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Review Article

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Pregabalin and gabapentin in neuropathic pain management after spinal cord injury: a systematic review and meta-analysis

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Neuropathic pain after spinal cord injury (SCI) has a significant negative impact on the patients' quality of life. The objective of this systematic review is to examine the safety and efficacy of pregabalin (PGB) and gabapentin (GBP) in the treatment of neuropathic pain due to SCI. PubMed, the Cochrane Library, Embase, Scopus, and the Web of Science were searched up to December 2018. The reference lists of key and review studies were reviewed for additional citations. The quality of the studies was evaluated using the Cochrane Collaboration's tools for assessing the risk of bias. A meta-analysis was performed for primary and secondary outcomes. Eight studies were eligible for inclusion. Meta-analysis of PGB *vs.* placebo showed that PGB was effective for neuropathic pain (standardized mean difference [SMD] = −0.40; 95% confidence interval [CI]: −0.78, −0.01), anxiety (MD = −0.68; 95% CI: −0.77, −0.59), depression (mean difference [MD] = −0.99; 95% CI: −1.08, −0.89), and sleep interference (MD = −1.08; 95% CI: −1.13, −1.02). Also, GBP was more effective than a placebo for reducing pain. No significant difference was observed between the efficacy of the two drugs (MD = −0.37; 95% CI: −1.67, 0.93). There was no significant difference between the two drugs for discontinuation due to adverse events (risk ratio = 3.00; 95% CI: 0.81, 11.15). PGB and GBP were effective *vs.* placebos in decreasing neuropathic pain after SCI. Also, there was no significant difference between the two drugs for decreasing pain and adverse events.

Key Words: Anxiety; Depression; Gabapentin; Meta-Analysis; Neuralgia; Pain; Pregabalin; Spinal Cord Injuries; Systematic Review.

INTRODUCTION

Neuropathic pain is one of the most challenging medical conditions after spinal cord injury (SCI) [1,2], which is associated with anxiety, depression, and sleep disorders [3-5]. It interferes with daily activities and normal functioning [6,7], and has a significant negative impact on the patients' quality of life [7-16]. More than half of those with SCI are estimated to suffer from neuropathic pain [13]. Pharmacological interventions such as anticonvulsant prescriptions have been mainly used to control various types of neuropathic pains [17].

Pregabalin (PGB) and gabapentin (GBP) are recommended as the first-line treatment for neuropathic pain

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due to SCI [18,19]. Both drugs have been shown to be effective in the treatment of neuropathic pain due to postherpetic neuralgia [20-26] and diabetic peripheral neuropathy [24-29]. PGB is the new generation of gabapentinoids that acts similar to GBP [30]. PGB is the only medication that is approved by the U.S. Food and Drug Administration for neuropathic pain management in SCI. Many individuals with SCI, regardless of receiving the standard treatments, still suffer from pain [31]. In recent years, several systematic reviews have been published about the efficacy and safety of PGB and GBP in management of neuropathic pain associated with SCI, which almost all compared PGB or GBP with placebos [17,19,32-36]. Lack of evidence for a direct comparison between interventions makes it difficult to choose the most effective treatment [37]. To our knowledge, to date, there is no systematic review comparing PGB and GBP in a head-to-head manner. This systematic review aims to examine the efficacy and safety of PGB and GBP in neuropathic pain management for patients with SCI.

MATERIALS AND METHODS

The study protocol was registered in international prospective reregister of systematic review (PROSPERO) with the registration number of CRD42019106997. We used the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist when writing our report [38].

1. Literature search

A systematic review of the relevant literature was conducted in PubMed, the Cochrane Library, Embase, Scopus, and the Web of Science up to December 2018. There were no restrictions on the year or type of publication. The references lists of the selected studies and review articles were reviewed for additional relevant articles. Additionally, to ensure identifying most of the relevant studies, key journals relevant to the topic were searched separately. SCI, neuropathic pain; PGB, and GBP were the search terms.

