BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023600
Article Type:	Research
Date Submitted by the Author:	17-Apr-2018
Complete List of Authors:	Onakpoya, Igho; University of Oxford, Primary Care Health Sciences Thomas, Elizabeth; Bond University Faculty of Health Sciences and Medicine, Faculty of Health Sciences and Medicine Lee, Joseph; University of Oxford, Nuffield Department of Primary Care Health Sciences Goldacre, Ben; University of Oxford, Primary Care Health Sciences Heneghan, Carl; Oxford University, Primary Health Care
Keywords:	pregabalin, benefits, harms, systematic review, meta-analysis

Benefits and harms of pregabalin in the management of neuropathic pain: a rapid systematic review and meta-analysis of randomized clinical trials

Igho J Onakpoya, research fellow[1], Elizabeth T Thomas, medical student[2], Joseph Lee, nihr in practice fellow[1], Ben Goldacre, senior clinical research fellow[1], Carl J Heneghan, director[1]

[1]University of Oxford, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Oxford, United Kingdom OX2 6GG

[2]Faculty of Health Sciences and Medicine, Bond University, 14 University Drive, Robina, Australia QLD 4226

Correspondence to IJ Onakpoya igho.onakpoya@phc.ox.ac.uk

ABSTRACT

Objective To assess the benefits and harms of pregabalin in the management of neuropathic pain

Design Rapid systematic review and meta-analysis of phase III randomized placebo-controlled trials.

Participants Adults aged 18 and above with neuropathic pain defined according to the International Association for the Study of Pain (IASP) criteria.

Interventions Pregabalin or placebo, with or without co-interventions.

Primary and secondary outcome measures Our primary outcomes were pain (as measured using validated scales) and adverse events. Our secondary outcomes were sleep disturbance, quality of life (QOL), patient global impression of change (PGIC), clinician global impression (CGI) scale, anxiety and depression scores, overall discontinuations and discontinuations because of adverse events.

Results We included 28 trials comprising 6087 participants. The neuropathic pain conditions studied were diabetic peripheral neuropathy, post-herpetic neuralgia, herpes zoster, sciatica, post-stroke pain and spinal cord injury-related pain. Patients who took pregabalin reported significant reductions in pain scores compared to placebo, SMD -0.49 (95% CI -0.66 to -0.32, P<0.00001); very low quality evidence. Pregabalin significantly reduced sleep interference scores (NRS) compared with placebo, SMD -0.38 (95% CI -0.50 to -0.26, P<0.00001) moderate quality evidence. Pregabalin significantly increased the risk of adverse events compared with placebo, RR 1.33 (95% CI 1.23 to 1.44, P<0.00001, low quality evidence). The risks of experiencing weight gain, somnolence, dizziness, peripheral oedema, fatigue, visual disturbances, ataxia, non-peripheral oedema, vertigo and euphoria were significantly increased with pregabalin. Pregabalin was significantly more likely than placebo to lead to

discontinuation of the drug because of adverse events, RR 1.91 (95% CI 1.54 to 2.37, P<0.00001), low quality evidence.

Conclusion Pregabalin has beneficial effects on some symptoms of neuropathic pain. However, its use significantly increases the risk of a number of adverse events and discontinuation due to adverse events. The quality of the evidence from journal publications is low.

Strengths and limitations of the study

- We undertook the same rigorous approach using Cochrane criteria for other systematic reviews within the time constraints.
- This is the first review that rates the quality of the evidence for each outcome assessed.
- The review may be prone to sampling bias, and we may have missed potentially eligible studies.
- We did not assess the extent to which different doses of pregabalin influenced the outcomes.

INTRODUCTION

Pregabalin is a gabapentinoid licensed for treatment of neurologic disorders. It is one of the earlier drugs approved by the United States Food and Drug Administration (FDA) (2004) for the treatment of painful diabetic neuropathy (PDN) and post-herpetic neuralgia (PHN).[1] Pregabalin is thought to exert its analgesic action through antagonistic activity at the voltage gated Ca2+ channels where it binds to the alpha-2-delta subunit.[1,2]

Prescriptions of pregabalin (and gabapentin) have markedly increased over the last few years. In the US, prescriptions for pregabalin rose from 39 million in 2012 to 64 million in 2016 *versus* (spend increased from approximately $2 billion to $4.4 billion over the same period. [3] In the UK, pregabalin use increased 350% over a five year period between 2008 and 2013. [4] In England alone, there were over 6.2 million prescriptions of pregabalin across GP practices in 2017 costing about $440 million.[5]

Pregabalin is recommended as first-line pharmacologic agent for management of neuropathic pain[6]. There is, however, some evidence of increased mortality attributed pregabalin in the UK,[7] and this has led some authors to caution clinicians about the risk of harms when prescribing. [8] The risks are thought to be particularly acute for patients who use heroin and those who misuse gabapentinoids. Indeed, the UK government is soon to classify the drug as a class C controlled substance because of its abuse potential and increased reports of deaths attributed to its use.[9] Practicing clinicians have also recently called for the evidence for the effectiveness of pregabalin to be re-examined in the light of its potential to cause harms.[3,4]

The objective of this rapid review was therefore to evaluate the evidence for benefits and harms of pregabalin in the treatment of neuropathic pain in adults, using evidence from published randomized clinical trials (RCTs).

METHODS

We conducted electronic searches in the Medline, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL). We searched each database from inception till January 2018. No language restrictions were imposed. [See appendix 1 for a full search strategy]. We also hand searched the bibliography of eligible studies.

We included phase III double-blinded placebo-controlled RCTs (efficacy studies) assessing the effects of pregabalin on neuropathic pain in adults aged 18 years and above. We included studies on neuropathic pain based on the definition of the International Association for the Study of Pain (IASP) definition.[10] These included trials on diabetic neuropathy, HIV-related neuropathy, lumbar radiculopathy, post-herpetic neuralgia, and chronic postsurgical pain. We included RCTs irrespective of study size and duration. If we included RCTs with a cross-over design, we used data from the first phase of the study. We excluded phase IV trials because they are typically unblinded. We also excluded studies that combined pregabalin with other types of pain intervention because the effects of such interventions would not be exclusively due to the actions of pregabalin; however, co-interventions used were allowed. Trials that randomized participants based on response to pregabalin therapy in the run-in phase were also excluded. Our main outcomes were pain (as measured using validated scales because such scales enhance the credibility of the measured outcomes[11]) and adverse events. Our secondary outcomes were sleep disturbance, quality of life (QOL), patient global impression

of change (PGIC), clinician global impression (CGI) scale, anxiety and depression, overall discontinuations and discontinuations because of adverse events.

The risk of bias for each included study was rated using Cochrane criteria.[12] Two reviewers (IJO and ETT) independently assessed the eligibility of studies, assessed the risk of bias. Three reviewers (IJO, ETT, JL) independently extracted the data. Any disagreements were resolved through discussion. For each included study, we extracted data on study ID, settings, populations, interventions, outcomes and results.

Using the random effects model (Mantel-Haenszel) of the standard meta-analysis software (RevMan 5.3),[13] we computed standardized mean differences (SMDs) and 95% confidence intervals (CIs) for continuous outcomes and risk ratios with 95% CI for binary outcomes. We used pre- to post-intervention changes to assess intervention effects between pregabalin and placebo. Where studies reported data on change from baseline but did not report standard deviations (SDs), we imputed SDs based on the SD of other studies included in the meta-analysis.[14] We used a value of P=0.05 as our threshold for statistical significance. We assessed heterogeneity using the I-squared statistic: values of 25%, 50% and 75% judged mild, moderate and substantial heterogeneity respectively. We investigated heterogeneity using subgroup (based on central or peripheral neuropathic pain) and sensitivity (based on study quality and/or duration) analyses. We used a funnel plot to assess publication bias.

Two reviewers (IJO and ETT) independently entered the data onto RevMan software and independently cross-checked each other's entry. Using the GRADEpro software (version 3.6),[15] we rated the overall quality of the body of evidence for each outcome using the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE)[16] criteria

which examines the following domains: study design; risk of bias; inconsistency; indirectness; and imprecision.

Patient public involvement

Because this was a rapid review, we did not enlist the services of patient representatives in this research.

RESULTS

Our searches identified 1349 non-duplicate citations, out of which 62 articles were considered eligible (Figure 1). We excluded 34 articles that did not fit our inclusion criteria. [See Appendix 2 for list of excluded studies and the reasons for exclusion]. In total, we included 28 studies[17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44] comprising 6087 participants (Table 1). The intervention duration was between three and 20 weeks (median 8 weeks) and all the trials were industry funded.

Twenty three studies examined the effectiveness of pregabalin in treatment of peripheral neuropathic pain including DPN, PHN and Herpes zoster (HZ) (Table 1). Five studies examined the effectiveness of pregabalin for treating central neuropathic pain including sciatica, post-stroke pain and spinal cord injury-related pain. Twenty five studies were conducted in two or more centres. Outcome measures for pain included numerical rating scale (NRS), visual assessment scale (VAS), Short-Form McGill Pain Questionnaire visual assessment scale (SF-MPQ VAS), and SF-MPQ personal pain intensity (SF-MPQ PPI) index [see Table 1 for full characteristics of included studies]. The overall risk of bias in the included studies was moderate to high (Figures 2a and 2b). This was mainly due to

inadequate reporting of blinding procedures, selective outcome reporting and financial conflicts of interest amongst study authors.

Pain

Twenty one studies provided adequate data on pain using the NRS or variants of it to allow meta-analysis. Meta-analysis showed a significant reduction in pain scores with pregabalin compared with placebo, SMD -0.49 (95% CI -0.66 to -0.32, P<0.00001, I^2=88%: Figure 3). A funnel plot showed that the studies were symmetrically distributed around the mean difference for all trials (Figure S1). The effect was significant for peripheral neuropathic pain (P<0.00001), but not for central neuropathic pain (P=0.08; Appendix table 1). The overall quality of the evidence was very low (Summary of Findings (SoF) Table 1). Sensitivity analyses revealed similar direction of effects (Appendix Table 2). Four studies that measured pain using NRS did not provide adequate data for meta-analysis; three of these reported significant reductions in pain scores favouring pregabalin over placebo, while one reported no significant difference between groups (See Appendix Table 3).

Three studies measured pain using the VAS, and all showed significant reduction in pain scores favouring pregabalin over placebo (Appendix Table 3). Nine studies measured pain using SF-MPQ VAS, and all reported significant reduction in pain scores favouring pregabalin over placebo. Four studies measured pain using SF-MPQ PPI index, and all reported significant reduction in pain scores favouring pregabalin over placebo.

Table 1: Main characteristics of RCTs assessing the effects of pregabalin in the management of central and peripheral neuropathic pain

Study ID	Design	Sample size	Duration	Setting	Population	Duration of neuropathic pain	Outcome measures	Interventions		
								Pregabalin	*Placebo*	*Co-interventions*
Arezzo 2008 [17]	Parallel-group	PGB 82; PLA 85	13 weeks	23 centres; USA	Men or women with T1DM or T2DM	≥3 months	**Primary:** Mean pain scores (MPS); proportion of responders; Adverse events≥3% **Secondary:** Sleep interference (11 point NRS), Present pain intensity (PPI) index; SF-MPQ VAS; CGIC; PGIC	600 mg/d Fixed	Not described	Aspirin (up to 325 mg/d for cardiac and stroke prophylaxis), acetaminophen (up to 4 g/d), SSRIs, and benzodiazepines such as lorazepam (dosed at bedtime with stable [>30 days] regimen for sleep problems) were allowed.
Cardenas 2013 [18]	Parallel-group	PGB 112; PLA 108	16 weeks	60 centres; Chile, China, Columbia, Czech Republic, Hong Kong, India, Japan, Phillipines, Russia, USA	Patients aged ≥18 years with C2-T12 complete/incomplete SCI	≥ 12 months	**Primary:** Duration-adjusted average change in pain (DAAC); **Secondary: C**hange in mean pain score (from baseline to endpoint); Percentage of patients with >/=30% reduction in mean pain score at end point; PGIC scores at endpoint; change in mean pain-related sleep interference score; change from baseline in mean pain at each study week; change from baseline in pain-related sleep interference scores at each week; Medical Outcomes Study-Sleep Scale (MOS-SS); Hospital Anxiety and Depression scale scores (at baseline and endpoint)	150-600mg/d Flexible phase followed by maintenance phase	Matching grey capsule	Nonsteroidal anti-inflammatory drugs, cyclo-oxygenase-2 inhibitors, and acetaminophen (≤1.5 g/d in Japan, ≤4 g/d in all other countries) were permitted as rescue therapy. Antidepressants were permitted if the patient was on a stable dose within 30 days before the first visit.
Dworkin 2003 [19]	Parallel-group	PGB 89; PLA 84	8 weeks	29 centres; USA	Men or women ≥18 years old with post-herpetic neuralgia	≥3 months	**Primary:** Pain reduction in last 24 hours; Safety and adverse events **Secondary:** SF-MPQ at baseline, weeks 1,3,5,8; daily sleep interference score; MOS-SS; SF-36; PGIC; CGIC	300mg/d, 600mg/d Fixed	Identical in appearance; administered 1 capsule three times daily	Permitted medications included narcotic and non-narcotic analgesics, acetaminophen (not to exceed 4g/day), nonsteroidal anti-inflammatory drugs, aspirin, and antidepressants, including selective serotonin reuptake inhibitors (provided that dosing had been stable for at least 30 days before baseline)
Freynhagen 2005 [20]	Parallel-group	PGB 273; PLA 65	12 weeks	60 centres; 9 European countries that were not specified	Men or women ≥18 years old with primary diagnosis of painful DPN or post-herpetic neuralgia	≥3 months PHN, ≥6 months DPN	**Primary:** Mean Pain Score; adverse events; **Secondary:** daily sleep interference diary; MOS-SS; PGIC	150-600mg/d Flexible; 300mg/d, 600mg/d Fixed	Matching capsules; matching twice daily dosing schedule	SSRIs for treatment of depression, aspirin for myocardial infarction and stroke prophylaxis, short-acting benzodiazepines for insomnia, and paracetamol as rescue medication were allowable medications during the study period.
Guan 2011 [21]	Parallel-group	PGB 206; PLA 102	8 weeks	11 centres; China	Males or females 18-75 years with primary diagnosis of painful DPN or PHN	≥3 months PHN, ≥1 year, <5 years DPN	**Primary:** Mean Pain score (DPRS) during preceding 24h; DAAC score; **Secondary:** Daily sleep interference scale; SF-MPQ; PGIC; CGIC; Safety and adverse events	150-600mg/d Flexible	Flexible dose placebo in matching capsules; doses titrated using same regimen	NSAIDs and SSRIs allowed to be continued on stable dose
Holbech 2015 [22]	Cross-over	PGB 18; PLA 19	5 weeks	3 centres; Denmark	Males or females 20-85 years with polyneuropathy due to dpn	≥6 months	**Primary:** Total pain intensity on NRS; adverse events; **Secondary:** pain-related sleep disturbances; pain relief on 6-point verbal scale; **Other:** specific pain symptoms on the NRS; number of paracetamol tablets used as escape medication; SF-36 (health related QoL); Major Depression Inventory; QST tests	150mg/d, 300mg/d Fixed	Matched placebos of identical appearance to the 2 trial drugs were dosed similarly using double-dummy technique.	Up to 6 tablets of 500 mg paracetamol could be used daily as escape medication
Huffman 2015 [23]	Cross-over	PGB 101; PLA 102	6 weeks	36 centres; USA (25), Sweden (4), South Africa (4), Czech Republic (3)	Men or women ≥18 years old with painful DPN and with pain on walking	Not described	**Primary:** Numeric Rating Scale (NRS); DPN Pain on Walking (NRS); **Secondary:** 30%, 50% responders**;** Brief Pain Inventory-Short Form (BPI-sf); Daytime Total Activity Counts per Day; Steps per Day; Walk 12 questionnaire; Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) Total Quality of Life (TQOL) Score; Euro QoL-5 Dimensions (EQ-5D); Mean Sleep Interference Rating Score; HADS	150-300 mg/day Fixed	Matching placebo also administered in 3 divided doses	Not described

