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Efficacy and safety of pregabalin for chronic neuropathic pain: A meta-analysis

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Abstract

To assess the efficacy and safety of pregabalin during short-term treatment in adults with neuropathic pain. We searched the PubMed, Embase, Web of Science, Cochrane Central Register of Controlled Trials, and Clinical Trials databases. Twelve eligible articles were finally selected. Efficacy outcomes included change in Daily Pain Rating Scale score (DPRS; 0 = 'no pain' to 10 = 'worst possible pain') and sleep interference score (0 = 'pain does not interfere with sleep' to 10 = 'completely interferes'). Safety was based on adverse events, serious adverse events (SAEs) and the incidence of treatment emergent adverse events (TEAEs) .The authors used the Cochrane Collaboration's Risk of Bias Tool to assess the risk of bias in included trials. Review Manager 5.3 was used for all statistical analyses. Data from 12 articles including 3,169 patients (pregabalin, n = 1,677; placebo, n =1,492) were analyzed. Mean changes in the daily pain rating scale score [MD=-0.65, 95%CI(-0.88,-0.41), P<0.001] and daily sleep interference score in patients that received pregabalin were compared to those that received placebo [MD=-0.81, 95%CI(-1.16,-0.46), P<0.001]. The incidence of any TEAE was significantly increased in patients that received pregabalin [OR=1.70, 95%CI (1.44,2.01), P<0.001]. Serious adverse events (SAEs) rate in the pregabalin group was higher than the placebo group [OR=2.09, 95%CI (1.49,2.93), P<0.001], while there was no significant difference in the incidence rate of discontinuation [OR=1.29, 95%CI (0.79,2.11), P = 0.31]. Comparative results revealed pregabalin (150-600 mg/day) significantly reduced the symptoms of neuropathic pain in adults and its safety was acceptable.

Keywords: Pregabalin, neuropathic pain, efficacy, safety, randomized controlled trial, meta-analysis

INTRODUCTION

Neuropathic pain (NP), defined as pain resulting from injury or dysfunction of the somatosensory system, tends to be more refractory to treatment than other forms of pain.[1] Depending on the origin, it is either categorized as peripheral or central pain. Among peripheral neuropathic pain, diabetic peripheral neuropathy (DPN), post-herpetic neuralgia (PHN), posttraumatic neuralgia, and iatrogenic injuries are common. Central neuropathic pain can be associated with stroke, spinal cord injury (SCI), multiple sclerosis, and Parkinson's disease. HIV-neuropathy and cancer-related pain are also included. Chronic neuropathic pain is considered a complex multidimensional condition, which is challenging to manage because of its associated comorbidities affecting many aspects of the patient's life, including sleep disturbance, depression, anxiety, disrupted daily routines, reduced social activities, absenteeism, presenteeism and low health related quality of life (QoL).[2-5]

Drugs from many different classes have been used to treat neuropathic pain, including tricyclic antidepressants (TCAs), selective serotonin–norepinephrine reuptake inhibitors (SNRIs), nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and antiepileptic drugs (AEDs). Each of these classes has demonstrated some degree of efficacy, while each has its limitations. Pregabalin is an anticonvulsant with analgesic and anxiolytic properties. It is a structural analogue of the neurotransmitter gamma-aminobutyric acid (GABA) that mediates its actions by binding to voltage-gated calcium channels in the central nervous system. Pregabalin is a selective, high-affinity ligand for the α2-δ subunit of voltage-

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gated calcium channels, which are thought to play an important role in modulating neuropathic pain.[6-8]

To better understand the onset of neuropathic pain relief, we retrospectively analyzed individual patient data from 13 large randomized placebo-controlled clinical trials of pregabalin in neuropathic pain.[9-20] The objective was to evaluate the efficacy and safety of pregabalin during short-term treatment in adults with chronic neuropathic pain.

METHODS

This meta-analysis was performed according to the protocol provided as supporting material (Supplement 1), and was reported based on as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplement 2).[21]

Search strategy

We systematically searched PubMed, Embase, Web of Science, Cochrane Central Register of Controlled Trials, and Clinical Trials databases to identify eligible articles using the key search terms "pregabalin" AND "neuropathic pain". Studies were searched from database inception to September 24, 2019. The searches were limited to RCTs in the English language. All references to relevant articles were manually retrieved and the corresponding authors of some of the experiments were contacted to find missing information. The search was updated on November 16, 2019 using the same strategy.

Inclusion and exclusion criteria. Inclusion criteria were: (1) Population: i. ≥18 years of age with a diagnosis of chronic neuropathic pain syndrome at least 3 months include peripheral neuropathic, central neuropathic pain and other types of neuralgia; ii. Patients were included if they had scores ≥40 mm on the visual analog scale of the Short-Form McGill Pain Questionnaire and had an average Daily Pain Rating Scale (DPRS) score ≥4 derived from at least 4 diary entries during the 1-week baseline period; iii. Stable usage of SSRIs for anxiety or depression starting ≥ 30 days prior to screening, or stable usage of NSAIDS or COX-2 inhibitors starting ≥ 7 days prior to screening were permitted to continue without change during the course of the study; iv. Stable night time use of hypnotics for insomnia was also permitted without change in dosing for the study duration. (2) Study design: placebo-controlled RCTs. (3) Intervention: pregabalin treatment for<6 months. (4) Outcomes: predefined efficacy and safety outcomes.

