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ORIGINAL RESEARCH

Gabapentin has Longer-Term Efficacy for the Treatment of Chronic Pelvic Pain in Women: A Systematic Review and Pilot Meta-analysis

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ABSTRACT

Introduction: Gabapentin has potential analgesic benefits in patients with neuropathic pain, such as post-herpetic neuralgia and diabetic peripheral neuropathy neuropathic pain. However, its efficacy in women with chronic pelvic pain (CPP) remains contradictory. In the present study, we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) to ascertain the efficacy of this treatment.

Methods: We systematically reviewed RCTs published in PubMed, Embase, the Cochrane Library, Web of Science, and Google Scholar databases, up to July 2021. These articles compared gabapentin with placebo or any other active treatment for CPP in women, with 'the change in pain scores from the baseline during the first 3 and 6 months of treatment' taken as the primary outcome. We considered reductions equivalent to 1.0 cm for primary outcomes to be clinically important.

Results: Four studies, comprising 469 participants, were included in our meta-analysis. Results revealed that the gabapentin group had significantly higher change in pain intensity scores from baseline to 3 months [weighted mean difference (WMD) − 0.61 cm; 95% confidence interval (CI) − 0.97 to − 0.25; I^2 = 0%; p = 0.0009] and 6 months (WMD − 1.38 cm; 95% CI − 1.89 to − 0.88; I^2 = 0%; $p < 0.00001$), relative to the control group. The difference of 6-month pooled result was more clinically important. Results from analysis of secondary outcomes showed that gabapentin had no beneficial efficacy during the first 3 months of treatment. Although gabapentin treatment was associated with a higher risk of dizziness and somnolence, no statistically significant differences were observed with regards to the total incidence of adverse events.

Conclusions: Overall, gabapentin could be a potential treatment option for CPP in women. However, as a pilot study, further studies are needed to explore the longer-term benefits and definite safety of this therapy in the future.

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Key Summary Points
Why carry out this study?
Although several clinical studies have evaluated gabapentin for treatment of chronic pelvic pain (CPP) in women, the efficacy and safety of this therapy remain controversial.
Therefore, there is an urgent need for specific pooled effect analysis to ascertain the methods efficacy and safety.
What was learned from the study?
The present meta-analysis evaluated efficacy and safety of gabapentin for treatment of CPP in women.
Results revealed that gabapentin has potential analgesic effects in this group of patients. However, gabapentin was also associated with non-severe dizziness and somnolence, compared to the placebo or standard analgesic treatment. The evidence of the therapy option gabapentin for CPP in women is clearly presented.
In the future, studies comprising longer-term medication and follow-up are needed to validate these findings.

INTRODUCTION

Chronic pelvic pain (CPP), which affects between 2.1% and 24% of all women worldwide, has been associated with poor quality-of-life and negative functional status [1–3]. Physical and psychological treatment therapies have been used to manage CPP, albeit with limited success [4–7]. Notably, pharmacotherapy remains the first-line treatment for CPP in women [8, 9], with the common analgesic gabapentin increasingly showing potential benefits for CPP patients [10].

Gabapentin, a type of γ-aminobutyrate acid analogue, plays an analgesic role mainly by affecting the nervous system [11]. Results from some previous clinical studies have demonstrated that gabapentin generates optimal analgesic effect compared to placebo during treatment of CPP in women [12–14]. However, these findings are not robust and conclusive due to limited sample sizes used. To address these controversies, a large-sample, multicenter, randomized, double-blind, placebo-controlled trial was performed [3]. Results revealed that pain scores were not significantly changed from baseline to 13–16 weeks in the gabapentin group [3]. Moreover, there were no significant differences in Brief Pain Inventory (BPI) pain interference scores between the gabapentin group and control group [weighted mean difference (WMD) 0.00, 95% confidence interval (CI) − 0.74 to 0.74] [3]. Overall, these studies reveal contradictory results, with regards to long- or short-term effects of gabapentin for treatment of CPP in women. What's more, although some studies have reported gabapentin-related adverse events, such as dizziness, drowsiness and mood changes, the overall safety of this therapy also remains inconclusive [3, 12–14].

To date, no high-quality evidence exists with regards to efficacy and safety of gabapentin for treatment of CPP in women, necessitating a comprehensive meta-analysis. In the present study, we aimed to quantify the benefits of gabapentin for treatment of CPP in women by analyzing safety and efficacy outcomes using a meta-analysis. The change in pain scores from baseline to 3 and 6 months treatment were designated as primary outcomes. Additionally, we assessed patients' overall satisfaction after treatment, with a view of improving their integrated judgment.

