Review Article
Efficacy of pregabalin in the treatment of postherpetic neuralgia: a meta-analysis of randomized controlled trials

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Abstract: We aimed to summarize the efficacy of pregabalin in the treatment of postherpetic neuralgia (PHN) in pain reduction, sleep improvement and overall improvement of the patients in published studies. A literature search for randomized clinical trials (RCTs) investigating the efficacy of pregabalin for PHN was carried out in PubMed, EMBASE and the Cochrane database. For each trial met the inclusion criteria, study design, treatment comparators, dosage and duration, patient demographics and efficacy outcomes were extracted. The primary end point was treatment efficacy outcomes and the secondary end points included endpoint mean sleep interference score, percentage of 30% or 50% pain responders, and Patient Global Impression of Change (PGIC). A total of 5 RCTs with 9 different dosing groups involving 811 patients in the pregabalin group and 814 patients in the control group were included. The pooled SMD of mean pain score reductions was -0.651 (95% CI, -0.866, -0.435, P<0.001) in the pregabalin group compared with the placebo group. Higher dosing regimens resulted in greater reduction in pain score within a certain study but were not consistent among studies. Higher rate of patients with more than 30% and 50% pain score reduction in the pregabalin group vs. the placebo group. Significant benefits in mean sleep interference score and PGIC were observed in the pregabalin group vs. the control group. Higher dosing regimens yielded more improvement within each study but were not consistent among different studies. Pregabalin is effective in reducing the mean pain score and sleep interference score, increasing the percentage of 30% and 50% pain responders in comparison with placebo. Future studies are warranted to elucidate the effect of different dosing regimens on the treatment outcome.

Keywords: Pregabalin, postherpetic neuralgia, pain reduction, meta-analysis, randomized controlled trials

Introduction

Postherpetic neuralgia (PHN) is the most frequent chronic complication of herpes zoster due to symptomatic reactivation of latent Varicella zoster virus [1, 2]. PHN results in pains and poor quality of life as well as health care costs. The definition of PHN is usually as pain persisting for at least 3 months after crusting of the acute zoster rash. It is seen in 7% to 27% of patients and as many as 50% of patients aged 70 years or older will have persistent pain 6 months after healing of the acute rash [3]. Current treatment options for PHN included the use of topical therapy (lidocaine or capsaicin) and systemic therapy which included tricyclic antidepressants, serotonin-norepinephrine reu-

ptake inhibitors, and anticonvulsants [4]. However, the results of current treatment options were still to be improved as fewer than half of the patients in clinical trials have 50% or greater reductions in pain [4].

Pregabalin is one of the antiepileptic medications approved by Food and Drug Administration of the United States (FDA) for the treatment of neuropathic pain. Pregabalin binds potently to the α2δ subunit protein of voltage-gated calcium channels in central nervous system (CNS) tissues [5]. The binding would lead to a reduction of calcium influx, modulating the release of several excitatory neuro-transmitters from presynaptic neurons [6]. Thus, it may lead to subsequent analgesia [7]. Currently, there are sev-

eral clinical trials that focused on the effectiveness of pregabalin for PHN, with an overall improvement in reduction of 24 h mean pain score. Nevertheless, it is still not an up-to-date meta-analysis that could reveal the exact effect of pregabalin or the proper dosing (150 mg/day or 300 mg/day), the best way of dosing (flexible or fixed) and proper treatment planning. This study intended to pool the results of all published randomized controlled trials on the efficacy of pregabalin in pain reduction, sleep improvements and overall improvements of the patients.

Methods

Publication search

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A literature search for randomized clinical trials (RCTs) was carried out in following databases: PubMed, EMBASE and the Cochrane database with no restrictions of publication year. The search strategy included the following key words: "postherpetic neuralgia" OR "post-herpetic neuralgia", AND "pregabalin". A manual search of the reference lists from selected articles was also carried out to further increase the number of publications with relevant data. Only articles in English were included.

Study selection

Titles and abstracts of citations identified from the searches were reviewed by two reviewers independently for potential inclusion in the study. Discrepancies were resolved by consensus through discussion between the two reviewers. Results published only in abstract form were not considered. Inclusion criteria were as following: (a) pain had to have been present for more than 3 months after the healing of the acute herpes zoster skin rash, (b) average pain scores of 4 or more on pain scale on the week before commencing study medication and (c) patients were grouped as the treatment of oral pregabalin vs. the placebo. Trials were excluded if they (a) included other antidepressants, or anticonvulsants or other treatments, (b) were clinical trials that involved other similar conditions such as diabetic neuropathy; (c) were with a study period shorter than 4 weeks.