2. Study selection

After removing duplicate records, two authors (ABa and ABe) independently reviewed the titles and abstracts of the articles that were included based on the inclusion criteria. Disagreements were resolved by discussion between the two researchers and, if necessary, by a third person (DM). The selected studies were included for analysis if the following criteria were met [21]: (1) the focus was on individuals with neuropathic pain due to SCI with no restriction to any specific age group; (2) PGB and GBP were compared with each other or with a placebo; (3) neuropathic pain was measured as an outcome [22]; (4) the study design was a randomized clinical trial, and [22] (5) was published in the English language. Observational studies, case reports, editorial comments, and studies on animals were excluded.

3. Data extraction and quality assessments

We used Cochrane Collaboration's tool to assess the risk of potential bias in the selected studies. The quality of the included randomized controlled trials (RCTs) was assessed independently by two researchers (ABa and AA).

Two reviewers (ABe and RS) independently extracted data using a constructed data extraction form including study characteristics (design, longitude, and following study), participants' characteristics (age, sex, and number of patients), dosage (primarily median and maximum), efficacy outcomes (pain, anxiety, sleep, and depression), and side effects. In case of a dispute, issues were solved by discussion and checking with the third person (MD). The primary efficacy outcome variables were the changes in pain score and secondary outcomes included sleep interference, depression, and anxiety. Safety outcomes, which included adverse events (AEs) and discontinuations, were also analyzed.

4. Data analysis

A meta-analysis was performed to compare the efficacy and safety of PGB *vs.* GBP and PGB *vs.* placebo. Meta-analysis for the GBP and placebo studies was not possible due to differences in the treatment received by the control group. For example, in one study the control group used a placebo while in another study an active placebo (diphenhydramine) was used. Additionally, in one study, a different scale was used for measuring and reporting the perceived pain. We performed the analysis using RevMan ver. 5.3 software.

For continuous variables, weighted mean difference (MD) and a 95% confidence interval (CI) were used.

For dichotomous variables, risk ratio (RR) and a 95% CI were used. Statistical heterogeneity has been evaluated using the I^2 and chi-square tests. The random-effects method and the fixed-effect method were used for studies with significant heterogeneity and for those without heterogeneity, respectively.

RESULTS

1. Literature search

The processes of literature search, removal of duplicates, and screening based on title, abstract, and full text is shown in **Fig. 1**. The 866 articles found in the initial search were narrowed down to 8 articles that were selected for further eligibility assessment. After checking for all inclusion and exclusion criteria, finally, eight articles [39-46] were included in this review. One head-to-head trial was excluded due to the fact that the type of disease was not specified [47].

2. Study characteristics

Of eight studies included in the review, two studies compared PGB with GBP, three studies compared PGB with a placebo, and three studies compared GBP with a placebo. In head-to-head studies [45,46], a total of 58 patients with neuropathic pain due to SCI in two crossover groups of PGB and GBP entered the studies. Of 58 participants, 40 individuals (69%) completed the studies. In both studies [45,46], pain scores were measured by the visual analogue scale (VAS). Sleep quality, depression, and anxiety were secondary outcomes. The prescribed dosage was 150-600 mg/day, two times per day, for PGB and 300-3,600 mg/day, three times per day for GBP. In three RCTs, 377 patients in two groups (PGB and placebo) were compared with each other [41,43,44]. Pain scores were measured by the VAS and duration-adjusted average change. The nine-item medical outcomes study-sleep scale problems index and the hospital anxiety and depression scale were used to measure sleep quality, depression, and anxiety, respectively. In three other RCTs, GBP was compared with a placebo [39,40,42] and an active placebo (diphenhydramine) in patients. The VAS, numeric rating scale, and neuropathic pain scale were used to measure pain scores. In one study, depressive symptomatology was measured by the center for epidemiologic studies depression scale short form. Study characteristics are presented in **Table 1** [39-46].

3. Quality assessment

Quality assessment of these studies, using the Cochrane Collaboration's tool, is presented in **Fig. 2** [39-46].

4. Efficacy outcomes

PGB *vs.* GBP: There is no significant difference between two drugs in the reduction of pain scores (MD = –0.37, 95% CI: –1.67, 0.93; $P > 0.05$, **Fig. 3**) [45,46].

