Int J Clin Exp Med 2017;10(1):16-29
www.ijcem.com /ISSN:1940-5901/IJCEM0041114

Review Article

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

Dong Wang[1,2], Jing-Bo Bao[3], Kai Zhang[2], Long-Fang Ju[4], Ling-Zhi Yu[1]

[1]Department of Pain Management, Jinan Central Hospital Affiliated to Shandong University, Jinan, Shandong, People's Republic of China; [2]Department of Anesthesia, Zhangqiu Hospital of Traditional Chinese Medicine, Zhangqiu, Shandong, People's Republic of China; [3]School Hospital, Yantai Vocational School, Yantai, Shandong, People's Republic of China; [4]Department of Anesthesia, Maternal and Child Health Care Hospital of Zhangqiu, Shandong, People's Republic of China

Received October 2, 2016; Accepted November 3, 2016; Epub January 15, 2017; Published January 30, 2017

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, Corchrane, 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 RR4.18 (95% CI 1.47, 1.87). Adverse effects were statistically significant, such as dizziness, peripheral edema, somnolence, RR3.23 (95% CI 2.78, 3.75), RR 2.91 (95% CI 2.24, 3.79), RR2.51 (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), posttraumatic pheripheral 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 relive 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

Table 1. Search strategy used in PubMed

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

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 Corchrane Central Trials Central (Corchrane 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. 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].

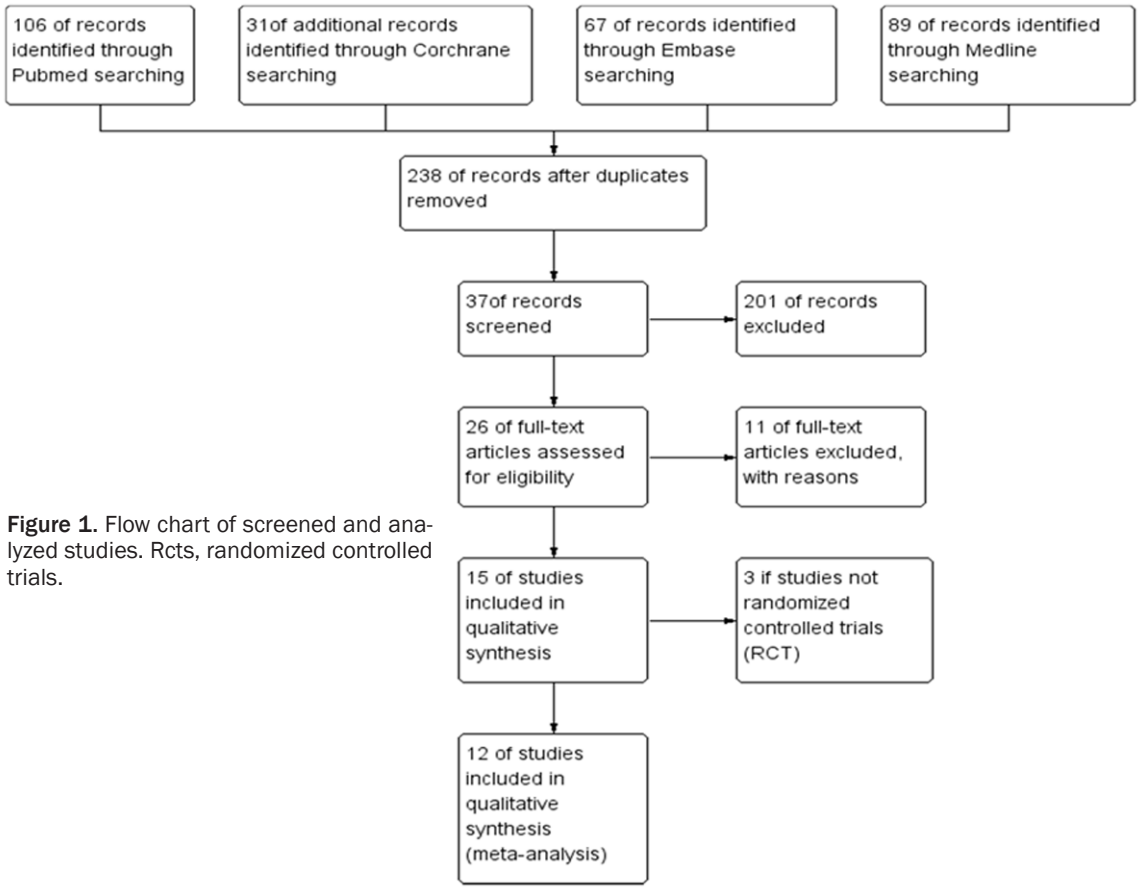

Figure 1. Flow chart of screened and analyzed studies. Rcts, randomized controlled trials.

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. Corchrane 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

