Review Article
Pregabalin for the treatment of neuropathic pain in adults: a systematic review of randomized controlled trials

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Abstract: Background: The treatment of neuropathic pain remains a significant challenge for the medical workers. Objectives: The chief aim of the systematic review was to quantitatively evaluate the efficacy, safety and tolerability of the use of pregabalin for neuropathic pain management. Methods: We searched the databases of PubMed, Cochrane, Medline, Embase for randomized controlled trials (RCTs) using pregabalin for neuropathic pain management. We extracted data about pain intensity, quality of life, global impression of change, treatment satisfaction and adverse events. RCTs comparing pregabalin with placebo in the management of neuropathic pain were included. Results: By retrieving we got 238 articles, 12 articles were included. Compared with the placebo group, the pregabalin group could reduce visual analog scale (VAS) WMD -0.89 cm (95% CI -1.15, -0.63). It was significant reduction in the pregabalin at both ‘anxiety’ and ‘depression’ of the Hospital Anxiety and Depression Scale (HADS) as follows WMD -1.39 (95% CI -2.26, -0.52), WMD -1.18 (95% CI -2.02, -0.34). It expressed difference at the patient perception of change (PGIC), the clinical perception of change (CGIC) as follows RR 4.18 (95% CI 1.47, 1.87). Adverse effects were statistically significant, such as dizziness, peripheral edema, somnolence, RR 3.23 (95% CI 2.78, 3.79), RR 2.91 (95% CI 2.24, 3.79), RR 2.51 (95% CI 1.78, 3.54). Conclusions: The meta-analysis demonstrated that pregabalin may be an effective pharmacological approach for the neuropathic pain.

Keywords: Pregabalin, neuropathic pain, visual analog scale, confidence interval, adverse events

Introduction
The issue of the management of Neuropathic pain (NP) has received considerable critical attention. It is a formidable challenge for medical workers. If NP is not managed effectively, it can contribute to many clinical risks, such as the patients’ physical and psychological health. They may experience many complications, including moderate, severe, or extreme pain and the disorder of emotional function. NP includes a wide range of manifestations, such as postherpetic neuralgia (PHN), HIV-associated distal sensory polyneuropathy (HIV-DSP), diabetic peripheral neuropathy (DPN), spinal cord injury (SCI), chronic lower pain (CLBP), post-traumatic peripheral neuropathic pain (PTNP) and so on. Pharmacological treatment remains the main effect for neuropathic pain. Traditional medicines are associated with the lack of clinical efficacy, undesirable adverse effects. It needs to find effective pharmacological treatment to manage and relieve the systems of neuropathic pain.

Pregabalin (PGB) is a high level of new drugs in the treatment of neuropathic pain (NP). PGB was developed in the search for a compound that would maintain the biologic activity of gabapentin while importing its pharmacokinetic properties; PGB was approved by the European Agency for the Evaluation of Medicinal Products in July 2004 for the treatment of peripheral neuropathic pain as an adjunctive treatment for
Pregabalin for neuropathic pain

Partial seizures [1]. Now it has been widely used in the management of NP all over the world. PGB targets α-2-δ (alpha-2-delta) ligands of calcium channel. It acts on voltage-gated calcium channels. PGB is a drug that binds to the α-2-δ subunit of calcium channels and there is evidence from reported RCTs supporting its use in the neuropathic pain caused by diabetic peripheral neuropathy (DPN), postherpetic peripheral neuralgia (PHN), spinal cord injury, and fibromyalgia [2]. Different authors have measured the efficacy and safety of pregabalin for NP in a variety of ways. More and more clinical trials have been conducted and PGB was used as primary or adjuvant treatment in those trials. We made the systematic review to evaluate the efficacy and safety of (PGB) in neuropathic pain (NP).