Data extraction and quality assessment

For each trial selected, study design, treatment comparators, dosage and duration, patient demographics and efficacy outcomes were extracted. The primary end point was treatment efficacy outcome: 11-point numeric rating scale (NRS) or 100-point visual analogue scale (VAS) measurements of mean 24 h pain severity at end point. The secondary end points included: endpoint mean sleep interference score, percentage of 30% or 50% pain responders, Patient Global Impression of Change (PGIC). Proportions of patients achieving pain reductions of ≥30% or ≥50% (30% responders and 50% responders) using either the NRS or VAS were considered of clinical relevance. The JADAD scale for reporting randomized controlled trials was used to assess the quality of each study, on a range of 0 (poor) to 5 (best) [8].

Statistical analysis

Heterogeneity of effect sizes across studies was assessed by the Cochrane Q statistic ($P > 0.05$ were considered relative homogeneity) and the I^2 statistic. I^2 is equivalent to the quantity of Cochran's Q minus its degrees of freedom divided by Cochran's Q, or $I^2 = (Q\text{-}df)/Q$. I^2 values of <40% was taken as heterogeneity might not be important and value was taken as > 75% considerable heterogeneity [2]. The fixed-effect model was applied for the analysis without significant heterogeneity. In the event of significant heterogeneity, we used a random-effect meta-analysis as an overall summary if appropriate. For dichotomous data, we summarized results as risk ratios (RRs) with 95% confidence intervals (CIs), and for continuous data we used the mean difference if outcomes were measured in the same way between trials. We used the standard mean differences (SMD) to combine trials that measured the same outcome but used different methods. When not reported, missing SD was estimated on the basis of the reported standard error (SE). Potential publication bias analysis was not performed because the number of trials was less than 10 (the recommended minimum number) [9]. All statistical tests were performed with STATA (version 11.0; Stata Corporation, College Station, TX). A P-value of <0.05 was considered statistically significant.

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

Trials, year	Design	Inclusion criteria	Intervention and control (Cases)	Duration and dosing regimen	Pain assess-ment	Quality assess-ment
Dworkin RH, 2003	Multicenter, random-ized, parallel-group, double-blind, placebo-controlled	At least 40 mm on the 100 mm VAS of the SF-MPQ at base-line and randomiza-tion visits and they also completed at least four daily pain diaries and had a minimum mean daily pain rating of 4 on an 11-point numerical pain rating scale during the base-line week preceding randomization.	300 or 600 mg/day (n = 89), placebo (n = 84)	8 weeks, TID (including 1-week dosage escalation)	VS.A	5
Sabatowski R, 2004	Multicenter, random-ized, double-blind, placebo-controlled	Pain present for more than 6 months after healing of the HZ rash; Completed at least four daily pain diaries during the 7 day baseline phase, with an average daily pain score 4 or over. Patients were also required to score 40 or over 40 mm on the 100 mm VAS of the SFMPQ at the baseline and randomization visits.	150 mg/day (n = 81), 300 mg/day (n = 76), placebo (n = 81)	8 weeks, TID (including 1-week dosage escalation)	NRS	5
Van Seventer R, 2006	Multicenter, random-ized, double-blind, placebo-controlled, parallel-group	Pain for > -3 months after healing of HZ lesions, with a VAS pain score > or = 40 mm at baseline and at randomization, and had at least 4 daily pain diary entries with a mean daily pain score > or = 4 prior to randomization.	150 mg/day (n = 87), 300 mg/day (n = 98), 600 mg/day (n = 90), placebo (n = 93)	13 weeks, BID (including 1-week dosage escalation)	NRS	5
Stacy BR, 2008	Randomized, double-blind, placebo-controlled, parallel-group	Age > 18 years, with neuropathic pain more than 6 months after healing of the herpes zoster rash, average daily pain score of 4 or greater (on a 0-10 NRS), and 40-mm score or greater on the VAS SF-MPQ.	Fixed dose 300 mg/day (n = 88), flexible dose 150-600 mg/day (n = 91), placebo (n = 90)	4 weeks, BID (with one additional trial-medication tapering phase)	VAS	5
Liu Q, 2015	Multicenter, random-ized, double-blind, placebo-controlled	Age > 18 years, diagnosed with PHN, with a visual analog scale pain score of > or = 40 mm on the 100 mm VAS of the SF-MPQ at screening and randomization. Completed at least 5 daily pain diary entries with an average daily pain score ≥4 over the 7 days prior to randomization.	300 mg/day (n = 111), placebo (n = 109)	8 weeks, TID (including 1-week dosage escalation)	VAS	5

VAS: visual analog scale; SF-MPQ: short-form-McGill pain questionnaire; NRS: numeric rating scale.

