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REVIEW

A Meta-analysis of Randomized Controlled Trials Comparing the Efficacy and Safety of Pregabalin and Gabapentin in the Treatment of Postherpetic Neuralgia

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ABSTRACT

Objective: To systematically evaluate the clinical efficacy of pregabalin and gabapentin in the treatment of postherpetic neuralgia (PHN), including the difference in pain control and occurrence of adverse reactions.

Methods: PubMed, MEDLINE, EMBASE, Cochrane Library, and Web of Science databases were searched for randomized controlled trials (RCTs) comparing the efficacy of pregabalin and gabapentin in patients with PHN. Data from studies meeting the inclusion criteria were extracted and the Cochrane Risk of Bias risk assessment tool was used to evaluate the quality of the included studies. Revman 5.3 and Stata17 were used to perform the meta-analysis and to detect publication bias.

Results: A total of 14 RCTs with 3545 patients were included in this study, including 926 in the pregabalin treatment group, 1256 in the gabapentin treatment group, and 1363 in the placebo control group. Pregabalin was better than gabapentin in alleviating pain and improving the global perception of change in pain and sleep ($P < 0.05$). Gabapentin was associated with a lower incidence of adverse events than pregabalin ($P < 0.05$). Funnel plot and Begg's and Egger's tests showed no significant publication bias.

Conclusion: Pregabalin appears to have a better overall therapeutic effect than gabapentin for patients with PHN, but gabapentin has a lower incidence of adverse reactions and a better safety profile. Clinicians should comprehensively consider patient factors and fully evaluate the advantages and disadvantages of each treatment option to select the most suitable drugs for patient use. Considering the limited quantity and quality of the existing literature, high-quality RCTs are needed to confirm the advantages of pregabalin over gabapentin in the treatment of PHN and guide clinical decision-making.

Keywords: Pregabalin; Gabapentin; Postherpetic neuralgia; Systematic review; Meta-analysis; Randomized controlled trial

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Key Summary Points

This meta-analysis evaluated the clinical efficacy of pregabalin and gabapentin in the treatment of postherpetic neuralgia.

Pregabalin was found to have a better overall therapeutic effect than gabapentin for patients with PHN.

However, gabapentin was found to have a lower incidence of adverse reactions and a better safety profile.

Further high-quality RCTs are needed to confirm the advantages of pregabalin over gabapentin in the treatment of PHN.

INTRODUCTION

Herpes zoster (HZ) is a common skin disease characterized by painful blisters and skin rashes in a segmental or root distribution, with a predilection for the intercostal nerves, cervical nerves, and trigeminal nerves. It can remain latent for a long time within a spinal cord root ganglion. HZ is caused by the reactivation of varicella zoster virus (VZV) [1]. The characteristic clinical manifestations of HZ include knife-like or burning pain, which may be accompanied by pruritus, hypoesthesia, or paresthesia, and occasionally fever, general malaise, and rash. The rash is mostly located on one side or near the midline. It starts as a red maculopapular rash, then evolves into vesicles, pustules, and finally crusts. Scarring and pigmentation are often left behind. Generally, the pain disappears after the vesicle recedes, but some patients experience persistent and severe pain, called postherpetic neuralgia (PHN) [2]. PHN is the commonest neuropathic pain syndrome and commonest complication of herpes zoster [3].

The antiepileptic drugs gabapentin and pregabalin were approved early by the US Food and Drug Administration (FDA) in the 1990s to treat PHN [4, 5]. Both are new generation antiepileptic drugs that can be used in the treatment of neuropathic pain; they have many things in common, but there are also some differences. Both are analogs of the neurotransmitter γ-aminobutyric acid (GABA) with no pharmacological activity on GABA receptors. They are not metabolized by the liver and have a low binding rate with plasma proteins. They have no inducible or inhibitory effect on liver microsomal enzymes and rarely interact with other drugs. Pregabalin is thought to exert its analgesic effect through the antagonistic activity of voltage-gated Ca^{2+} channels, and its main antagonistic target is the type I α2-δ subunit of voltage-dependent Ca^{2+} channels in the central nervous system [6]. The analgesic effects of gabapentin include: increasing the inhibitory input of GABA-mediated pathway, antagonistic *N*-methyl-D-aspartic acid receptor (NMDA) activity, antagonism of calcium channels in the central nervous system, and inhibition of peripheral nerve conduction [7]. In addition, Roberta et al. [8] showed that gabapentin can also act on the type I α2-δ subunits of voltage-dependent calcium channels.

Although pregabalin is a new antiepileptic drug, it has no obvious advantage compared with other antiepileptic drugs in the treatment of partial epilepsy. However, the treatment of chronic pain, especially chronic neuropathic pain, is challenging, so the use of pregabalin in chronic pain has received increasing attention. Previous systematic reviews of PHN regimens have shown that gabapentin and pregabalin can significantly improve pain in patients with PHN compared with placebo [9]. Tarride et al. [10] conducted a comparative analysis of gabapentin and pregabalin in diabetic neuralgia and PHN in Canada, and found that pregabalin had better efficacy than gabapentin. However, there are other studies that indicate that gabapentin is preferable as a first-line drug over pregabalin and abundant previous clinical data [11]. There are currently few reports comparing pregabalin with gabapentin in the literature. Further studies are needed to fully and accurately understand the differences between the two in regards to clinical application. Therefore, this paper describes a meta-analysis and systematic review

of published clinical randomized controlled trials (RCTs) to more comprehensively compare and understand the efficacy and safety of pregabalin and gabapentin in the treatment of PHN, and provide more powerful evidence to guide the selection of clinical medication.

METHODS

This systematic review and meta-analysis followed the guidelines in the Cochrane Collaboration handbook and has been registered on PROSPERO (CRD42022363670). We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement for the realization of this work [12]. 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.

Literature Retrieval Strategy

Searches were performed in PubMed, MEDLINE, EMBASE, Cochrane Library, and Web of Science databases with no publication time limit. The following search terms were used: "postherpetic neuralgia" (Title/Abstract) OR "neuralgia, Postherpetic" (Mesh) AND ["Pregabalin" (Mesh) OR "Gabapentin" (Mesh)] OR ["Pregabalin" (Title/Abstract) OR "Gabapentin" Title/Abstract].