PGB *vs.* placebo: The meta-analysis demonstrated a significant effect of PGB in comparison to a placebo on the reduction of pain scores (standardized mean difference [SMD] = –0.40; 95% CI: –0.78, –0.01; $P < 0.05$). For second-

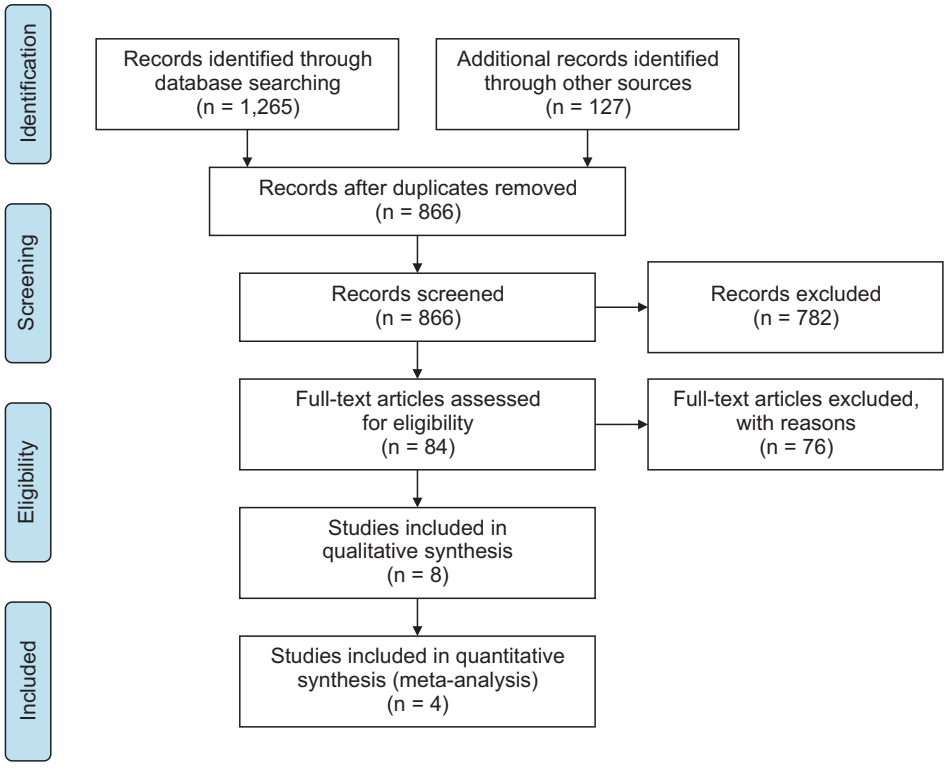

Fig. 1. Study flow diagram preferred reporting items for systematic reviews and meta-analyses (PRISMA).

Table 1. Characteristics of the Included Studies

Study	Design	Patients	Intervention/ Control	Study duration (wk)	Dosage (mg/day)	Pain measure scales
Cardenas et al. [44] Chile, China, Columbia, Czech Republic, Hong Kong, India, Japan, Philippines, Russian Federation, USA	Parallel	111 PGB, 108 PBO	PGB/PBO	17	PGB: 150-600 PBO: 150-600	DAAC
Kaydok et al. [45] Turkey	Crossover	28	PGB/GBP	8	PGB: 150-600 GBP: 300-3,600	VAS, NPS
Levendoglu et al. [40] Turkey	Crossover	20	GBP/PBO	20	GBP: 900-3,600 PBO: -	VAS, NPS
Rintala et al. [42] USA	Crossover	38	GBP/PBO	8	GBP: 100-1,200 PBO: 25	VAS, NRS
Siddall et al. [41] Australia	Parallel	70 PGB, 67 PBO	PGB/PBO	12	PGB: 150-600 PBO: 150-600	VAS
Tai et al. [39] USA	Parallel	7	GBP/PBO	4	GBP: 300-1,800 PBO: 300-1,800	NPS
Vranken et al. [43] Netherlands	Parallel	11PGB, 10 PBO	PGB/PBO	4	PGB: 150-600 PBO: -	VAS
Yilmaz et al. [46] Turkey	Crossover	21	PGB/GBP	16	PGB: up to 300 GBP: up to 1,800	VAS

PGB: pregabalin, PBO: placebo, DAAC: duration-adjusted average change, GBP: gabapentin, VAS: visual analog scale, NPS: neuropathy pain scale, NRS: numeric rating scale.