Kanodia 2011 [24]	Parallel-group	PGB 23; PLA 22	4 weeks	1 centre; India	Patients with acute herpes zoster presenting within 72 hours of onset	< 3 days	**Primary:** Pain on linear VAS; Adverse events	150mg/d Fixed	Not described	Oral acyclovir 800mg was given 5 times per day for 7 days
Kim 2011 [25]	Parallel-group	PGB 110; PLA 109	12 weeks	32 centres; Asia-Pacific	Males or females ≥18 years with diagnosis of central post-stroke pain	≥3 months	**Primary:** Mean pain score; **Secondary:** Daily sleep interference scale (DSIS); Weekly mean pain scores; proportion of 30%, 50% responders; quantitative assessment of Neuropathic pain (QANeP); Neuropathic Pain Symptom Inventory (NPSI); Weekly mean sleep interference scores; MOS-SS; HADS; SF-MPQ VAS- Part B; Euro Quality of Life (EQ-5D); PGIC; CGIC; Safety and tolerability	300,600mg/d Dose adjustment followed by fixed maintenance phase	Matching placebo	Stable medications for pain or insomnia if used normally >30 days before screening
Krcevski Skvarc 2010 [26]	Parallel-group	PGB 14; PLA 15	3 weeks	1 centre; Slovenia	Men or women 30-80 years with herpes zoster pain.		**Primary:** Assessment of pain severity (11 point Likert scale); Secondary: patients' ratings of the severity of allodynia, hyperalgesia, and burning, prickling and tingling sensations; rating of quality of sleep and physical activity; consumption of analgesics; occurrence of adverse events; SHN; PHN	150 or 300mg/d Fixed	Placebo also administered twice daily	Oxycodone, naproxen and/or tramadol, morphine, diclofenac
Lesser 2004 [27]	Parallel-group	PGB 240; PLA 97	5 weeks	45 centres; USA	Men or women ≥18 years old who were diagnosed with diabetes mellitus (type 1 or 2) and had distal symmetric sensorimotor polyneuropathy.	1-5 years	**Primary:** Pain (11-point NRS); **Secondary:** daily sleep interference diary; SF-MPQ; CGIC; PGIC; SF-36; POMS; **Safety outcomes**	75, 300, 600mg/d Fixed	Placebo administered three times daily	Acetaminophen and SSRIs permitted
Liu 2015 [28]	Parallel-group	PGB 112; PLA 110	8 weeks	22 centres; China	Male and female ethnically Chinese patients aged ≥ 18, diagnosed with post-herpetic neuralgia	Symptoms persisting ≥ 3 months after the healing of HZ lesions	**Primary:** Mean score of Daily Pain Rating Score; **Secondary:** Change from baseline on Pain VAS; Change from baseline on Present Pain Intensity (PPI) of the SF-MPQ; 30% pain responders at endpoint; change from baseline in weekly mean pain score; change from baseline in sleep interference score (11-point NRS); CGIC; PGIC; MOS-SS; Adverse events	150mg/d, 300mg/d Fixed	Matched placebo capsules on the same dosing schedule	Concomitant use of medications permitted except antidepressants, epileptics, analgesics or corticosteroids, skeletal muscle relaxants, mexelitine, and dextromethorphan as well as electrotherapy, transcutaneous electrical nerve stimulation, acupuncture, and neurosurgical therapy.
Mathieson 2017 [29]	Parallel-group	PGB 108; PLA 101	8 weeks	Number not specified; Australia	Patients with sciatica	≥1 week, <1 year	**Primary:** Average leg-pain intensity score over the course of previous 24 hours as assessed at 8 weeks and 52 weeks; **Secondary:** extent of disability (Roland Disability Questionnaire for sciatica); back pain intensity; global perceived effect; Quality of Life as measured on Short Form Health Survey 12; adverse events	150-600mg/d Flexible	Matching placebo capsules were packaged in white, opaque, sealed containers at a central pharmacy	Concomitant therapies included physical therapies as well as other analgesic medications (except for adjuvant analgesic agents), which would ideally be prescribed in accordance with the World Health Organization pain ladder. Trial clinicians were asked not to prescribe certain medicines (antiepileptic medications, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, topical lidocaine, and benzodiazepines) or to schedule interventional procedures.

Moon 2010 [30]	Parallel-group	PGB 162; PLA 78	10 weeks	Multicentre (number not specified); Korea	Korean patients aged 18 years with neuropathic pain (diabetic peripheral neuropathy, postherpetic neuralgia, or posttraumatic neuropathic pain)	Mean duration of pain pregabalin patients- 3 years, placebo patients 3.2 years	**Primary:** Endpoint mean DPRS score, Secondary: weekly mean DPRS score, duration adjusted average change (DAAC) of adjusted mean DPRS from baseline to endpoint, proportion of responders (whose scores reduced by 30% or 50%), Daily Sleep Interference Scale (DSIS), Euro Quality of Life assessment (EQ-5D): utility and VAS score; MOS-SS; HADS; PGIC; CGIC; **Tolerability evaluation** of adverse events and vital signs	150-600mg/d Flexible	Matching placebo capsules provided by Pfizer	Most patients were taking drug therapy at baseline, and the majority (83.8%) remained on concomitant drug therapy during the study, including one-third who received tricyclic antidepressants.
Rauck 2013 [31]	Parallel-group	PGB 56; PLA 112	20 weeks	85 centres; USA	Men or women ≥18 years old who were diagnosed with diabetes mellitus (type 1 or 2) and had pain attributed to DPN, defined as painful distal symmetric sensorimotor polyneuropathy.	≥6 months, <5 years	**Primary:** Change from baseline in pain intensity score (11 point PI-NRS); **Secondary:** Change from baseline in mean 24-hour average pain intensity score, daytime average pain intensity socre, nighttime average pain intensity score, current pain intensity score, daytime worst pain intensity score, nighttime worst pain intensity score, sleep interference score, and rescue analgesia consumption (mg); Neuropathic Pain Scale (NPS); SF-MPQ; pre- and post-50-foot (15 meter) walk pain scores; PGIC; CGIC; proportion of subjects achieving various levels of reduction in the 24-hour average pain intensity score; time to onset of sustained improvement in the 24-hour average pain intensity score; POMS; SF-36 health-related quality of life questionnaire; **Safety assessments**	300mg/d Fixed	Matching placebo in blister card	Acetaminophen, up to 3 g/day, was allowed as rescue medication for pain throughout the trial but was not allowed within 24 hours of any site visit for assessments.
Richter 2005 [32]	Parallel-group	PGB 161; PLA 85	6 weeks	Multicentre; not specified	Patients with diabetes and painful distal symmetrical sensorimotor polyneuropathy	1-5 years	**Primary:** Pain; Adverse events; **Secondary:** Pain characteristics (SF-MPQ, PPI); sleep interference (11 point NRS 0 to 10); health status (SF-36); psychologic state (POMS); global improvement (PGIC, CGIC)	150mg/d, 600mg/d Fixed	Matching dose and schedule	Aspirin (for prophylaxis of myocardial infarction and transient ischemic attacks), acetaminophen (3 g/day), and stable doses of serotonin reuptake inhibitors were allowed.
Rosenstock 2004 [33]	Parallel-group	PGB 76; PLA 70	8 weeks	25 centres	Men or women ≥18 years old with type 1 or 2 diabetes mellitus who reported symmetrical painful symptoms in distal extremities for a period of 1–5 years prior to study	1-5 years	**Primary:** Endpoint mean score **Secondary:** SF-MPQ-Sensory, affective and total score; daily sleep interference score; PGIC; CGIC; SF-36; Profile of Mood States (POMS); **Safety**	300mg/d Fixed	Lactose USP, 1 capsule three times daily	Acetaminophen (up to 4 g/day), aspirin (up to 325 mg/day for myocardial infarction or transient ischemic attack prophylaxis), and serotonin reuptake inhibitors provided no dose changes occurred within 30 days prior to randomization or during the study)
Sabatowski 2004 [34]	Parallel-group	PGB 157; PLA 81	8 weeks	53 centres; Europe, Australia	Men or women ≥18 years old with post-herpetic neuralgia	≥6 months	**Primary:** Endpoint mean score; **Secondary:** mean sleep interference scores, PGIC, CGIC, SF-36 health survey, Zung Self-Rating Depression Scale, VAS of the SF-MPQ, **Adverse events**	150mg/d, 300mg/d Fixed	Identical in appearance	Patients allowed to continue acetaminophen (up to 3 g/day), non-steroidal anti-inflammatory drugs, opioid or non-opioid analgesics, or antidepressants.
Satoh 2011 [35]	Parallel-group	PGB 179; PLA 90	13 weeks **intervention period	62 centres; Japan	Men or women ≥18 years old with diabetic peripheral neuropathy	≥ 1 year	**Primary:** Change from baseline in mean weekly pain score at week 13 using a 11 point NRS; **Secondary:** weekly mean pain scores, responder rates, SF-MPQ score, weekly mean sleep interference scores using 11-point NRS; MOS-Sleep Scale, SF-36, PGIC, CGIC, **Safety:** Adverse events.	300mg/d, 600mg/d Fixed	Not described, same schedule	Not described
Shabbir 2011 [36]	Parallel-group	PGB 70; PLA 70	6 weeks	2 centres; Mayo Hospital and Services Hospital, Lahore.	Men or women ≥18 years old with diabetic peripheral neuropathy	≥6 months	**Primary:** Reduction in pain (measured with NRS); responders who experienced 50% or more reduction in baseline pain score on NRS	150-600mg/d Flexible	Not described	Not described
Siddall 2006 [37]	Parallel-group	PGB 70; PLA 67	12 weeks	8 centres; Australia	Patients with central neuropathic pain in spinal cord injury	Persisted continuously for at least 3 months or with relapses and remission for at least 6 months	**Primary:** Endpoint mean pain scores, Sleep-interference scores, SF-MPQ Total, sensory and affective scores, from which VAS and PPI score was derived. MOS-sleep scale and HADS, PGIC; T**olerability and safety**	150-600mg/d Flexible	Placebo also administered twice daily	70% of patients taking other medications too: opiates, tricyclics, AEDs, NSAIDS/Cox2, Benzos, SSRI/SSNI, Muscle relaxants.
Simpson 2010 [38]	Parallel-group	PGB 151; PLA 151	14 weeks	44 centres; USA, Puerto Rico	Men or women ≥18 years old with painful HIV-DSP	≥ 3 months	**Primary:** Change from baseline in mean NPRS score; **Secondary:** change in sleep interference scores; MOS-Sleep Scale; PGIC; Pain- modified Brief Pain Inventory; Gracely Pain Scale (GPS); **Safety:** adverse events	150-600mg/d Flexible	Placebo also administered twice daily	Neurotoxic antiretroviral (ARV) drugs known to cause sensory neuropathy clinically similar to HIV-DSP must have been on stable doses for ≥3 months before screeningDoses of other pain medications had to be stable for ≥1 month before treatment and throughout the study.
Simpson 2014 [39]	Parallel-group	PGB 183; PLA 194	16 weeks	45 centres; South Africa, USA, India, Columbia, Thailand, Peru, Puerto Rico, Poland.	Men and women ≥18 years of age with HIV neuropathy	≥ 3 months	**Primary:** Change in Pain scores (NRS); **Secondary:** PGIC/CGIC; Brief Pain Symptom Inventory short form (BPI-sf);MOS-SS; Pain-related sleep interference and overall sleep disturbance (NRS-Sleep scale); Safety	150-600mg/d Flexible	Matching placebo delivered through system for randomization and drug dispensing	NSAIDs, if taken at stable dose for ≥4 weeks before study, antidepressants without efficacy for neuropathic pain if taken at stable dose for ≥30 days before study [SSRIs, bupropion, trazodone], nonbenzodiazepine hypnotics no more than