Inclusion and Exclusion Criteria

Before the literature search, the inclusion and exclusion criteria were determined. The study types of interest were RCTs or cohort studies evaluating the efficacy of pregabalin versus gabapentin for PHN. The primary outcome measure was the pain score (treatment effect) of patients receiving pregabalin and gabapentin for the treatment of PHN, and the secondary outcome measures included the rate of adverse reactions after medication, sleep score, and global perception of change in pain [using the Patients' Global Impression of Change (PGIC) scale].

The inclusion criteria were as follows: (1) study: RCT; (2) subjects: patients with PHN; and (3) interventions: pregabalin group, oral pregabalin or placebo; gabapentin group, oral gabapentin or placebo. The exclusion criteria were as follows: (1) nonrandomized controlled trials; (2) primary outcome measure did not describe efficacy; (3) duration of treatment was less than 1 month; (4) treatment with or without other medications; and (5) other medical conditions, such as cognitive impairment, alcohol and drug abuse, diabetes, or Acquired immunodeficiency syndrome (AIDS) that could interfere with treatment.

Literature Screening and Data Extraction

Based on the inclusion and exclusion criteria described above, two researchers independently screened the literature and extracted data, which were then cross-checked and discussed with each other to reach agreement on contentious issues. Data extracted included title, year of publication, author, country, number of subjects, study design, intervention, and outcome measures.

Evaluation of the Quality of the Included Studies

The Cochrane Risk of Bias Assessment Tool [13] was used to evaluate the quality of all the included RCTs in terms of the following six aspects: (1) selection bias (random sequence generation and allocation concealment); (2) implementation bias (investigator and subject blinding); (3) measurement bias (blinded evaluation of the study results); (4) follow-up bias (integrity of the results); (5) reporting bias (selective reporting of the research results); and (6) other bias (in addition to the above biases, the information provided was assessed to have other factors causing bias). RevMan 5.3 software was used to assess the risk of bias in all included studies.

Data Analysis

In this study, RevMan 5.3 and Stata17 software were used to analyze the data and create forest plots for the results of all included studies. Chi-square (P-value) and I^2 tests were used to assess heterogeneity. When the I^2 test result was less than 50% and $P > 0.1$, this indicated that the heterogeneity was not obvious, the fixed effects model was adopted, and the inverse-variance method was used to analyze the fixed effects model. If the I^2 test result was $> 50\%$ and $P < 0.1$, this indicated obvious heterogeneity, the random effect model was adopted, and the Dersimonian–Laird method was adopted on the basis of the inverse-variance method. The combined effect size and its 95% confidence interval (CI) were calculated after correction factors were introduced to correct the weights in the fixed-effects model [14]. Sensitivity analyses were conducted to check the robustness of the results when the heterogeneity among studies was high. Studies that seriously affected heterogeneity were excluded before the analysis and subsequent analysis of heterogeneity, such as sensitivity analysis or subgroup analysis, were performed. For continuous variables, the standardized mean difference (SMD) and its 95% CI were used as pooled statistics. For dichotomous variables, the hazard ratio (RR) and its 95% CI were used as pooled statistics, and $P < 0.05$ was considered statistically significant.

Detection of Publication Bias

RevMan 5.3 software was used to create funnel plots, and Begg's and Egger's tests were performed in Stata17 software to evaluate the publication bias of the included studies. In the funnel plots, scatter plots were drawn with the effect values as abscissas and accuracy as ordinates. If there was no publication bias in the included studies, the graph had an inverted funnel shape. If the funnel plot was asymmetric or incomplete, publication bias could exist [15]. Since the funnel plot method can only make qualitative determination of the results, and the visual inspection results are random and relatively approximate, we also conducted Egger's weighted linear regression test and Begg's rank correlation test to further evaluate whether the included studies had publication bias. When Begg's test result is $P < 0.05$, it indicates possible publication bias; if $P > 0.05$, it is considered that there is no publication bias. The criteria of Egger's test results were as follows: if $Z > 1.96$, $P < 0.05$, publication bias may exist; if $Z < 1.96$, $P > 0.05$, it is considered that there is no publication bias [16].

RESULTS

Literature Search Results and Quality Evaluation

This meta-analysis initially retrieved 2795 articles, and after reviewing these articles, 2781 studies were excluded, mainly because they were case reports or reviews or did not meet the inclusion criteria. The meta-analysis finally included only 14 studies. The article retrieval process is shown in Fig. 1. These final studies included 3534 patients, including 926 in the pregabalin group, 1256 in the gabapentin group, and 1363 in the placebo control group. Most of the included studies were conducted in the USA. Other details of the included studies are presented in Table 1. The results of the Cochrane Risk of Bias assessment using Revman5.3 software for all 14 included studies are shown in Fig. 2.

Pain Score

Eleven studies provided sufficient data on pain using the Numerical Pain Rating Scale (NRS) or a variant of it that allowed for meta-analysis. The results of the meta-analysis showed that patients taking pregabalin and gabapentin reported significantly less pain compared with the placebo group, and the standardized mean difference (SMD) was −0.78 (95% CI −0.98 to −0.58, $P < 0.05$) in the pregabalin group. Gabapentin group −2.16 (95% CI −3.40 to −0.92, $P < 0.05$), when the two were combined for subgroup analysis, pregabalin