Table 2. Main results of involved studies

Trials	Pregabalin	Placebo	Reduction in mean pain score, SMD (95% CI), P	Endpoint sleep interference score, SMD (95% CI), P	30% pain responders	50% pain responders	PGIC (much/ very much improved)	PGIC (at least minimal improved)
Dworkin RH, 2003 150/300 mg	89	84	-1.69 (-2.33, -1.05), 0.0001	-1.58 (-2.19, -0.97), 0.0001	63% vs. 25%	50% vs. 20%	NA	84% vs. 26%
Sabatowski R, 2004 150 mg	81	81	-1.20 (-1.81, -0.58), 0.0002	-1.11 (-1.71, -0.51), 0.0003	37% vs. 19%	25% vs. 10%	31% vs. 14%	54% vs. 35%
Sabatowski R, 2004 300 mg	76	81	-1.57 (-2.20, -0.95), 0.0001	-1.43 (-2.04, -0.82), 0.0001	50% vs. 19%	28% vs. 10%	38% vs. 14%	58% vs. 35%
van Seventer R, 2006 150 mg	87	93	-0.88 (-1.53, -0.23), 0.0077	-1.03 (-1.62, -0.44), 0.0007	39.1% vs. 17.2%	26.4% vs. 7.5%	23% vs. 16%	52% vs. 35%
van Seventer R, 2006 300 mg	98	93	-1.07 (-1.70, -0.45), 0.0016	-1.26 (-1.84, -0.68), 0.0002	40.8% 17.2%	26.5% vs. 7.5%	28% vs. 16%	48% vs. 35%
van Seventer R, 2006 600 mg	90	93	-1.79 (-2.43, -1.15), 0.0003	-1.93 (-2.52, -1.34), 0.0002	52.3% vs. 17.2%	37.5% vs. 7.5%	36% vs. 16%	67% vs. 35%
Stacy BR, 2008 flexible-does 150-600 mg	88	90	NA	NA	70% vs. 31%	46.7% vs. 18.4%	NA	NA
Stacy BR, 2008 fixed-does 300 mg	91	90	NA	NA	58% vs. 31%	39.8% vs. 18.4%	NA	NA
Liu Q, 2015 300 mg	111	109	-0.71 (-1.08, -0.34), 0.0002	-0.54 (-0.93, -0.14), 0.0079	52.6% vs. 30.6%	NA	41% vs. 18%	NA