Materials and methods

In the writing of the meta analysis, we always adhered to the principles of QUROM guidelines. We have searched requirements of clinical case reports published in terms of pregabalin in the treatment of neuropathic pain. The Cochrane Central Trials Central (Cochrane Library, from 2006 to June 2016), MEDLINE (from June 1980 to June 2016), EMBASE (from July 1986 to June 2016), PUBMED (from December 1986 to 29 June 2016) were searched. We applied no language restrictions.

Table 1. Search strategy used in PubMed

<table>
<thead>
<tr>
<th>#</th>
<th>Search Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>randomized controlled trial [pt]</td>
</tr>
<tr>
<td>#2</td>
<td>controlled clinical trial [pt]</td>
</tr>
<tr>
<td>#3</td>
<td>randomized [tiab]</td>
</tr>
<tr>
<td>#4</td>
<td>placebo [tiab]</td>
</tr>
<tr>
<td>#5</td>
<td>drug therapy [sh]</td>
</tr>
<tr>
<td>#6</td>
<td>randomly [tiab]</td>
</tr>
<tr>
<td>#7</td>
<td>trial [tiab]</td>
</tr>
<tr>
<td>#8</td>
<td>groups [tiab]</td>
</tr>
<tr>
<td>#9</td>
<td>#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8</td>
</tr>
<tr>
<td>#10</td>
<td>Animals [mh] not (human [mh] and animals [mh])</td>
</tr>
<tr>
<td>#11</td>
<td>#9 not #10</td>
</tr>
<tr>
<td>#12</td>
<td>neuropathic pain [mh]</td>
</tr>
<tr>
<td>#13</td>
<td>neuropathy [mh]</td>
</tr>
<tr>
<td>#14</td>
<td>neuropathic [mh]</td>
</tr>
<tr>
<td>#15</td>
<td>pain [mh]</td>
</tr>
<tr>
<td>#16</td>
<td>#12 or #13 or #14 or #15</td>
</tr>
<tr>
<td>#17</td>
<td>pregabalin [mh]</td>
</tr>
<tr>
<td>#18</td>
<td>#11 and #16 and #17</td>
</tr>
</tbody>
</table>

Free text and MeSH terms ‘pregabalin’, ‘neuropathic pain’, ‘neuropathic’, ‘pain’, ‘neuropathy’, ‘randomized controlled trial’, ‘controlled clinical trial’, ‘randomized’, ‘placebo’, ‘drug therapy’, ‘randomly’, ‘trial’, ‘group’ were used for searching (Table 1). The last literature search was in June 2016. The articles retrial works were screened by two independent reviewers. The retrieved documents were offered in full text.

Study selection

Selection for criteria: The researchers selected the studies according to the following criteria: (1) All the studies must be random controlled trials. (2) The participants’ age need more than 18 years old. After the subjects were required to be involved in the surgical treatment, the studies are involved. (3) The experiment group accept pregabalin treatment. (4) The control group accept placebo treatment.

Outcome measures

Primary outcomes: (1) The time point for the observation included the modified baseline observation carried forward (mBOCF) and the last observation carried forward (LOCF). (2) The evaluation intensity of pain was measured by a self-reported instrument. Visual analog scale (VAS) was a 10 centimeter (cm) horizontal line labeled ‘no pain’ at one end and ‘worst pain imaginable’ on the other end. The patients was asked to mark on this line where the intensity of the pain. The distance form ‘no pain’ to the patients’ mark numerically quantifies the pain. The VAS was a simple and efficient method that correlates well with other reliable method. (3) The assessment of changes in pain was measured by numeric pain rating scale (NPRS). Subjects rated pain experienced during the previous 24 hours on an 11-point NRPS ranging from 0 (no pain) to 10 (worst possible pain) [3].