First author	Year	Setting	Number PR/PL	Age (years) PR/PL	Design	Population	Origin of pain	Primary outcome	Secondary outcomes	Adverse Events
Simpson D.M	2010	America	151/151	(48.2 ± 8.1)/ (46.8 ± 7.5)	open-label, 3-months, pregabalin and placebo	40 centers in the United States	HIV-DSP	NRS (from mBOCF to LOCF)	NRS sleep Interference score, MOS sleep scale, HADS, PGIC, mBPI-sf, NPSI, GPS	Yes
Simpson Dvid M	2014	America	183/192	(41.2 ± 9.0)/ (42.3 ± 8.4)	Open-label, 6-months, pregabalin and placebo	45 centers in South Africa, United States, India, Thailand, Poland, Puerto Rico	HIV-DSP	NRS (from mBOCF to LOCF)	Responder status, PGIC, CGIC, NRS-sleep scores, HADS	Yes
Cardenas Diana D	2013	Ameri-can	111/108	(46.1 ± 12.7)/ (45.6 ± 13.8)	1,4,12-week dose opti-mization period, double-blinded manner	American Spinal injury Association	SCI	NRS (from mBOCF to LOCF)	Responder status, PGIC, MOS-SS, HARDS	Yes
Gilron Ian	2011	America	80/77	(58 ± 8.3)/ (61 ± 9.3)	9-week (4-week single-blind, Flexible dosing+5-week placebo-controlled double blind)	America clinical patients	DPN,PHN	Pain intensity	MOS-SS, mBPI-sf, HADS, PGIC, PTSS, EQ-5D	Yes
Dworkin R.H	2003	England	89/84	(72.4 ± 10.5)/ (70.5 ± 11.3)	at least 18 years,pain present for more than 3 month	English clinical patients	PHN	VAS	SF-MPQ	Yes
van Seventer R.	2010	America	127/127	(52 ± 14)/ (51 ± 13)	18-80 years, pain for morethan 3 month	American clinical patients	PT NeP (DPN, PHN, trigeminal, carpal tunnel syndrome, central neuropathic pain, CRPSII)	NRS	MOS-SS, HADS, mBPI-sf, PGIC	Yes
Freynhagen Rainer	2005	Germany	132/65	(61.8 ± 11.0)/ (61.7 ± 12.6)	randomized, double-blind, placebo-controlled	German Clinical patients	DPN, PHN	VAS	SF-MPQ	Yes
Freynhagen Rainer	2015	Germany	4884/2626	(60.6 ± 13.3)/ (59.1 ± 13.7)	Randomized, controlled trials	May 1998 to May 2012, Asia, Australia, Canada, Europe, Latin America, The Middle East, South Africa, the United States	DPN, PHN, CLBP, HIV neuropathy, cancer related NeP, and other NeP condi-tions (TGN and disturbed sleep concurrent with NeP)	AEs	No	Yes
Sabatowski Rianer	2004	Germany	76/81	(71.9 ± 10.3)/) (73.2 ± 10.3)	17 February 1999	Europe, Australia	PHN	VAS of SF-MPQ	MSIS, PGIC, CGIC, SF-36, Zung SRDS	Yes
Freeman Roy	2008	America	266/557	(59.10 ± 10.93)/ (58.78 ± 11.24)	5 to 13 weeks	America	DPN	NRS (from mBOCF to LOCF)	Responders (pain level), PGIC	Yes
Mishra Seema	2012	India	30/30	Not mentioned	4-week	India	NeP	VAS,	LANSS, ECOG	Yes
Tolle Thomas	2008	America	99/96	(57.28 ± 10.5)/ (58.93 ± 11.7)	Randomized, double-blinded, placebo-controlled	Europe (Germany, Hungary, Poland, The United Kingdom)	DPN, PHN	NRS	Responders (pain level), PGIC, CGIC, EQ-5D	Yes

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, SCI = 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.

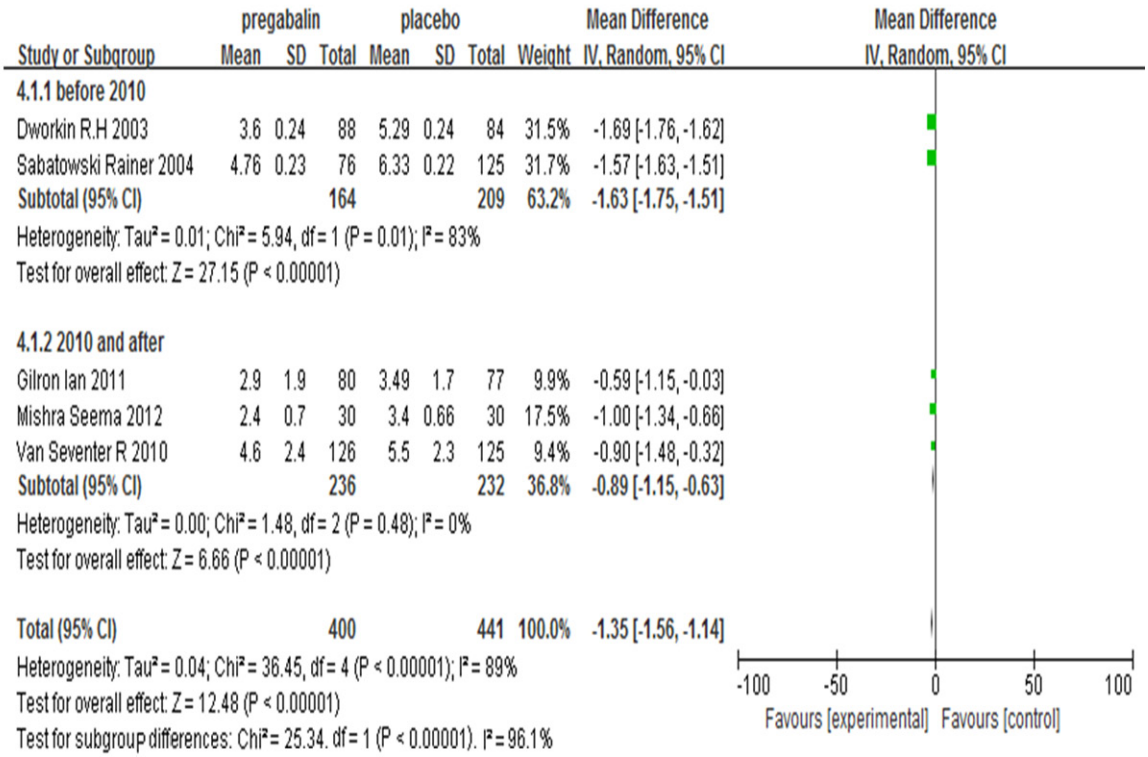

Figure 2. Review: Pregabalin and neuropathic pain (systematic review). Comparison: 01 Pregabalin vs placebo control. Outcome: 01 Pain intensity score (VAS).