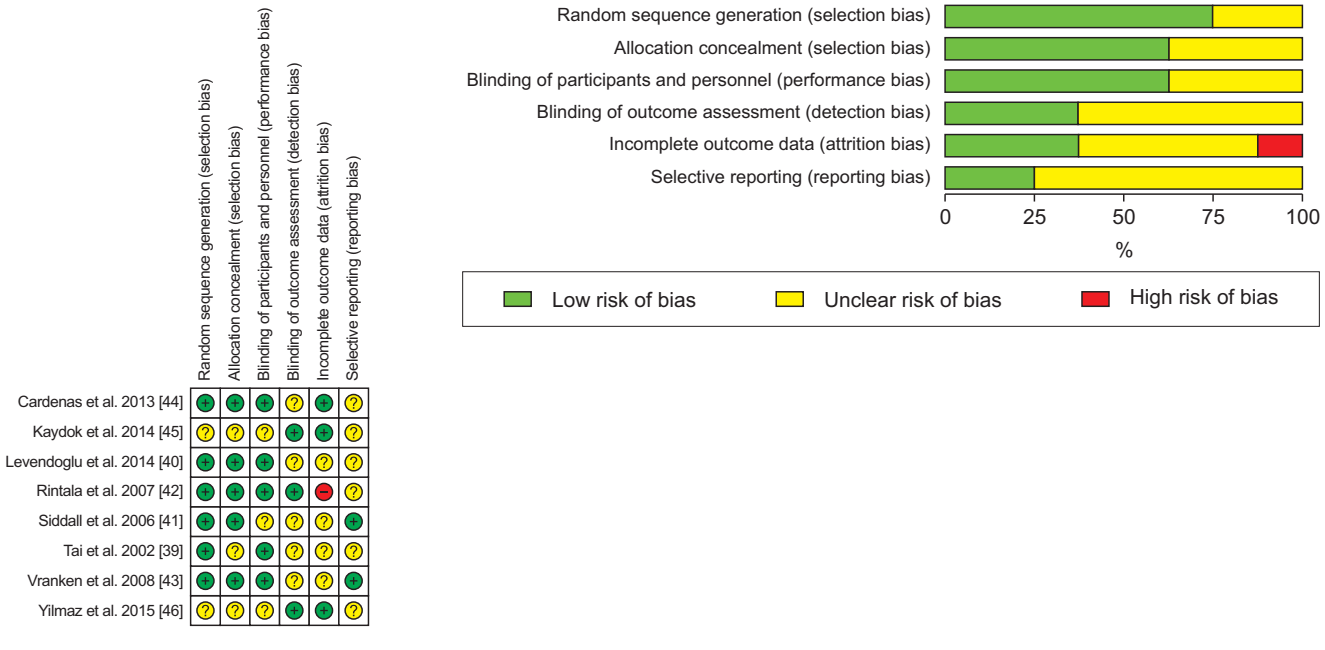

Fig. 2. Risk of bias.

ary outcomes, PGB was more effective than a placebo for anxiety (MD = –0.68; 95% CI: –0.77, –0.59; $P < 0.05$), depression (MD = –0.99; 95% CI: –1.08, –0.89; $P < 0.05$), and sleep interference (MD = –1.08; 95% CI: –1.13, –1.02; $P < 0.05$, **Fig. 4**) [41,44].

GBP *vs.* placebo: In two studies [39,40,42], GBP was only effective in some aspects of neuropathic pain such as pain intensity, unpleasantness, and hot sensation. In one study [42], there was no significant difference between GBP and an active placebo (diphenhydramine) in terms of pain scores. Generally, GBP *vs.* a placebo was more effective.