Trials were excluded if they included patients with: (1) A clinically significant abnormal ECG results, creatinine clearance <30 mL/min, liver function test results that were >3 times the upper limit of normal or abnormal hematology findings were excluded. (2) Drugs banned for increased use during the study period included drugs for antidepressants, epileptics, analgesics or corticosteroids, skeletal muscle relaxants. (3) Nonpharmacological treatments, such as physical therapy, massage, mind cure, electrotherapy, acupuncture, neurosurgical therapy, and Chinese traditional medication were also prohibited.

Data extraction

Two authors independently assessed the quality of the included studies and extracted the data using the data extraction form. The extracted information included first author's name, year of publication, study design, patient population, sample, age, sex distribution, intervention, treatment duration, and efficacy and safety outcomes. Disagreements were resolved by joint discussion.

Outcomes and definitions

The primary efficacy outcome was the mean change in Daily Pain Rating Scale (DPRS; an 11-point numeric rating scale ranging from 0 = 'no pain' to 10 = 'worst possible pain') from baseline to endpoint. Patients who experience a ≥30 % reduction in pain are considered to have a moderately important improvement in pain and those who experience a ≥50 % reduction in pain, a substantial improvement in pain.[22] Furthermore, a pain score of ≤3 on the DPRS (no worse than mild pain) at endpoint represents an ideal outcome for patients with chronic pain.[23] The key secondary efficacy outcomes were mean changes in the daily sleep interference score (0 = 'pain does not interfere with sleep' to 10 = 'pain completely interferes with sleep/unable to sleep'). Safety outcomes were discontinuation rate due to AEs and commonly reported TEAEs including dizziness, edema peripheral, somnolence, dry mouth, and fatigue.

Quality assessment

To assess the risk of bias in included trials. The Cochrane Collaboration's Risk of Bias Tool was used by two review authors independently.[24] Reviewers examined seven domains as follows:

random sequence generation, allocation concealment, blinding of outcome assessment, blinding of participants and personnel, incomplete outcome data, selective reporting, and other bias. Risk of bias was categorized as low, high, or unclear. Disagreements were resolved by joint discussion.

Statistical analysis

The Review Manager 5.3 was used for this meta-analysis. Mean differences (MDs) with 95 % confidence intervals (CIs) were calculated for continuous variables, and odds ratios (ORs) with 95% CIs were calculated for dichotomous variables. A random-effects model was used to pool studies with substantial heterogeneity, as determined by the chi-squared test ($P<0.05$) and the inconsistency index ($I^2 \geq 50\%$).[25-26] Additionally, we estimated the adverse events rate to evaluate drug safety. An assessment of publication bias was performed using funnel plots and the Begg's/Egger's test using Stata 15.0 software.

RESULTS

Characteristics of included studies

We searched a total of 554 articles in the database. We eliminated 93 duplicate articles. By reading the title and abstract of the article, 374 irrelevant articles were excluded and the full text of 87 articles were read. Finally, 12 eligible articles that described 13 RCTs were considered eligible for inclusion in our meta-analysis (Figure 1). The characteristics of the included trials were shown in (Table 1). The 13 RCTs were conducted between 2003 and 2019. The trials included 3,169 adult patients with chronic neuropathic pain, defined as the Daily Pain Rating Scale (higher score represents great neuropathic pain severity; max score = 10). Among the included patients, 1,677 were treated with pregabalin, and 1,492 were treated with placebo. Two of the trials lasted 6 weeks, four lasted 8 weeks, and the rest lasted 10,12,13,14,15,16 and 17 weeks, respectively. Five trials administered fixed doses of pregabalin at 150 mg/day, 300 mg/day, or 600 mg/day; other trials administered flexible doses of 150-600 mg/day. Visual inspection of the funnel plot, and the Begg's/Egger's test revealed no significant publication bias ($P=0.237$) (Figure 2). Sensitivity analysis was performed if heterogeneity was found. When we converted fixed effect model to random effect model in heterogeneity outcomes, the pooled ORs were all located in the significant range of overall effect, indicating that the results of the meta-analysis showed low sensitivity and high stability.[27]

Quality assessment

Overall, risk of bias in the included RCTs was low or unclear, seen in Figure 3, risk of bias across studies was shown in Figure 3A and risk of bias in individual studies was shown in Figure 3B.

Primary efficacy outcome

Change in the Daily Pain Rating Scale score from baseline to the end of the study was reported in twelve trials [9-20] (pregabalin, n = 1677; placebo, n = 1492). Mean change in the Daily Pain Rating Scale score was significantly greater in patients with chronic neuropathic pain that received pregabalin compared to those that received placebo (MD=-0.65, 95%CI -0.88, -0.41, $P<0.001$) (Figure 4). In this case, heterogeneity was detected ($I^2 = 62\%$, $P = 0.002$) so we used a random-effects model.