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.corchrane.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. $I^2 = (Q\text{-}df)/Q \times 100\%$. 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%,

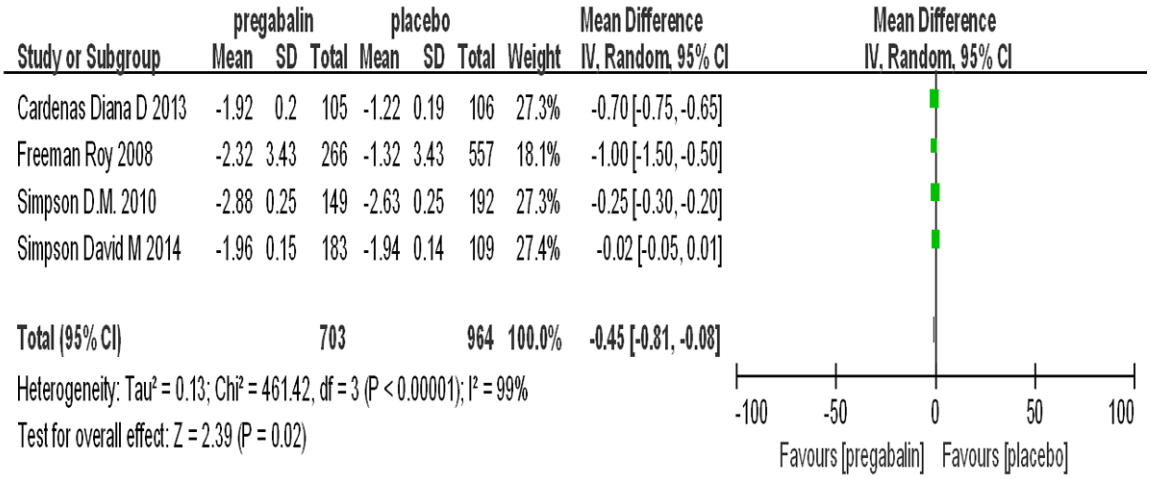

Figure 3. Review: Pregabalin and neuropathic pain (systematic review). Comparison: 01 Pregabalin vs placebo control. Outcome: 02 NPRS(mBOCF to LOCF).

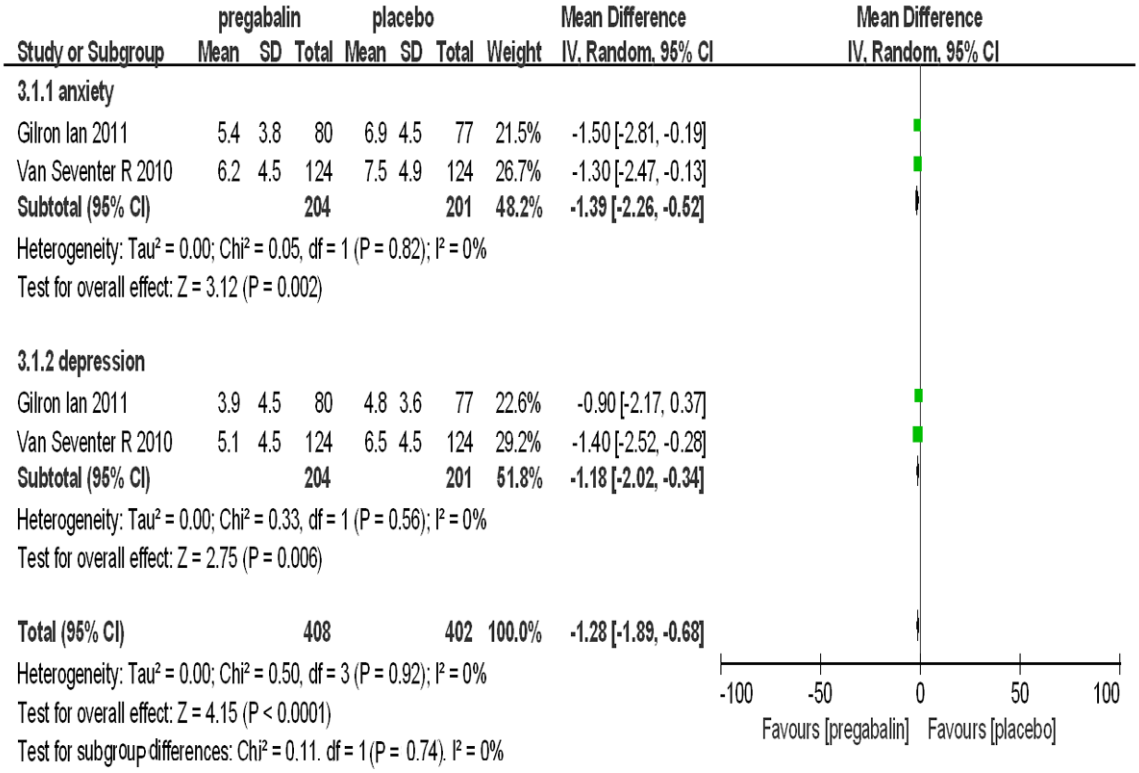

Figure 4. *Review:* Pregabalin and neuropathic pain (systematic review). Comparison: 01 Pregabalin vs placebo control. Outcome: 03 HADS (anxiety and depression).

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 signi ficant.

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

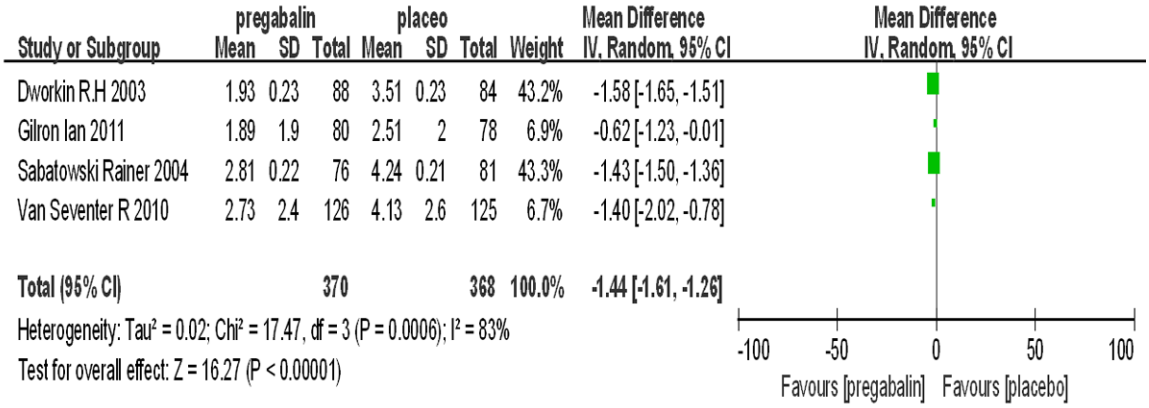

Figure 5. Review: Pregabalin and neuropathic pain (systematic review). Comparison: 01 Pregabalin vs placebo control. Outcome: 04 Sleep interfere score (LOCF).