METHODS

Search Strategy

This systematic review and meta-analysis was performed based on the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and recommendations from the Cochrane Collaboration [15–17]. Additionally, the meta-analysis was registered at International Prospective Register of Systematic Reviews (PROSPERO), under registration number CRD42021249421 (https://www.crd.york.ac.uk/PROSPERO/) in May 2021. Briefly, we searched five electronic bibliographic databases, namely PubMed, Embase, the Cochrane Library, Web of Science, and Google Scholar, for articles published before April 2021. To completely include all studies that met our inclusion criteria, we performed a final search before July 2021.

Our search strategy included the following keywords: CPP, gabapentin, and randomized controlled trial (RCT). A summary of this process is shown in the Supplement Materials (eMethods 1–5). To ensure no studies were left out, we performed a manual search of the reference lists in the downloaded articles.

Eligibility Criteria and Study Selection

RCTs were included in the analysis if: (1) they randomly evaluated efficacy of gabapentin in women with CPP and compared with placebo or standard analgesic; and (2) reported at least 1 of the following outcomes: change in pain scores at multiple timepoints, the BPI pain interference scores, the proportion of patients reporting 30% or more reduction in pain scores, the overall satisfaction rate, and the rate of drug-related adverse events. On the other hand, articles were excluded if they were abstracts, conference papers, and protocols. In addition, studies with incomplete or redundant data were also excluded. There were no language restrictions during searches. What's more, this article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Next, two reviewers (XMF and YFR) independently screened titles and abstracts of the included studies, followed by reading of the corresponding full texts. Any disagreements between them were adjudicated through a discussion with two other reviewers (YFJ and FMY).

Data Extraction

The two reviewers (HW and XY) retrieved information, namely name of the first author, year of publication, administration route, sample size, details of intervention and control, as well as outcomes, using a standardized data extraction form. Notably, authors of the articles were contacted via e-mail, for access of important data that were either unclear or missing.

Assessment of Methodologic Quality and Risk of Bias

Assessment of methodological quality was independently conducted by two reviewers (XMF and YFR) using the Cochrane Collaboration's risk of bias tool [18, 19]. All included studies were evaluated based on six aspects, namely random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Two other reviewers (YFJ and FMY) were called upon to discuss any inconsistencies and reach a consensus. The risk of bias in each study was categorized as high, low, or unclear, and if one or more items fell into the high-risk group, the study would be considered to have a high risk of bias. A risk-of-bias summary table for this parameter was generated using the Review Manager, version 5.3 (Cochrane Collaboration, Nordic Cochrane Centre, London, United Kingdom) as shown in Table 1 [20].

Moreover, two reviewers (XMF and XF) independent adopted the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach to evaluate evidence of bias, inconsistency, indirectness, imprecision, and publication bias for each

Table 1 Risk of bias assessment

Study	Overall assessment	Random sequence generation	Allocation concealment	Blinding: performance bias	Blinding: detection bias	Incomplete outcome data	Selective outcome reporting
AbdelHafee [13]		Randomization was performed using a computer-generated randomization system (SPSS Random Number Generator; SPSS Inc., Chicago, IL, USA) using randomization sequence 1:1 ratio 5	Computer-generated randomization cards were produced and kept in the hospital pharmacy to prepare packages and provide supply and resupply	This was a double-blinded placebo-controlled randomized clinical trial	No information	Missing data is likely to have a significant effect on the study	Pre-specified outcomes reported
Risk of bias	Unclear	Low	Low	Low	Unclear	Unclear	Low
Horne [3]		Participants were randomly assigned in a 1:1 ratio to receive either gabapentin or matched placebo through a secure online randomization system	Sharp Clinical Services UK over-encapsulated the gabapentin, and dispensed all capsules into numbered	Patients, clinicians, and research staff were unaware of the trial group assignments throughout the trial	Patients, clinicians, and research staff were unaware of the trial group assignments throughout the trial	Missing data is unlikely to have a significant effect on the study	Pre-specified outcomes reported
Risk of bias	Low	Low	Low	Low	Low	Low	Low