										once/week for sleep disturbance if clinically essential, rescue therapy of oral acetaminophen (max 3g/day), low dose (≤650mg/day) aspirin and stable antiretroviral treatment >8 weeks before study
Stacey 2008 [40]	Parallel-group	PGB 179; PLA 90	4 weeks	42 centres; United States, Germany, Italy, Spain, and United Kingdom	Men or women ≥ 18 years old with post-herpetic neuralgia	≥3 months	**Primary:** Pain reduction; time to onset of meaningful pain relief; **Secondary:** Daily sleep interference score; PGIC; VAS of the SF-MPQ; VAS anxiety; VAS allodynia; **Safety evaluation**	150-600mg/d Flexible dose; 300mg/d Fixed dose	Placebo also administered twice daily	Concomitant pain treatments permitted given that it must be stable for at least 30 days
Tolle 2008 [41]	Parallel-group	PGB 299; PLA 96	12 weeks	58 centres; Germany, Hungary, Poland, United Kingdom, Australia, and South Africa	Men or women ≥18 years old with painful symmetrical sensorimotor polyneuropathy due to diabetes	≥1 year	**Primary:** Pain reduction (according to 11-point NRS) from baseline; treatment responders; **Secondary:** PGIC; CGIC; EuroQoL Health Utilities Index; Daily pain-related sleep-interference scores; EQ-5D (VAS); **Safety evaluation**	150, 300, 300/600mg/d Fixed	Placebo also administered twice daily	SSRIs for depression or anxiety given in a stable dose for >30 days
Van Seventer 2006 [42]	Parallel-group	PGB 275; PLA 93	13 weeks	76 centres	Men or women ≥ 18 years old with post-herpetic neuralgia	>3 months	**Primary:** Endpoint mean pain scores; patients with ≥50% and ≥30% reduction in pain score from baseline; weekly mean pain scores; **Secondary:** endpoint mean sleep-interference scores, weekly mean sleep-interference scores, PGIC	150, 300, 600mg/d Fixed	Placebo also administered twice daily	non-narcotic analgesics, e.g., noramidopyrine and paracetamol, and stable regimens of opioids, anti-inflammatories, and antidepressants
Van Seventer 2010 [43]	Parallel-group	PGB 127; PLA 127	8 weeks	44 centres; Belgium, Canada, Denmark, Finland, Italy, Netherlands, Portugal, Romania, Sweden, Switzerland, United Kingdom	Men or women aged 18–80 with post- traumatic peripheral neuropathic pain	≥3 months	**Primary:** End-point mean pain score; **Secondary:** rating of extent to which pain interfered with sleep; MOS-SS;HADS; mBPI-sf; PGIC; **Tolerability and safety assessment**	150-600mg/d Flexible	Placebo also administered twice daily	NSAIDS, COX-2 inhibitors, opioid and non-opioid analgesics, anti-epileptic drugs, antidepressant medications, other concomitant medications if they had been stable for at least 1 month before the study and would remain stable throughout the study
Vranken 2008 [44]	Parallel-group	PGB 20; PLA 20	4 weeks	1 centre; Netherlands	Men and women ≥18 years old with central neuropathic pain	≥6 months	**Primary:** Pain intensity score (VAS); Mean endpoint pain score; Pain Disability Index (PDI); EQ-5D; Medical Outcomes Short-form Health Survey questionnaire 36 (SF36); **Safety**	150-600mg/d Flexible	Flexible dose placebo (1-4 capsules per day); matching capsules; on same dosing schedule	Adjuvant analgesics

ABBREVIATIONS: CGIC: Clinician global impression of change; PGB: Pregabalin; PGIC: Patient global impression of change; PLA: Placebo; SF-MPQ PPI: Short-Form McGill Pain Questionnaire *personal pain intensity;* SF-MPQ VAS: Short-Form McGill Pain Questionnaire visual assessment scale; VAS: Visual assessment scale

Summary of Findings Table 1: Effect of pregabalin on NRS scores in patients with neuropathic pain

Patient or population: patients with neuropathic pain
Settings:
Intervention: Effect of pregabalin on pain

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Control**	Corresponding risk **Effect of pregabalin in pain**				
Mean Pain Score		The mean mean pain score in the intervention groups was **0.49 standard deviations lower** (0.66 to 0.32 lower)		5093 (21 studies)	⊕⊖⊖⊖ **very low**[1,2]	SMD -0.49 (-0.66 to -0.32)
Mean Pain Score - Central neuropathic pain (including sciatica)		The mean mean pain score - central neuropathic pain (including sciatica) in the intervention groups was **0.38 standard deviations lower** (0.8 lower to 0.04 higher)		785 (4 studies)	⊕⊖⊖⊖ **very low**[2,3,4]	SMD -0.38 (-0.8 to 0.04)
Mean Pain Score - Peripheral neuropathic pain (includes PDN, HZ & PHN)		The mean mean pain score - peripheral neuropathic pain (includes pdn, hz & phn) in the intervention groups was **0.52 standard deviations lower** (0.71 to 0.33 lower)		4308 (17 studies)	⊕⊖⊖⊖ **very low**[1,2]	SMD -0.52 (-0.71 to -0.33)

*The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **NRS:** Numerical rating scale; **SMD:** Standard mean deviation**; PDN:** Painful diabetic neuropathy; **HZ:** Herpes zoster; **PHN:** Post-herpetic neuralgia

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Inconsistency in allocation concealment and blinding, selective reporting, authors had financial ties to industry sponsor
[2] Substantial heterogeneity
[3] Industry-sponsored, selective reporting
[4] Wide confidence interval

Adverse events

Figure 4 shows that pregabalin was significantly more likely to cause adverse events compared with placebo, RR 1.33 (95% CI 1.23 to 1.44, P<0.00001, I^2=52%) (Figure 4). This translates into an absolute effect of 145 (95% CI 101 to 194) more adverse events per 1000 treated. The overall quality of the evidence was low (SoF Table 2). Sensitivity analyses revealed similar direction of effects (Appendix Table 2). The risk of experiencing individual adverse events of weight gain, somnolence, dizziness, peripheral oedema, fatigue, visual disturbances, ataxia, non-peripheral oedema, dry mouth, vertigo and euphoria were significantly increased with pregabalin compared with placebo (see Appendix Table 1 and Figures S2 to S12). Pregabalin was also significantly more likely to cause discontinuation because of adverse events (RR 1.91, 95% CI 1.54 to 2.37, P<0.00001, I^2=0%); the quality of the evidence was low (SoF Table 2; Appendix Table 1; and Figure S13). Sensitivity analyses by study duration revealed similar direction of effects, but there was no significant difference with higher quality studies (Appendix Table 2).

There was no significant difference in the risk of serious adverse events (RR 0.9; 95% CI 0.66 to 1.24, P=0.50, I^2=0%; SoF Table 2; Appendix Table 1; and Figure S14); the quality of the evidence was moderate. Sensitivity analyses showed a significant effect in favour on pregabalin with three higher quality studies, but there was no difference based on study duration (Appendix Table 2). In total, six deaths were reported across four trials, five in pregabalin group and one in placebo: RR 0.86, 95% CI 0.18 to 4.06, P = 0.85, I^2=0%.

Summary of Findings Table 2: Effect of pregabalin on adverse events in patients with neuropathic pain

Patient or population: patients with Neuropathic pain
Settings:
Intervention: Effect of pregabalin on adverse events

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Number needed to harm (NNH)
	Assumed risk Control	Corresponding risk Effect of pregabalin on adverse events				
Adverse events	**Study population**		**RR 1.33** (1.23 to 1.44)	4010 (19 studies)	⊕⊕⊖⊖ **low**[1,2]	6 (5 to 9)
	523 per 1000	**696 per 1000** (643 to 753)				
	Moderate					
	440 per 1000	**585 per 1000** (541 to 634)				
Discontinuations because of adverse events	**Study population**		**RR 1.91** (1.54 to 2.37)	5426 (24 studies)	⊕⊕⊖⊖ **low**[1,3]	22 (15 to 37)
	51 per 1000	**98 per 1000** (79 to 121)				
	Moderate					
	47 per 1000	**90 per 1000** (72 to 111)				
Serious adverse events	**Study population**		**RR 0.9** (0.66 to 1.24)	4272 (16 studies)	⊕⊕⊕⊖ **moderate**[1]	289 (-121 to 85)
	35 per 1000	**31 per 1000** (23 to 43)				
	Moderate					
	20 per 1000	**18 per 1000** (13 to 25)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Selective reporting, authors had financial ties to industry sponsor
[2] Moderate heterogeneity
[3] Wide confidence interval

Sleep disturbance

Twenty-one studies measured sleep interference using the NRS sleep interference scale or variants of it. Pregabalin significantly reduced sleep interference scores compared with placebo: SMD -0.38, 95% CI -0.50 to -0.26, P<0.00001, I^2=32%; the quality of the evidence was moderate (SoF Table 3; Appendix Table 1; and Figure S15). Fourteen studies reported sleep interference outcome measures with the NRS scale but did not provide adequate data for statistical pooling; 12 of these reported significant reductions in sleep interference scores favouring pregabalin over placebo, while two studies reported no significant difference between groups (Appendix Table 3). Seven studies measured sleep outcomes using the Medical Outcomes Study Sleep Scale (MOS-Sleep). We could not pool results from these studies because of insufficient data. All the studies reported significant improvements in sleep scores in favour of pregabalin over placebo (Appendix Table 3).

Quality of life (QOL)

Four studies assessed QOL using EQ-5D scores or variants of it. Two of these reported significant improvements with pregabalin compared with placebo, while the other two reported no significant differences between groups (Appendix Table 3).

Patient Global Impression of Change (PGIC)

Thirteen studies reported this outcome. Ten studies reported significant improvements in PGIC scores with pregabalin compared with placebo, while three studies found no significant differences between groups (Appendix Table 3). We could not pool results from these studies because insufficient data were published.

Summary of Findings Table 3: Effect of pregabalin on sleep scores in patients with neuropathic pain

Patient or population: patients with Neuropathic pain
Settings:
Intervention: Effect of pregabalin on sleep

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Control**	Corresponding risk **Effect of pregabalin on sleep**				
Sleep interference		The mean sleep interference in the intervention groups was **0.38 standard deviations lower** (0.5 to 0.26 lower)		1641 (7 studies)	⊕⊕⊕⊖ **moderate**[1]	SMD -0.38 (-0.5 to -0.26)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **SMD:** Standardized mean difference

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Selective reporting, authors had financial ties to industry sponsor

Clinician Global Impression of Change

Six studies reported this outcome; four of these reported significant improvements with pregabalin compared with placebo, while two found no significant differences between groups (Appendix Table 3).

Hospital Anxiety Depression Scores (HADS)

Four studies were pooled for this outcome. There was no significant difference in HADS-Anxiety scores between groups: SMD -0.12, 95% CI -0.29 to 0.04, P=0.14, I^2=44%; the quality of the evidence was moderate (SoF Table 4; Figure S16). There was also no significant difference in HADS-Depression scores between groups: SMD -0.06, 95% CI -0.26 to 0.13, P=0.54, I^2=60%; the quality of the evidence was low (SoF Table 4; Appendix Table 1 and Figure S17). One study[41] that did not provide sufficient data for statistical pooling reported significant improvement in the HADS-Anxiety scores in favour of pregabalin, but no significant difference in HADS-depression scores between groups (Appendix Table 1). One study[40] measured anxiety using the VAS anxiety scale and reported significant improvements in QOL scores with fixed- and flexible-dose pregabalin compared with placebo (P=0.03 and P=0.02 respectively.

Overall discontinuations

In total, there were 1,203 drop-outs (approximately 20%) in the 28 trials (n=5972) that reported the data (Appendix Table 1). There was no significant difference in overall discontinuation rates between groups, RR 1.09 (95% CI 0.93 to 1.28, P=0.29, I^2=51%).

Summary of Findings Table 4: Effect of pregabalin on anxiety and depression scores in patients with neuropathic pain

Patient or population: patients with Neuropathic pain
Settings:
Intervention: Effect of pregabalin on anxiety and depression

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Control**	Corresponding risk **Effect of pregabalin on anxiety and depression**				
HADS-Anxiety		The mean hads-anxiety in the intervention groups was **0.12 standard deviations lower** (0.29 lower to 0.04 higher)		1041 (4 studies)	⊕⊕⊕⊖ **moderate**[1]	SMD -0.12 (-0.29 to 0.04)
HADS-Depression		The mean hads-depression in the intervention groups was **0.06 standard deviations lower** (0.26 lower to 0.13 higher)		1041 (4 studies)	⊕⊕⊖⊖ **low**[1,2]	SMD -0.06 (-0.26 to 0.13)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **HADS:** Hospital anxiety and depression scale; **SMD:** Standardized mean difference

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Selective reporting, authors had financial ties to industry sponsor
[2] Moderate heterogeneity

DISCUSSION

Summary of the evidence

The evidence from published RCTs suggests that pregabalin reduces pain scores in patients with neuropathic pain. The effect is significant in peripheral neuropathic pain, but does not achieve statistical significance with central neuropathic pain (P=0.08). Pregabalin significantly increases the risk of adverse events including weight gain, somnolence, dizziness, dry mouth, peripheral oedema, fatigue, visual disturbances, ataxia, non-peripheral oedema, vertigo and euphoria. Pregabalin significantly reduces sleep interference scores compared with placebo. There was insufficient evidence to assess an effect on quality of life. The evidence for PGIC and CGIC scores was mixed among studies that reported these outcomes and there was no significant effects on HADS anxiety and depression scores compared with placebo. There were five deaths in the pregabalin arms and one in the placebo, but insufficient power to detect an overall effect.