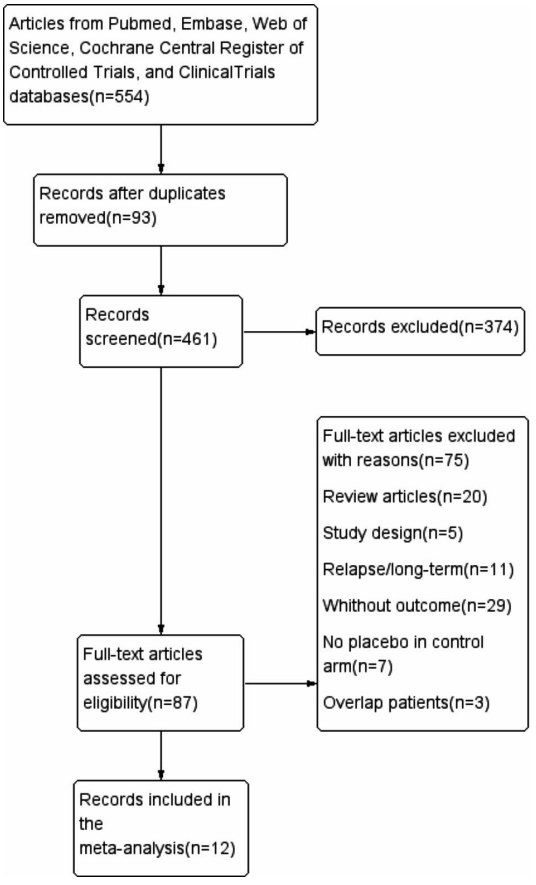


Figure 1. Flow diagram of the literature search.

Table I. Characteristics of included RCTs

Number	Study	Year	Design	Sample size(N)	Male/ Female (N)	Diagnosis criteria	Treatment/ control	Age years (mean±SD)	PGB Dose (mg/d)	Duration (weeks)	Baseline Daily Pain Rating Scale (mean±SD)	Mean change of the daily sleep interference score(SE)	Adverse events (AEs) recorded	Location
1	Dworkin	2003[4]	Double-blind	173(89/84)	81/92	Postherpetic neuralgia	PGB/PBO	72.4±10.5/ 70.5 ±11.3	300mg OR 600mg	8	6.3±1.4/ 6.4±1.5	\	121/33	the United States
2	Richter (A)	2005[4]	Double-blind	164(79/85)	103/61	Diabetic peripheral neuropathy	PGB/PBO	56.3±9.4/ 57.1±10.3	150mg	6	6.5±1.3/ 6.9±1.6	\	49/55	the United States
3	Richter (B)	2005[4]	Double-blind	167(82/85)	92/75	Diabetic peripheral neuropathy	PGB/PBO	57.8±9.5/ 57.1±10.3	600mg	6	6.7±1.7/ 6.9±1.6	\	164/55	the United States
4	Siddall	2006[11]	Double-blind	137(70/67)	114/23	Central neuropathic pain associated with spinal cord injury.	PGB/PBO	50.3/49.8	150–600 mg	12	6.54±1.3/ 6.73 ±1.4	-1.43±3.61/- 0.27±3.75	130/41	Australia
5	Arezzo	2008[9]	Double-blind	167(82/85)	103/64	Diabetic peripheral neuropathy	PGB/PBO	58.2±9.6/ 58.3 ±10.9	600mg	13	6.28±1.47/ 6.58 ±1.58	\	14/10	the United States
6	Simpson	2010[2]	Double-blind	302(151/151)	245/57	HIV neuropathy	PGB/PBO	48.2±8.1/ 46.8±7.5	150–600 mg	14	6.9 ±1.5/ 6.7±1.5	\	123/106	the United States and Puerto Rico
7	van	2010[8]	Double-blind	254(127/127)	125/129	Post-traumatic peripheral neuropathic pain	PGB/PBO	52±14/ 51 ±13	150–600 mg	8	6.0±1.6/ 6.3 ±1.7	-1.37±2.4/- 0.67±2.7	109/74	8 countries
8	Moon	2010[12]	Double-blind	240(162/78)	111/129	Peripheral Neuropathic Pain	PGB/PBO	59.7±10.8/ 61.3±12.9	150-600mg	10	6.28±1.52/ 6.31±1.45	\	71/23	Korea
9	Guan	2011[2]	Double-blind	308(206/102)	143/165	Peripheral Neuropathic Pain	PGB/PBO	60.1±8.9/ 60.0±10.2	150-600mg	8	6.3±1.58/ 6.4 ±1.53	\	103/41	China
10	Simpson	2014[10]	Double-blind	375(183/192)	138/237	Human immunodeficiency virus neuropathy	PGB/PBO	41.2±9.0/ 42.3±8.4	150-600mg	17	6.8±1.2/ 6.9±1.2	\	126/117	45 countries
11	Liu	2017[1]	Double-blind	220(111/109)	119/101	PHN	PGB/PBO	65.7±8.6/ 64.1±9.6	300mg	8	5.93±1.30/ 6.08±1.26	-1.24±1.58/- 0.07±1.57	71/48	China
12	Markman	2018[12]	Double-blind	542(275/265)	\	Post-traumatic peripheral neuropathic pain	PGB/PBO	52.8±12.9/ 53.5±12.6	150–600 mg	15	6.41±1.3/ 6.5±1.3	-2.29±1.82/- 1.86±1.79	138/106	The UK
13	Jiang	2019[1]	Double-blind	128(64/64)	77/51	Radiotherapy-related neuropathic pain	PGB/PBO	55.5±8.7/ 56.8±8.1	150–600 mg	16	6.47±1.5/ 6.34±1.37	-2.4±1.2/ -1.5±1.8	74/41	China