SMD: standard mean differences; 95% CI: 95% confidence interval.
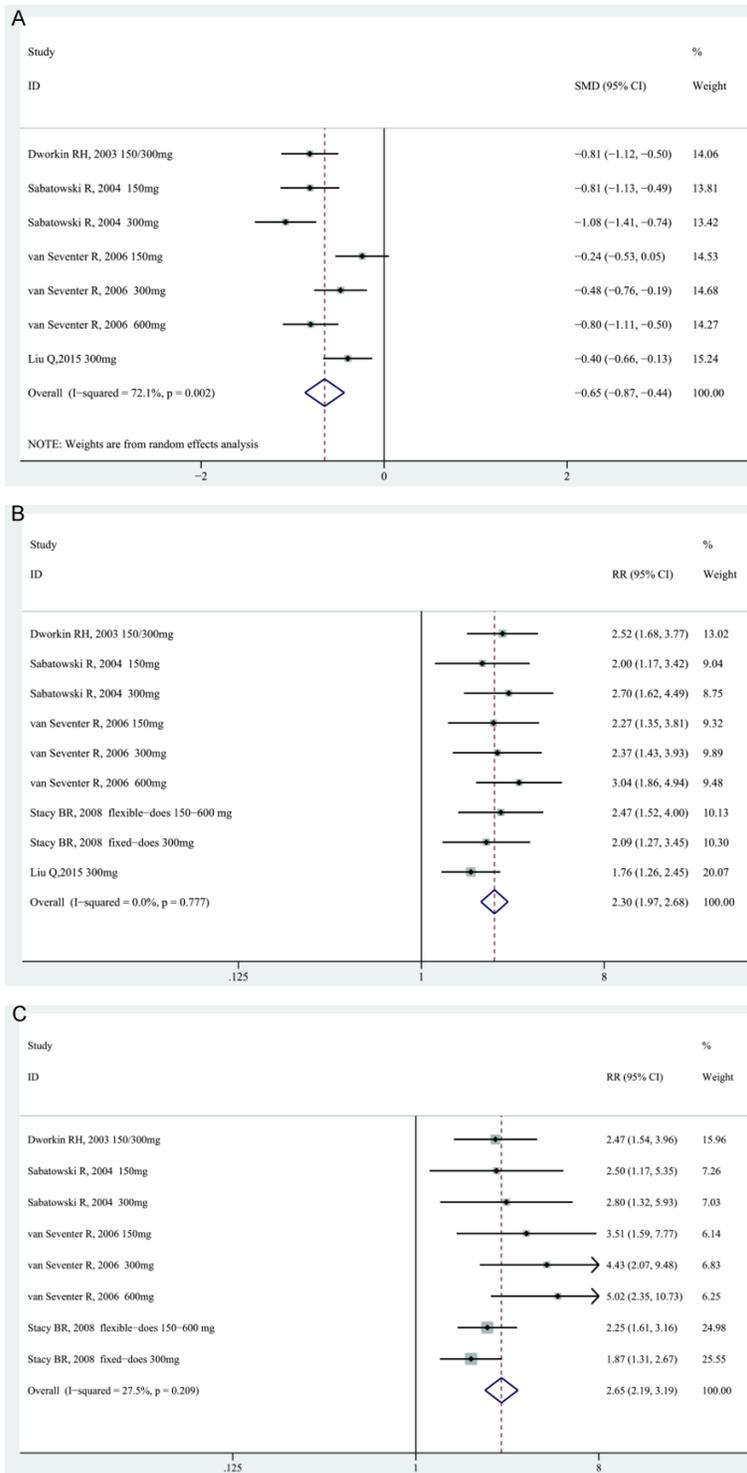
Figure 1. The pooled results of involved studies in (A) reduction in pain score; (B) 30% pain responder; (C) 50% pain responder.

Results

Study characteristics

After the literature search, review articles, case and series studies were excluded. A total of

164 articles were retrieved. Reviewing the full-text articles was performed in 31 articles. Finally, we identified a total of 5 RCTs with 9 different dosing groups [10-14] involving 811 patients in the pregabalin group and 814 patients in the control group (**Table 1**). Studies focused on both diabetic neuropathy and PHN patients were excluded because of failure in extracting data for PHN alone [15-18]. Following results of these study was pooled: reduction in endpoint mean pain score (4 trials with 7 groups); endpoint mean sleep interference score (3 trials with 6 groups); percentage of 30% pain responders (5 trials with 9 groups) or 50% pain responders (4 trials with 8 groups), PGIC score of much improved or very much improved (3 trials with 6 groups); PGIC score of at least minimally improved (3 trials with 6 groups).