Secondary outcomes

The evaluation of mood disorder was measured by the Hospital Anxiety and Depression Scale (HADS). The degree of ‘anxiety’ was assessed according to 7 different questions; the evaluation of ‘depression’ was assessed according to another 7 different questions. Each items had been answered by the patients on a four point (0-3) response category and the possible scores arranged from 0 to 21 for anxiety and 0 to 21 for depression [4].
The evaluation of the improvement of pain was measured by the correlations between the patient global impression of change (PGIC), the clinical perception of change (CGIC) by the therapist. The patients’ report of changes in pain (VAS endpoint-baseline) were calculated by nonparametric Spearman rank correlation coefficients [5]. The degree of the improvement of pain was also assessed by responder rate in the meta. Responder rate was consisted of 2 parts, including ≥30% and ≥50%. Responder rate ≥30% in the mean score was used to evaluate the effect of the treatment.

The evaluation of quantity sleep was measured by the daily sleep interference score. It is an 11-point numerical rating scale (0 = did not interfere with sleep, 10 = completely interfere with sleep). When patients woke up each day, they evaluated the sleep situation.

The possible side effects of drug treatment were also evaluated. Side effects included dizziness, peripheral edema, nausea, somnolence, weight gain and so on. The number of cases that were left out of the trials because serious side effects were recorded.

Quality of assessment

Two independent reviewers made the risk assessment of each article. Cochrane Collaboration’s risk of bias tool was used in the process. It included 7 different parts, such as random sequence generation, allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), other bias. There are 3 different literature evaluation standards, including low risk, unclear risk and high risk. The considered aspect is classified when the evaluation requires that all the keys are included. The considered aspect is classified when the evaluation requires that one or key factors are included. The paradox of the part has a mild effect on the results. The state of high risk corresponds to no key factors.
### Table 2. Randomized, double-blinded, placebo-controlled trials included in the analysis