PHN, post-herpetic neuralgia; PGB, pregabalin; PBO, placebo.

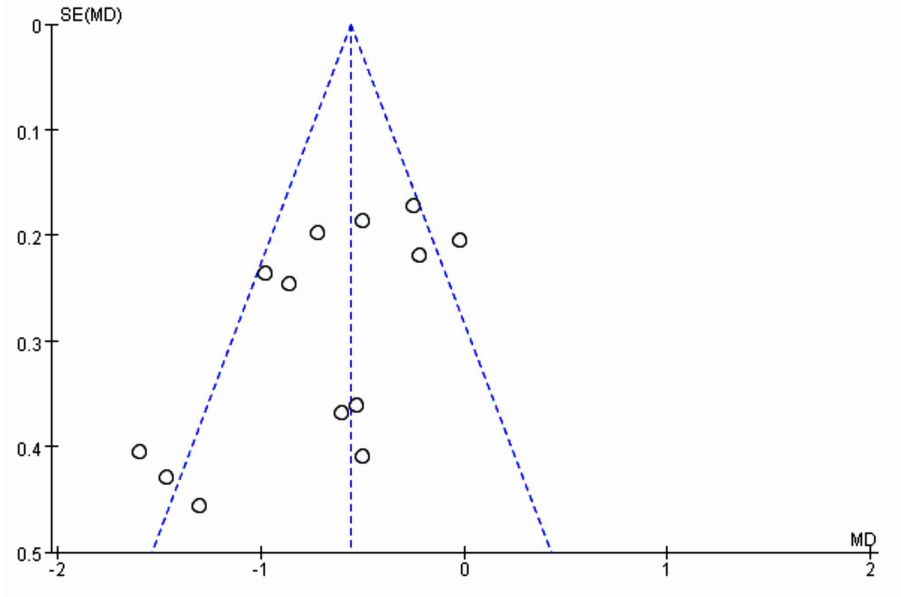


Figure 2. Funnel plot of publication bias.

Secondary efficacy outcomes

Change in daily sleep interference score from baseline to the end of the study was reported in five trials[12-16] (pregabalin, n = 644; placebo, n = 629). Mean change in daily sleep interference score was greater in patients with chronic neuropathic pain that received pregabalin compared to those that received placebo (MD=-0.81, 95%CI -1.16,-0.46, P<0.0001) (Figure 5). Heterogeneity was detected (I^2 = 55%, P = 0.06), thus, a random-effects model was used.