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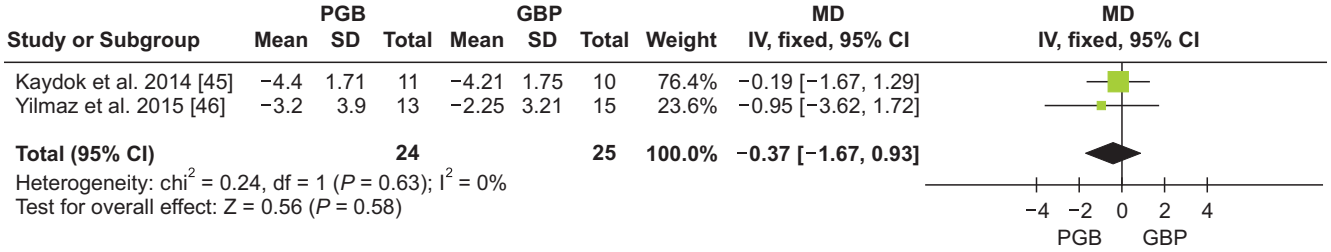

Fig. 3. Pooled mean difference (MD) of pregabalin (PGB) *vs.* gabapentin (GBP) for pain outcome. There was no significant difference between two drugs for reducing pain. SD: standard deviation, CI: confidence interval, df: degree of freedom.