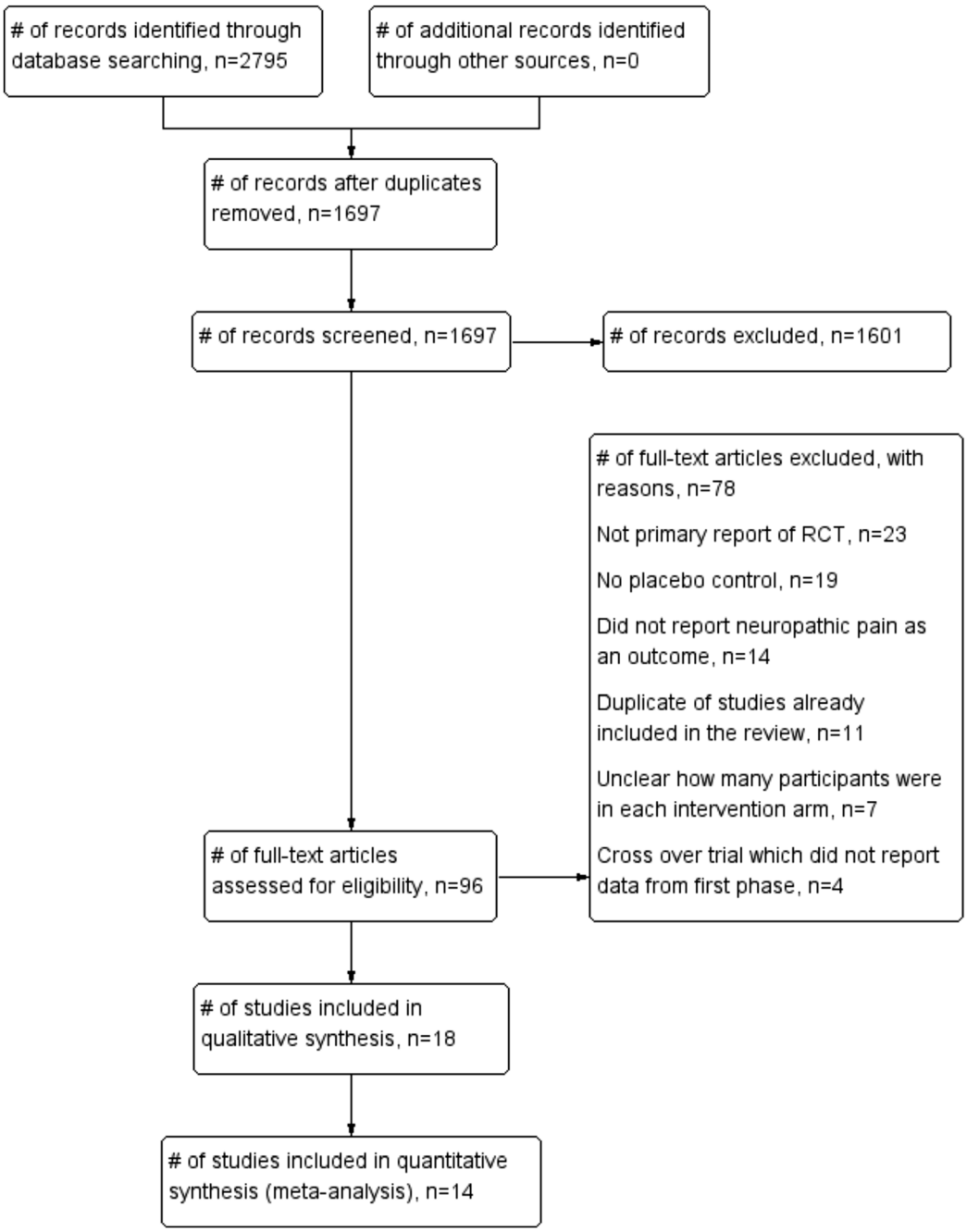

Fig. 1 Flow diagram of the literature screening process

appeared to improve the pain of patients more than gabapentin; this difference was statistically significant −1.65 (95% CI −2.42 to −0.87, $P < 0.05$), as shown in Fig. 3.

Patient Global Impression of Change (PGIC)

The PGIC scale was used in 12 studies to evaluate treatment outcomes. The results of the meta-analysis showed that the PGIC score for

Table 1 Summary of clinical trials included in the meta-analysis

Study	Year	Design	Country	Sample size	Duration	Interventions	Outcome measures
Dworkin et al. [17]	2003	Parallel-group, double-blind, randomized clinical trial	USA	Pregabalin 89, placebo 84	8 weeks	Pregabalin: 300 mg/day, 600 mg/day fixed Placebo: PLA also administered three times daily	Primary: pain score, safety, and adverse events. Secondary: SF-MPQ at baseline, daily sleep interference score, MOS-SS, SF-36, PGIC, CGIC
Huffman et al. [18]	2017	Double-blind, randomized withdrawal, placebo-controlled	USA, Sweden, South Africa, and Czech Republic	Pregabalin 101, placebo 102	6 weeks	Pregabalin: 150–300 mg/day fixed Placebo: matched PLA capsules on the same dosing schedule	Primary: DPN pain on walking (NRS). Secondary: ≥ 30% improvement; ≥ 50% improvement; BPI-SF; daytime total activity counts per day; norfolk QOL-DN; total quality of life score; EQ-5D; mean sleep interference rating score; HADS, safety and adverse events
Krcevski Skvarc and Kamenik [19]	2010	Double-blind, randomized, placebo-controlled	Slovenia	Pregabalin 14; placebo 15	4 weeks	Pregabalin: 150 or 300 mg/day fixed Placebo: PLA also administered twice daily	Primary: assessment of pain severity (11-point Likert scale) Secondary: patients' ratings of the severity of allodynia, hyperalgesia, and burning; sleep interference score; safety and adverse events; SHN; PHN
Liu et al. [20]	2017	Double-blind, randomized, parallel-group	China	Pregabalin 112; placebo 110	8 weeks	Pregabalin: 150 mg/day, 300 mg/day fixed Placebo: PLA also administered twice daily	Primary: average daily pain score Secondary: VAS; SF-MPQ at baseline; ≥ 30% improvement; change from baseline in weekly MPS; sleep interference score (11-point NRS); CGIC; PGIC; MOS-SS; adverse events

Table 1 continued

Study	Year	Design	Country	Sample size	Duration	Interventions	Outcome measures
Sabatowski et al. [21]	2004	Randomized, placebo-controlled	Europe and Australia	Pregabalin 157; placebo 81	8 weeks	Pregabalin: 150 mg/day, 300 mg/day fixed Placebo: Matched PLA capsules on the same dosing schedule	Primary: average daily pain score Secondary: mean sleep interference scores, PGIC, CGIC, SF-36 health survey, Zung Self-Rating Depression Scale, VAS of the SF-MPQ, safety and adverse events
Stacey et al. [22]	2008	Randomized, placebo-controlled	USA, Germany, Italy, Spain, and UK	Pregabalin 179; placebo 90	4 weeks	Pregabalin: 150–600 mg/day, 300 mg/day fixed Placebo: PLA also administered twice daily	Primary: pain reduction; time to onset of meaningful pain relief Secondary: daily sleep interference score; PGIC; VAS of the SF-MPQ; VAS anxiety; VAS allodynia; safety and adverse events
van Seventer et al. [23]	2006	Double-blind, randomized, placebo-controlled	USA, UK, and France	Pregabalin 275; placebo 93	13 weeks	Pregabalin: 150–600 mg/day flexible Placebo: PLA also administered twice daily	Primary: average daily pain score Secondary: daily sleep interference score; MOS-SS; HADS; BPI-SF; PGIC; safety and adverse events
Rice et al. [24]	2001	Double-blind, randomized, placebo-controlled	UK and Ireland	Gabapentin 223; placebo 111	7 weeks	Gabapentin: 1800 mg/day, 2400 mg/day fixed Placebo: PLA also administered three times daily	Primary: average daily pain score Secondary: $\geq$ 30% improvement; $\geq$ 50% improvement; sleep interference score; SF-MPQ; PGIC/CGIC; SF-36; safety and adverse events