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Setting</th>
<th>Number PR/PL</th>
<th>Age (years) PR/PL</th>
<th>Design</th>
<th>Population</th>
<th>Origin of pain</th>
<th>Primary outcome</th>
<th>Secondary outcomes</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simpson D.M</td>
<td>2010</td>
<td>America</td>
<td>151/151</td>
<td>(48.2 ± 8.1)/</td>
<td>open-label, 3-months, pregabalin and placebo</td>
<td>40 centers in the United States</td>
<td>HIV-DSP</td>
<td>NRS</td>
<td>NRS sleep interference score, MOS sleep scale, HADS, PGIC, mBPI-sf, NPSI, GPS</td>
<td>Yes</td>
</tr>
<tr>
<td>Simpson David M</td>
<td>2014</td>
<td>America</td>
<td>183/192</td>
<td>(41.2 ± 9.0)/</td>
<td>Open-label, 6-months, pregabalin and placebo</td>
<td>45 centers in South Africa, United States, India, Thailand, Poland, Puerto Rico</td>
<td>HIV-DSP</td>
<td>NRS</td>
<td>Responder status, PGIC, CGIC, NRS-sleep scores, HADS</td>
<td>Yes</td>
</tr>
<tr>
<td>Cardenas Diana D</td>
<td>2013</td>
<td>America</td>
<td>111/108</td>
<td>(46.1 ± 12.7)/</td>
<td>1,4,12-week dose optimization period, double-blinded manner</td>
<td>American Spinal injury Association</td>
<td>SCI</td>
<td>NRS</td>
<td>Responder status, PGIC, MOS-SS, HARDS</td>
<td>Yes</td>
</tr>
<tr>
<td>Gilron Ian</td>
<td>2011</td>
<td>America</td>
<td>80/77</td>
<td>(58 ± 8.3)/</td>
<td>9-week (4-week single-blind, Flexible dosing+5-week placebo-controlled double blind)</td>
<td>America clinical patients</td>
<td>DPN, PHN</td>
<td>Pain intensity</td>
<td>MOS-SS, mBPI-sf, HADS, PGIC, PTSS, EQ-5D</td>
<td>Yes</td>
</tr>
<tr>
<td>Dworkin R.H</td>
<td>2003</td>
<td>England</td>
<td>89/84</td>
<td>(72.4 ± 10.5)/</td>
<td>at least 18 years, pain present for more than 3 month</td>
<td>English clinical patients</td>
<td>PHN</td>
<td>VAS</td>
<td>SF-MPQ</td>
<td>Yes</td>
</tr>
<tr>
<td>van Seventer R.</td>
<td>2010</td>
<td>America</td>
<td>127/127</td>
<td>(52 ± 14)/</td>
<td>18-80 years, pain for more than 3 month</td>
<td>American clinical patients</td>
<td>PT NeP (DPN, PHN, trigeminal, carpal tunnel syndrome, central neuropathic pain, CRPSII)</td>
<td>NRS</td>
<td>MOS-SS, HADS, mBPI-sf, PGIC</td>
<td>Yes</td>
</tr>
<tr>
<td>Freynhagen Rainer</td>
<td>2005</td>
<td>Germany</td>
<td>132/65</td>
<td>(61.8 ± 11.0)/</td>
<td>randomized, double-blind, placebo-controlled</td>
<td>German Clinical patients</td>
<td>DPN, PHN</td>
<td>VAS</td>
<td>SF-MPQ</td>
<td>Yes</td>
</tr>
<tr>
<td>Freynhagen Rainer</td>
<td>2015</td>
<td>Germany</td>
<td>4884/2626</td>
<td>(60.6 ± 13.3)/</td>
<td>Randomized, controlled trials</td>
<td>May 1998 to May 2012, Asia, Australia, Canada, Europe, Latin America, The Middle East, South Africa, the United States</td>
<td>DPN, PHN, CLBP, HIV neuropathy, cancer related NeP, and other NeP conditions (TGN and disturbed sleep concurrent with NeP)</td>
<td>AEs</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Sabatowski Rainer</td>
<td>2004</td>
<td>Germany</td>
<td>76/81</td>
<td>(71.9 ± 10.3)/</td>
<td>17 February 1999</td>
<td>Europe, Australia</td>
<td>PHN</td>
<td>VAS of SF-MPQ</td>
<td>MSIS, PGIC, CGIC, SF-36, Zung SRDS</td>
<td>Yes</td>
</tr>
<tr>
<td>Freeman Roy</td>
<td>2008</td>
<td>America</td>
<td>266/557</td>
<td>(59.10 ± 10.93)/</td>
<td>5 to 13 weeks</td>
<td>America</td>
<td>DPN</td>
<td>NRS</td>
<td>Responders (pain level), PGIC</td>
<td>Yes</td>
</tr>
<tr>
<td>Mishra Seema</td>
<td>2012</td>
<td>India</td>
<td>30/30</td>
<td>Not mentioned</td>
<td>4-week</td>
<td>India</td>
<td>NeP</td>
<td>VAS</td>
<td>LANS, ECOG</td>
<td>Yes</td>
</tr>
<tr>
<td>Tolle Thomas</td>
<td>2008</td>
<td>America</td>
<td>99/96</td>
<td>(57.28 ± 10.5)/</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>Europe (Germany, Hungary, Poland, The United Kingdom)</td>
<td>DPN, PHN</td>
<td>NRS</td>
<td>Responders (pain level), PGIC</td>
<td>Yes</td>
</tr>
</tbody>
</table>