Reductions in end point mean pain score

There were four studies that reported the reductions in endpoint mean pain score (**Table 2**; **Figure 1A**). The pooled SMD of mean pain score reductions was -0.651 (95% CI, -0.866, -0.435, P<0.001) in the pregabalin group compared with the placebo group calculated with the random-effect model with relatively high heterogeneity (I^2 = 72.1%). Although all of these studies indicated an advantage of pain score reductions in the pregabalin group compared with the placebo group, there was one study showed that the advantage in pain score reduction was not statistically significant (SMD = -0.240, 95% CI, -0.533, -0.050, P = 0.054). It was observed that higher dosing regimen would result in greater reduction in pain score within a
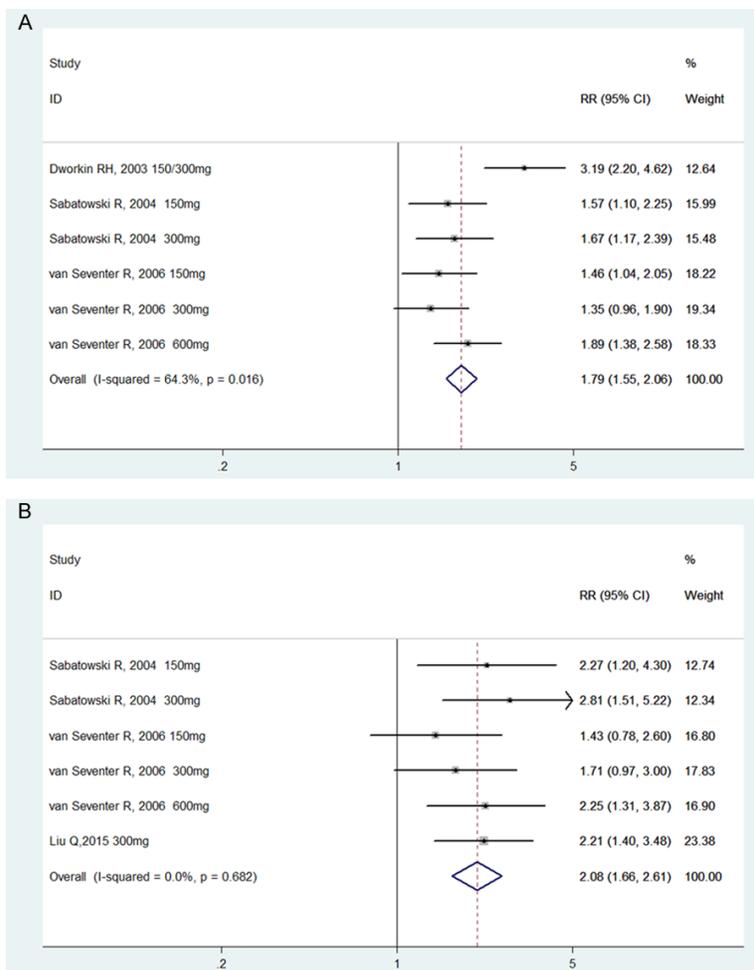
Figure 2. The pooled results of involved studies in (A) at least minimal improvement and (B) much improvement or very much improvement in Patient Global Impression of Change score.

There was no heterogeneity (I^2 = 0%, P = 0.777) across the included trials. Except for one study using 600 dosing regimen [12] showed an RR over 3, all comparisons yield advantages of pregabalin vs. placebo with RRs ranged from 1.76 to 2.52.

The percentage of patients experienced more than 50% pain score reduction ranged from 25% in the study group of 150 mg pregabalin in the study in 2004 [11] to 50% in the study group in 2003 [10]. The pooled results showed that pregabalin had a significant improvement in 50% reduction in pain intensity (RR = 2.65; 95% CI 2.19, 3.19; P<0.001) in the fixed-effect model (I^2 = 27.5%, P = 0.209) (**Figure 1C**). There was only one study showed that more than half of these patients experienced more than 50% reduction in pain score and the treatment response of pregabalin was still not of satisfactory. Higher dosing regimens showed higher RR within each study but not among different studies.

certain study [11, 12], but is not consistent between studies. For instance, the 600 mg regimen was more effective than the 300 mg regimen and the 150 mg regimen within one study [12], however, the 600 mg regimen did not result in greater pain score reduction compared with the 150 mg and 300 mg regimen in another study [11].

The percentage of 30% and 50% pain responders

All 5 trials in this meta-analysis reported the portion of patients with 30% pain score reduction. Higher percentage of patients experienced more than 30% reduction in pain score in the pregabalin group vs. the placebo group with pooled RR = 2.30 (95% CI, 1.97, 2.68; P<0.001) in the fixed-effect model (**Figure 1B**).