Comparison with the existing literature

We have identified several published reviews assessing the effectiveness of pregabalin the management of neuropathic pain, and our results are partly consistent with these. Zhang et al[45] and Wang et al[46] showed that pregabalin was more efficacious than placebo for treatment of DPN-associated pain and PHN-associated pain respectively; however, the two reviews did not base their results on changes from baseline between groups. Semel et al[47] and Freeman et al[48] also concluded that pregabalin was more effective than placebo for neuropathic pain; however, both reviews did not account for the quality of the included primary studies. Finnerup et al[49] concluded that there was modest evidence supporting the use of pregabalin for treatment of neuropathic pain; however, the authors used GRADE criteria to assess the strength of recommendation but not the quality of the evidence. In an overview of Cochrane

reviews, Wiffen et al[50] concluded that there was clinical trial evidence supporting the use of pregabalin for treatment of some aspects of neuropathic pan; however, the authors did not rate the quality of the evidence for the outcomes reported.

Two reviews[51,52] that examined the safety profile of pregabalin concluded that pregabalin use was significantly more associated with adverse events than placebo; however, both reviews did not rate the quality of the evidence for the outcomes reported

Comparison with existing guidelines

We identified several guidelines that recommend the use of pregabalin for treatment of neuropathic pain, and some of their specifications are consistent with our results. For instance, the European Federation of Neurological Societies (EFNS) guideline[53] based on data from comparative studies recommended pregabalin as first line treatment for neuropathic pain; however, the guidance assessed only the level, but not the quality, of the evidence; and also notes that there are too few large scale comparative studies to make definite conclusions about the benefits and harms. Similarly, the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitationn guidance[54] recommends pregabalin as first line treatment based on levels (and not quality) of the evidence; however, they guidance recommends that clinical trials of longer duration should be conducted. The Canadian Pain Society (CPS) guidance[55] recommends pregabalin as first-line treatment for neuropathic pain, but acknowledges that paucity of longer-duration trials limit the conclusions that can be drawn about its benefits and harms on the long-term.

Strengths and limitations

This rapid review has limitations due to its streamlined methods and search strategy. Firstly, the lack of a published a priori protocol could have introduced selective outcome reporting bias in this rapid review; nevertheless, most of the outcomes reported in this review have been listed as outcomes of interest to be considered when designing trials of neuropathic pain interventions.[56] There is a risk that our review may be prone to sampling bias, and that we may have missed potentially eligible studies, which could have been identified by searching clinical trials registries and grey literature. However, we undertook the same rigorous approach using Cochrane criteria for other systematic reviews within the time constraints. It has also been reported that generally the conclusions of rapid reviews and full reviews do not greatly differ[57]; and enhanced rapid reviews where data is independently checked by a second reviewer could help policy makers with quicker access to the evidence base.[58] This review therefore provides the most up to date comprehensive summary of the available literature, as it accounts for study quality and reports clinically meaningful patient outcomes. We did not assess the extent to which different doses of pregabalin influenced the outcomes assessed.

Implications for research

The quality of the included studies examining efficacy of pregabalin for pain was rated as low or very low according to the GRADE framework. This highlights the need for larger, robust, high-quality clinical trials to be conducted, with particular attention paid to minimizing selective reporting of outcomes. Concerns about selective reporting could be mitigated if drug manufacturers enabled access to clinical study reports (CSRs), especially as industry-sponsored trials are likely to skew reports in favour of benefits over harms.[59,60] This would allow for a more comprehensive assessment of the benefits and harms of pregabalin. Of note, all the included trials were industry-sponsored, and an overwhelming majority of the

authors of the include studies had financial ties to the pharmaceutical industry. Of note, the results of the only published charity-funded phase IV placebo-controlled trial that assessed the effectiveness of pregabalin in management of neuropathic (radicular) pain contrast our meta-analysis results – there was no significant difference in pain scores between groups.[61] Independent and publicly funded trials assessing the benefits and harms of pregabalin should be conducted. Only a few studies assessed the effect of pregabalin in improving quality of life, anxiety and depression and CGIC. Future trials should further assess the role of pregabalin for these outcomes. Studies investigating the type of neuropathic pain pregabalin relieves (e.g. stimulus-dependent pain such as hyperalgesia or allodynia), or spontaneous pain could be an area of consideration for future research.

That the median duration of intervention was nine weeks suggests that the intermediate to longer term benefits of pregabalin for neuropathic pain are unproven. Indeed in real life clinical care, it has been reported that the initial benefits seen with use of the drug in patients with neuropathic pain were no longer apparent after 6 to 12 months of therapy.[62] Therefore, RCTs that are adequately powered, and with longer durations of interventions are desirable. The finding of 5 deaths among 891 participants on pregabalin, vs 1 death among 320 participants on placebo, is somewhat concerning. Given the low frequency of this outcome (coupled with the short trial durations), RCTs are unlikely to be informative; we suggest pharmacoepidemiological studies in routinely collected electronic health records and spontaneous reporting databases to assess the impact of pregabalin on mortality.

Implications for clinical practice

Very low-to-moderate quality evidence suggests that pregabalin improves some symptoms of neuropathic pain. However, it significantly increases the risk of adverse events including

somnolence, oedema, visual disturbances, ataxia, vertigo and euphoria. Pregabalin also increases the risk of drug discontinuation because of adverse events. Clinicians should be cautious about prescribing pregabalin, and should consider whether its benefits outweigh potential harms in individual patients.

Conclusions

The evidence from RCTs in journal publications suggests that pregabalin has beneficial effects on some symptoms of neuropathic pain. However, its use significantly increases the risk of adverse events and discontinuation due to adverse events. The quality of the evidence from journal publications is overall low, and the duration of trials is short. Greater transparency in the reporting of outcomes is advocated; independent and publicly funded trials assessing the effects of pregabalin in neuropathic pain should be encouraged. Allowing researchers access to full CSRs of pregabalin trials should be a priority for drug companies and regulators.

Acknowledgement

IJO, BG and CJH are part of the Evidence Synthesis Working Group. The Evidence Synthesis Working Group is funded by the National Institute for Health Research School for Primary Care Research (NIHR SPCR) [ProjectNumber 390]. JL is supported by an NIHR In Practice Fellowship. The views expressed are those of the author(s) and not necessarily those of the NIHR, the NHS or the Department of Health.

Funding

None

Data sharing statement

No additional data available

Authors' Contribution

IJO was involved with devising the review methods, conducting electronic searches, screening of abstracts, data extraction, data analysis and interpretation, and co-drafting of the review. ETT was involved with devising the review methods, screening of abstracts, data extraction, data analysis and interpretation, and co-drafting of the review. JL was involved with data extraction, data analysis and interpretation, and co-drafting of the review. BG was involved with devising the review methods, data analysis and interpretation, and co-drafting of the review. CJH was involved with devising the review methods, data analysis and interpretation, and co-drafting of the review.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). CJH has received expenses and fees for his media work. He has received expenses from the WHO, FDA, and holds grant funding from the NIHR, the NIHR School of Primary Care Research, The Wellcome Trust and the WHO. He has received financial remuneration from an asbestos case. He has also received income from the publication of a series of toolkit books published by Blackwells. On occasion, he receives expenses for teaching EBM and is also paid for his GP work in NHS out of hours. CEBM jointly runs the EvidenceLive Conference with the BMJ and the Overdiagnosis Conference with some international partners which are based on a non-profit making model. BG receives funding from the Laura and John Arnold Foundation and reports personal fees from intermittent additional personal income

from speaking and writing for lay audiences on problems in science and medicine including regulatory shortcomings. IJO, ETT and JL have no interests to disclose.

Transparency declaration

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Figure legends

Figure 1: Flow chart showing the process for inclusion of RCTs assessing the effects of pregabalin in the management of neuropathic pain

Figure 2a: Graphical representation of the risk of bias in RCTs assessing the effects of pregabalin in the management of neuropathic pain

Figure 2b: Risk of bias summary for RCTs assessing the effects of pregabalin in the management of neuropathic pain

Figure 3: Effect of pregabalin on pain scores in patients with neuropathic pain

Figure 4: Effect of pregabalin on the risk of adverse events in patients with neuropathic pain

Figure 1: Flow chart showing the process for inclusion of RCTs assessing the effects of pregabalin in the management of neuropathic pain

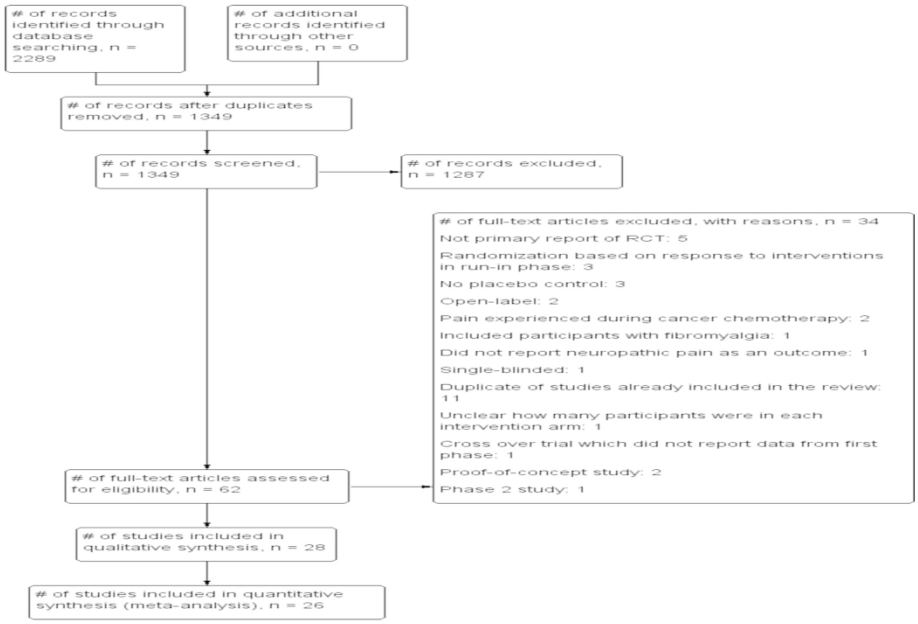

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Figure 2a: Graphical representation of the risk of bias in RCTs assessing the effects of pregabalin in the management of neuropathic pain

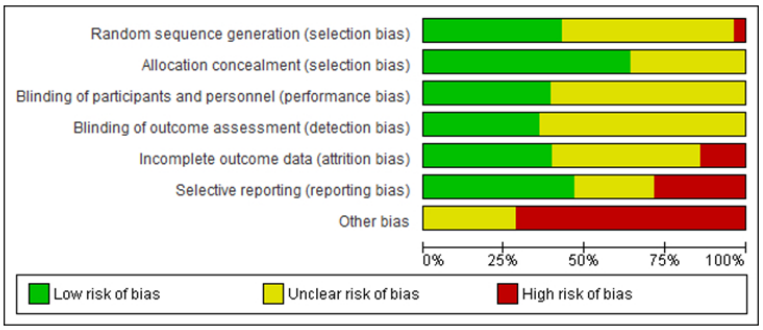

Figure 2b: Risk of bias summary for RCTs assessing the effects of pregabalin in the management of neuropathic pain

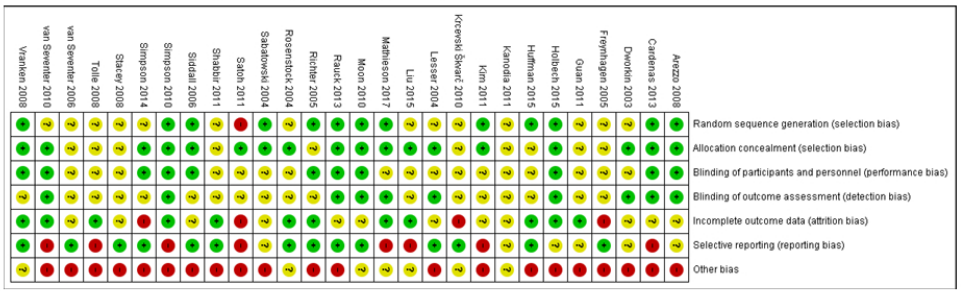

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Figure 3: Effect of pregabalin on pain scores in patients with neuropathic pain