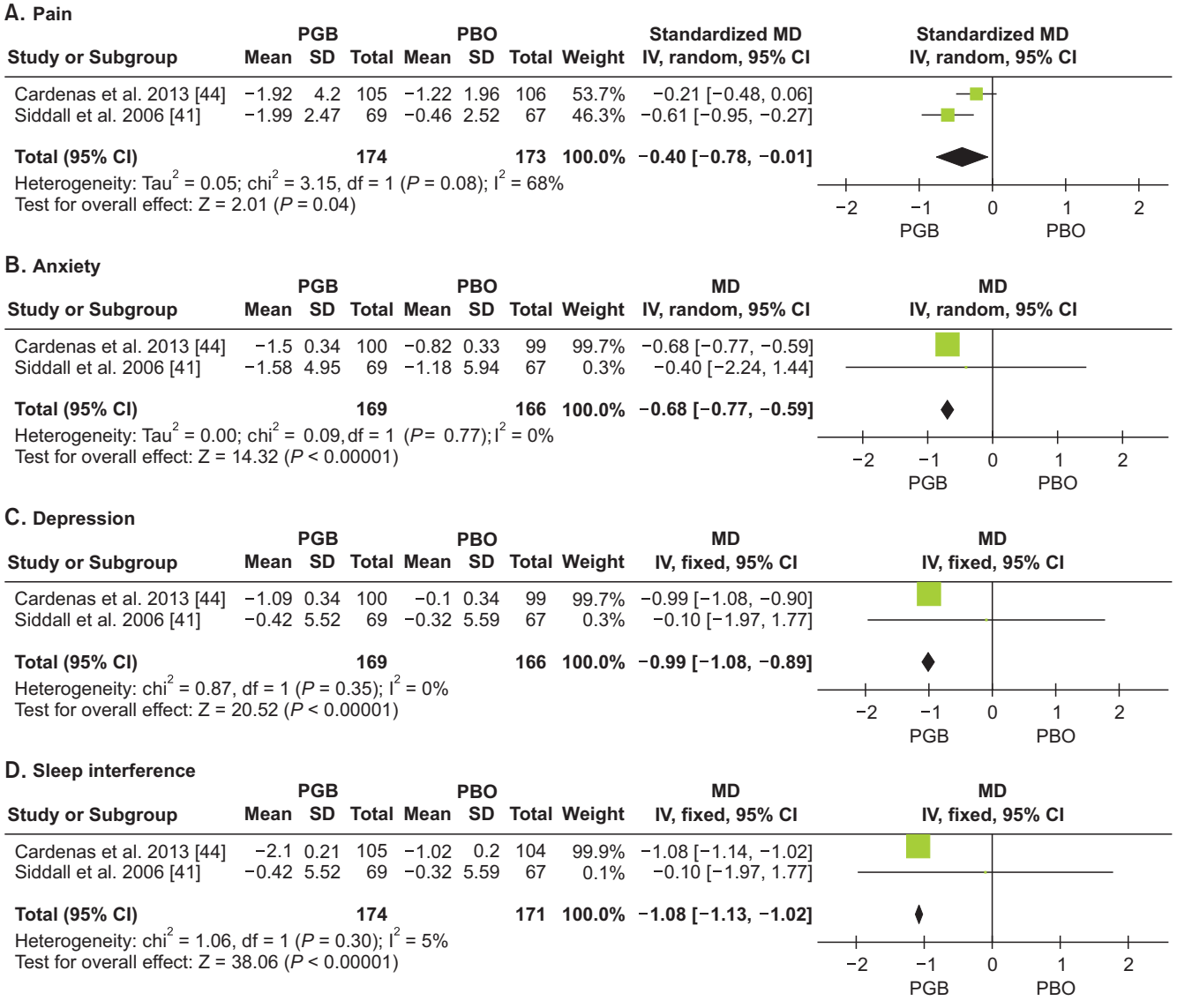

Fig. 4. Pooled mean difference (MD) of pregabalin (PGB) *vs.* placebo (PBO) for outcomes of pain (A), anxiety (B), depression (C), and sleep interference (D). PGB is effective *vs.* PBO for all outcomes. SD: standard deviation, CI: confidence interval, df: degree of freedom.

5. Safety outcomes

PGB *vs.* GBP: Drowsiness and somnolence were the commonly reported AEs for PGB and GBP [45,46]. Patients in the PGB group experienced a greater number of AEs than in the GBP group. Seven patients in the PGB group and two patients in the GBP group had to discontinue their medication therapy due to AEs. No significant difference was

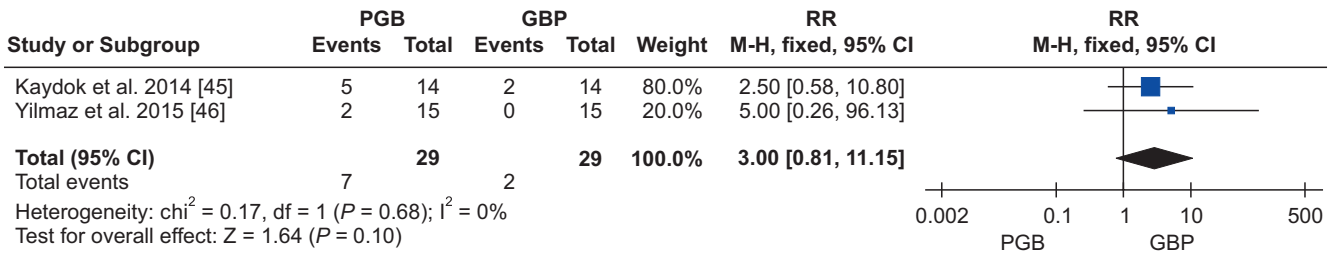

Fig. 5. Pooled risk ratio (RR) of pregabalin (PGB) *vs.* gabapentin (GBP) for adverse events (AEs). There was no significant difference between two drugs for AEs. CI: confidence interval, df: degree of freedom.