Table 1 continued

Study	Year	Design	Country	Sample size	Duration	Interventions	Outcome measures
Irving et al. [25]	2009	Double-blind, randomized, placebo-controlled	USA	Gabapentin 107; placebo 51	4 weeks	Gabapentin: 1800 mg/day (600 + 1200) fixed Placebo: PLA also administered twice daily	Primary: average daily pain score Secondary: ≥ 30% improvement; ≥ 50% improvement; sleep interference score; SF-MPQ; NPS; PGIC/CGIC; safety and adverse events
Backonja et al. [26]	2011	Double-blind, randomized, placebo-controlled	USA	Gabapentin 47; placebo 54	4 weeks	Gabapentin: 1200 mg/day fixed Placebo: PLA also administered twice daily	Primary: average daily pain score Secondary: ≥ 30% improvement; ≥ 50% improvement; sleep interference score; POMS; PGIC; SF-MPQ; safety and adverse events
Rowbotham et al. [27]	1998	Double-blind, randomized, placebo-controlled	USA	Gabapentin 113; placebo 116	8 weeks	Gabapentin: 3600 mg/day fixed Placebo: PLA also administered three times daily	Primary: average daily pain score Secondary: sleep interference score; SF-MPQ; PGIC/CGIC; SF-36; POMS; safety and adverse events
Sang et al. [28]	2013	Double-blind, randomized, placebo-controlled	USA, Russia, and Argentina	Gabapentin 221; Placebo 231	10 weeks	Gabapentin: 1800 mg/day fixed Placebo: PLA also administered once a day	Primary: average daily pain score Secondary: ≥ 50% improvement; PGIC/CGIC; sleep interference score; safety and adverse events

Table 1 continued

Study	Year	Design	Country	Sample size	Duration	Interventions	Outcome measures
Wallace et al. [29]	2010	Double-blind, randomized, placebo-controlled	USA	Gabapentin 269; placebo 131	10 weeks	Gabapentin: 1800 mg/day fixed Placebo: PLA also administered twice daily	Primary: average daily pain score Secondary: ≥ 50% improvement; sleep interference score; SF-MPQ; NPS; BPI; PGIC/CGIC; safety and adverse events
Zhang et al. [30]	2013	Double-blind, randomized, placebo-controlled	USA	Gabapentin 276; placebo 95	14 weeks	Gabapentin: 1200 mg/day, 2400 mg/day, 3600 mg/day fixed Placebo: PLA also administered twice daily	Primary: average daily pain score Secondary: ≥ 30% improvement; ≥ 50% improvement; pain intensity; sleep interference score; NPS; SF-MPQ; BPI; SF-36; dynamic allodynia; POMS-B; PGIC/CGIC; safety and adverse events

CGIC clinical global impression of change, *DPN* diabetic peripheral neuropathy, *HADS* hospital anxiety and depression scale, *BPI-SF* brief pain inventory-short form, *NRS* numerical pain rating scale, *PGIC* patients' global impression of change, *PHN* postherpetic neuralgia, *SF-MPQ* short-form McGill pain questionnaire, *SHN* subacute herpetic neuralgia, *VAS* visual analog scale, *Norfolk QOL-DN* Norfolk quality of life-diabetic neuropathy, *EQ-5D* EuroQol five dimensions questionnaire, *MOS-SS* medical outcomes study sleep scale, *SF-36* 36-item short-form, *POMS* profile of mood states, *NPS* neuropathic pain scale, *BPI* brief pain inventory, *POMS-B* profile of mood states bipolar, *MPS* Machiavellian personality scale

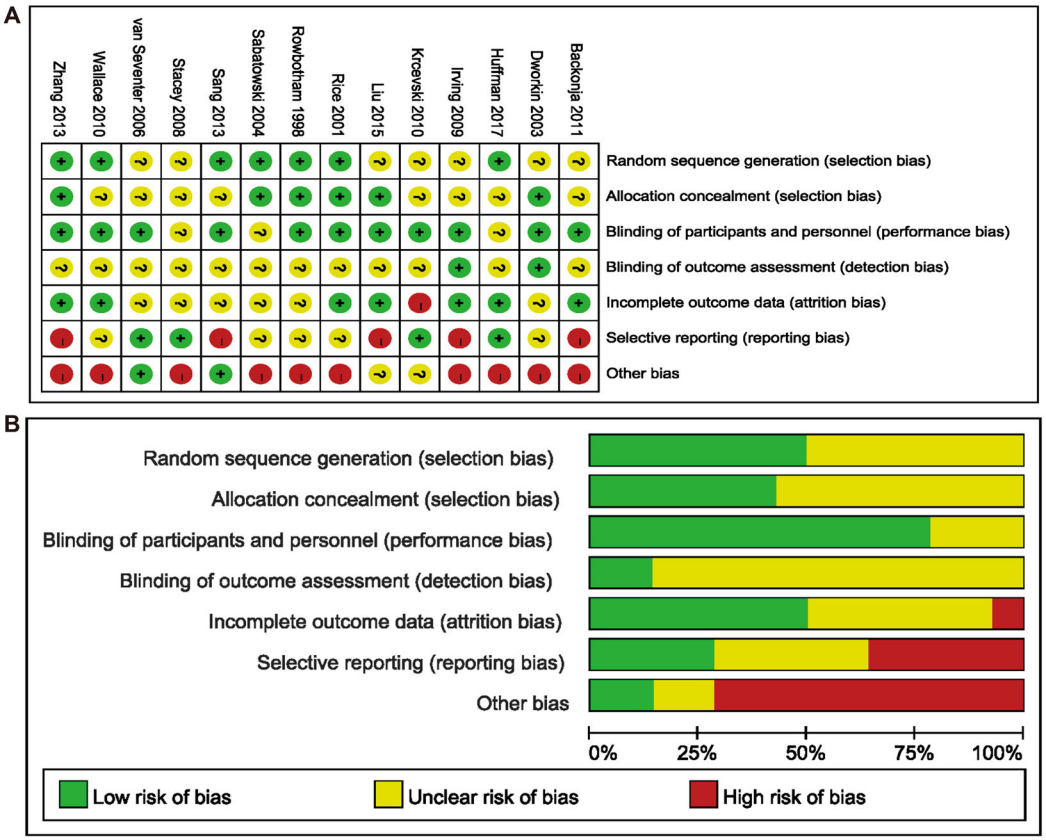

Fig. 2 Quality evaluation of included studies. **A** A plot of the distribution of review authors' judgements across studies for each risk of bias item. **B** A summary table of review authors' judgements for each risk of bias item for each study