Table 1 continued

Study	Overall assessment	Random sequence generation	Allocation concealment	Blinding: performance bias	Blinding: detection bias	Incomplete outcome data	Selective outcome reporting
Lewis [12]		This was a two-arm prospective parallel group 1:1 randomized controlled pilot trial, in two centers in Scotland, UK (NHS Lothian and NHS Grampian)	Eligible women were randomized by the clinical research team to either gabapentin or an identical-looking placebo using a web-based system that ensured allocation concealment	Participants, all clinical staff, and those recording outcomes were blind to the allocated treatment until all outcome data had been recorded	Participants, all clinical staff, and those recording outcomes were blind to the allocated treatment until all outcome data had been recorded	Missing data is likely to have a significant effect on the study	Some outcomes are not reported, but they have been mentioned in the Methods section
Risk of bias	Unclear	Unclear	Low	Low	Low	Unclear	Unclear
Sator-Katzenschlager [14]		They tried to achieve a balanced study design by randomization	No information	Open label	Open label	Missing data are unlikely to have a significant effect on the study	The satisfaction rate is not reported, but it has been mentioned in the Methods section
Risk of bias	High	Unclear	High	High	High	Low	Unclear

UK United Kingdom, *NHS* National Health Service, *SPSS* Statistical Product and Service Solutions, *USA* United States of America

outcome [21]. Results of these were rated high (⊕⊕⊕⊕), moderate (⊕⊕⊕◯), low (⊕⊕◯◯) , or very low (⊕◯◯◯). Any discrepancies during assessment were discussed by two other reviewers (YFJ and FMY).

Measurement of Primary and Secondary Outcomes

The primary outcome of this meta-analysis was the change in pain scores from the baseline during the first 3 and 6 months of treatment. Pain scores were defined using either the visual analogue scale (VAS) or the numeric rating scale (NRS), both of which consisted of an 11-point scale ranging from 0 to 10, representing no pain and worst imaginable pain, respectively. Secondary pain-related outcomes were defined using the BPI pain interference score, which measures pain interference in the patient's life. The score rages from 0 to 10, with higher values denoting greater interference. Another pain-related outcome was the proportion of patients reporting 30% or more reduction in pain score. Other secondary outcomes included the proportion of patients whose improvement was 'very marked or marked' or felt 'satisfied or very satisfied' about the efficacy, as well as the rate of drug-related adverse events. Notably, the overall satisfaction rate was mainly based on patients report, while the rate of drug-related adverse events was mainly defined by the total incidence as well as occurrence of common adverse events, namely dizziness, somnolence, and mood changes. Finally, in some cases, the data of 13 and 16 weeks were approximated as 3-month data for calculating the pooled effect.

Meta-analysis

Statistical analysis was performed using Review Manager 5.3. For the observation level weight, continuous and dichotomous variables were set as 'inverse variance' and 'Mantel–Haenszel' methods, respectively. For the primary outcome, we calculated WMD using the random-effects model, with a 95% CI, two-sided p values and Z-statistics. The negative mean difference implied that gabapentin treatment generated better efficacy for treatment of CPP in women, as evidenced by a significant decrease in pain scores relative to the baseline. With regard to the BPI pain interference scores, we calculated two-sided p values, Z-statistics, WMD and 95% CI. For the proportion of patients reporting 30% or more reduction in pain score, the rate of overall satisfaction, and the rate of drug-related adverse events, the two-sided p values, Z-statistics, risk ratio (RR), and 95% CI were calculated. Data followed by $p < 0.05$ were considered statistically significant.

Interpretation of Outcome Results

We applied the minimally clinically important difference (MCID) in pain scores to interpret results on changes in pain scores from baseline to 3 and 6 months [22]. The difference was defined to be a 1-cm change in pain score during the course of the treatment with gabapentin for CPP in women [23].

Heterogeneity, Sensitivity, and Subgroup Analysis

We applied the I^2 statistics to determine heterogeneity among studies [24]. We applied the random-effects model for analysis of studies that showed significant heterogeneity ($I^2 >$ 50%), whereas the fixed-effects model was used for studies with $I^2 <$ 50%. Furthermore, we applied sensitivity analysis to further explore sources of heterogeneity in studies that had $I^2 >$ 50%.

Assessment of Publication Biases

Funnel plots, based on Egger's test, are recommended in the assessment of publication bias for a meta-analysis comprising at least ten trials [25, 26]. In the present study, we did not generate funnel plots owing to the fact that only four trials were included.