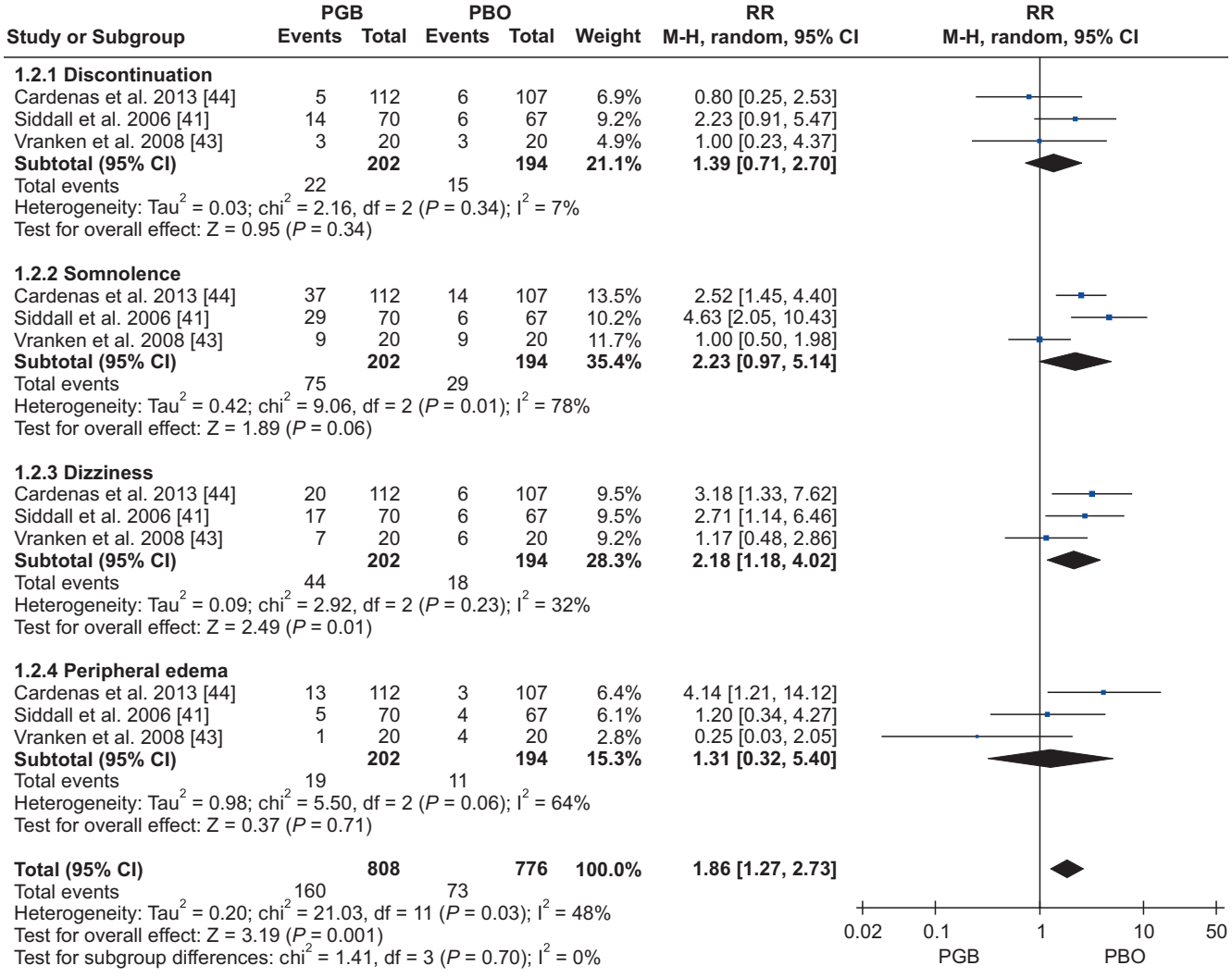

Fig. 6. Pooled risk ratio (RR) of pregabalin (PGB) *vs.* placebo (PBO) for adverse events. There was no significant difference between PGB and PBO for discontinuation, somnolence, and peripheral edema. The incidence of dizziness was higher for PGB. CI: confidence interval, df: degree of freedom.

observed in discontinuation due to AEs in the two treatment groups (RR = 3.00; 95% CI: 0.81, 11.15; $P > 0.05$, **Fig. 5**) [45,46].

PGB *vs.* placebo: Drowsiness, dizziness, edema, and peripheral edema were the most common AEs in the selected studies [41,43,44]. According to the analyses performed on the results reported by the studies, no significant difference was observed between PGB and the placebo for discontinuation due to AEs (RR = 1.39; 95% CI: 0.71, 2.70; $P > 0.05$), somnolence (RR = 2.23; 95% CI: 0.97, 5.14; $P > 0.05$), and peripheral edema (RR = 1.31; 95% CI: 0.32, 5.40; $P > 0.05$). However, there was a significant difference between PGB and the placebo for dizziness (RR = 2.23; 95% CI: 0.97, 5.14; $P < 0.05$, **Fig. 6**) [41,43,44]. GBP *vs.* a placebo: The most

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common AEs reported for GBP were dry mouth, drowsiness, fatigue, dizziness, constipation, edema, and vertigo [39,40,42]. Nonetheless, one of the selected studies showed no significant difference in AEs between the recipients of GBP and the placebo [39,40,42].