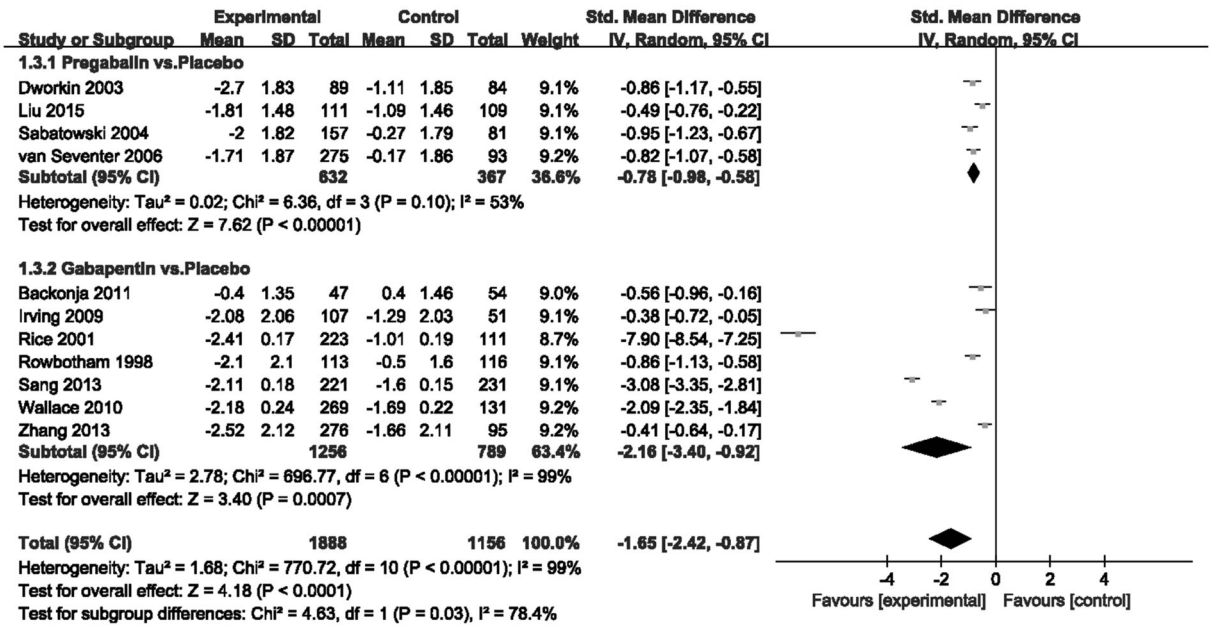

Fig. 3 Forest plot of pain scores in patients with PHN treated with pregabalin and gabapentin

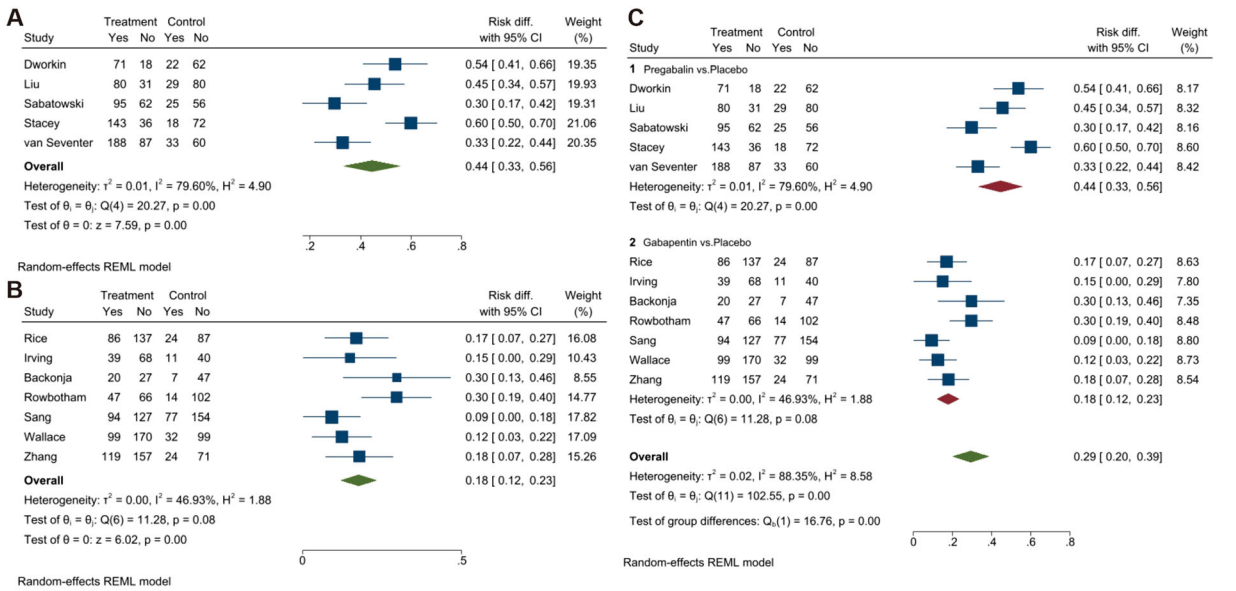

Fig. 4 Forest plot of PGIC scores in patients with PHN treated with pregabalin and gabapentin. **A** Pregabalin versus placebo; **B** gabapentin versus placebo; **C** comparison between the pregabalin and gabapentin groups