RESULTS

A total of 152 studies were identified across the aforementioned databases. However, only four [3, 12–14] met our inclusion criteria and were therefore included in the meta-analysis (Fig. 1). A total of 148 studies were excluded for various reasons. Summarily, 14 studies were excluded due to duplication, 119 studies were excluded due to unrelated intervention or comparator (n = 28), or not an RCT (n = 91) at the title and abstract screening stages. In addition, 15 articles were excluded after evaluation of full texts, of which 11 and four had no research results and missing data, respectively.

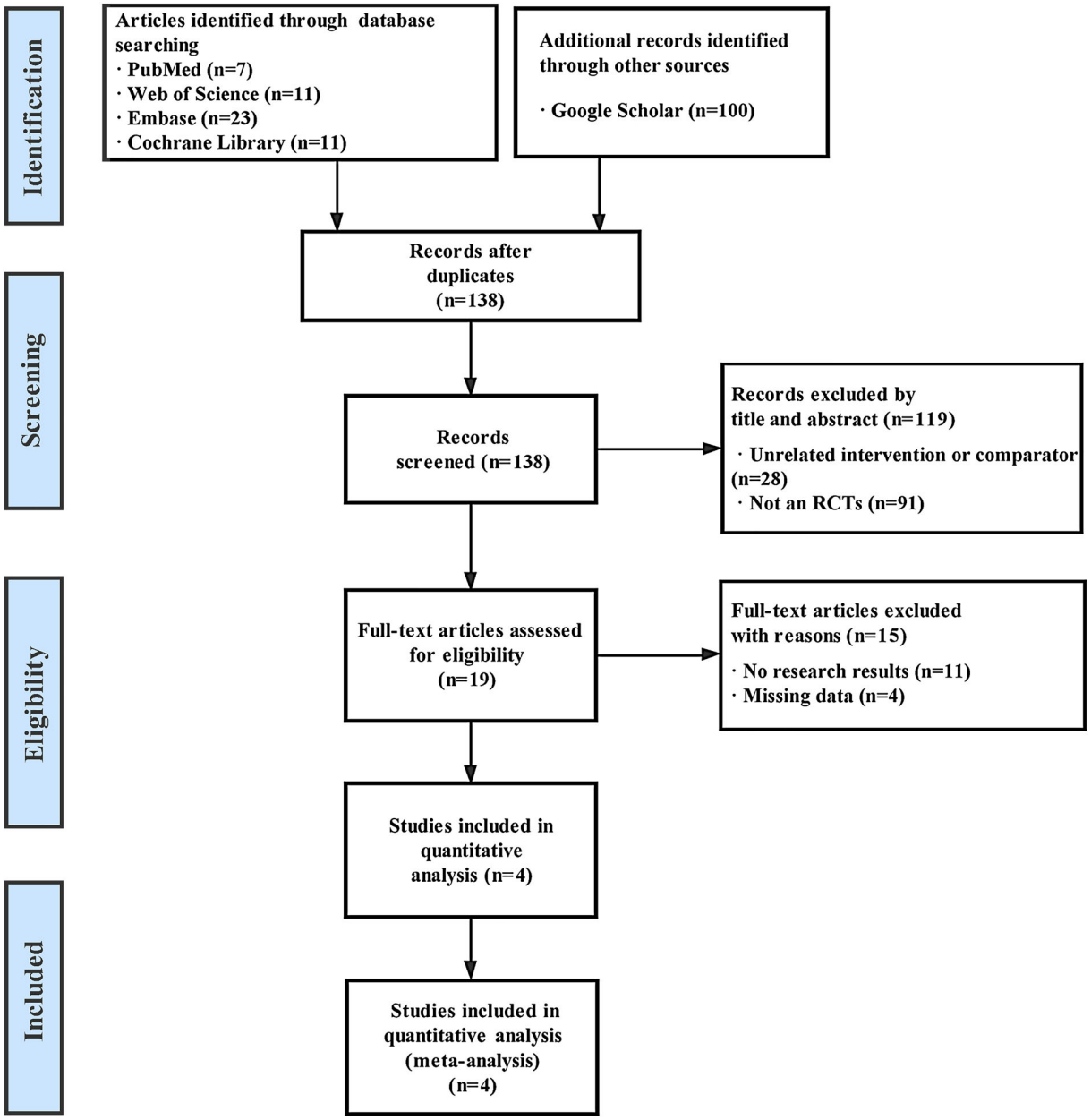

Fig. 1 Flowchart of identification and selection of studies included in the meta-analysis