Improvement in PGIC

A total of 4 studies evaluated the improvement in PGIC. As shown in **Figure 2A**, the pregabalin group yielded higher rate of patient with at least minimal improvement of PGIC (RR = 1.79, 95% CI, 1.55, 2.06, P<0.001). There was relatively high heterogeneity (I^2 = 64.3%, P = 0.016) across the included trials and thus the random-effect model was applied. There was not substantial difference among different dosing regimens. There were no significant heterogeneity between studies in the result of much improvement or very much improvement (I^2 = 0.0%, P = 0.682). The pooled results based on fixed-effect model showed that the pregabalin groups were associated with a 2.08-fold risk of experiencing much or very much improvement (95% CI, 1.66, 2.61, P<0.001) (**Figure 2B**).
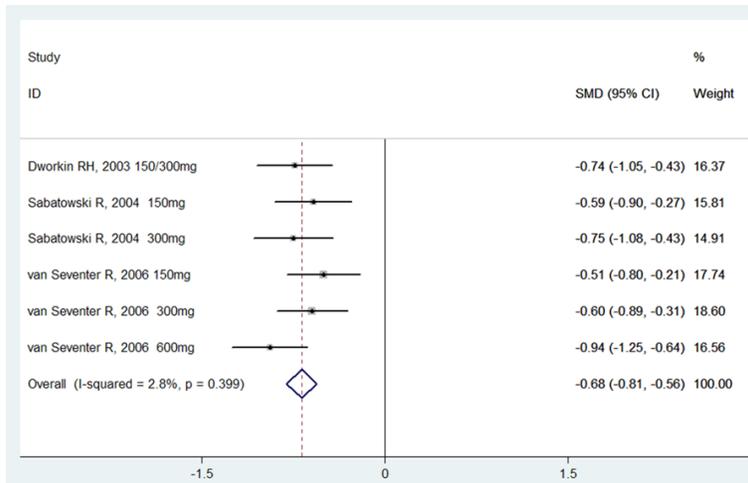
Figure 3. The pooled results of involved studies in endpoint mean sleep interference score.

Endpoint mean sleep interference score

Three studies with 6 different dosing-regimen groups were involved in the evaluation of endpoint mean sleep interference score. The pooled results showed a significant benefit in the pregabalin group with a mean sleep interference score (SMD = -0.68, 95% CI, -0.81, 0.56, P<0.001) (**Figure 3**). The effect of 150 mg dosing regimen and the 300 mg dosing regimen showed similar effects in two studies [11, 12], while the 600 mg dosing regimen resulted greater reduction compared with the 300 mg and 150 mg dosing regimen [12].

Subgroup analyses and sensitivity analyses

We performed subgroup analysis based on the differences in dosing regimen, administration methods and duration of treatment for the endpoint mean pain score and the percentage of patients with 30% or 50% reduction in endpoint pain score.

Patients receiving 150 mg regimen had an advantage over the placebo with a reduction of 0.52 points in endpoint mean pain score, but the differences was not significant (P = 0.068). Patients receiving 300 mg had an advantage in mean pain score with a reduction of 0.76 points compared with the placebo group (P<0.001) (**Table 3**). Both analyses were based on random-effect model. The other two subgroup analyses indicated similar extent of benefit in endpoint mean pain score reduction in the pre-

gabalin group compared with the control group with SMD ranging from -0.76 to -0.50.

For the results regarding the percentage of 50% pain responders, all subgroups indicated RRs of 2.14 to 2.44 in the pregabalin group vs. the placebo group. The RR for the percentage of 30% pain responders ranged from 2.55 to 2.96 in most subgroups; however, the RR was as high as 4.33 in the study with the treatment duration of 13 weeks by pooling the results from the study by van Seventer R [19], indicating that the prolonged regimen might lead to higher percentage of 30% pain responders but not 50% pain responders (**Table 3**).

Discussion

This meta-analysis confirmed that pregabalin was effective for the treatment of PHN with a significant improvement in 50% and 30% pain responders, sleep interference scores and PGIC compared to placebo. Pregabalin was associated with an advantage of endpoint mean pain score reduction compared with the placebo in the random-effect model (P = 0.002) although there were substantial heterogeneity between the studies (I^2 = 72.1%). This effect strengthened as the dose increased within a certain study; but this trend was not consistent among different studies. The mean pain score reduction was higher in some studies with lower dosing regimens than higher dosing regimens in other studies, indicating that the optimal dosing regimen was still to be investigated. Pregabalin was also confirmed to yield a higher percentage of 30% or 50% pain responders in comparison to the placebo, with a much lower degree of heterogeneity. This finding suggested that the percentage of 30% or 50% responder may be a more universal indicator than mean pain score reduction in evaluating the effectiveness of pregabalin. In addition, this study validated that pregabalin would lead to an improvement of mean sleep interference score and the PGIC.