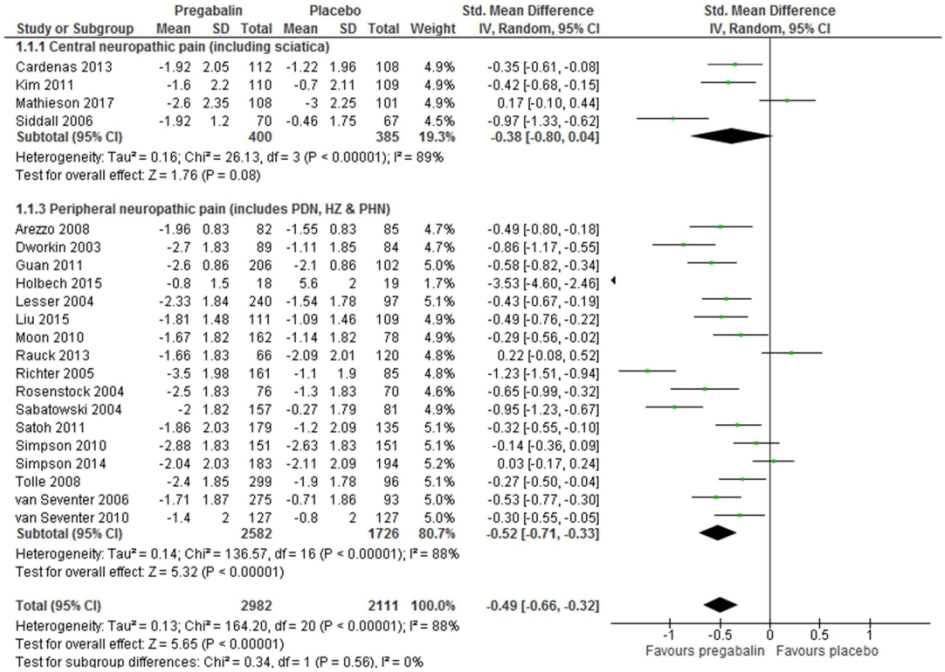

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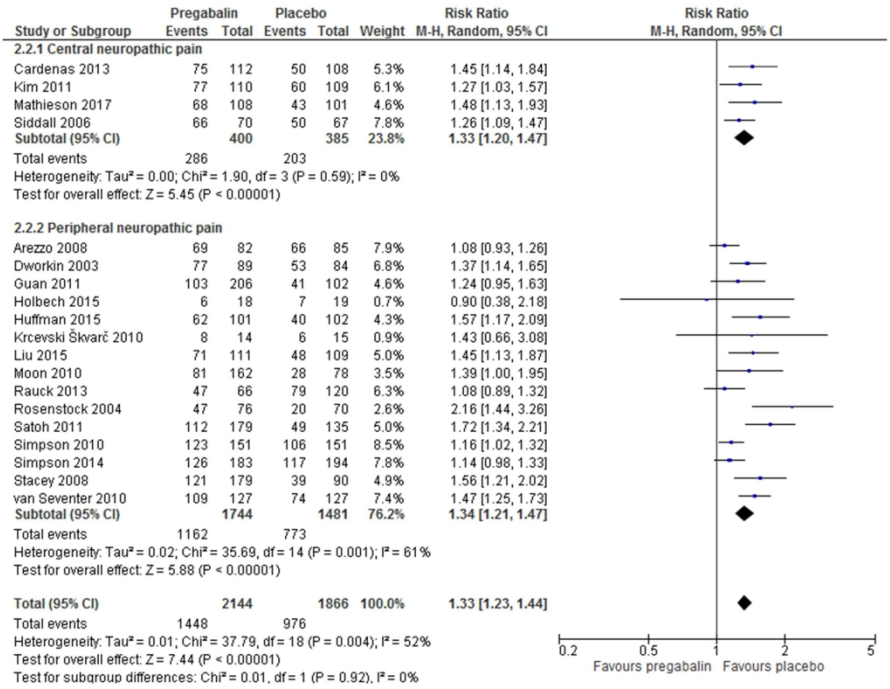
Figure 4: Effect of pregabalin on the risk of adverse events in patients with neuropathic pain



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Appendix Table 1: Benefits and harms of pregabalin in the management of neuropathic pain

Outcome	Overall analysis	Subgroup analyses		Test for subgroup differences
		Central neuropathic pain	*Peripheral neuropathic pain*	
Mean change in pain scores - NRS	(n = 5093): SMD -0.49 (-0.66 to -0.32, P < 0.00001, I^2=88%	(n = 785): SMD -0.38 (-0.80 to 0.04), P = 0.08, I^2=89%	(n = 4308): SMD -0.52 (-0.71 to -0.33), P < 0.00001, I^2=88%	P = 0.56, I^2=0%
Mean change in sleep interference scores - NRS	(n = 1641): SMD -0.38 (-0.50 to -0.26, P < 0.00001, I^2=32%	(n = 357): SMD -0.49 (-0.70 to -0.28), P < 0.00001, I^2=0%	(n = 1284): SMD -0.35 (-0.50 to -0.19), P < 0.0001, I^2=45%	P = 0.30, I^2=8%
Mean change in HADS-anxiety scores	(n = 1041): SMD -0.12 (-0.29 to 0.04, P = 0.14, I^2=44%	(n = 418): SMD -0.27 (-0.46 to -0.08, P = 0.006, I^2=0%	(n = 623): SMD -0.00 (-0.16 to 0.15, P = 0.97, I^2=0%	P = 0.04, I^2=77.2%
Mean change in HADS-depression scores	(n = 1041): SMD -0.06 (-0.26 to 0.13, P = 0.54, I^2=60%	(n = 418): SMD -0.16 (-0.41 to 0.10, P = 0.23, I^2=44%	(n = 623): SMD 0.02 (-0.28 to 0.32, P = 0.90, I^2=71%	P = 0.38, I^2=8%
Overall adverse events	(n = 4010): RR 1.33 (1.23 to 1.44), P < 0.00001, I^2=52%	(n = 489): RR 1.33 (1.20 to 1.47), P < 0.00001, I^2=0%	(n = 3225): RR 1.34 (1.21 to 1.47), P < 0.00001, I^2=61%	P = 0.92, I^2=0%
Adverse event: weight gain	(n = 3636): RR 4.58, (2.88 to 7.28), P < 0.00001, I^2=0%	(n = 428): RR 3.77 (0.94 to 15.08), P = 0.06, I^2=0%	(n = 3636): RR 4.69 (2.87 to 7.68), P < 0.00001, I^2=0%	P = 0.77, I^2=0%
Adverse event: somnolence	(n = 5695): RR 2.84, (2.36 to 3.42), P < 0.00001, I^2=0%	(n = 785): RR 3.18 (2.16 to 4.68), P < 0.00001, I^2=0%	(n = 4910): RR 2.74 (2.22 to 3.40), P < 0.00001, I^2=1%	P = 0.51, I^2=0%
Adverse event: dizziness	(n = 5732): RR 2.94 (2.30 to 3.74), P < 0.00001, I^2=63%	(n = 785): RR 3.38 (2.46 to 4.63), P < 0.00001, I^2=0%	(n = 4947): RR 2.89 (2.17 to 3.85), P < 0.00001, I^2=67%	P = 0.48, I^2=0%
Adverse event: peripheral edema	(n = 5001): RR 2.63 (1.86 to 3.73), P < 0.00001, I^2=41%	(n = 439): RR 3.90 (1.63 to 9.36), P = 0.002, I^2=0%	(n = 4562): RR 2.53 (1.74 to 3.68), P < 0.00001, I^2=44%	P = 0.37, I^2=0%
Adverse event: fatigue*	(n = 3958): RR 1.83 (1.32 to 2.54), P = 0.0003, I^2=14%	N/A	N/A	N/A
Adverse event: visual disturbance	(n = 2814): RR 2.50 (1.53 to 4.09), P = 0.0003, I^2=6%	(n = 566): RR 4.05 (1.27 to 12.91), P = 0.02, I^2=0%	(n = 2248): RR 2.36 (1.32 to 4.22), P = 0.004, I^2=16%	P = 0.42, I^2=0%
Adverse event: ataxia**	(n = 1045): RR 5.49 (1.84 to 16.36), P = 0.002, I^2=0%	N/A	N/A	N/A
Adverse event: dry mouth	(n = 3873): RR 2.39 (1.66 to 3.44), P < 0.0001, I^2=16%	(n = 357): RR 3.75 (1.43 to 9.83), P = 0.007, I^2=0%	(n = 3516): RR 2.28 (1.52 to 3.41), P < 0.0001, I^2=20%	P = 0.35, I^2=0%
Adverse event: non-peripheral edema	(n = 2337): RR 3.51 (1.93 to 6.40), P < 0.0001, I^2=0%	(n = 785): RR 3.82 (1.65 to 8.85), P = 0.002, I^2=0%	(n = 1552): RR 3.70 (1.36 to 10.06), P = 0.01, I^2=19%	P = 0.96, I^2=0%
Adverse event: vertigo**	(n = 1031): RR 3.08 (1.01 to 9.40), P = 0.05, I^2=30%	N/A	N/A	N/A
Adverse event: euphoria*	(n = 1274): RR 8.80 (2.72 to 28.54), P = 0.0003, I^2=0%	N/A	N/A	N/A
Discontinuation due to adverse events	(n = 5426): RR 1.91 (1.54 to 2.37), P < 0.00001, I^2=0%	(n = 576): RR 1.42 (0.79 to 2.55), P = 0.24, I^2=0%	(n = 4850): RR 2.00 (1.58 to 2.55), P < 0.00001, I^2=6%	P = 0.29, I^2=12%

Abbreviations: HADS: Hospital anxiety depression scale; NRS: Numerical rating scale; RR: Risk ratio; SMD: Standardized mean difference

*only one RCT on central neuropathic pain reported adequate data
**all RCTs were in patients with peripheral neuropathic pain

Appendix Table 2: Sensitivity analyses by study quality and duration in clinical trials assessing the benefits and harms of pregabalin in neuropathic pain

Outcome	Sensitivity analysis based on higher quality studies*	Sensitivity analysis based on shorter duration of intervention**	Sensitivity analysis based on longer duration of intervention***
Pain	5 studies (n = 932): SMD -0.56 (-1.07 to -0.05; P = 0.03; I^2=92%)	10 studies (n = 2408): SMD -0.68 (-0.96 to -0.40; P < 0.00001; I^2=90%)	10 studies (n = 2685): SMD -0.31 (-0.49 to -0.13; P = 0.0006; I^2=79%)
Adverse events	6 studies (n = 1152): RR 1.17 (1.06 to 1.29; P = 0.002; I^2=23%)	11 studies (n = 2088): RR 1.46 (1.34 to 1.58; P < 0.00001; I^2=0%)	8 studies (n = 1922): RR 1.23 (1.12 to 1.35; P < 0.0001; I^2=55%)
Serious adverse events	3 studies (n = 627): RR 0.59 (0.38 to 0.92; P = 0.02; I^2=0%)	8 studies (n = 2088): RR 0.72 (0.49 to 1.07; P = 0.11; I^2=0%)	7 studies (n = 1674): RR 0.93 (0.55 to 1.59; P = 0.79; I^2=26%)
Discontinuation due to adverse events	6 studies (n = 1152): RR 1.22 (0.79 to 1.87; P = 0.37; I^2=0%)	13 studies (n = 2403): RR 1.95 (1.34 to 2.84; P = 0.0005; I^2=27%)	11 studies (n = 3023): RR 1.88 (1.40 to 2.53; P < 0.0001; I^2=0%)

*studies that adequately reported randomization and blinding procedures

**Studies duration lasting less than 12 weeks

***Studies duration lasting at least 12 weeks

Appendix Table 3: Main results* of RCTs assessing the benefits and harms of pregabalin in the management of neuropathic pain

		Pain			Sleep Disturbance				
Study ID	**NRS**	**VAS Score**	**SF-MPQ VAS**	**SF-MPQ PPI**	**Sleep Interference Scores**	**MOS-Sleep**	**Quality of Life (EQ-5D)**	**PGIC**	**CGIC**
Arezzo 2008			Significantly favoured PGB over PLA (MD -11.06, 95% CI, -18.89 to -3.22; P = 0.006)					Significant improvement with PGB compared to PLA, P= 0.002	
Cardenas 2013						Significant improvement with PGB over PLA on domains of sleep disturbance, awaken short of breath, sleep quantity, and optimal seep subscales (P<0.05)		PGIC reported as binary outcome; significantly improved with PGB compared with PLA, P<0.001	Significant improvement in the PGB arm (P= 0.0294)
Dworkin 2003			Significantly favoured PGB over PLA (MD -17.62, 95% CI, -25.37 to -9.86; P = 0.0001		Significantly favoured PGB over PLA (MD -1.58, 95% CI, -2.19 to -0.97; P = 0.0001)	Significantly favoured PGB over PLA (MD -9.80, 95% CI, -14.49 to -5.11; P = 0.0001)		Significantly improved with PGB versus PLA, P = 0.001	
Freynhagen 2005	Both flexible- and fixed-dose PGB significantly reduced endpoint mean pain score versus PLA (P=0.002 and P<0.001 respectively)				Significantly improved at endpoint in each PGB treatment group over PLA (P<0.001)	Significantly favoured PGB over PLA (P<0.05)			
Guan 2011			Significantly improved with PGB vs PLA LSMD -6.56, 95% CI -11.65 to -1.47, P=0.012		Significantly improved with PGB vs PLA: LSMD -0.5, 95% CI -0.93 to -0.07, P=0.023				
Holbech 2015					Significantly improved with PGB vs PLA LSMD -0.55, 95% CI -0.93 to -0.17, P=0.004				
Huffmann 2015	Significant treatment difference favouring PGB over PLA for DPN pain (P=0.034) and DPN pain on walking (P=0.001)							Significant improvements with PGB compared to PLA (P=0.002)	
Kanodia 2011		Significantly improved with PGB compared to PLA: MD -21, 95% CI: -23.8 to -18.2; P = 0.004)							
Kim 2011					Significantly favoured PGB over PLA (P<0.05)	Significant improvement with PGB over PLA in sleep quantity (P=0.03), sleep adequacy (P=0.13), snoring (P=0.39), and reduced the sleep problems index (P=0.049)	No significant difference between groups at endpoint, MD 0 (95% CI -0.1, 0,1) P= 0.566	No significant difference between groups at endpoint, -0.2 (95% CI -0.5, 0.1) P=0.144	Significant improvement of in PGB group vs PLA: MD -0.3 (95% CI -0.6, 0) (P=0.049)
Krcevski Skvarč 2010	No significant difference between groups, P values not reported								
Lesser 2004					Significantly favoured PGB over PLA (P=0.0001)				
Liu 2015			Significant decrease with PGB compared with PLA: MD -8.18, 95% CI: -11.99 to -4.37; P<0.0001)	Significant decrease in with PGB compared with PLA: MD -0.37, 95% CI: -0.58 to -0.16; P=0.0007).		Significantly greater improvements with PGB in subscales of sleep disturbance (P=0.0039) and quantity of sleep (P=0.0035) compared with PLA		Significantly improved with PGB versus PLA: LSMD -0.49 95% CI -0.72 to -0.27, P<0.0001	Significant improvement with PGB versus PLA, LSMD -0.62 95% (CI -0.86, -0.39), P<0.0001
Mathieson 2017									
Moon 2010					Significantly favoured PGB over PLA: LSMD -0.51 (95% CI, -0.96 to -0.07; P = 0.024)	Significantly greater improvements with PGB in subscales of sleep disturbance (P=0.0034) and quantity of sleep (P=0.018) compared with PLA	No significant differences in endpoint scores of EQ-5D utility score least squares means 0.03, 95% CI -0.04, 0.09 P= 0.429, or EQ-5D VAS at endpoint LSMD 3.50 (95% CI -1.18, 8.18) P= 0.142	No statistically significant difference between groups	No statistically significant difference between groups
Rauck 2013					No significant difference between groups: MD 0.11 (95% CI -0.60 to 0.82)				
Richter 2005			Significantly favoured PGB 600mg/day over PLA (MD -14.67, 95% CI, -21.92 to -7.41; P = 0.0002). No significant	Significantly favoured PGB 600mg/day over PLA (MD -0.66, 95% CI, -0.97 to -0.35; P = 0.0002). No significant difference	Significantly favoured PGB over PLA: LSMD -1.152; 95% CI -1.752 to -0.551; P=0.0004				