PR = pregabalin, PL = placebo, NRPS = numeric rate pain scale, LOCF = last observation carried forward, NRS = numeric rating scale, HADS = hospital anxiety and depression scale, PGIC = patient global impression of change, mBPI-sf = the modified brief pain inventory-short form, NPSI = neuropathic pain symptom inventory, VAS = visual analog scale, HIV = human immunodeficiency virus, DSP = distal sensory polyneuropathy, mBOCF = the modified baseline observation carried forward, SD = spinal cord injury, DAAC = duration-adjusted average change, MOS SS = medical outcomes study sleep scale, DPN = diabetic peripheral neuropathy, PHN = postherpetic neuralgia, PTSS = pain treatment satisfaction scale, EQ-5D = health state profile, SF-MPQ = the short-form McGill pain questionnaire, CLBP = chronic lower back pain, Cancer-related NeP = chemotherapy induced neuropathy and cancer induced bone pain, PT NeP = posttraumatic peripheral neuropathic pain, TGN = idiopathic trigeminal neuralgia, NeP = neuropathic pain, MSIS = mean sleep interference scores, SF-36 = SF-36 Health Survey, Zung SRDS = Zung self-rating depression scale, ECOG = eastern co-operative oncology group, HIV-DSP = human immunodeficiency virus associated distal sensory polyneuropathy, CRPS = complex regional pain syndrome, NRSSIS = numeric rate scale sleep interference score.
Data extraction and management

Data extraction is mainly determined according to visual analog score (VAS), the Hospital Anxiety and Depression Scale (HADS), the patient perception of change (PGIC), the clinical perception of change (CGIC), Responder rate and the Medical Outcome Survey (MOS) sleep scale. When the articles didn’t provide enough data, we would contact the authors to get enough information. When the articles had more comparisons, we confirmed the criterion and incorporated them.

Statistical analysis

Review Manager Software 5.3 was used in the data analysis. The software could be downloaded from the link below (http://tech.cochrane.org/revman/download). Dichotomous data is possible response. On the other hand, continuous is a measurement of a numerical quantity. For each study, relative (RR) with 95% confidences intervals (CI) would have been calculated for dichotomous outcomes; for continuous outcomes reported using the same scale, pooled results would have been presented as mean difference (MD); standardized mean different (SMD) would have been calculated where appropriate; analyses based on this effect has historically been termed weighed mean difference (WMD) analyses in the Corchrane Database of Systematic Reviews (CDSR) [6]. Relative effect (95% CI) will typically be a risk ratio or odds ratio (or occasionally a hazard ratio) with its accompanying 95% confidence interval, obtained from a meta-analysis performed on the basis of the same effect measure. When dealing with continuous data, weighted mean differences (WMD) and 95% confidence interval (CI) were used to process the data. For dichotomous data, risk and 95% CI were used to calculated to analyze this type of data. Methods for identifying statistical heterogeneity should be stated by using \( I^2 \) and a chi-squared test. \( I^2 \) is a useful statistic for quantifying inconsistency. \( I^2 = \frac{Q-df}{Q} \times 100\% \). When \( I^2 \) is in the range of 0 to 30%, the heterogeneity might be important. When \( I^2 \) is in the range of 30% to 60%, the heterogeneity may be represent moderate. When \( I^2 \) is in the range of 50% to 90%, the heterogeneity may represent substantial. When \( I^2 \) is in the range of 75% to 100%,
heterogeneity may be considerable. When the heterogeneity is not high, the comparison of data is meaningful. While the test of the data of statistical significance produce P values, P value has guiding significance. When P≤0.05, the result was considered statistically significant.

Results

We have got 238 articles after duplication. 201 articles were excluded for various reasons after screening (Figure 1). 12 articles were left by the inclusion criterion (Table 2). All the articles were written in English. The use of Pregabalin’s
Pregabalin for neuropathic pain

The main content of the articles is the treatment of neuropathic pain. The total number of patients in these articles was 10311, of which 6117 patients were treated with pregabalin.

Neuropathic pain and pregabalin intervention

The retrieval of cases included various types of neuropathic pain (Table 2). The largest number of type of disease was postherpetic neuralgia (PHN) (six studies). There were other types of diseases in the studies, including diabetic peripheral neuropathy (DPN) (five studies), human immunodeficiency virus associated distal sensory polyneuropathy (HIV-DSP) (five studies), spinal cord injury (SCI) (one study), complex regional pain syndrome (CRPS) (one study). Another important factor was the ages of the patients. The age of the patients ranged from 48 to 84 in the studies. The patients came from different regions, mostly from American. At the same time, there were patients from Germany, India, England. These articles were written at different times, respectively. 6 articles were written before 2010 and 7 articles were in 2010 or after 2010.