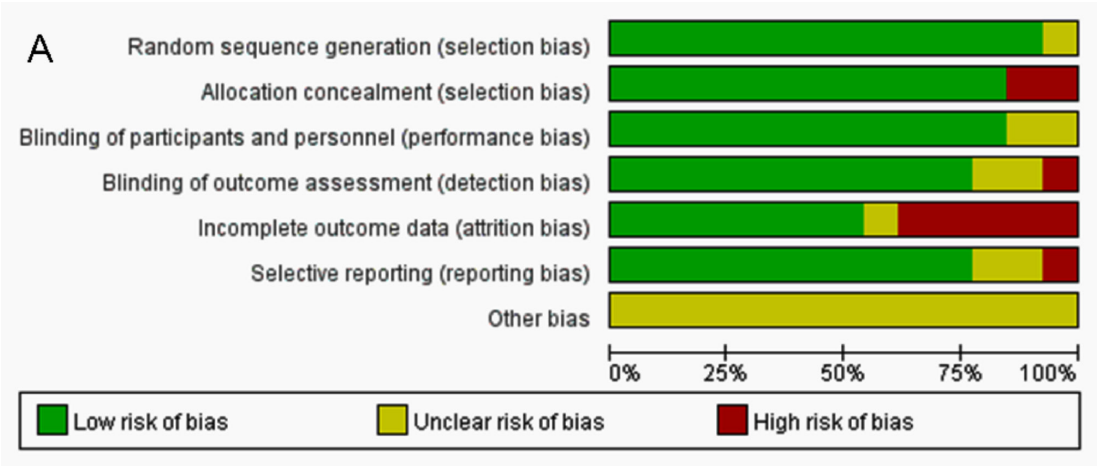
Safety

Discontinuation due to AEs was reported in twelve trials[9-20] (pregabalin, n = 1,680; placebo, n = 1,494) (Figure 6A) and the pooled rate in the pregabalin group was higher than the placebo group (OR = 2.09, 95 %CI 1.49,2.93, P<0.001). Heterogeneity was detected (I^2 = 45 %, P = 0.04). Overall incidence of TEAEs (any AE) was reported in twelve trials[9-20] (pregabalin, n = 1,680; placebo, n = 1,494) (Figure 6B). The incidence of any AE was increased in patients with chronic neuropathic pain that received pregabalin compared to those that received placebo (OR = 1.70, 95 %CI 1.44,2.01, P<0.001). Heterogeneity was detected (I^2 = 49 %, P = 0.05). There was no significant difference in the incidence of serious adverse events (SAEs) between the treatment groups and the control groups (pregabalin, n = 1,680; placebo, n = 1494; OR = 1.29, 95 %CI 0.79,2.11, P = 0.31) (Figure 6C). The most frequently reported TEAEs included dizziness, edema peripheral, somnolence, dry mouth and fatigue.

DISCUSSION

This meta-analysis introduced the efficacy and safety of pregabalin in adults with chronic neuropathic pain. Results showed that mean changes in the Daily Pain Rating Scale score and daily sleep interference score were significantly greater in patients with chronic neuropathic pain that received pregabalin compared to those that received placebo. The most common AEs were dizziness, edema peripheral, somnolence, dry mouth and fatigue. Although there was discontinuation rate due to AEs, the incidence of any AE and TEAEs were significantly increased in patients that received pregabalin. Furthermore there was no significant difference in the incidence of SAEs and therefore pregabalin was highly safe.

The selection of all multicenter, randomized, double-blind, placebo-controlled trials was a major advantage of our meta-analysis. From the database we searched, this is the first meta-analysis to evaluate the efficacy and safety of pregabalin in the treatment of chronic neuropathic pain in adults and the incidence of TEAEs. The chronic neuropathic pain treatment landscape is challenged by the lack of an evidence base to support clinical decision-making for treatment interventions. Selection of a pharmacologic agent is influenced by patient characteristics and adverse drug events. The current meta-analysis of placebo



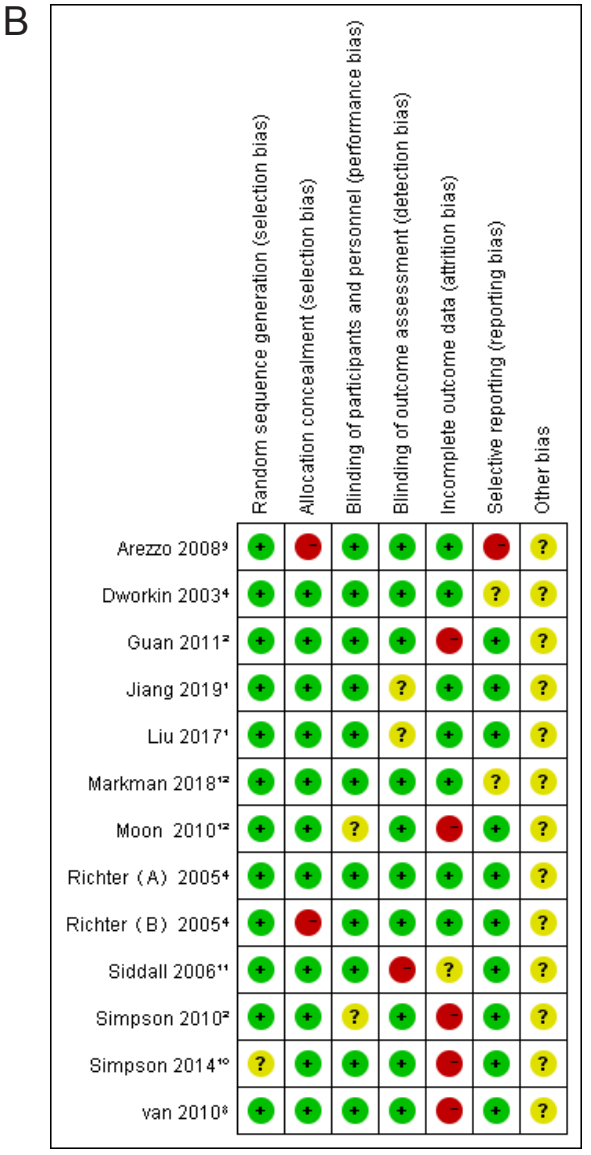


Figure 3. Assessment of the quality of included studies. (A) risk of bias graph. (B) risk of bias summary.