DISCUSSION

The purpose of this systematic review was to examine the safety and efficacy of PGB and GBP in the treatment of neuropathic pain due to SCI. This study is the first systematic review and meta-analysis in which the two drugs have been compared directly with each other. A systematic review of head-to-head trails provides the highest quality evidence to compare the effectiveness of the two interventions [48].

In recent years, several recommendations have been published considering the efficacy and safety of PGB and GBP in the management of neuropathic pain after SCI [17,19,32-36,49]. To our knowledge, these recommendations [17,19,32-36,49] were limited to randomized placebo-controlled trials only and, due to the lack of head-to-head studies, had important limitations. Recently, A limited number of studies performed head-to-head comparison of these drugs and the results of these studies showed that both drugs were effective in the treatment of neuropathic pain [45,46].

The results of our meta-analysis showed that both PGB and GBP have similar efficacy in reducing pain, and there was no significant difference between the two interventions. In previous systematic reviews [17,19,32-36,49], both drugs were found to be effective in reducing neuropathic pain due to SCI, which is similar to the findings of the present study. However, studies included in these reviews did not compare PGB and GBP with each other [39-44,50-52].

In several systematic reviews [17,35,36], no significant difference was reported between the efficacy of PGB and GBP in individuals with SCI, which, from the statistical point of view, is similar to the findings of our study. On the other hand, evidence shows that results of indirect comparisons are usually in accordance with the results of direct comparisons [53]. The findings of the current study vary from several other review studies [32-34] which compared PGB and GBP with a placebo. In those studies, it was concluded that PGB is more effective than GBP in the treatment of neuropathic pain due to SCI. These differences can be attributed to the lack of head-to-head trials in those studies.

In a meta-analysis conducted by Mehta et al. [36], lack of a direct comparison between PGB and GBP was considered a barrier to making a conclusive statement about difference in efficacy (decreasing neuropathic pain after SCI) of the two drugs, but such limitations did not exist in the present study. Ghosh et al. [47] studied the efficacy and safety of PGB and GBP in 100 patients with neuropathic pain in a head-to-head design using an unclear indication. At the end of the study, consistent with our findings, VAS pain scores were similar in the PGB and GBP groups, and both drugs lead to a decrease in neuropathic pain. But PGB showed better results in comparison to GBP based on the pain quality assessment scale.

The findings of this meta-analysis showed that PGB, compared to a placebo, was more effective in reducing neuropathic pain, sleep disorders, anxiety, and depression, while, GBP *vs.* a placebo, was shown to be effective in some aspects of pain.

Drowsiness and somnolence were the most reported side effects of PGB and GBP in crossover studies [45,46]. The number of adverse events and discontinuations due to treatment were higher for PGB in comparison to GBP. Our meta-analysis showed that dizziness was a side effect of PGB in comparison with a placebo. However, the results of a study [54] showed the long-term safety and tolerability of PGB in patients with central neuropathic pain due to SCI. Results of a systematic review by Tzellos et al. [32] indicated that PGB had greater side effects in comparison to GBP.

The poor methodological quality of the head-to-head studies, small sample sizes, and lack of enough data limited our ability to perform further in-depth meta-analysis on findings of the previous studies. Restriction of the reviewed studies to the English language was another limitation of this study. However, expanding the inclusion criteria to the studies with English abstracts increased the pool of the potential studies to be chosen for further analyses.

The findings of this study suggest that both PGB and GBP are effective in the treatment of neuropathic pain associated with SCI. Likewise, head-to-head studies showed that there was no significant difference between the two drugs in reducing pain scores. Similarly, there was no significant difference in the safety profiles of the two drugs. We suggest a network meta-analysis for future studies.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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