Characteristics of the Included Studies

Among the studies, two were single-center ($n_1 = 60$, $n_2 = 56$) ($n_1 = 60$, $n_2 = 56$) [13, 14], one was multicenter ($n = 306$) [3], while the other was a two-center ($n = 47$) RCTs [12]. These subjects who were included were women with a range of 30–40 years of age. With regards to pain levels, all studies analyzed women who had CPP beyond 6 months [3, 12–14]. Moreover, the subjects were given an oral dose of gabapentin, ranging from 300 to 3600 mg daily [3, 12–14]. Intervention methods in the control group applied two different methods, as evidenced by three trials that reported placebos [3, 12, 13] while the other one used standard treatment, as controls [14]. Details on characteristics of each study are shown in Table 2.

Risk of Bias

A summary of results on assessment of risk of bias across the four studies is shown in Supplement Materials (Fig. S1 and Fig. S2) [3, 12–14]. Overall, one study recorded a low risk of bias [3] and the other study recorded a high risk of bias [14], whereas the remaining two exhibited unclear risk of bias [12, 13]. Specifically, two trials had an unclear risk of randomization sequences [12, 14], owing to lack of detailed description of the random allocation approach. On the other hand, allocation concealment, blinding of participants, personnel and outcome assessors were not described in one trial [14], while another trial recorded unclear risk towards blinding of outcome assessors [13]. With regards to selective reporting, we found unclear risk of bias in two trials [12, 13]. For the risk of attrition bias, one exhibited 'unclear risk of bias' [13] and the other showed a 'high risk of bias' [14].

Primary Outcomes

Four trials reported 'the change in pain scores from the baseline during the first 3 months treatment' [3, 12–14]. The included subjects reported their CPP intensity change on VAS (three studies, $n = 116$) [12–14] or NRS (1 study, $n = 244$) [3]. In addition, three trials reported on 'the change in pain scores from the baseline during the first 6 months treatment' [12–14]. The changes in pain intensities were analyzed from baseline to 6 months (three studies, $n = 99$) [12–14] and 3 months (four studies, $n = 360$) [3, 12–14] for assessing the pooled effects.

Compared with the control group, the gabapentin group had a greater change in pain intensity scores from baseline to 3 months (WMD: − 0.61 cm; 95% CI − 0.97 to − 0.25; $I^2 = 0\%$; $p = 0.0009$) as well as at 6 months (WMD − 1.38 cm; 95% CI − 1.89 to − 0.88; $I^2 = 0\%$; $p < 0.00001$) (Fig. 2; Table 3). Changes in pain scores failed to meet the threshold for MCID (a 1-cm change at any single time point) during the 3-month period, but the changes were higher than MCID during the 6-month period. Overall, quality of evidence, for this parameter, was rated as 'moderate' due to a high risk of bias.

Secondary Pain-Related Outcomes

The BPI Pain Interference Score

Two studies comprising 249 participants reported BPI pain interference scores [3, 12] during the first 3 months of treatment, although the pooled effect was not statistically significant (WMD − 0.01, 95% CI − 0.70 to 0.68; $I^2 = 0\%$; $p = 0.97$) (Table 3). For this parameter, the quality of evidence was 'moderate' due to a wide CI.

The Proportion of Patients Reporting 30% or More Reduction in Pain Score

Two studies, comprising 278 participants, reported this parameter [3, 13]. Notably, we could not calculate the pooled RR owing to differences in data extraction periods. One of the two studies revealed no statistically significant differences between the gabapentin (71/123) and placebo (56/121) groups during 16 weeks of treatment, whereas the other one reported a higher proportion in the gabapentin (19/20) compared to placebo (5/14) group over a 6-month period (Table 3).

Table 2 Basic characteristics of the included studies

Authors (year)	The route of administration	Groups (*n*): treatment (dose)	Duration of therapy	Follow-up time	Groups: age (mean ± SD) years	Prior surgery: percent of totals	Outcomes
AbdelHafeez [13] (2019)	Oral	Gabapentin (30): gabapentin (300–2700 mg) Control (30): placebo	6 months	3, 6 months	Gabapentin: (32.70 ± 4.91) years Control: (30.27 ± 5.32) years	Gabapentin: 16.67% Control: 6.67%	(1) The change in pain scores from the baseline during the first 3 months of treatment (2) The change in pain scores from the baseline during the first 6 months of treatment (3) The proportion of patients reporting 30% or more reduction in pain score (4) The overall satisfaction rate (5) The incidence of dizziness, somnolence, and mood changes
Horne [3] (2020)	Oral	Gabapentin (153): gabapentin (300–2700 mg) Control (153): placebo	16 weeks	13–16 weeks	Gabapentin: (30.50 ± 7.70) years Control: (30.10 ± 8.60) years	No information	(1) The change in pain scores from the baseline during the first 3 months of treatment (2) The BPI pain interference score (3) The proportion of patients reporting 30% or more reduction in pain score (4) The overall satisfaction rate (5) The incidence of dizziness, somnolence, and mood changes

