3.

When fewer than 10 studies were included, funnel plots were not constructed.

Meta-analysis outcomes

Efficacy

For the prevention setting, we identified two trials comparing the pregabalin prevention setting with placebo.[13 25] There is not a statistically significant effect on the improvement of average pain (SMD −0.14, 95% CI −0.51 to 0.23; I^2=26% (95% CI 0% to >98%)) compared with placebo. Pregabalin, compared with placebo, for the prevention of CIPN shows a trend towards a reduction in worst pain, but without statistical significance (SMD −0.28, 95% CI −0.57 to 0.01; I^2=0% (95% CI 0% to 98%; p=0.06)); we also analyse quality of life (MD 2.5, 95% CI −4.67 to 9.67; p=0.49) and CTCAE grade 3 (Relative Risk (RR): 0.20, 95% CI 0.01 to 3.92; p=0.29), both are non-statistically significant. There seems to be a statistical difference in the prevention of CIPN CTCAE grades 2 and 3 (RR 0.05, 95% CI 0.01 to 0.36; p=0.003). However, since the evidence is only from a small study, more evidence is needed (figure 4). Due to the heterogeneity of the studies, we did not conduct a pooled analysis for the treatment setting.

Safety and AEs

We identified four trials that compare the safety of gabapentinoids with placebo, there is not a statistically significant effect on the risk of dropping out due to AE (RR 3.77, 95% CI 0.43 to 33.17; I^2=0% (95% CI