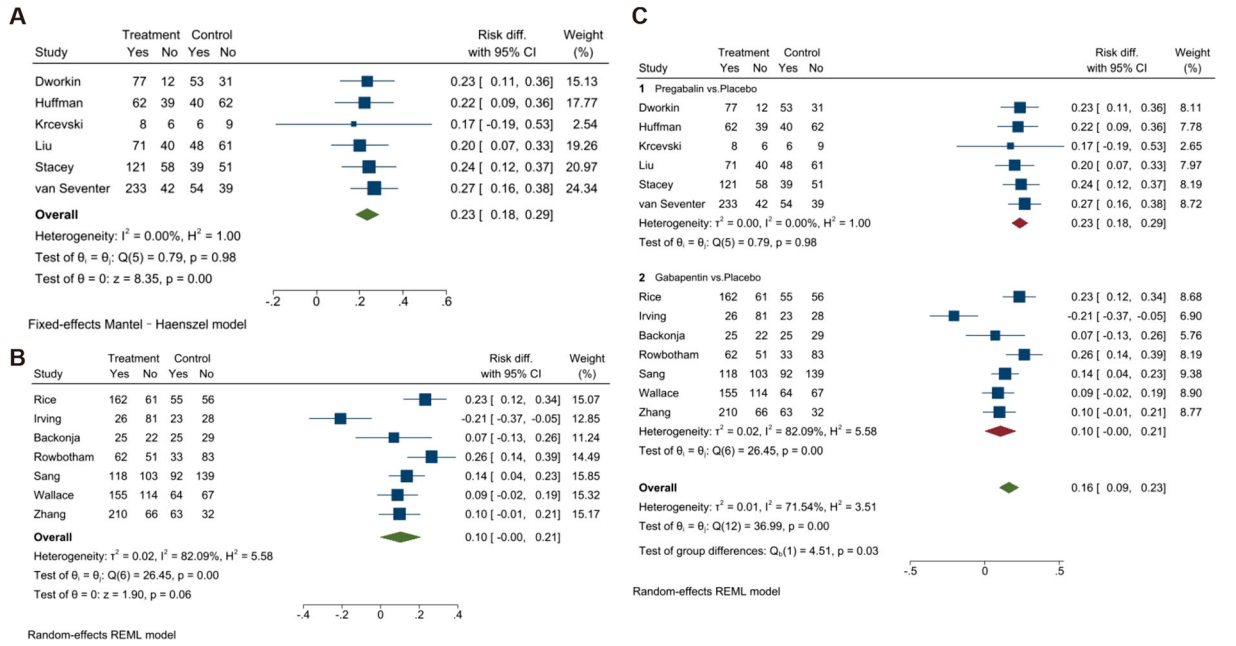

Fig. 5 Forest plot of adverse reactions in patients with PHN treated with pregabalin and gabapentin. **A** Pregabalin versus placebo; **B** gabapentin versus placebo; **C** comparison between the pregabalin and gabapentin groups

pain in patients taking pregabalin and gabapentin was significantly improved compared with the placebo group, with the RR of the pregabalin group being 0.44 (95% CI 0.33–0.56, $P < 0.05$), as shown in Fig. 4A, and that of the gabapentin group being 0.18 (95% CI 0.12–0.23, $P < 0.05$), as shown in Fig. 4B. When the two were combined for the subgroup

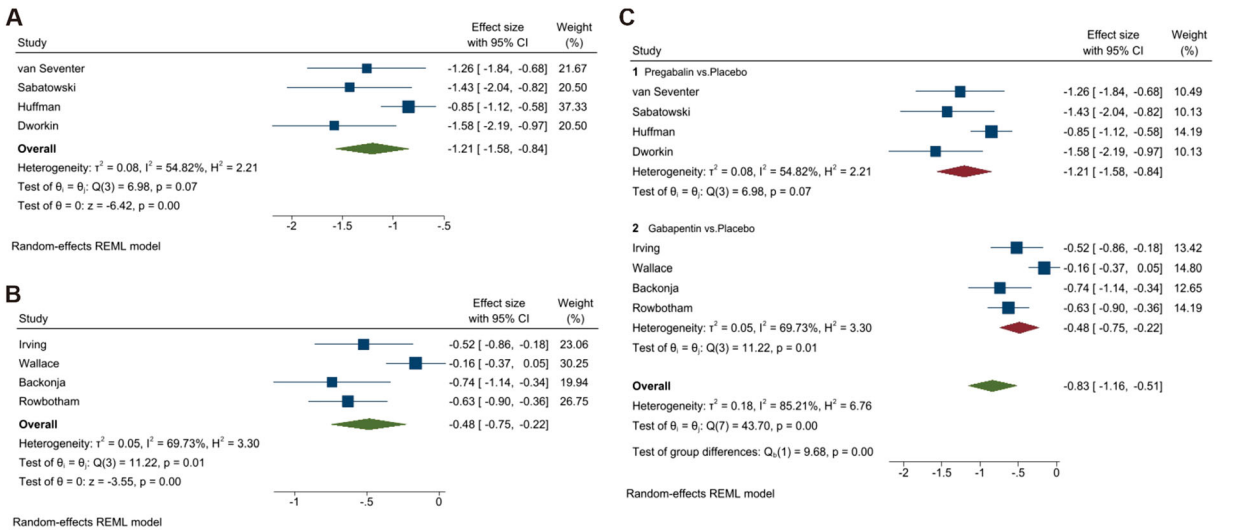

Fig. 6 Forest plot of sleep disturbance scores in patients with PHN treated with pregabalin and gabapentin. **A** Pregabalin versus placebo; **B** gabapentin versus placebo; **C** comparison between pregabalin group and gabapentin group