Table 2 continued

Authors (year)	The route of administration	Groups (*n*): treatment (dose)	Duration of therapy	Follow-up time	Groups: age (mean ± SD) years	Prior surgery: percent of totals	Outcomes
Lewis [12] (2016)	Oral	Gabapentin (22): gabapentin (300–2700 mg) Control (25): placebo	6 months	3, 6 months	No information	No information	(1) The change in pain scores from the baseline during the first 3 months of treatment (2) The change in pain scores from the baseline during the first 6 months of treatment (3) The BPI pain interference score (4) The total incidence of adverse events
Sator-Katzenschlager [14] (2005)	Oral	Gabapentin (20): gabapentin (300–3600 mg) Control (20): amitriptyline (25–150 mg)	24 months	1, 3, 6, 12, 24 months	Gabapentin: (40.40 ± 12.90) years Amitriptyline: (36.70 ± 11.00) years	Gabapentin: 80.00% Amitriptyline: 80.00%	(1) The change in pain scores from the baseline during the first 3 months (2) The change in pain scores from the baseline during the first 6 months of treatment (3) The total incidence of adverse events

n numbers, *SD* standard deviation, *mg* milligram, *BPI* Brief Pain Inventory

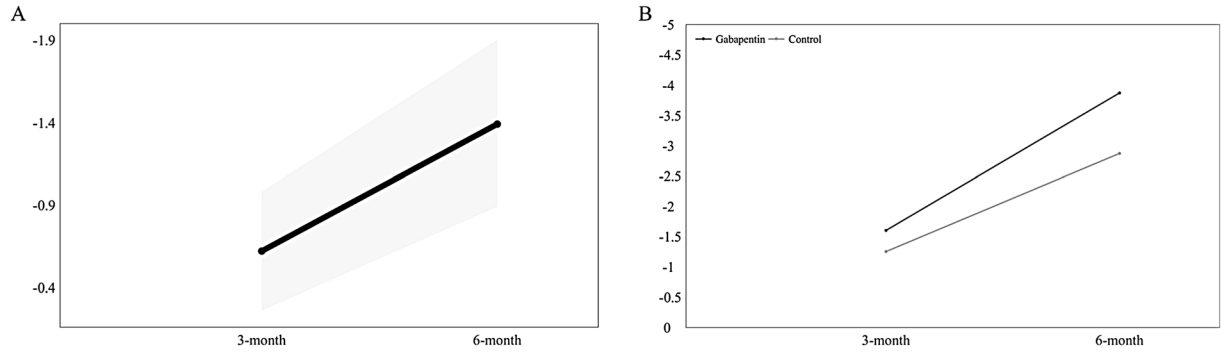

Fig. 2 **A** Band plot for weighted mean difference (WMD) of the change in pain scores from baseline to 3 and 6 months between gabapentin versus control. Pooled estimates of the WMD for each time point are represented by a *dark line* and 95% confidence intervals are represented by the surrounding *shaded region*; **B** line chart for mean values of the change in pain scores from baseline to 3 and 6 months in two groups

Other Secondary Outcomes

The Overall Satisfaction Rate

Two studies reported the proportion of patients who felt 'very marked or marked' or felt 'very satisfied or satisfied' after treatment [3, 13]. Notably, we could not calculate the pooled RR due to the fact that the data had been collected across different timepoints. Moreover, we found no statistically significant differences between groups during both 16-week (RR = 1.49; 95% CI 0.93–2.38) and 6-months (RR = 1.31; 95% CI 0.78–2.21) treatment periods (Table 3).

The Rate of Drug-Related Adverse Events

In the included trials, there have been some drug-related adverse events in the treatment of CPP in women. Two studies [12, 14] evaluated the total incidence of adverse events (n = 87) during 6 months of treatment, while the other two [3, 13] described occurrence of common adverse events during the whole treatment period, including dizziness (n = 296), somnolence (n = 300), and mood changes (n = 290).