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 pragabalin.

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) (fives 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). Fives studies were reported as VAS (**Figure 2**) [7-11]. Two studies were published before 2010 [7, 8], while three studies were in or after 2010 [9-11]. The results were respectively as WMD -1.62 cm (95% CI -1.67,-1.58), I^2 = 83%, P<0.0001; WMD -0.89 cm (95% CI-1.15, -0.63), I^2 = 0% P<0.00001. There were both statistically significant differences, low heterogeneity in the latter.

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), I^2 = 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.

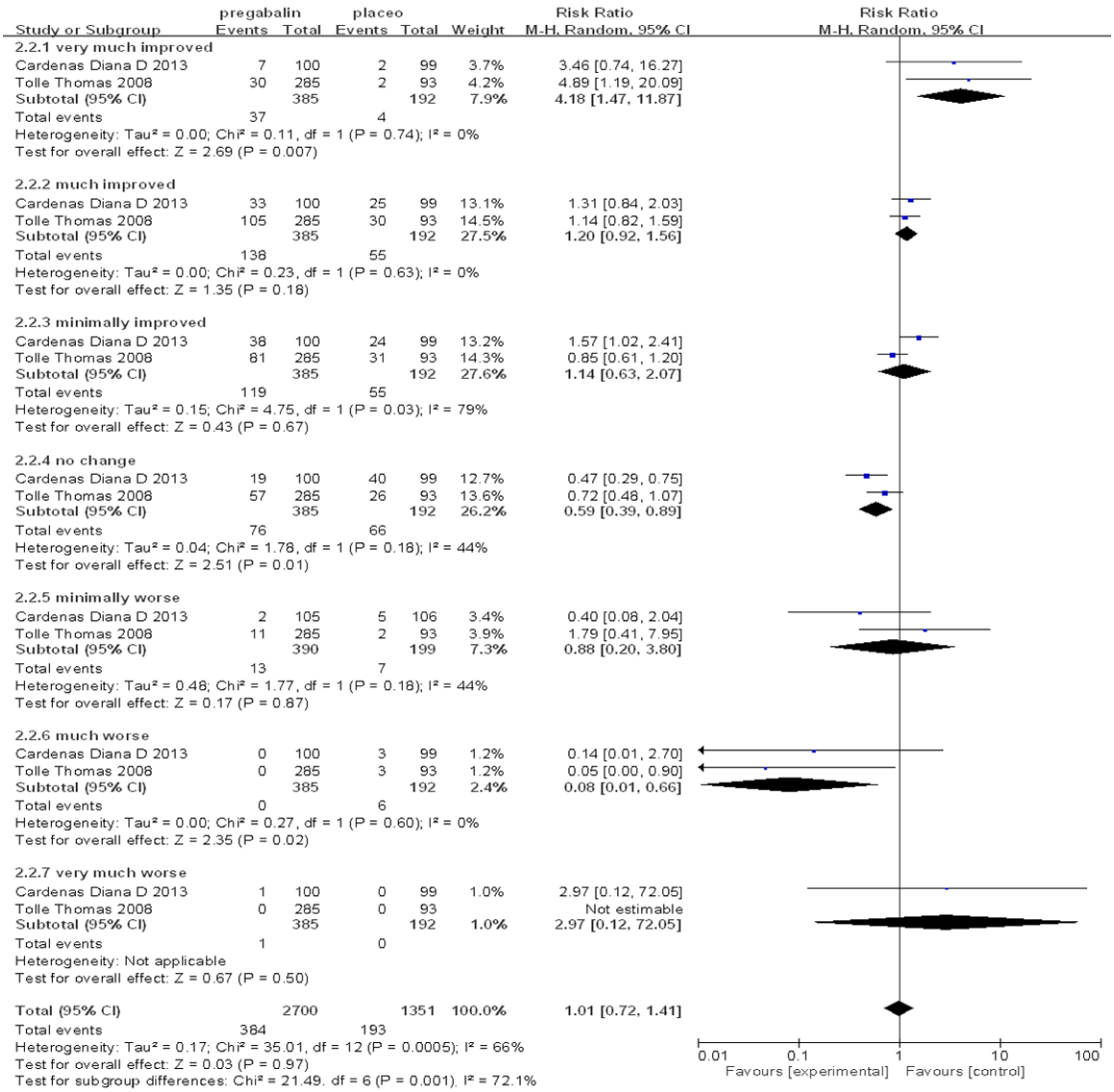

Figure 6. Review: Pregabalin and neuropathic pain (systematic review). Comparison: 01 Pregabalin vs placebo control. Outcome: 05 PGIC and CGIC.

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 interfere 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, I^2 = 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, I^2 = 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,