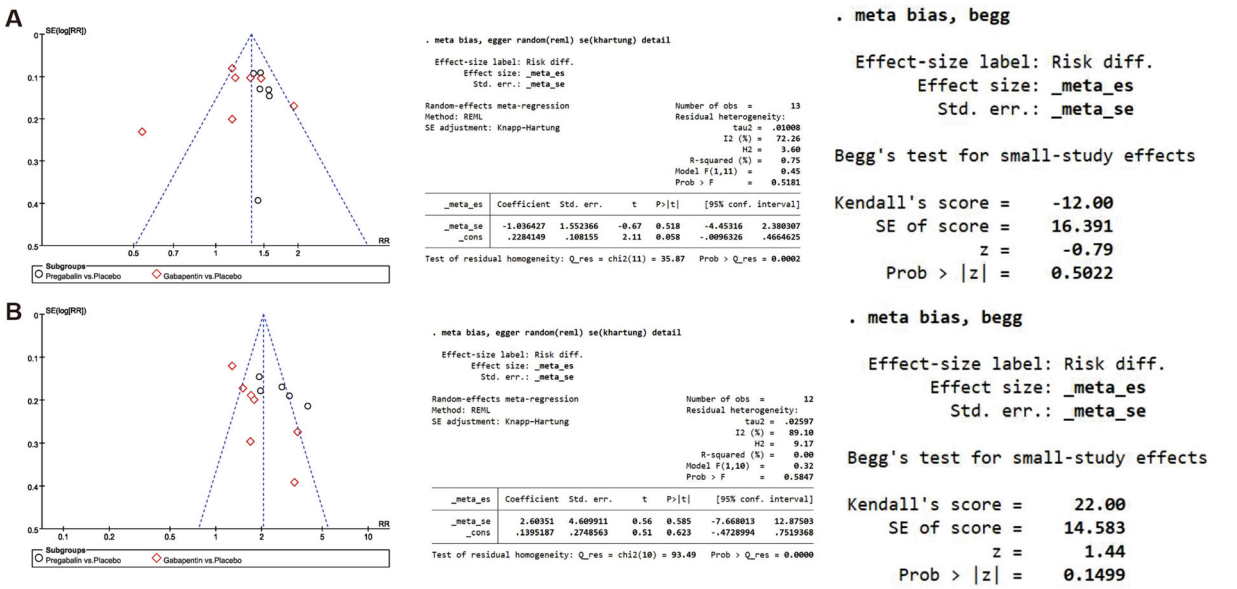

Fig. 7 Funnel plots as well as Begg's and Egger's test results in patients with PHN treated with pregabalin and gabapentin. **A** results of the subgroup analysis of adverse reactions; **B** results of the PGIC score subgroup analysis

analysis, pregabalin improved the PGIC score of patients more than gabapentin, and the difference was statistically significant 0.29 (95% CI 0.20–0.39, $P < 0.05$), as shown in Fig. 4C.

Adverse Reactions

Adverse effects were evaluated in 13 studies. Compared with placebo, patients taking pregabalin had a significantly increased risk of adverse events such as weight gain, drowsiness, dizziness, peripheral edema, fatigue, visual

impairment, ataxia, non-peripheral edema, and vertigo. The RR in the pregabalin group was 0.23 (95% CI 0.18–0.29, $P < 0.05$), as shown in Fig. 5A. However, compared with placebo, gabapentin did not significantly increase the incidence of these adverse events, with a RR of 0.10 (95% CI 0.00–0.21, $P = 0.06$). As shown in Fig. 5B, when the two were combined for subgroup analysis, the incidence of adverse events in the gabapentin group was lower than that in the pregabalin group. The difference was statistically significant at 0.16 (95% CI 0.09–0.23, $P < 0.05$), as shown in Fig. 5C.

Sleep Disturbance Score

Eight studies measured sleep disturbance scores. RR values and 95% confidence intervals were used as the pooled data in the meta-analysis, and the results showed that compared with the placebo group, the sleep disturbance score of patients taking pregabalin and gabapentin was decreased: −1.21 (95% CI −1.58 to −0.84, $P < 0.05$) in the pregabalin group, as shown in Fig. 6A, and −0.48 (95% CI −0.75 to −0.22, $P < 0.05$) in the gabapentin group, as shown in Fig. 6B. When the two were combined for subgroup analysis, the score for sleep disturbance in the pregabalin group was lower than that in the gabapentin group, and the difference was statistically significant at −0.83 (95% CI −1.16 to −0.51, $P < 0.05$), as shown in Fig. 6C.

Detection of Publication Bias

We tested for publication bias in 13 studies that included the adverse effects subgroup (Fig. 7A) and 12 studies that included the PGIC subgroup (Fig. 7B). The funnel plot results showed that the left and right sides were essentially symmetric, and Begg's test results confirmed $P > 0.05$, indicating that there was no publication bias. Egger's test results revealed a Z score of < 1.96 and $P > 0.05$, also indicating that there was no publication bias in the included studies.

DISCUSSION

It has been reported that the global incidence of herpes zoster in the general population is 3–5‰ [31], which is about 9–34%, and PHN occurs in more than 50% of patients with herpes zoster [32]. The clinical manifestations of PHN include sleep and emotional disorders in addition to pain. Data indicate that 40% of PHN patients have insomnia, anxiety, depression, inattention, and other manifestations, which have an immeasurable impact on the quality of life of patients [33]. Therefore, the goal of PHN treatment is to effectively control pain as early as possible, relieve accompanying sleep and emotional disturbances, and thus improve the quality of life of patients. At present, there are many treatment methods for PHN, and the rational selection of drugs is the basis for the treatment of patients with PHN. Compared with other treatment methods such as interventional therapy, drug therapy is relatively simple, safe, and easy to manage, with higher patient compliance, better treatment effects, and is more conducive to the remission of the disease [34].

Pregabalin and gabapentin, both derivatives of the inhibitory neurotransmitter GABA, are also the only FDA-approved first-line oral drugs for the treatment of PHN [35, 36]. These drugs bind to presynaptic angular voltage-gated calcium channels to reduce the release of excitatory neurotransmitters such as glutamate and substance P [37]. However, no head-to-head comparison study has been performed between pregabalin and gabapentin for the treatment of PHN. Ling et al. [38] analyzed the efficacy and safety of 11 drugs in the treatment of neuropathic pain (NP) after spinal cord injury (SCI) in adults. The results showed that gabapentin, botulinum toxin type A, and pregabalin were the most effective in alleviating psychiatric or sleep-related symptoms, while lamotrigine and gabapentin caused fewer side effects and were more effective in alleviating mental or sleep-related symptoms caused by SCI-related NP. Owing to poor safety and/or efficacy, the use of tramadol, levetiracetam, carbamazepine, or cannabinoids is not recommended. Markman

et al. [39] analyzed and compared the treatment response of pregabalin in patients with NP who had previously received gabapentin with that of patients who had not received gabapentin. Results showed that all doses of pregabalin resulted in a significant reduction in mean pain scores compared with placebo; however, the degree of pain reduction mediated by pregabalin did not differ significantly between those who had not previously used gabapentin and those who had. Overall, these findings provide evidence that pregabalin has some benefits in patients with NP who do not respond well to gabapentin therapy. Although the mechanism of action of the same class of drugs is similar, the failure of one drug in the same class of drugs may be considered justification for treatment with another drug. Chen et al. [35] studied the efficacy and safety of pregabalin and gabapentin in patients with neuropathic pain caused by SCI to determine which treatment is most suitable for such patients. Through a comprehensive analysis and exploration of the eight included RCTs, it was concluded that according to the average pain intensity after treatment, the efficacy of different study drugs was, in decreasing order of efficacy: pregabalin, gabapentin, amitriptyline, carbamazepine, and placebo. According to the proportion of patients who discontinued treatment due to adverse effects, the descending order was as follows: pregabalin, amitriptyline, carbamazepine, gabapentin, and placebo. Furthermore, the drug with the highest overall incidence of treatment-related adverse effects was pregabalin, followed by gabapentin and placebo. It was concluded that pregabalin was the most effective for pain relief in patients with SCI-related neuropathic pain, while gabapentin performed better in terms of safety associated with the drug therapy. Through comparison of the effects of the two drugs in patients with other types of NP, it can be seen that the effect of pregabalin is superior to gabapentin, and PHN is a common neuropathic pain. Therefore, it is speculated that pregabalin may be better than gabapentin in terms of the treatment effects in patients with PHN.