We found no statistically significant differences in the pooled effect, with regard to total incidence of adverse events (RR 0.50; 95% CI 0.03–7.31; I^2 = 73%; p = 0.61). Quality of the evidence was considered 'low' due to the wide CI and high risk of bias. Furthermore, pooled results revealed no significant differences in the risk of mood changes between the groups (RR 1.23; 95% CI 0.91–1.67; I^2 = 0%; p = 0.17). The quality of evidence for this parameter was 'moderate', due to the wide CI. However, the gabapentin group of CPP women recorded higher incidence of dizziness and somnolence, relative to the placebo. For both outcomes, the quality of the evidence was categorized as 'moderate' due to wide CI. The details are shown in Table 3.

DISCUSSION

The findings of this pilot systematic review and meta-analysis provide useful insights into the longer-term potential role of gabapentin for the treatment of CPP in women. Our results revealed significant differences in pain relief outcomes between the gabapentin and placebo groups, from baseline to the first 3 and 6 months, after treatment. With regards to MCID, our results demonstrated that gabapentin is efficacious over a 6-month period but not over a 3-month treatment period. Notably, results from secondary outcomes, namely BPI pain interference scores, proportion of patients reporting 30% or more reduction in pain score, and the overall satisfaction rate, corroborated the primary results for the first 3 months. However, analysis of the proportion of patients with reduced pain scores and the overall satisfaction rates was only performed as a qualitative description. Finally, although we found no

Table 3 Primary and secondary endpoint results

Outcome	Studies included	Gabapentin, mean (SD) or *n*/*N*	Control, mean (SD) or *n*/*N*	WMD or RR (95% CI)	*p* value for statistical significance	*p* value for heterogeneity	I^2 test for heterogeneity	Quality of evidence (GRADE)
Primary outcomes								
The change in pain scores from the baseline during the first 3 months of treatment	4	− 1.60 (4.04)	− 1.25 (4.09)	− 0.61 (− 0.97 to − 0.25)	0.0009	0.82	0%	⊕⊕⊕◯ Moderate
The change in pain scores from the baseline during the first 6 months of treatment	3	− 3.87 (2.31)	− 2.87 (2.63)	− 1.38 (− 1.89 to − 0.88)	< 0.00001	0.55	0%	⊕⊕⊕◯ Moderate
Secondary pain-related outcomes								
The BPI pain interference score during the first 3 months	2	3.55 (2.76)	3.56 (2.78)	− 0.01 (− 0.70 to 0.68)	0.97	0.93	0%	⊕⊕⊕◯ Moderate
The proportion of patients reporting 30% or more reduction in pain score								
During 16 weeks	1	71/123	56/121	1.25 (0.98 to 1.59)	N/A	N/A	N/A	N/A
During 6 months	1	19/20	5/14	2.66 (1.31 to 5.41)	N/A	N/A	N/A	N/A
Other secondary outcomes								
The overall satisfaction rate								
During 16 weeks	1	34/112	22/108	1.49 (0.93 to 2.38)	N/A	N/A	N/A	N/A
During 6 months	1	15/20	8/14	1.31 (0.78 to 2.21)	N/A	N/A	N/A	N/A
The rate of adverse events								

Table 3 continued

Outcome	Studies included	Gabapentin, mean (SD) or *n/N*	Control, mean (SD) or *n/N*	WMD or RR (95% CI)	*p* value for statistical significance	*p* value for heterogeneity	I^2 test for heterogeneity	Quality of evidence (GRADE)
The total incidence of adverse events	2	17/42	20/45	0.50 (0.03 to 7.31)	0.61	0.05	73%	⊕⊕◯◯ Low
Mood changes	2	56/148	43/142	1.23 (0.91 to 1.67)	0.17	0.58	0%	⊕⊕⊕◯ Moderate
Dizziness	2	74/152	33/144	2.11 (1.51 to 2.94)	< 0.0001	0.16	49%	⊕⊕⊕◯ Moderate
Somnolence	2	67/154	35/146	1.80 (1.29 to 2.49)	0.0005	0.64	0%	⊕⊕⊕◯ Moderate

⊕⊕⊕⊕ High-quality evidence, ⊕⊕⊕◯ Moderate-quality evidence, ⊕⊕◯◯ Low-quality evidence, ⊕◯◯◯ Very low quality evidence
SD standard deviation, *n/N* numbers/numbers, *WMD* weighted mean difference, *RR* risk ratio, *CI* confidence interval, *GRADE* grades of recommendation, assessment, development, and evaluation, *BPI* Brief Pain Inventory, *N/A* not applicable

statistically significant differences in the total incidence of adverse events, additional analysis revealed that gabapentin treatment was strongly associated with a higher rate of dizziness and somnolence. Notably, gabapentin-related side effects were mild and transient, without any significant mood changes.