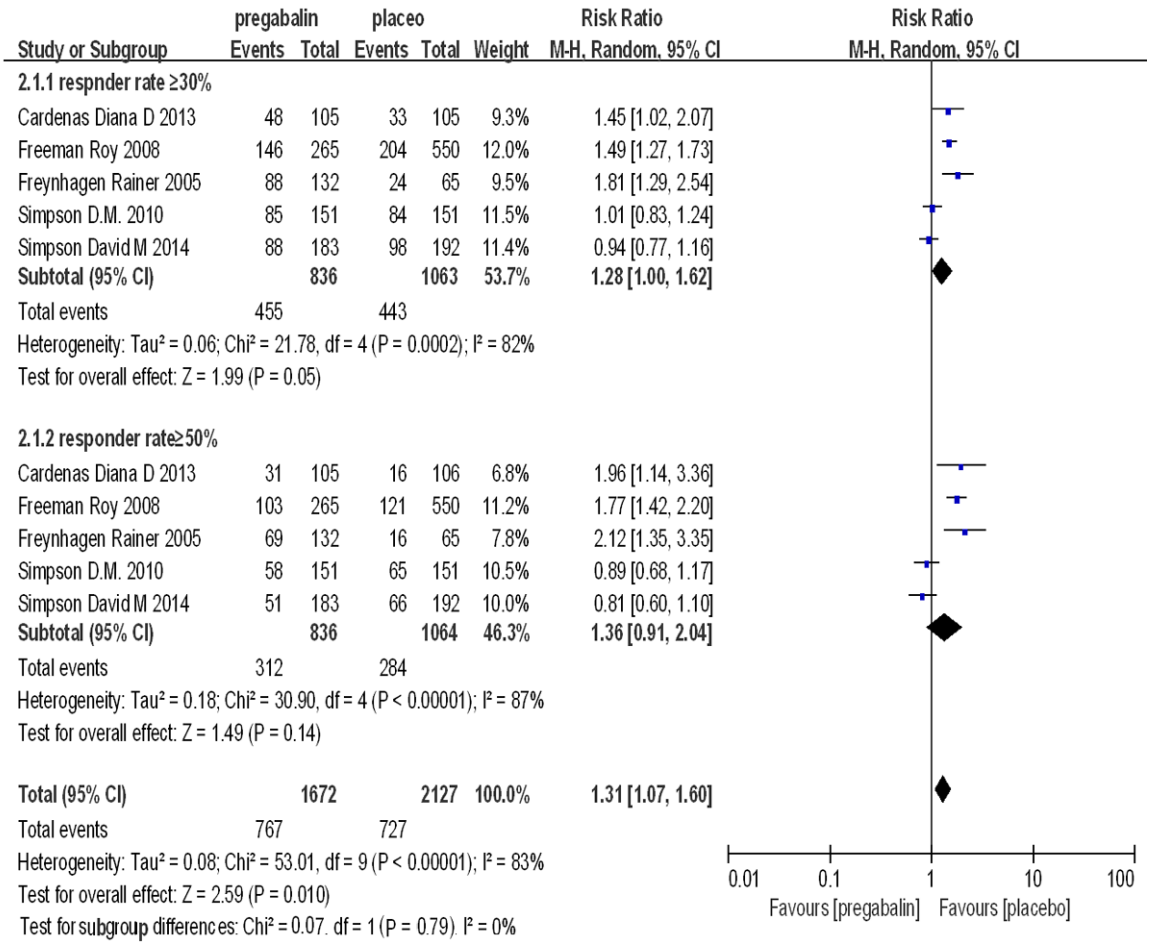

Figure 7. Review: Pregabalin and neuropathic pain (systematic review). Comparison: 01 Pregabalin vs placebo control. Outcome: 06 Responder rate.

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 3.38 (95% CI 1.28, 8.95), RR 2.04 (95% CI 1.57, 2.66), RR 2.36 (95% CI 1.71, 51.38). 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 so far to conclude that pregabalin was an effective pharmacological approach to reduction of neuropathic pain. The results suggested that, compared

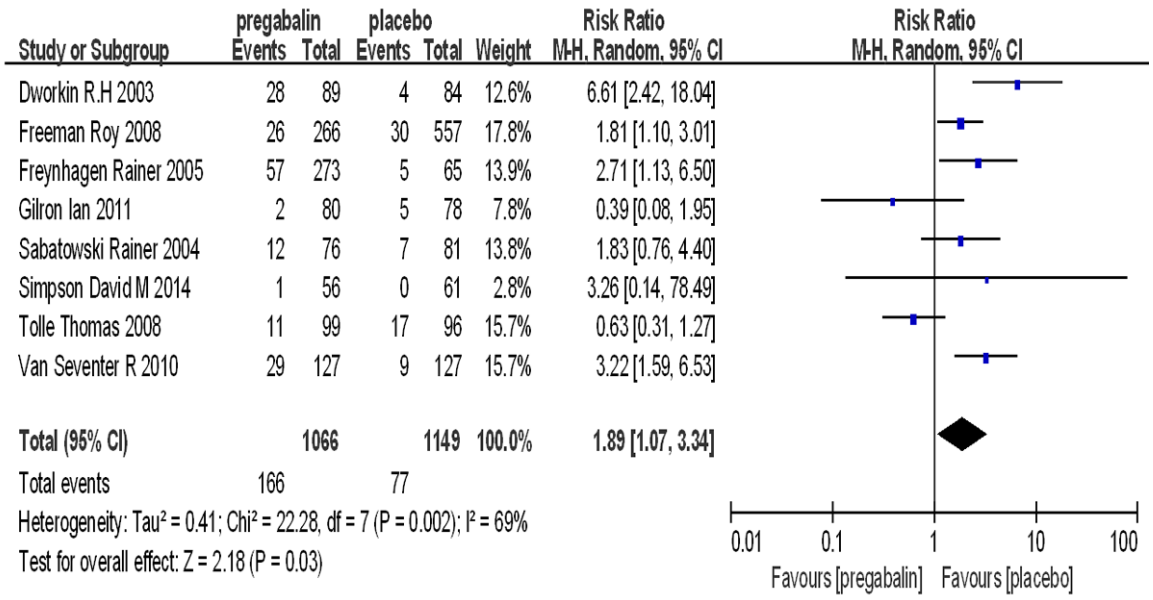

Figure 8. Review: Pregabalin and neuropathic pain (systematic review). Comparison: 01 Pregabalin vs placebo control. Outcome: 07 Withdraw.