Table 3. Subgroup analysis of reduction in mean pain scores, 30% and 50% pain responders

Subgroups	Number of study groups	Effect model	Pooled effect sizes	95% CI	P-value	Pregabalin/ Placebo
Reduction in mean pain scores						
Duration of treatment						
8 weeks	4	Random	-0.76	-1.052, -0.474	<0.001	356/355
13 weeks	3	Random	-0.50	-0.820, -0.188	0.002	275/279
Dosing regimen						
150 mg	2	Random	-0.52	-1.081, 0.038	0.068	168/174
300 mg	3	Random	-0.64	-1.035, -0.244	0.002	285/283
Administration methods						
BID	3	Random	-0.50	-0.820, -0.188	0.002	273/279
TID	4	Random	-0.76	-1.052, -0.474	<0.001	356/355
50 percentage pain responders						
Duration of treatment						
8 weeks	3	Fixed	2.16	1.746, 2.664	<0.001	247/246
13 weeks	3	Fixed	2.56	1.915, 3.419	<0.001	285/279
Dosing regimen						
150 mg	2	Fixed	2.14	1.473, 3.103	<0.001	168/174
300 mg	3	Fixed	2.37	1.770, 3.170	<0.001	285/283
Administration methods						
BID	5	Fixed	2.44	1.956, 3.050	<0.001	463/459
TID	3	Fixed	2.16	1.746, 2.664	<0.001	247/246
30 percentage pain responders						
Duration of treatment						
8 weeks	4	Fixed	2.55	1.791, 3.642	<0.001	357/355
13 weeks	3	Fixed	4.33	2.774, 6.752,	<0.001	275/279
Dosing regimen						
150 mg	2	Fixed	2.96	1.714, 5.125	<0.001	168/174
300 mg	3	Random	2.63	1.532, 4.520	<0.001	285/283
Administration methods						
BID	5	Random	2.83	1.943, 4.126	<0.001	454/459
TID	4	Fixed	2.55	1.791, 3.642	<0.001	357/355

This is the first meta-analysis that pooled the efficacy of pregabalin vs. placebo which involved 5 studies with different dosing regimens. Besides what we have confirmed, the results indicated that inter-study differences are huge in the mean pain score. In addition, the effect of different dosing regimens was not consistent among different studies, since lower-dose regimen led to more substantial effect than the higher doses in some studies. Subgroup analyses suggested that the duration of treatment, dosing regimen, and administration methods did not significantly change the effect of pregabalin; except that there was possibilities that the prolonged treatment period of 13 weeks would led to higher rate of 30% pain responders but not in the rate of 50% pain responder compared with treatment of 8 weeks. This could be explained by the theory that with the longer treatment period, there were higher chance for the patients to have an moderate pain score reduction (of more than 30%), nevertheless, but not a substantial reduction (of more than 50%). The percentage of 30% pain responders may increase in a long, stable treatment but not the percentage of the 50% pain responders.

Pregabalin is recommended as the first-line treatment for PHN by the American Academy of Neurology and European Federation of Neurological Societies. Nevertheless, the effi-

cacy of pregabalin is still not satisfactory, just as shown in this study. The percentage of patients who had more than 30% or 50% reduction in endpoint mean score remained limited. Combined treatments of pregabalin and other medications should be considered if the current treatment failed. In this circumstance, the efficacy of controlled-release oxycodone was evaluated. The combination of these two medicines resulted not only greater improvements in quality of life but also reduced the dose of these two medicines compared with using them alone [20]. Taking the current efficacy of pregabalin and other medications, none of which were ever shown to reduce the pain by more than 50% in more than half of the patients repeatedly [4].

Several limitations of this meta-analysis should be noted. First, this study was significant heterogeneity (I^2 = 72.1%) among the findings with regard to the change in mean pain intensity scores. Second, different dosing regimens were included in these studies, despite the fact that subgroup analyses were performed. The characteristics of the involved patients were uneven; such variability may become a contributor to the heterogeneity among these studies. However, we could not perform further analysis based on current information.

Conclusion

This meta-analysis evaluated the efficacy of pregabalin in the treatment of PHN in comparison with the placebo from 5 RCTs with 9 study groups. The results indicated that pregabalin is effective in reducing the mean pain score and the sleep interference score, increasing the percentage of 30% and 50% pain responders in comparison with placebo. Higher dosing regimens yield more significant improvement within each study but heterogeneous results among different studies.

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Disclosure of conflict of interest

None.

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