Pain intensity

The study recorded the VAS score at the end of the treatment. The VAS scores were used to evaluate the analgesic effect of pregabalin intervention. We described the comparison between pregabalin and the placebo groups at the last observation carried forward (LOCF).

Combined data from the change of NPRS (mBOCF to LOCF) were recorded. Four studies were reported as NRS (mBOCF to LOCF) (Figure 3) [3, 12-14]. The combined data got the result as WMD -0.45 (95% CI -0.81, -0.08), I² = 99%, P = 0.02. It was statistically difference, not significant, but it was high heterogeneity.

Mood disorder: Two studies reported HADS at rest at mean with standard deviation (Figure 4) [9, 10]. HADS included the evaluation of ‘anxiety’ and ‘depression’. Combined data from two aspects were respectively WMD -1.39 (95% CI -2.26, -0.52), WMD -1.18 (95% CI -2.02, -0.34). There were both statistically significant difference and low heterogeneity.

The improvement of pain relief

Five studies reported Responder rate (Figure 6) [3, 12-15]. Two degrees of Responder rate were compared as ≥30%, ≥50%. Combined data from two aspects were respectively RR 1.28 (95% CI 1.00, 1.62), P = 0.05; RR 1.36 (95% CI 0.91, 2.04), P = 0.14. There were no statistically difference. Two studies reported PGIC and CGIC (Figure 5). Seven degrees were studied as follows: very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse.

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For the treatment of neuropathic pain is the main content of the articles. The total number of the patients in these articles was 10311, of which 6117 patients were treated with pregabalin.
Combined data from seven degrees were respectively RR 4.18 (95% CI 1.47, 11.87), P = 0.007; RR 1.20 (95% CI 0.92, 1.56), P = 0.18; RR 1.14 (95% CI 0.63, 2.07), P = 0.67; RR 0.59 (95% CI 0.39, 0.89), P = 0.01; RR 0.88 (95% CI 0.20, 3.80), P = 0.87; RR 0.88 (95% CI 0.01, 0.66), P = 0.02; RR 2.97 (95% CI 0.12, 72.05). The differences were statistically significant at very much improved group and no change group.

**Sleep interference**

Four studies reported sleep interference score (Figure 7) [7-10]. Combined data were calculated and got the result WMD -1.40 (95% CI -1.61, -1.26), P<0.00001, I² = 83%). It was statistically significant.

**Adverse effects**

Eight studies reported withdrew patients for adverse events (Figure 8) [7-10, 13-16]. In total, 16% (166/1066) patients with neuropathic pain in the pregabalin group and 6% (77/1149) in the placebo group withdrew from the trials because of severe adverse effects. The result was RR 1.89 (1.07, 3.34), P = 0.03, I² = 69%. The data result was statistically different with substantial heterogeneity. There were a number of side effects that have been reported, such as dizziness, peripheral edema, nausea,
somnolence, weight gain, vertigo, asthenia, dry mouth, headache, fatigue, blurred vision, constipation, euphoria (Figure 9). Through the comparison of the corresponding data, we obtained the following results, RR 2.91 (95% CI 2.24, 3.79), RR 2.51 (95% CI 1.78, 3.54), RR 1.11 (95% CI 0.68, 1.80), RR 3.23 (95% CI 2.78, 3.75), RR 4.86 (95% CI 3.53, 6.69), RR 3.81 (95% CI 1.45, 10.02), RR 1.79 (95% CI 0.63, 5.09), RR 2.60 (95% CI 2.01, 3.38), RR 0.93 (95% CI 0.80, 1.08), RR 1.51 (95% CI 1.00, 2.29), RR 5.18 (95% CI 1.28, 8.95), RR 2.04 (95% CI 1.57, 2.66), RR 7.36 (95% CI 1.71, 31.38). The differences were statistically significant in the aspects of dizziness, peripheral edema, somnolence, weight gain, vertigo, dry mouth, blurred vision, constipation, euphoria.