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 Admi nistration 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 pregabalins' 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

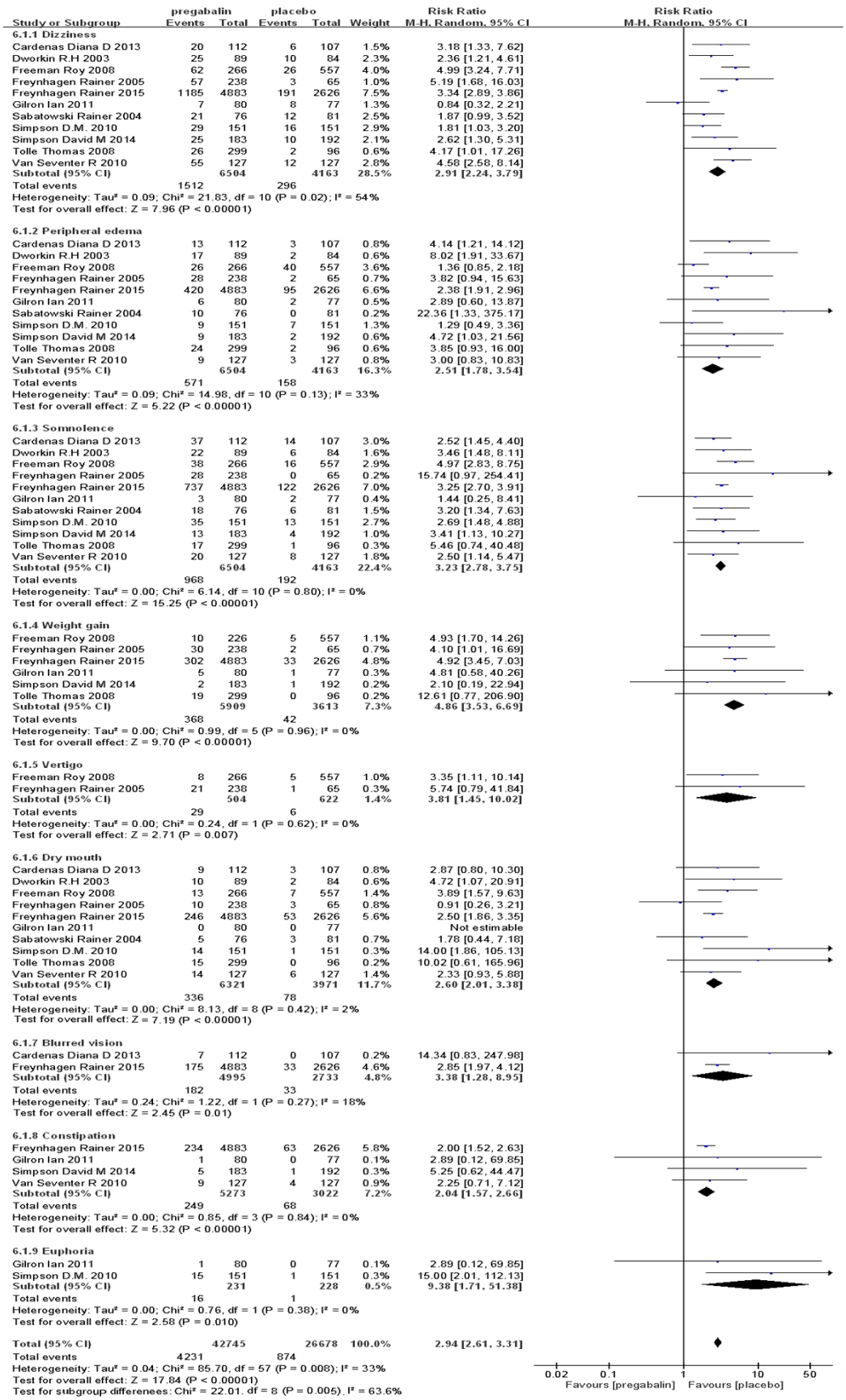
pregabalin
placebo
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
6.1.1 Dizziness
Cardenas Diana D 2013 20 112 6 107 1.5% 3.18 [1.33, 7.62]
Dworkin R.H 2003 25 89 10 84 2.3% 2.36 [1.21, 4.61]
Freeman Roy 2008 62 266 26 557 4.0% 4.99 [3.24, 7.71]
Freynhagen Rainer 2005 57 238 3 65 1.0% 5.19 [1.68, 16.03]
Freynhagen Rainer 2015 1185 4883 191 2626 7.5% 3.34 [2.89, 3.86]
Gilron Ian 2011 7 80 8 77 1.3% 0.84 [0.32, 2.21]
Sabatowski Rainer 2004 21 76 12 81 2.5% 1.87 [0.99, 3.52]
Simpson D.M. 2010 29 151 16 151 2.9% 1.81 [1.03, 3.20]
Simpson David M 2014 25 183 10 192 2.1% 2.62 [1.30, 5.31]
Tolle Thomas 2008 26 299 2 96 0.6% 4.17 [1.01, 17.26]
Van Seventer R 2010 55 127 12 127 2.8% 4.58 [2.58, 8.14]
Subtotal (95% CI) 6504 4163 28.5% 2.91 [2.24, 3.79]
Total events 1512 296
Heterogeneity: Tau² = 0.09; Chi² = 21.83, df = 10 (P = 0.02); I² = 54%
Test for overall effect: Z = 7.96 (P < 0.00001)
6.1.2 Peripheral edema
Cardenas Diana D 2013 13 112 3 107 0.8% 4.14 [1.21, 14.12]
Dworkin R.H 2003 17 89 2 84 0.6% 8.02 [1.91, 33.67]
Freeman Roy 2008 26 266 40 557 3.6% 1.36 [0.85, 2.18]
Freynhagen Rainer 2005 28 238 2 65 0.7% 3.82 [0.94, 15.63]
Freynhagen Rainer 2015 420 4883 95 2626 6.6% 2.38 [1.91, 2.96]
Gilron Ian 2011 6 80 2 77 0.5% 2.89 [0.60, 13.87]
Sabatowski Rainer 2004 10 76 0 81 0.2% 22.36 [1.33, 375.17]
Simpson D.M. 2010 9 151 7 151 1.3% 1.29 [0.49, 3.36]
Simpson David M 2014 9 183 2 192 0.6% 4.72 [1.03, 21.56]
Tolle Thomas 2008 24 299 2 96 0.6% 3.85 [0.93, 16.00]
Van Seventer R 2010 9 127 3 127 0.8% 3.00 [0.83, 10.83]
Subtotal (95% CI) 6504 4163 16.3% 2.51 [1.78, 3.54]
Total events 571 158
Heterogeneity: Tau² = 0.09; Chi² = 14.98, df = 10 (P = 0.13); I² = 33%
Test for overall effect: Z = 5.22 (P < 0.00001)
6.1.3 Somnolence
Cardenas Diana D 2013 37 112 14 107 3.0% 2.52 [1.45, 4.40]
Dworkin R.H 2003 22 89 6 84 1.6% 3.46 [1.48, 8.11]
Freeman Roy 2008 38 266 16 557 2.9% 4.97 [2.83, 8.75]
Freynhagen Rainer 2005 28 238 0 65 0.2% 15.74 [0.97, 254.41]
Freynhagen Rainer 2015 737 4883 122 2626 7.0% 3.25 [2.70, 3.91]
Gilron Ian 2011 3 80 2 77 0.4% 1.44 [0.25, 8.41]
Sabatowski Rainer 2004 18 76 6 81 1.5% 3.20 [1.34, 7.63]
Simpson D.M. 2010 35 151 13 151 2.7% 2.69 [1.48, 4.88]
Simpson David M 2014 13 183 4 192 1.0% 3.41 [1.13, 10.27]
Tolle Thomas 2008 17 299 1 96 0.3% 5.46 [0.74, 40.48]
Van Seventer R 2010 20 127 8 127 1.8% 2.50 [1.14, 5.47]
Subtotal (95% CI) 6504 4163 22.4% 3.23 [2.78, 3.75]
Total events 968 192
Heterogeneity: Tau² = 0.00; Chi² = 6.14, df = 10 (P = 0.80); I² = 0%
Test for overall effect: Z = 15.25 (P < 0.00001)
6.1.4 Weight gain
Freeman Roy 2008 10 226 5 557 1.1% 4.93 [1.70, 14.26]