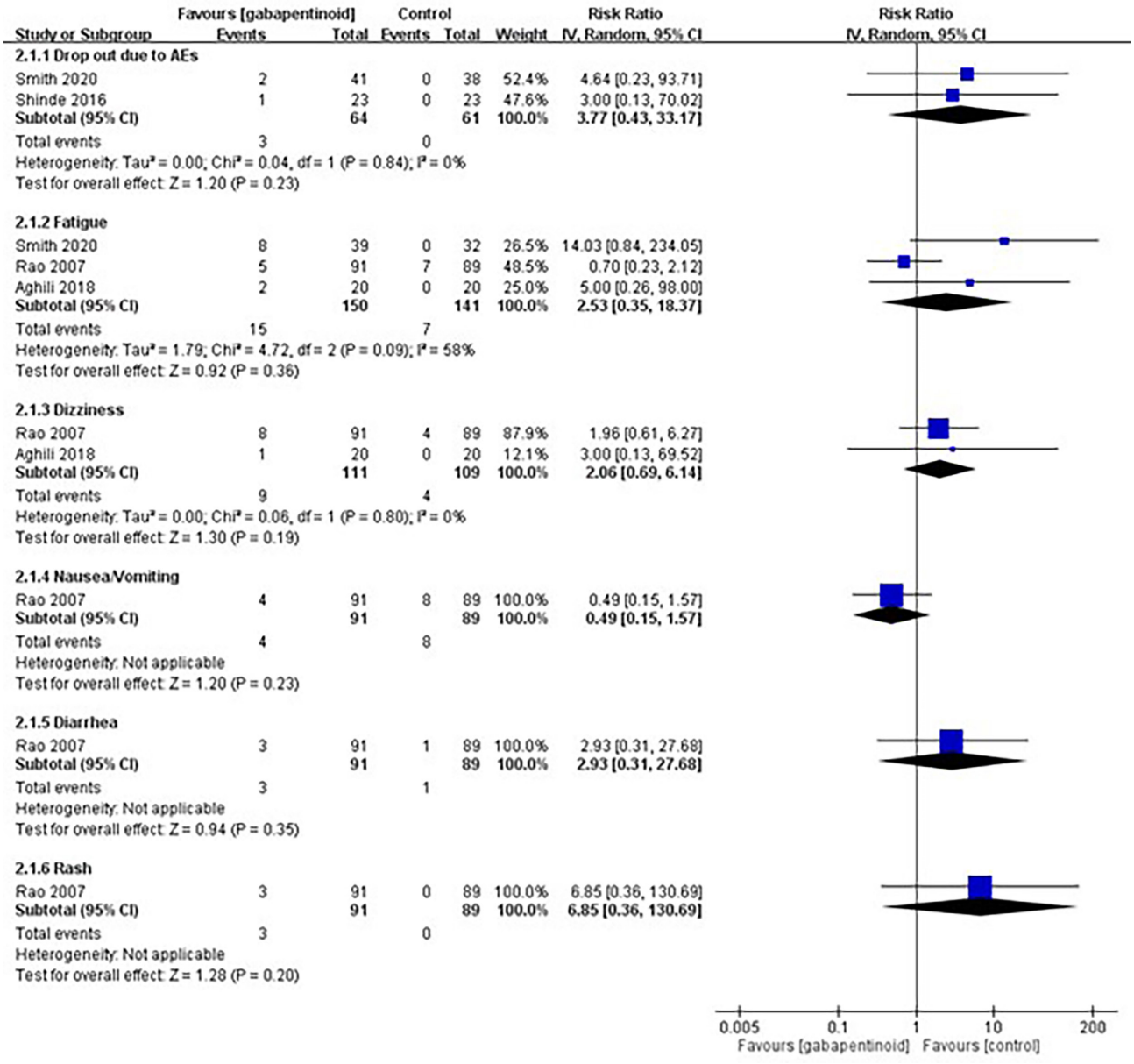

Figure 5 Safety of gabapentinoids compared with placebo. AEs, adverse events.

0% to 97%)) and fatigue (RR 2.53, 95% CI 0.35 to 18.37; I^2=58% (95% CI 0% to 98%)) compared with placebo. It has a similar effect on dizziness (RR 2.06, 95% CI 0.69 to 6.14; I^2=0% (95% CI 0% to 97%)), nausea/vomiting (RR 0.49, 95% CI 0.15 to 1.57), diarrhoea (RR 2.93, 95% CI 0.31 to 27.68) and rash (RR 6.85, 95% CI 0.36 to 130.69) (figure 5).[13 15 26 30]

Descriptive outcomes

Gabapentin versus placebo prevention

Two studies were conducted to investigate the prevention of CIPN, comparing gabapentin to placebo.[15 29] Aghili *et al* used CTCAE version 4 to assess the effectiveness of preventing CIPN in patients with breast cancer who received paclitaxel; in the gabapentin group (300 mg for day 1; 600 mg for day 2; and 900 mg divided into three doses for day 3 up to the day 14 of each cycle), nearly all patients had grade 1 neuropathy (75–95%) and no grade 3 neuropathy; in contrast, the placebo group had more toxicities in grade 2 (55–85%) and grade 3 (5–20%).[15]

Smith *et al* [26] demonstrated that patients with HNC who took gabapentin during chemotherapy and radiation experienced significantly less pain (p=0.004). At week 7, the treatment group's pain score was lower than that of the control group. The use also led to a decrease in other symptoms. In summary, gabapentin can effectively alleviate painful mucositis and reduce the overall burden for patients with HNC.

Gabapentin versus placebo treatment

A study was conducted to investigate the treatment of CIPN, comparing gabapentin to a placebo. Rao *et al*

used a cross-over design with two 6-week phases separated by a 2-week 'washout' period to balance marginal distributions of stratification variables between enrolled groups and evaluated CIPN-related symptoms by questionnaires. In adult patients with symptomatic CIPN for longer than 1 month, gabapentin (target dose=2.7 g/day) is ineffective.[30]

Pregabalin versus placebo prevention

Pregabalin was compared with placebo in two studies to look into the prevention of CIPN. Pregabalin may reduce the incidence of chronic oxaliplatin-induced peripheral neuropathy, according to the research by de Andrade *et al*. A study shows that there were no significant differences between the pregabalin group (150–600 mg per day) and the placebo group in the following measures: Brief Pain Inventory (BPI), McGill Pain Questionnaire (MPQ), Douleur Neuropathique 4 (DN-4), Neuropathic Pain Symptom Inventory (NPSI), nerve conduction studies (NCS), quality of life (QOL), and pain intensity. At the last visit, pain intensity in the pregabalin group was 1.03 (95% CI = 0.79-1.26) compared to 0.85 (95% CI = 0.64-1.06) in the placebo group, which was not significant. Scores from BPI, MPQ, DN-4, NPSI, and NCS, as well as side-effect profiles, incidence of death, QOL scores, and mood scores, did not differ significantly between the two groups. According to Shinde *et al*'s study, pregabalin (75 mg two times per day) does not help patients with breast cancer avoid paclitaxel-associated acute pain syndrome or paclitaxel-associated CIPN (p=0.88).[13 25]