**Subgroup analysis**

We performed a subgroup base on whether the studies reported before or after 2010. As far as VAS was concerned, the difference was statistical significance when the studies were reported in or after 2010 WMD -0.89 cm (95% CI -1.15, -0.63), In terms of the degree of Responder rate, 3 studies were reported before 2010 [14, 15] and 2 studies were reported after 2010 [12, 13]. We got two results as follows: WMD 1.47 (95% CI 0.88, 2.48), P = 0.14; WMD 0.75 (95% CI 0.60, 0.95), P = 0.02. The difference was statistically significant when the studies were reported after 2010. Eleven studies reported the incidence of dizziness, and eleven studies reported peripheral edema.

**Discussion**

In this meta-analysis, it was determined that there was sufficient evidence thus far to conclude that pregabalin was an effective pharmacological approach to reduction of neuropathic pain. The results suggested that, compared
with placebo, PGB therapy protocol used in the study provided improved analgesia and the reduced pain intensity. The meta-analysis of overall effects from 12 trials showed that the pregabalin intervention significantly reduced NP, as measured by VAS scores. The change of NPRS was also obvious, but it was high heterogeneity. We got the result of \( I^2 = 99\% \). The importance of heterogeneity between studies on summary estimates of relative hazard is difficult to assess; some of the heterogeneity observed might reflect difference in methodology and criteria used to assess status [17]. Then we dealt with the high heterogeneity. At first, we used RE (random effects) in the analysis model when \( I^2 > 50\% \). The other way was to carry out a subgroup analysis. So it may not be clinical relevant. It could be carried out on a number of aspects of subgroup analysis and the most commonly used were gender classification, age, location and time of occurrence and so on. In our studies, the patients' ages ranged from 32 to 85. It was closely related to neuropathic pain treatment with the patients' age. So we took subgroup analysis of the time of clinical trials. Pregabalin was approved by the European Agency for the Evaluation of Medicinal Products in July 2004 for the treatment of peripheral neuropathic pain and as an adjunctive treatment for partial seizures at first; it was provisionally approved by the US Food and Drug Administration and Drug Administration in December 2004 for the treatment of diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN) [1]. It was about 12 years since PGB was widely used for the treatment for neuropathic pain in clinical. We took the year of 2010 as a time point for the medium in the subgroup analysis. As far as VAS was concerned, it was statistically significant and very low heterogeneity in and after 2010. Subgroup analysis was used in the analysis of the changes in NRS. There was a very high heterogeneity in both and after 2010. But four articles respectively indicated that pregabalin's treatment was effective [3, 12-14].

The meta-analysis showed that PGB reduced the agitation of the patients with NP. For example, the reduction in HADS achieved with pregabalin was statistically significant and extremely low heterogeneity at both 'anxiety' and 'depression'. Two articles were included in the meta for the change of HADS [9, 10]. Patients with neuropathic pain could be accompanied by mood changes. The evaluation of score of 'anxiety' and 'depression' in the pregabalin group was significant lower than that in the placebo group. It was an important consideration and could significantly reduce psychological symptoms and improve the quality of life.

The analysis showed that the effect of sleep-disturbance of PGB was not much stronger
than placebo effects. PGB and placebo interventions have showed similar effect. The reduction in NRS sleep scores achieved with PGB was statistically significant and could be not clinically relevant for considerable heterogeneity. Therefore, it could be concluded that the effect of pregabalin on patients sleep was not clear. Sleep problems have a great impact on patients. Surveys of patients with painful DPN have estimated that >50% of patients experience extensive pain-related sleep interference; patients with PHN, and also those with spinal cord injury, are also highly susceptible to pain-related sleep interference [18].