Freynhagen Rainer 2005 30 238 2 65 0.7% 4.10 [1.01, 16.69]
Freynhagen Rainer 2015 302 4883 33 2626 4.8% 4.92 [3.45, 7.03]
Gilron Ian 2011 5 80 1 77 0.3% 4.81 [0.58, 40.26]
Simpson David M 2014 2 183 1 192 0.2% 2.10 [0.19, 22.94]
Tolle Thomas 2008 19 299 0 96 0.2% 12.61 [0.77, 206.90]
Subtotal (95% CI) 5909 3613 7.3% 4.86 [3.53, 6.69]
Total events 368 42
Heterogeneity: Tau² = 0.00; Chi² = 0.99, df = 5 (P = 0.96); I² = 0%
Test for overall effect: Z = 9.70 (P < 0.00001)
6.1.5 Vertigo
Freeman Roy 2008 8 266 5 557 1.0% 3.35 [1.11, 10.14]
Freynhagen Rainer 2005 21 238 1 65 0.3% 5.74 [0.79, 41.84]
Subtotal (95% CI) 504 622 1.4% 3.81 [1.45, 10.02]
Total events 29 6
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 2.71 (P = 0.007)
6.1.6 Dry mouth
Cardenas Diana D 2013 9 112 3 107 0.8% 2.87 [0.80, 10.30]
Dworkin R.H 2003 10 89 2 84 0.6% 4.72 [1.07, 20.91]
Freeman Roy 2008 13 266 7 557 1.4% 3.89 [1.57, 9.63]
Freynhagen Rainer 2005 10 238 3 65 0.8% 0.91 [0.26, 3.21]
Freynhagen Rainer 2015 246 4883 53 2626 5.6% 2.50 [1.86, 3.35]
Gilron Ian 2011 0 80 0 77 Not estimable
Sabatowski Rainer 2004 5 76 3 81 0.7% 1.78 [0.44, 7.18]
Simpson D.M. 2010 14 151 1 151 0.3% 14.00 [1.86, 105.13]
Tolle Thomas 2008 15 299 0 96 0.2% 10.02 [0.61, 165.96]
Van Seventer R 2010 14 127 6 127 1.4% 2.33 [0.93, 5.88]
Subtotal (95% CI) 6321 3971 11.7% 2.60 [2.01, 3.38]
Total events 336 78
Heterogeneity: Tau² = 0.00; Chi² = 8.13, df = 8 (P = 0.42); I² = 2%
Test for overall effect: Z = 7.19 (P < 0.00001)
6.1.7 Blurred vision
Cardenas Diana D 2013 7 112 0 107 0.2% 14.34 [0.83, 247.98]
Freynhagen Rainer 2015 175 4883 33 2626 4.6% 2.85 [1.97, 4.12]
Subtotal (95% CI) 4995 2733 4.8% 3.38 [1.28, 8.95]
Total events 182 33
Heterogeneity: Tau² = 0.24; Chi² = 1.22, df = 1 (P = 0.27); I² = 18%
Test for overall effect: Z = 2.45 (P = 0.01)
6.1.8 Constipation
Freynhagen Rainer 2015 234 4883 63 2626 5.8% 2.00 [1.52, 2.63]
Gilron Ian 2011 1 80 0 77 0.1% 2.89 [0.12, 69.85]
Simpson David M 2014 5 183 1 192 0.3% 5.25 [0.62, 44.47]
Van Seventer R 2010 9 127 4 127 0.9% 2.25 [0.71, 7.12]
Subtotal (95% CI) 5273 3022 7.2% 2.04 [1.57, 2.66]
Total events 249 68
Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 3 (P = 0.84); I² = 0%
Test for overall effect: Z = 5.32 (P < 0.00001)
6.1.9 Euphoria
Gilron Ian 2011 1 80 0 77 0.1% 2.89 [0.12, 69.85]
Simpson D.M. 2010 15 151 1 151 0.3% 15.00 [2.01, 112.13]
Subtotal (95% CI) 231 228 0.5% 9.38 [1.71, 51.38]
Total events 16 1
Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 2.58 (P = 0.010)
Total (95% CI) 42745 26678 100.0% 2.94 [2.61, 3.31]
Total events 4231 874
Heterogeneity: Tau² = 0.04; Chi² = 85.70, df = 57 (P = 0.008); I² = 33%
Test for overall effect: Z = 17.84 (P < 0.00001)
Test for subgroup differenees: Chi² = 22.01. df = 8 (P = 0.005). I² = 63.6%
0.02 0.1 1 10 50
Favours [pregabalin] Favours [placebo]