			difference between PGB 150mg/day and PLA (MD -4.78, 95% CI, -12.20 to -2.64; P = 0.20)	between PGB 150 mg/day and PLA (MD -0.17, 95% CI, -0.49 to 0.14; P = 0.28)					
Rosenstock 2004			Significantly favoured PGB over PLA (MD -16.19, 95% CI, -24.52 to -7.86; P = 0.0002)	Significantly favoured PGB over PLA (MD -0.37, 95% CI, -0.72 to -0.02; P = 0.036)	Significantly favoured PGB over PLA: LSMD -1.54, 95% CI -2.28 to -0.80, P=0.0001				
Sabatowski 2004					Significantly favoured PGB over PLA: LSMD -1.11, 95% CI -1.71 to -0.51, P=0.0003 for 150 mg/day; LSMD -1.43, 95% CI -2.04 to -0.82, P=0.0001 for 300 mg/day				
Satoh 2011			Significantly favoured PGB 300 mg/day and 600 mg/day over PLA (P < 0.05)		Significantly improved in the 300 and 600 mg/ day PGB groups compared with PLA (P < 0.0001 and P = 0.0273 respectively)				
Shabbir 2011	Significant improvement in pain of DPN was observed in patients receiving PGB (48.1%) and compared to those receiving PLA (10.5%), P values not reported								
Siddall 2006			Significantly favoured PGB over PLA (MD -17.6, 95% CI, -25.2 to -10.0; P<0.001)	Significantly favoured PGB over PLA (MD -0.66, 95% CI, -0.99 to -0.32; P<0.001)					
Simpson 2010								Significant self-reported improvement favouring PGB over PLA: 82.8% vs 66.7% (P= 0.008)	
Simpson 2014					No significant difference between groups: LSMD 0.04, 95% CI 0.43 to 0.35, P =0.840			No significant differences between groups: (P=0.505)	No significant differences between groups (P=0.427)
Stacey 2008		Significant improvement in VAS allodynia scores with PGB compared to PLA (flexible-dose: MD -14.4 mm [P<0 .0001] and fixed-dose, MD -8.98 mm [P =0.0075])	Significant improvement in with PGB compared to PLA (flexible-dose: MD -16.33 mm [P<0 .0001] and fixed-dose, MD -11.97 mm [P =0 .0008])		Significant improvements with flexible- and fixed-dose PGB. Results of between-group differences not reported		Fixed or flexible dose PGB demonstrated significant improvement in VAS anxiety scores over PLA (fixed-dose, 19.95, P = 0.025, and flexible-dose, -17.81; P= 0.024)	Patients treated with any PGB treatment regimen were significantly more likely to rate themselves as minimally, much, or very much improved on the PGIC at end point compared with PLA	
Tolle 2008							Significant improvements in utility scores for 150, 300, 600mg/day respectively compared to PLA, all P ≤ 0.0263	Significant improvement with 600 mg/day PGB versus PLA in subjects reporting “improved” or “much improved” (50.5% vs 33.3%, P = 0.02)	Significant superiority of PGB 600 mg/day over PLA (P= 0.009)
Van Seventer 2006						Significant improvement in MOS sleep scale problems with PGB compared with PLA MD – 7.54, 95% CI -11.52 to -3.56, P<0.001		Patients in the 150 mg/day (P = 0.02) and 600 mg/day (P = 0.003) groups were more likely to report global improvement than those in the PLA group	
Van Seventer 2010								Significant improvement in favour of PGB over PLA (P = 0.006)	
Vranken 2008		Significant decrease in with PGB compared with PLA: MD 2.18, 95% CI: 0.57 to 3.80; P = 0.01)					Statistically significant improvement for both the EQ-5D utility score (p<0.001) and EQ-5D VAS score with PGB compared to PLA (P<0.001)		

ABBREVIATIONS: CGIC: Clinician global impression of change; LSMD: Least square mean difference; MD: Mean difference; MOS-Sleep: Medical Outcomes Study Sleep Scale; NRS: numerical rating scale; PGB: Pregabalin; PGIC: Patient global impression of change; PLA: Placebo; SF-MPQ PPI: Short-Form McGill Pain Questionnaire personal pain intensity; SF-MPQ VAS: Short-Form McGill Pain Questionnaire visual assessment scale; VAS: Visual assessment scale

*These outcome results have been presented narratively because there was inadequate data to pool results across studies

Figure S1: Funnel plot for publication bias in RCTs assessing the effect of pregabalin in neuropathic pain. The broken line represents the mean difference for all trials.

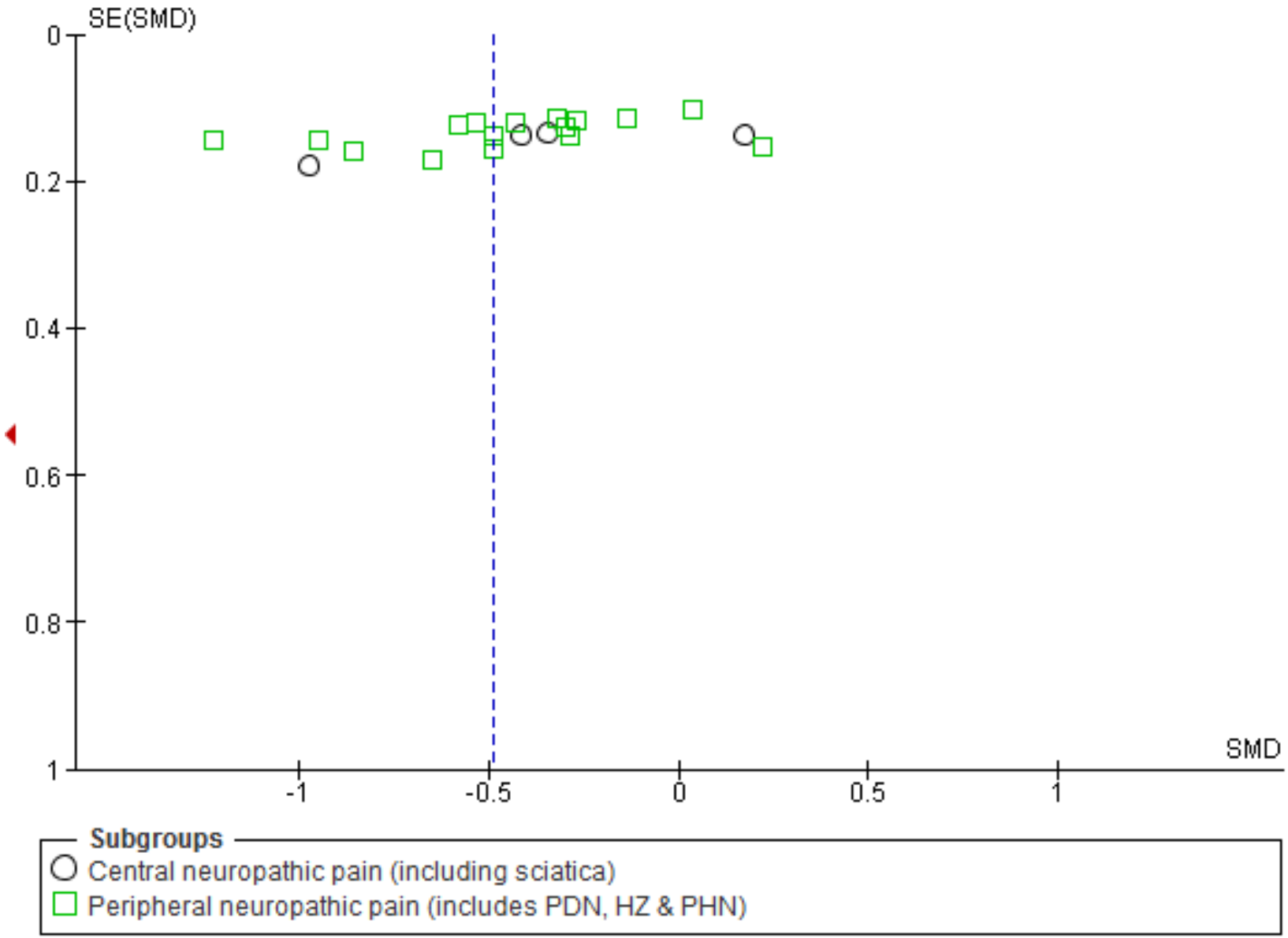


Figure S2: Effect of pregabalin on the risk of weight gain in patients with neuropathic pain

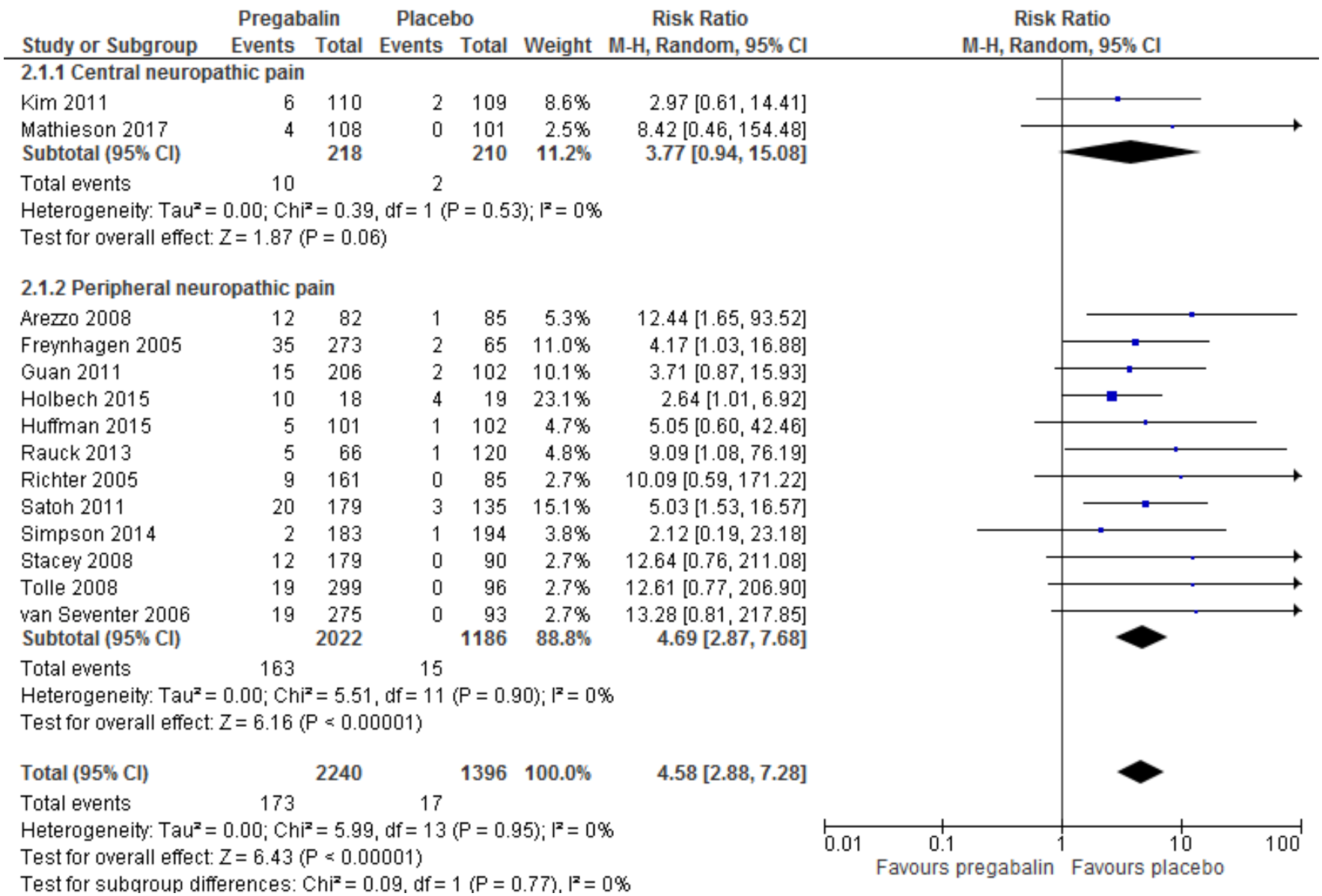


Figure S3: Effect of pregabalin on the risk of somnolence in patients with neuropathic pain