Collectively, our results are novel and clinically relevant. Although previous studies have described success of this therapy in the treatment of other chronic pain conditions, such as chronic neuropathic pain [27–29], evidence of gabapentin administration in the treatment of women with CPP remains dearth. To date, only one previous review has attempted to answer this question [10]. However, the precision and validity of findings were limited by paucity of available evidence and non-quantitative analysis, hence no intuitive answer has been obtained regarding the benefits of this therapy. We therefore designed and performed this pilot meta-analysis.

Overall, our findings revealed the potential efficacy of gabapentin for the treatment of CPP in women. Although pain relief failed to reach the MCID threshold during the first 3 months of treatment, results of pain scores over a 6-month period indicated that gabapentin requires a longer period to be embodied. Results from a previous multicenter double-blind trial indicated that gabapentin did not relieve pain in women with CPP [3]. However, it is important to note that the cycles of this trial were only performed for approximately 16 weeks. Conversely, results from another pilot trial study by Horne showed that gabapentin had a significant analgesic effect after 6 months of treatment [30]. With regards to the mechanism of action, one plausible explanation for the observed differences in time-dependent efficacy observed herein is that gabapentin exerts long-term effects on HVA ICa in medium-sized and small (IB4-) DRG neurons, which play a significant role in pain relief [31–33]. However, further studies using high-quality clinical designs are needed to validate gabapentin's longer-term effects in the treatment of CPP in women.

Results of secondary outcomes corroborated those from primary outcomes, and suggested that gabapentin can generate longer-term efficacy in CPP patients. Since BPI can be used to comprehensively evaluate pain, we found two studies indicating that gabapentin does not significantly exert therapeutic effects on pain relief over a short treatment period (3 months). Generally, 30% or more pain relief is considered a good treatment outcome [22]. Our results revealed that the number of people experiencing 30% or more pain relief was higher after gabapentin treatment, relative to the placebo, over a 6-month period. However, an additional caveat is 'the overall satisfaction rate' used as the patient-related outcome showed that patients were not so satisfied with the efficacy of gabapentin during 16 weeks or 6 months. Therefore, gabapentin may have longer-term efficacy ($\geq$ 6 months) in CPP patients, although further studies are warranted to validate this finding.

Our findings revealed no statistically significant differences with regards to 'the total incidence of adverse events' and 'mood changes', between the treatment and control groups, suggesting that it was a less-obvious hazard for women with CPP to receive the gabapentin treatment. However, gabapentin is closely involved in high risks of dizziness and somnolence, which are central nervous system adverse effects [34]. Therefore, patients with major neurologic conditions are advised to avoid gabapentin-based treatment [35, 36].

This review has several strengths. Firstly, we employed a comprehensive search strategy to identify and summarize our evidence. Secondly, the primary outcomes were interpreted with the MCID under a clinical context, which helped improve credibility. Thirdly, our results revealed that gabapentin has statistically significant longer-term effects ($\geq$ 6 months) in the treatment of CPP in women, which provides a platform for future clinical studies. Finally, the low heterogeneity of the pooled effect observed herein enhanced external validity of our findings.

However, the study also had some limitations. Firstly, our study had a small sample size, which may affect the findings and conclusions of our study. Further studies using high-quality and large-scale RCTs are needed to validate our findings. Secondly, the possibility of small

sample effect cannot be fully ruled out, despite that the homogeneity of data dilutes this possibility. Thirdly, it is difficult to determine the effect of age, adjuvant pain therapies, and previous pelvic surgery on efficacy of gabapentin for treatment of CPP in women using subgroup analysis owing to the lack of sufficient relevant studies. Similarly, we did not perform tests of heterogeneity and publication bias due to a limited number of relevant studies.

CONCLUSIONS

Our results demonstrate that gabapentin is a potential treatment option for CPP in women, and generates a longer-term analgesic effect. Based on results on adverse effects, we hypothesize that gabapentin treatment may not be suitable for patients with serious neurological diseases, hence they should seek alternative therapies. Further studies based on high-quality clinical trials are needed to validate our findings.

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