The results of this meta-analysis extracted from existing data showed that both pregabalin and gabapentin have definite therapeutic effects on PHN. In general, pregabalin has more advantages than gabapentin in improving patients' pain and sleep, which corroborates the findings of Cory [40] and Maria et al. [41]. The finding that pregabalin is more effective than gabapentin in relieving pain in PHN may be because although both pregabalin and gabapentin can reduce Ca^{2+} influx and excitatory transmitter release by inhibiting α2δ protein, a subunit of voltage-dependent Ca^{2+} channels in the central nervous system, the binding efficiency of pregabalin to the α2δ subunit is more than six times that of gabapentin [42]. This results in less excitatory transmitter release, causing more of the abnormally fired neurons to return to a normal state and allowing them to control pain more effectively. In addition, pregabalin is a second-generation antiepileptic drug, which retains the biological activity of gabapentin and also improves on its pharmacokinetic characteristics. The absorption and distribution rate of pregabalin is constant within the dose range, and the interindividual differences are small. The efficacy can be predicted when the dosage is adjusted, and the bioavailability is not related to the dose and is above 90%. Gabapentin has nonlinear pharmacokinetic characteristics, and is only absorbed in the small intestine with a relatively slow absorption rate. The maximum blood concentration is generally reached about 3 h after taking the drug, and the absorption is nonlinearly related to the dose. The pharmacokinetics after taking the drug cannot be predicted, and the blood concentration cannot increase with an increase in the drug dose. The absorption of gabapentin is limited by the carrier on the transporter. The bioavailability is only 30–60%, and the bioavailability decreases with the increase in drug dose [43]. These results are similar to those of the studies included in this meta-analysis. PHN is a common neuropathic pain in clinical practice. Because of its diverse nature, severe degree, and long duration of pain, it is often secondary to insomnia, depression, anxiety, and other psychiatric symptoms. Some patients even use large doses of nonsteroidal analgesics for a long time, which seriously affects their quality of life. So the most

urgent need for such patients is relieving pain rapidly. Our results support the use of pregabalin compared with gabapentin. Although both regimens are clinically acceptable, studies have found that gabapentin has a stronger dose-dependent effect and an inverse association with quality of life, meaning that patients are less likely to use the multiple dose of drugs than a single dose. At the same time, pregabalin improved PHN-related somnipathy for only 1.6 days, compared with gabapentin for an average of about 7 days [44]. Therefore, the use of pregabalin can quickly meet patients' demands, improve patients' clinical satisfaction and trust in doctors, and also improve patients' compliance with subsequent treatment.

Drugs are a double-edged sword. While treating diseases, drugs may also affect the normal physiological function of the body, and some may even cause serious adverse drug reactions. This can lead to the forced withdrawal of drugs and even life-threatening problems, so we need to closely monitor and explain the possible adverse reactions to patients in clinical practice. Clinical studies have found that the common adverse reactions caused by pregabalin treatment are dry mouth, drowsiness, dizziness, edema, and peripheral edema [45]. Treatment with pregabalin significantly increases the incidence of these adverse effects compared with placebo. Common side effects of gabapentin and placebo include nausea, dizziness, vomiting, edema, and pruritus [46]. Gabapentin did not significantly increase the incidence of these adverse effects compared with placebo. However, compared with gabapentin, pregabalin tends to increase the incidence of adverse reactions such as dizziness, drowsiness, and edema [47, 48]. This is consistent with the analysis results of this paper. Although pregabalin is an effective means to alleviate PHN, its increased incidence of adverse reactions may reduce both patient compliance and the effectiveness of treatment. Compared with pregabalin, the efficacy of gabapentin in relieving PHN is slightly lower, but the adverse reactions are significantly fewer. Therefore, clinicians should also consider the impact of adverse effects of such drugs on patients while pursuing curative effect. For example, if a student has adverse reactions such as drowsiness and inattention after taking medicine, which affect his academic performance, this may lead to drug intolerance, and then doctor needs to adjust the dosage or treatment plan. Elderly patients that have obvious dizziness, ataxia and other adverse reactions after taking medicine may lead to an increased risk of falls and fractures, which requires doctors to choose a safer treatment plan. About patients with diabetes mellitus taking pregabalin, they would readjust the hypoglycemic regimen owing to weight gain. At this time, doctors may consider whether gabapentin is more suitable. In clinical work, according to the specific needs of patients, we may choose different drugs, different doses, and even different speeds of dosage. Then, curative effect and adverse drug reactions are the two aspects which doctors need to carefully balance and find the most suitable plan, according to the specifics of each individual patients, to maximize the benefit to patients, and take into account the patients' condition to minimize drug adverse reaction as far as possible. In conclusion, our study may provide some basis for drug selection for PHN.

There are some limitations to this study. Different studies used different cutoffs for evaluating the efficacy and adverse events for each intervention. Although the results of this study suggest that pregabalin has a better effect on PHN than gabapentin, the trials included in this analysis have insufficient dose limitations and observations, which cannot fully reflect the therapeutic effects of the drugs. Therefore, studies to improve these limitations are necessary to obtain more accurate and specific conclusions that can be used to guide clinical treatment.

CONCLUSION

This study shows that pregabalin is the most effective treatment for pain relief in patients with PHN, and that gabapentin has better safety characteristics associated with medical therapy. In addition, it may be worth noting that a well-designed head-to-head randomized controlled trial would resolve the issue of relative efficacy

and adverse effects. However, a possible ethical issue is that pharmaceutical companies may not be motivated to conduct or support such a trial. In the future, more multicenter, double-blind clinical randomized controlled trials with larger sample sizes need to be carried out to support the results of this study.

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