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 Central neuropathic pain						
Cardenas 2013	37	112	14	108	11.2%	2.55 [1.46, 4.44]
Kim 2011	24	110	5	109	4.0%	4.76 [1.88, 12.01]
Mathieson 2017	9	108	4	101	2.6%	2.10 [0.67, 6.62]
Siddall 2006	29	70	6	67	5.2%	4.63 [2.05, 10.43]
Subtotal (95% CI)		**400**		**385**	**23.1%**	**3.18 [2.16, 4.68]**
Total events	99		29			
Heterogeneity: Tau² = 0.00; Chi² = 2.68, df = 3 (P = 0.44); I² = 0%						
Test for overall effect: Z = 5.87 (P < 0.00001)						
2.5.2 Peripheral neuropathic pain						
Arezzo 2008	11	82	5	85	3.4%	2.28 [0.83, 6.28]
Dworkin 2003	22	89	6	84	4.8%	3.46 [1.48, 8.11]
Freynhagen 2005	32	273	0	65	0.4%	15.66 [0.97, 252.40]
Guan 2011	16	206	3	102	2.4%	2.64 [0.79, 8.86]
Huffman 2015	12	101	4	102	2.9%	3.03 [1.01, 9.08]
Krcevski Škvarč 2010	9	14	4	15	4.0%	2.41 [0.96, 6.08]
Lesser 2004	44	240	4	97	3.5%	4.45 [1.64, 12.04]
Liu 2015	6	111	5	109	2.6%	1.18 [0.37, 3.75]
Rauck 2013	9	66	5	120	3.1%	3.27 [1.14, 9.36]
Richter 2005	22	161	3	85	2.5%	3.87 [1.19, 12.57]
Rosenstock 2004	15	76	2	70	1.7%	6.91 [1.64, 29.13]
Sabatowski 2004	30	157	6	81	5.0%	2.58 [1.12, 5.94]
Satoh 2011	46	179	11	135	9.0%	3.15 [1.70, 5.86]
Simpson 2010	35	151	13	151	9.8%	2.69 [1.48, 4.88]
Simpson 2014	13	183	4	194	2.8%	3.45 [1.14, 10.37]
Stacey 2008	27	179	2	90	1.7%	6.79 [1.65, 27.91]
Tolle 2008	17	299	1	96	0.9%	5.46 [0.74, 40.48]
van Seventer 2006	42	275	4	93	3.5%	3.55 [1.31, 9.64]
van Seventer 2010	20	127	8	127	5.7%	2.50 [1.14, 5.47]
Vranken 2008	9	20	9	20	7.4%	1.00 [0.50, 1.98]
Subtotal (95% CI)		**2989**		**1921**	**76.9%**	**2.74 [2.22, 3.40]**
Total events	437		99			
Heterogeneity: Tau² = 0.00; Chi² = 19.24, df = 19 (P = 0.44); I² = 1%						
Test for overall effect: Z = 9.25 (P < 0.00001)						
Total (95% CI)		**3389**		**2306**	**100.0%**	**2.84 [2.36, 3.42]**
Total events	536		128			
Heterogeneity: Tau² = 0.00; Chi² = 22.21, df = 23 (P = 0.51); I² = 0%						
Test for overall effect: Z = 10.99 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.43, df = 1 (P = 0.51), I² = 0%						

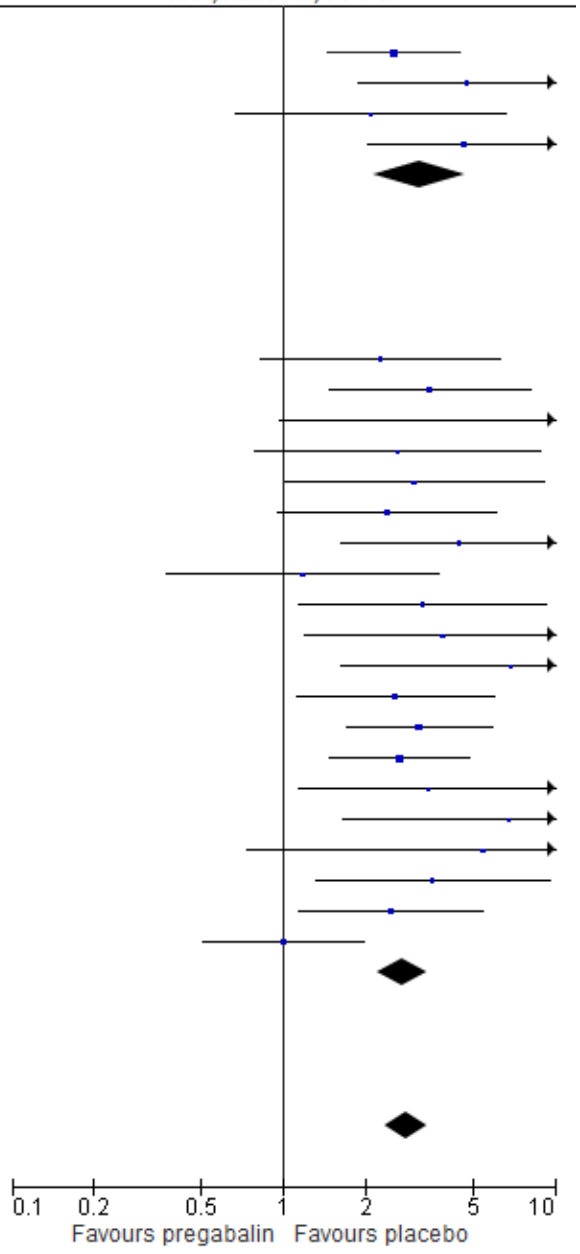


Figure S4: Effect of pregabalin on the risk of dizziness in patients with neuropathic pain

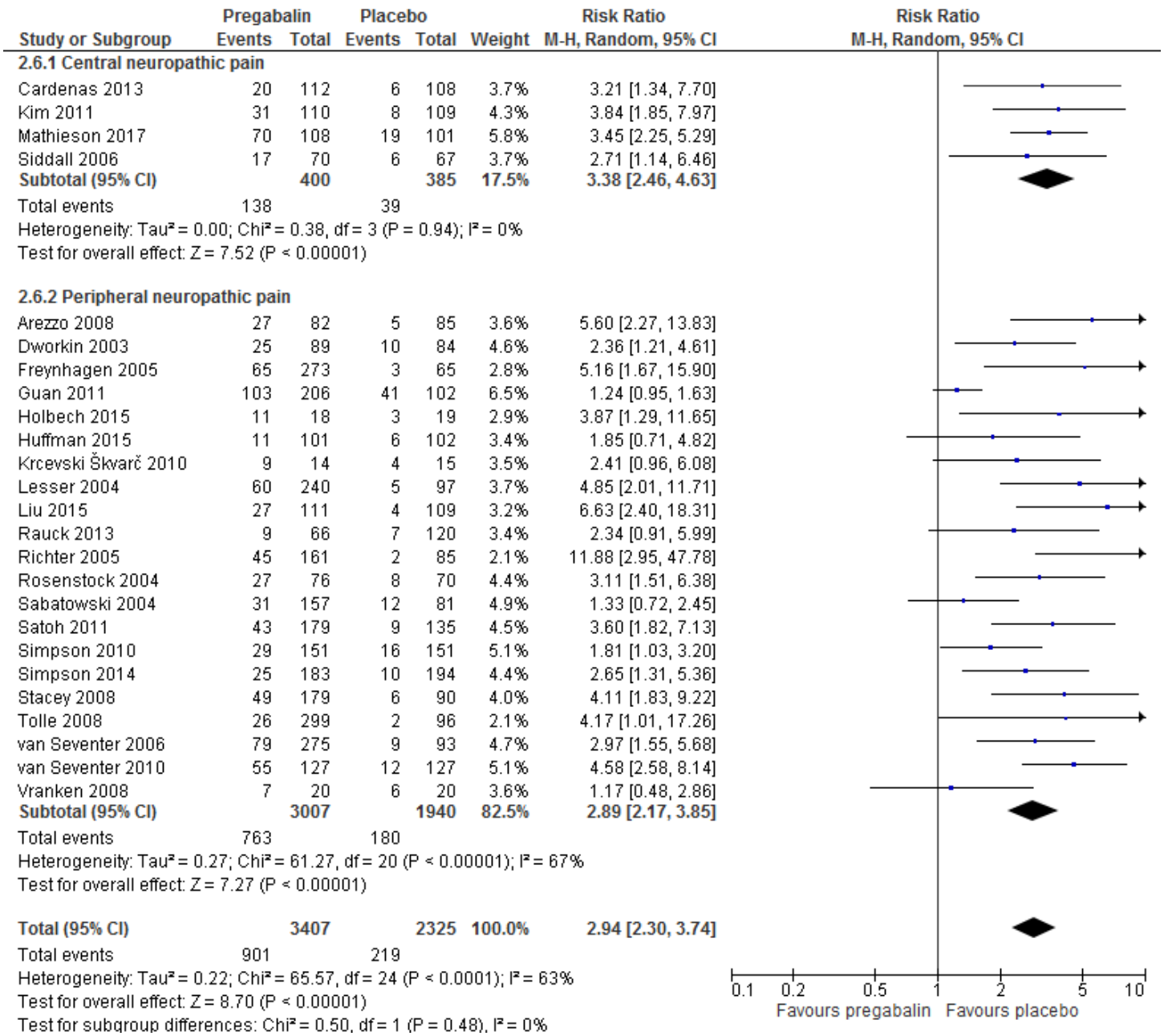


Figure S5: Effect of pregabalin on the risk of peripheral edema in patients with neuropathic pain

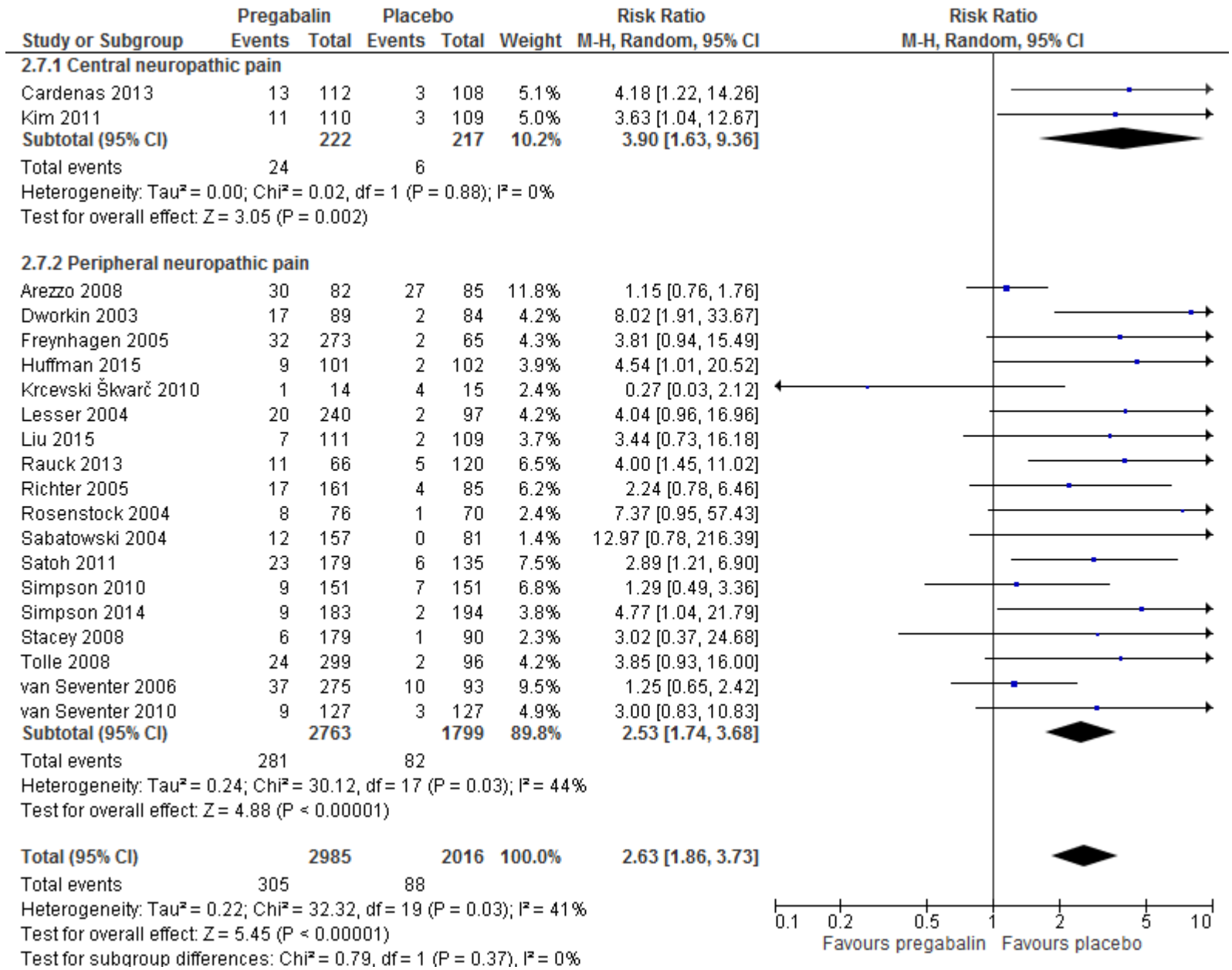


Figure S6: Effect of pregabalin on the risk of fatigue including asthenia in patients with neuropathic pain

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Arezzo 2008	8	82	1	82	2.4%	8.00 [1.02, 62.53]
Cardenas 2013	8	112	1	108	2.4%	7.71 [0.98, 60.65]
Freynhagen 2005	21	273	0	65	1.3%	10.36 [0.64, 168.79]
Guan 2011	23	206	7	102	11.9%	1.63 [0.72, 3.66]
Holbech 2015	7	18	3	19	6.5%	2.46 [0.75, 8.09]
Huffman 2015	11	101	3	102	6.0%	3.70 [1.06, 12.88]
Krcevski Škvarč 2010	8	14	8	15	15.9%	1.07 [0.56, 2.06]
Lesser 2004	13	240	3	97	6.1%	1.75 [0.51, 6.01]
Liu 2015	5	111	1	109	2.2%	4.91 [0.58, 41.35]
Rauck 2013	4	66	3	120	4.5%	2.42 [0.56, 10.51]
Richter 2005	13	161	3	85	6.1%	2.29 [0.67, 7.81]
Rosenstock 2004	3	76	2	70	3.2%	1.38 [0.24, 8.03]
Sabatowski 2004	7	157	4	81	6.4%	0.90 [0.27, 2.99]
Stacey 2008	13	179	1	90	2.5%	6.54 [0.87, 49.18]
Tolle 2008	10	299	0	96	1.3%	6.79 [0.40, 114.81]
van Seventer 2006	12	275	5	93	8.4%	0.81 [0.29, 2.24]
van Seventer 2010	15	127	10	127	13.0%	1.50 [0.70, 3.21]
Total (95% CI)		**2497**		**1461**	**100.0%**	**1.83 [1.32, 2.54]**
Total events	181		55			