Figure 9. Review: Pregabalin and neuropathic pain (systematic review). Comparison: 01 Pregabalin vs placebo control. Outcome: 08 adverse events.

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-relate 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], pharyngtis [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 frequ ently.

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.

Address correspondence to: Ling-Zhi Yu, Department of Pain Management, Jinan Central Hospital Affiliated to Shandong University, 105 Jiefang Road, Lixia District, Jinan 250013, Shandong, People's Republic of China. Tel: +86-531-85695150; Fax: +86-531-85695150; E-mail: tracy15953191260-@163.com

References

[1] Guay DR. Pregabalin in neuropathic pain: a more "pharmaceutically elegant" gabapentin? Am J Geriatr Pharmacother 2005; 3: 274-87.

[2] Raman S, DeAngelis C, Bruera E, Chow R, Lechner B, Chow E. Does Pregabalin Still Have a Role in Treating Cancer-Induced Bone Pain? J Clin Oncol 2016; 34: 524-6.

[3] Simpson DM, Schifitto G, Clifford DB, Murphy TK, Durso-De Cruz E, Glue P, Whalen E, Emir B, Scott GN, Freeman R; 1066 HIV Neuropathy Study Group. Pregabalin for painful HIV neuropathy: a randomized, double-blind, placebo-controlled trial. Neurology 2010; 74: 413-20.

[4] Snaith RP. The Hospital anxiety and depression scale. Health and Quality of Life Outcomes 2003; 1: 1-4.

[5] Swanenburg J, Gruber C, Brunner F, Wirth B. Patients' and therapists' perception of change following physiotherapy in an orthopedic hospital's outpatient clinic. Physiother Theory Pract 2015; 31: 293-8.

[6] Julian PT, Higgins SS. Cochrane Handbook for Systematic Reviews of Interventions. England: A John Wiley & Sons, Ltd; 2008. pp. 256-303.

[7] Dworkin RH, Corbin AE, Young JP Jr, Sharma U, LaMoreaux L, Bockbrader H, Garofalo EA, Poole RM. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 2003; 60: 1274-83.

[8] Sabatowski R, Galvez R, Cherry DA, Jacquot F, Vincent E, Maisonobe P, Versavel M; 1008-045 Study Group. Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. Pain 2004; 109: 26-35.

[9] Gilron I, Wajsbrot D, Therrien F, Lemay J. Pregabalin for peripheral neuropathic pain: a multicenter, enriched enrollment randomized withdrawal placebo-controlled trial. Clin J Pain 2011; 27: 185-93.

[10] van Seventer R, Bach FW, Toth CC, Serpell M, Temple J, Murphy TK, Nimour M. Pregabalin in the treatment of post-traumatic peripheral neuropathic pain: a randomized double-blind trial. Eur J Neurol 2010; 17: 1082-9.

[11] Mishra S, Bhatnagar S, Goyal GN, Rana SP, Upadhya SP. A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: a prospective randomized double-blind placebo-controlled study. Am J Hosp Palliat Care 2012; 29: 177-82.

[12] Cardenas DD, Nieshoff EC, Suda K, Goto S, Sanin L, Kaneko T, Sporn J, Parsons B, Soulsby M, Yang R, Whalen E, Scavone JM, Suzuki MM, Knapp LE. A randomized trial of pregabalin in patients with neuropathic pain due to spinal cord injury. Neurology 2013; 80: 533-9.

[13] Simpson DM, Rice AS, Emir B, Landen J, Semel D, Chew ML, Sporn J. A randomized, double-blind, placebo-controlled trial and open-label extension study to evaluate the efficacy and safety of pregabalin in the treatment of neuropathic pain associated with human immunodeficiency virus neuropathy. Pain 2014; 155: 1943-54.

[14] Freeman R, Durso-Decruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. Diabetes Care 2008; 31: 1448-54.

[15] Freynhagen R, Strojek K, Griesing T, Whalen E, Balkenohl M. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. Pain 2005; 115: 254-63.

[16] Tolle T, Freynhagen R, Versavel M, Trostmann U, Young JP Jr. Pregabalin for relief of neuropathic pain associated with diabetic neuropathy: a randomized, double-blind study. Eur J Pain 2008; 12: 203-13.
[17] Popat S, Matakidou A, Houlston RS. Thymidylate synthase expression and prognosis in colorectal cancer: a systematic review and meta-analysis. J Clin Oncol 2004; 22: 529-36.
[18] Nicholson B, Verma S. Comorbidities in chronic neuropathic pain. Pain Med (Malden, Mass) 2004; 5 Suppl 1: S9-S27.
[19] Baron R, Brunnmuller U, Brasser M, May M, Binder A. Efficacy and safety of pregabalin in patients with diabetic peripheral neuropathy or postherpetic neuralgia: Open-label, non-comparative, flexible-dose study. Eur J Pain 2008; 12: 850-8.
[20] Choy E, Richards S, Bowrin K, Watson P, Lloyd A, Sadosky A, Zlateva G. Cost effectiveness of pregabalin in the treatment of fibromyalgia from a UK perspective. Curr Med Res Opin 2010; 26: 965-75.
[21] Freynhagen R, Serpell M, Emir B, Whalen E, Parsons B, Clair A, Latymer M. A comprehensive drug safety evaluation of pregabalin in peripheral neuropathic pain. Pain Pract 2015; 15: 47-57.
[22] Parsons B, Emir B, Clair A. Temporal analysis of pain responders and common adverse events: when do these first appear following treatment with pregabalin. J Pain Res 2015; 8: 303-9.
[23] Khan TM, Alhafez AA, Syed Sulaiman SA, Bin Chia DW. Safety of pregabalin among hemodialysis patients suffering from uremic pruritus. Saudi Pharm J 2015; 23: 614-20.
[24] Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, Bushnell MC, Farrar JT, Galer BS, Haythornthwaite JA, Hewitt DJ, Loeser JD, Max MB, Saltarelli M, Schmader KE, Stein C, Thompson D, Turk DC, Wallace MS, Watkins LR, Weinstein SM. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Arch Neurol 2003; 60: 1524-34.