Pregabalin versus gabapentin treatment

The effectiveness and safety of gabapentin and pregabalin in CIPN are being investigated by Manjushree *et al*. In the study, paclitaxel (42.85%) and carboplatin combined were the two chemotherapy drugs most frequently found to cause CIPN. Pregabalin 75 mg was given to group B, and gabapentin 300 mg was given two times per day for 8 weeks to group A. The visual analogue scale and the Pain Quality Assessment Scale were statistically significant after 8 weeks of intervention in both the pregabalin and gabapentin groups (p<0.0001).[28]

Pregabalin versus duloxetine treatment

There have been two studies comparing pregabalin and duloxetine for the treatment of CIPN. Pregabalin and duloxetine were examined by Salehifar *et al* and Avan *et al* for their effectiveness and safety in treating taxane-induced peripheral neuropathy in patients with breast cancer. At baseline, the pregabalin and duloxetine groups have no significant differences in pain score, QOL and neuropathy score. Compared with using pregabalin, the use of duloxetine may have a higher likelihood of insomnia as a side effect (p<0.001), but there is a statistically significant difference in the improvement of emotional functioning scores.[27 29]

DISCUSSION

The safety and effectiveness of gabapentin and pregabalin in the treatment of CIPN are being evaluated in this systematic review and meta-analysis for the first time. Eight RCTs with a total of 631 patients were included in our analysis, and no significant differences were found between the average amount of pain that CIPN caused compared with placebo. The meta-analysis also did not show a significant improvement in the prevention of the worst pain, and only one study reported on quality of life, which did not show a significant improvement. The incidence of adverse reactions to gabapentin was slightly higher than that of pregabalin.

Gabapentinoids (gabapentin and pregabalin) have shown clinical activity in the management of seizures and pain, but the intact mechanisms remain unclear. Possible mechanisms might originate from binding to α2δ subunits of the calcium channel leading to less amount of norepinephrine, glutamate and neurotransmitter passing the pain sensation called substance P.[31]

Although gabapentinoids have been hopeful in the review articles to treat or prevent CIPN, the quality of the literature and heterogeneity of the sparse data may lead to inconsistent research results, and no significant clinical benefit has been observed in the integrated analysis. Currently, there are no clear data to support the use of gabapentinoids for the treatment or prevention of CIPN.

Pregabalin and gabapentin were included in a comprehensive review and meta-analysis of 16 drug classes for the treatment of CIPN. The benefits of gabapentin treatment were inconsistent, and pregabalin had moderate efficacy according to previous evidence. However, in this study, no meta-analysis was performed and the findings were based on critical evaluations by two researchers. An RCT of somatosensory predictors showed that pregabalin was effective in reducing pain compared with placebo. A retrospective study comparing mirogabalin and pregabalin found that both improved CIPN, but mirogabalin was more effective in pain relief and improvement in quality of life due to its different α2δ subunit affinity.[32]

Our study has limitations, such as a smaller number of included studies and an insufficient sample size including the inability to perform subgroup analyses due to differences in study design and inconsistency between the experimental and control groups in the reviewed studies. Insufficient data and low methodological quality of research limit the strength of evidence. The inclusion of patients with different types and treatments may also increase uncertainty in the research results. Further data collection is needed for analysis. An ongoing phase III study is evaluating the

efficacy of oral gabapentin in preventing paclitaxel-induced neuropathy.[33] Some experts recommend integrated care approaches, such as acupuncture, exercise and scrambler therapy, for treatment and prevention. Future research could focus on evaluating larger scale integrated healthcare and which combinations of treatments offer the most effective relief for patients' side effects.[34]

CONCLUSIONS

There is limited evidence to support the use of gabapentinoids in CIPN. For CIPN prevention, gabapentinoids do not significantly lower neuropathy incidence or severity in chemotherapy patients. Although there are some studies showing a protective effect, the overall evidence is insufficient. For CIPN treatment, some studies have shown a potential therapeutic effect of gabapentinoids. However, the results are not consistent between studies. Therefore, the use of gabapentinoids in CIPN should be approached with caution.

Contributors C-HH served as the lead for the integrated analysis. Y-FU and TWC were responsible for literature review and manuscript writing. Y-CL also provided consultation on the disease and polished the manuscript. C-HH, as the guarantor, accepted full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Patient consent for publication Not applicable.

Ethics approval Not applicable.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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