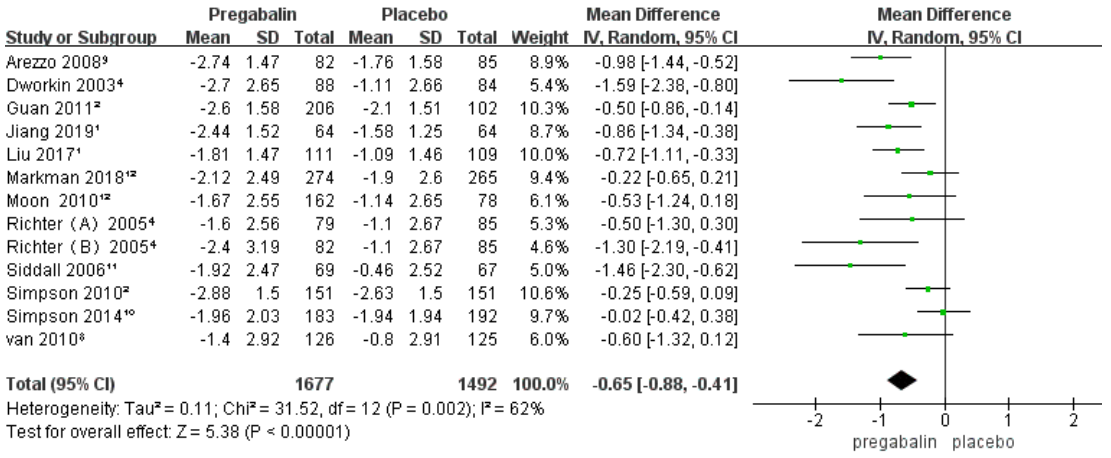


Figure 4. Forest plots of the Daily Pain Rating Scale score

controlled trials adds to the empirical evidence supporting a role of pregabalin for chronic neuropathic pain and increases the quality of the database used by physicians to develop opinions about the efficacy and safety of pregabalin in adult patients with chronic neuropathic pain. Additional high-quality RCTs with larger sample sizes are necessary to clearly define the efficacy and safety of pregabalin in chronic neuropathic pain.

We set strict inclusion criteria and had a large sample size, however, our review is with its limitations. First, no restriction was imposed on dose and treatment duration, which may increase heterogeneity. If there is heterogeneity, we try to apply sensitivity analysis to solve this problem. Second, we excluded articles without complete data from these studies and tried to pursue the integrity and authenticity of data. Third, we utilized a funnel plot to assess potential publication bias; generally, funnel plots should only be used to assess publication bias in reviews that include ≥10 studies, and even then researchers may be misled by their shape.[28,29]

In conclusion, the results of our meta-analysis indicate that pregabalin is an effective pharmacological treatment option in efficacy and high safety for adults with chronic neuropathic pain.

DISCLOSURE

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Conflict of interest: None.

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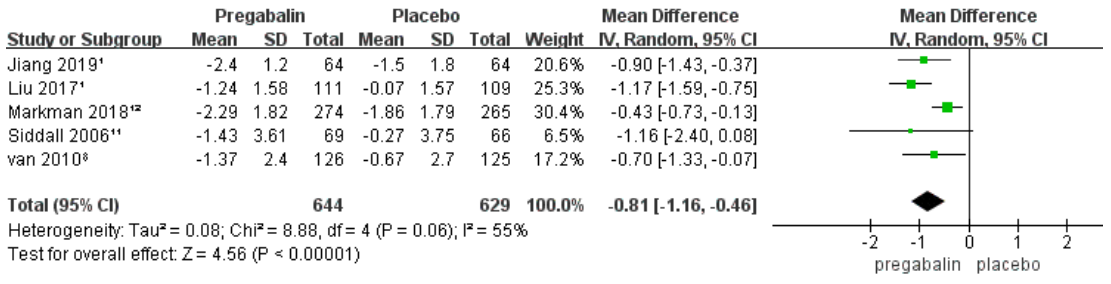
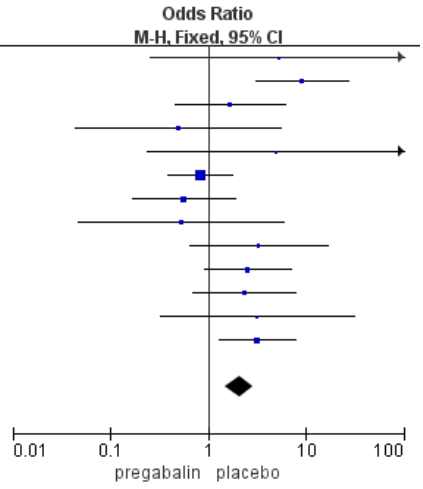


Figure 5. Forest plots of daily sleep interference score

(A)