Data of retrials articles are consistent with the current showing that PGB has efficient treatment in reducing NP. Compared to the placebo group, PGB provided effective treatment of NP. For example, PGIC and CGIC were involved in the evaluation of the overall status correlation. Treatment effects were consistently reflected across various scale, and there was good correlation between the changes in general status as assessed by PGIC and CGIC [19]. The comparison was statistically significant in the levels of ‘very much improved’, ‘no change’, ‘much worse’. The effect was significant better. The placebo group was significant stronger in the stage of ‘much worse’. Another comprehensive evaluation was response rate. The degree of it included ≥30% and ≥50%. Response was defined as a ≥30% improvement over baseline in pain score and a patient global impression of change rating of much improved or a very much improved [20]. Through the comparison of the data, we found that there was no statistical significance. The meaning of clinical application was not clear.

Despite its safety and efficacy, the use of PGB suffers from several drawbacks. The numbers of withdraws due to adverse events in the studies were calculated. It was statistical difference and the heterogeneity was moderate. More patients proposed adverse events with PGB than with placebo. So we could make a conclusion that these withdraws were not clinical significance. Furthermore, this meta-analysis showed a significant different in the incidence of adverse effects, including dizziness, peripheral edema, somnolence, weight gain, vertigo, dry mouth, blurred vision, constipation, euphoria. Several side effects were relatively easy to occur in the pregabalin group, including dizziness (23%), somnolence (15%), weight gain (6%), headache (6%). Only one articles mentioned some adverse effects, such as balance disorder [21], influenza [13], upper respiratory tract infection [13], back pain [13], pharyngitis [13], gastroenteritis [13], amblyopia [7], abnormal gait [7], speech disorder [7], disturbance in attention [10], accidental injury [14]. A greater understanding of when the most common adverse events (AEs) emerge or worsen could acid physicians and patients, particularly in cases where anticipation of mild AEs could facilitate improved medication adherence [22]. Dizziness and somnolence appeared frequently.

The limitation of the study may affect the results of the studies. The methods of some articles were not described elaborately, such as randomization, blinding. It led to make quality assessment difficult. As far as the patients' situation were concerned, they brought out influence factors. It included gender, age, course of disease, region, history of previous treatment, kidneys work, heart condition, drug or alcohol problems. As far as neuropathic pain was concerned, the patients' own situation had a certain impact on treatment. For example, it was noticed that female patients aged less than 50 years were found to be at a higher risk in comparison with men [23].

Another investigators have demonstrated the limitation were the different types of NP. Neuropathic pain is a pain that comes from problems with signals from the nerves. The diseases may act on different parts of the body. There may be differences in the response to drugs. However, the mechanisms of action of these diseases are similar. The underlying causes of neuropathic pain are wide and varied and clinical presentation is heterogeneous [24].

The wide variability in dose and duration of PGB might be another factor that limited the strength of the analysis results. The recom-
mended dose of PGB for neuropathic pain is 150 mg to 600 mg a day. Based on individual patient response and tolerability, the dose may be increased to a maximum dose of 600 mg a day. Pain reductions associated with PGB appear to be positively correlated with dosage, with the greatest effect observed in patients treated with 600 mg/day [14]. In the study, we selected 300 mg or the last dose a day. The duration of PGB use is also an influence factor. In the study, the course of treatment was at least 4 weeks. The duration of treatment also included 6 weeks, 8 weeks, 12 weeks. Different courses of treatment may have an impact on the efficacy and the side effects of the drug.

In summary, pregabalin has shown efficacy pain relief for neuropathic pain. At the same time, psychological symptoms of the patients is improved. Given the effect of pain relief, the adverse events are not hard to be tolerable. Of course, we have to pay attention to the adverse effect according to patients’ tolerability.

Disclosure of conflict of interest

None.

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