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Arezzo 2008[9]	2	82	0	85	1.0%	5.31 [0.25, 112.31]
Dworkin 2003[4]	28	89	4	84	5.7%	9.18 [3.06, 27.56]
Guan 2011[2]	10	206	3	102	7.7%	1.68 [0.45, 6.26]
Jiang 2019[1]	1	64	2	64	3.9%	0.49 [0.04, 5.57]
Liu 2017[1]	2	111	0	109	1.0%	5.00 [0.24, 105.35]
Markman 2018[12]	13	274	15	265	29.1%	0.83 [0.39, 1.78]
Moon 2010[12]	6	162	5	78	13.0%	0.56 [0.17, 1.90]
Richter (A) 2005[4]	1	79	2	85	3.8%	0.53 [0.05, 5.99]
Richter (B) 2005[4]	6	82	2	85	3.7%	3.28 [0.64, 16.73]
Siddall 2006[11]	14	70	6	67	9.8%	2.54 [0.91, 7.07]
Simpson 2010[2]	9	151	4	151	7.5%	2.33 [0.70, 7.73]
Simpson 2014[10]	3	183	1	192	1.9%	3.18 [0.33, 30.88]
van 2010[8]	20	127	7	127	11.8%	3.20 [1.30, 7.88]
Total (95% CI)		**1680**		**1494**	**100.0%**	**2.09 [1.49, 2.93]**
Total events	115		51			

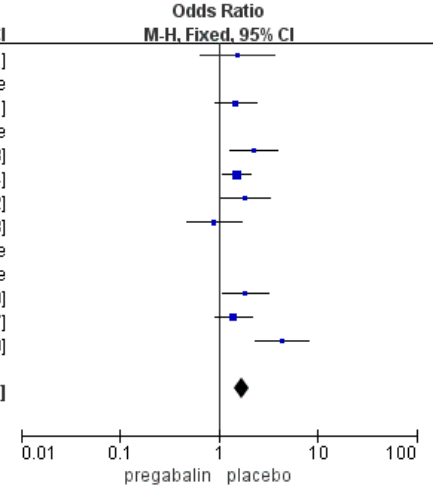
Heterogeneity: Chi² = 21.89, df = 12 (P = 0.04); I² = 45%
Test for overall effect: Z = 4.29 (P < 0.0001)



(B)

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Arezzo 2008[9]	14	82	10	85	3.9%	1.54 [0.64, 3.71]
Dworkin 2003[4]	121	89	33	84		Not estimable
Guan 2011[2]	103	206	41	102	13.1%	1.49 [0.92, 2.41]
Jiang 2019[1]	74	64	41	64		Not estimable
Liu 2017[1]	71	111	48	109	8.3%	2.26 [1.31, 3.88]
Markman 2018[12]	138	274	106	265	25.5%	1.52 [1.08, 2.14]
Moon 2010[12]	71	162	23	78	8.3%	1.87 [1.05, 3.32]
Richter (A) 2005[4]	49	79	55	85	9.6%	0.89 [0.47, 1.68]
Richter (B) 2005[4]	164	82	55	85		Not estimable
Siddall 2006[11]	130	70	41	67		Not estimable
Simpson 2010[2]	123	151	106	151	9.4%	1.86 [1.09, 3.20]
Simpson 2014[10]	126	183	117	192	17.0%	1.42 [0.92, 2.17]
van 2010[8]	109	127	74	127	5.0%	4.34 [2.35, 7.99]
Total (95% CI)		**1680**		**1494**	**100.0%**	**1.70 [1.44, 2.01]**
Total events	1293		750			

Heterogeneity: Chi² = 15.71, df = 8 (P = 0.05); I² = 49%
Test for overall effect: Z = 6.20 (P < 0.00001)



(C)

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Arezzo 2008[9]	0	82	0	85		Not estimable
Dworkin 2003[4]	0	89	0	84		Not estimable
Guan 2011[2]	3	206	2	102	9.3%	0.74 [0.12, 4.49]
Jiang 2019[1]	0	64	2	64	8.8%	0.19 [0.01, 4.12]
Liu 2017[1]	2	111	0	109	1.7%	5.00 [0.24, 105.35]
Markman 2018[12]	2	274	7	265	25.0%	0.27 [0.06, 1.32]
Moon 2010[12]	0	162	0	78		Not estimable
Richter (A) 2005[4]	0	79	0	85		Not estimable
Richter (B) 2005[4]	7	82	0	85	1.6%	16.99 [0.95, 302.42]
Siddall 2006[11]	13	70	8	67	23.5%	1.68 [0.65, 4.36]
Simpson 2010[2]	0	151	0	151		Not estimable
Simpson 2014[10]	7	183	7	192	23.2%	1.05 [0.36, 3.06]
van 2010[8]	4	127	2	127	6.8%	2.03 [0.37, 11.30]
Total (95% CI)		**1680**		**1494**	**100.0%**	**1.29 [0.79, 2.11]**
Total events	38		28			

Heterogeneity: Chi² = 10.13, df = 7 (P = 0.18); I² = 31%
Test for overall effect: Z = 1.01 (P = 0.31)

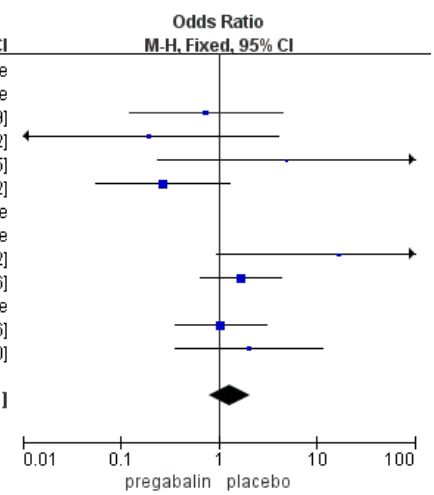


Figure 6. Forest plots of safety. (A) Discontinuation due to AEs. (B) Incidence of any AE. (C) Incidence of SAEs.

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Supplement 1

Review question(s)

Although efficacy of pregabalin for peripheral neuropathy (DPN) and postherpetic neuralgia (PHN) has been reported in previous analysis, the issue that improvement in neuropathic pain and treatment-emergent adverse effects in adults during short-term treatment has not been evaluated.

Searches

Literature databases include PubMed, Embase, Web of Science, Cochrane Central Register of Controlled Trials, and ClinicalTrials databases. We conduct manual searches of the reference lists of relevant articles.

Contact of experts: we attempt to contact the authors of relevant articles when needed. There were no restrictions on the date of publication. Language was limited to English.

Type of study to be included

Study designs: experimental (randomized controlled trials).

Participants/ population

Patients aged or older than 18 years meeting the chronic neuropathic pain

Exposure(s)

Pregabalin

Comparator(s)/ control

Placebo-controlled

Outcome(s)

Efficacy outcome: assessed by the daily pain rating scale (DPRS) and daily sleep interference score.

Tolerability outcome: assessed by discontinuation rate due to adverse events, the incidence of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs).

Data extraction, (selection and coding)

Selection process: Title and abstract screening: Teams of two reviewers will use the above eligibility criteria to screen titles and abstracts of identified citations in duplicate and independently for potential eligibility. We will get the full text for citations judged as potentially eligible by at least one of the two reviewers.

Full-text screening: Teams of two reviewers will use the above eligibility criteria to screen the full texts in duplicate and independently for eligibility. The teams of two reviewers will resolve disagreement by discussion or with the help of a third reviewer.

We use standardized and pilot tested screening forms. We will conduct calibration exercises to ensure the validity of the selection process.

Data abstraction process: Teams of two reviewers will abstract data from eligible studies in duplicate and independently. They will resolve disagreements by discussion or with the help of a third reviewer.

We collect the following data: the first author's name, year of publication, age, sex distribution, sample, study design, patient population, treatment duration, intervention, outcomes.

We use standardized and pilot tested data abstraction forms.

We conduct calibration exercises to ensure the validity of the data abstraction process.

Risk of bias (quality) assessment:

Teams of two reviewers assess the risk of bias in each study in duplicate and independently. They resolve disagreements by discussion or with the help of a third reviewer.

We use the Cochrane Risk of Bias tool to assess the risk of bias in randomized trials.

We will calculate the risk of bias using the following criteria: The likelihood of risk of bias included random sequence generation, allocation concealment, blinding of outcome assessment, blinding of participants and personnel, incomplete outcome data, selective reporting and other bias.

We grade each potential source of bias as high, low or unclear risk of bias. We will use unclear when the authors did not report enough information for us to make the judgment.

We did not exclude any study based on quality.

Strategy for data synthesis

We conduct a meta-analysis to pool the results across studies for pregabalin as the exposure of interest, and 'efficacy and safety' as the outcome of interest.

We carry out statistical analysis using RevMan(version 5.3). For Dichotomous data, we will calculate the ORs for each study. For continuous data, we will calculate the mean difference for each study.

We test the results for homogeneity using the I^2 test and considered heterogeneity present if $I^2 \geqslant 50\%$ and $P<0.05$. We will conduct the sensitivity analysis.

We assess publication bias using the funnel plot and the Begg's/Egger's test via Stata Version 15.0 software.

Section/topic	#	Checklist item	Reported in section
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract and Author summary
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction, 1st, 2nd and 3rd paragraph
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction, 4th paragraph
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Methods
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods, Search strategy
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods, Search strategy
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Methods, Search strategy
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods, Inclusion criteria
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods, Data extraction

Section/topic	#	Checklist item	Reported in section
METHODS			
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods, Data extraction
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods, Quality assessment
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods, Outcomes and definitions and Statistical analysis
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	Methods, Statistical analysis
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Methods, Quality assessment
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Methods, Sensitivity analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results, Characteristics of included studies and Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Results, Quality assessment and Fig 2B
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Results, Fig 4, Fig 5,Fig 6, Fig 7, Fig 8, and table 2

Section/topic	#	Checklist item	Reported in section
RESULTS			
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Results, Fig 4, Fig 5,Fig 6, Fig 7, Fig 8, and table 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results, Quality assessment and Fig 2A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Methods, Sensitivity analysis
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion, Paragraphs 1 to 4
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion, Paragraph 5
Limitations	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion, Paragraph 6
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Online submission system

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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