Heterogeneity: Tau² = 0.06; Chi² = 18.63, df = 16 (P = 0.29); I² = 14%

Test for overall effect: Z = 3.62 (P = 0.0003)

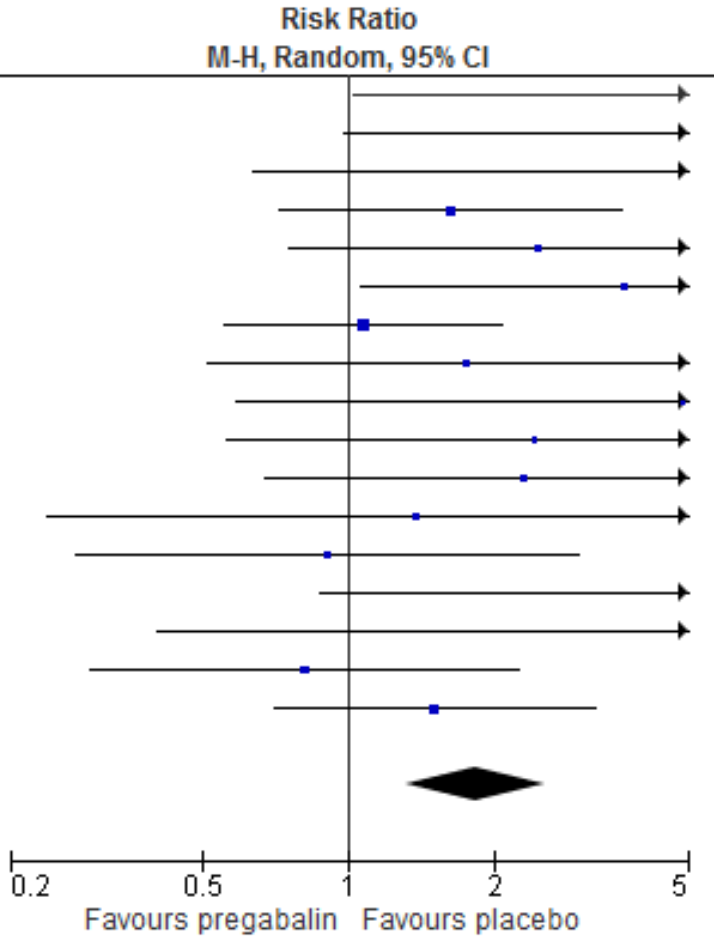
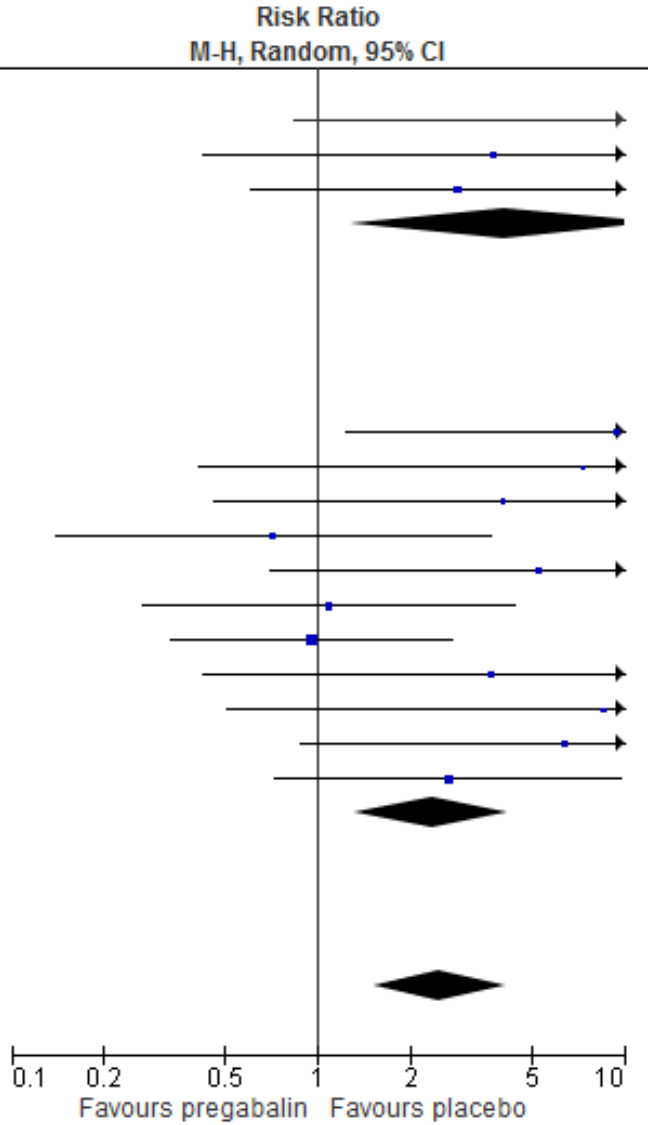


Figure S7: Effect of pregabalin on the risk of visual disturbances* in patients with neuropathic pain

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.8.1 Central neuropathic pain						
Cardenas 2013	7	112	0	108	2.9%	14.47 [0.84, 250.29]
Mathieson 2017	4	108	1	101	4.9%	3.74 [0.43, 32.91]
Siddall 2006	6	70	2	67	9.1%	2.87 [0.60, 13.73]
Subtotal (95% CI)		**290**		**276**	**17.0%**	**4.05 [1.27, 12.91]**
Total events	17		3			
Heterogeneity: Tau² = 0.00; Chi² = 1.03, df = 2 (P = 0.60); I² = 0%						
Test for overall effect: Z = 2.36 (P = 0.02)						
2.8.2 Peripheral neuropathic pain						
Dworkin 2003	10	89	1	84	5.6%	9.44 [1.23, 72.14]
Holbech 2015	3	18	0	19	2.8%	7.37 [0.41, 133.37]
Huffman 2015	4	101	1	102	4.9%	4.04 [0.46, 35.52]
Krcevski Škvarč 2010	2	14	3	15	8.4%	0.71 [0.14, 3.66]
Lesser 2004	13	240	1	97	5.7%	5.25 [0.70, 39.62]
Rauck 2013	3	66	5	120	11.2%	1.09 [0.27, 4.42]
Richter 2005	9	161	5	85	18.1%	0.95 [0.33, 2.75]
Rosenstock 2004	4	76	1	70	5.0%	3.68 [0.42, 32.17]
Stacey 2008	8	179	0	90	2.9%	8.59 [0.50, 147.25]
van Seventer 2006	19	275	1	93	5.8%	6.43 [0.87, 47.34]
van Seventer 2010	8	127	3	127	12.7%	2.67 [0.72, 9.82]
Subtotal (95% CI)		**1346**		**902**	**83.0%**	**2.36 [1.32, 4.22]**
Total events	83		21			
Heterogeneity: Tau² = 0.16; Chi² = 11.95, df = 10 (P = 0.29); I² = 16%						
Test for overall effect: Z = 2.90 (P = 0.004)						
Total (95% CI)		**1636**		**1178**	**100.0%**	**2.50 [1.53, 4.09]**
Total events	100		24			
Heterogeneity: Tau² = 0.06; Chi² = 13.90, df = 13 (P = 0.38); I² = 6%						
Test for overall effect: Z = 3.64 (P = 0.0003)						
Test for subgroup differences: Chi² = 0.66, df = 1 (P = 0.42), I² = 0%						



*includes blurring of vision and amblyopia

Figure S8: Effect of pregabalin on the risk of ataxia in patients with neuropathic pain

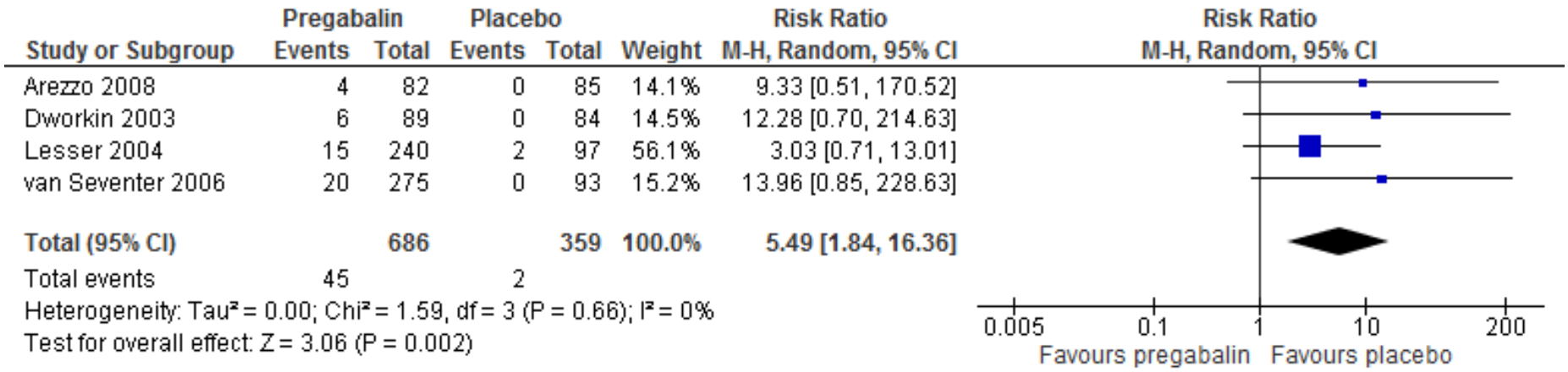


Figure S9: Effect of pregabalin on the risk of non-peripheral edema in patients with neuropathic pain

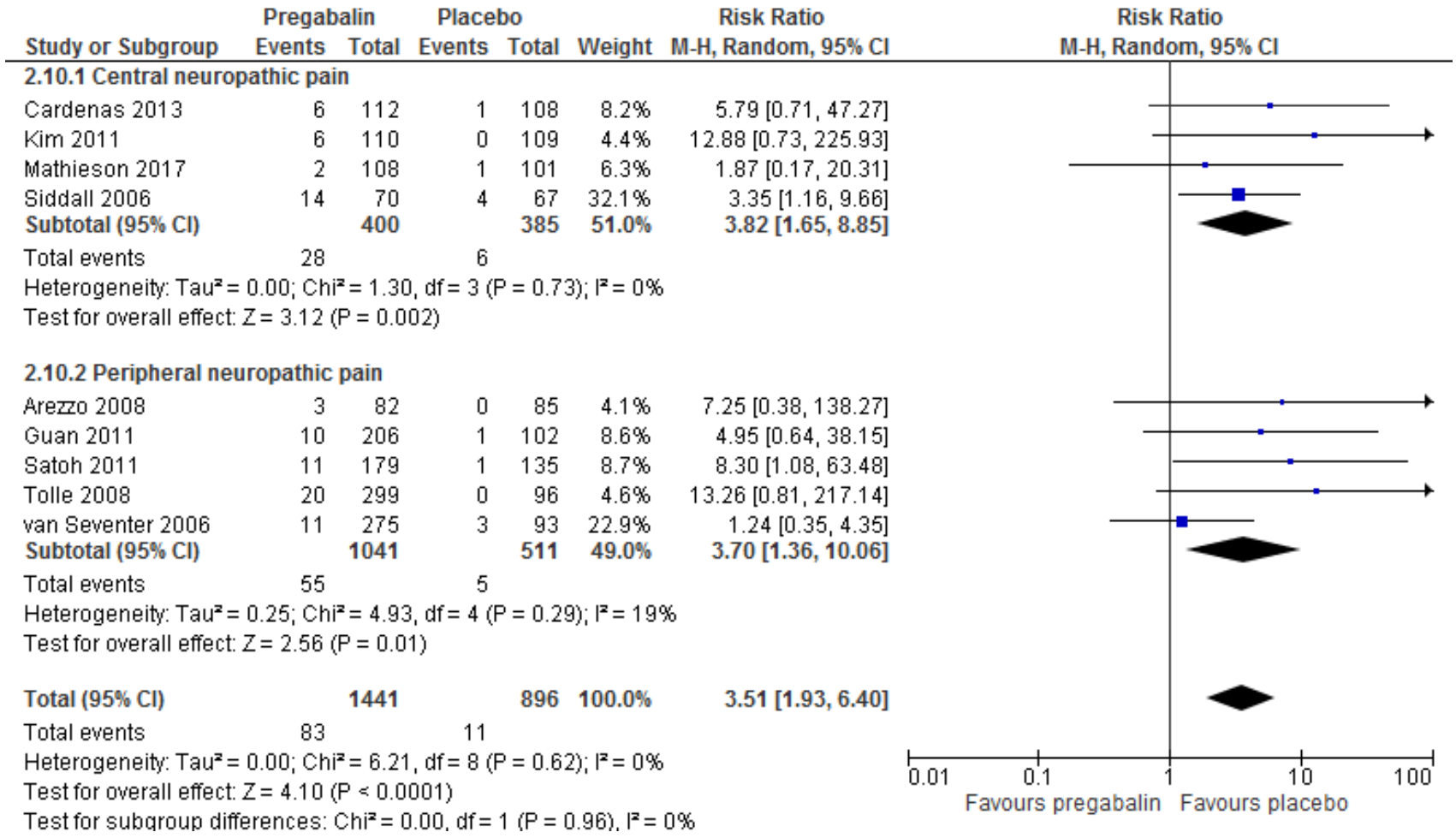


Figure S10: Effect of pregabalin on the risk of vertigo in patients with neuropathic pain

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Freynhagen 2005	24	273	1	65	22.5%	5.71 [0.79, 41.47]
Krcevski Škvarč 2010	7	14	5	15	51.8%	1.50 [0.62, 3.64]
Stacey 2008	6	179	0	90	12.7%	6.57 [0.37, 115.38]
Tolle 2008	13	299	0	96	13.1%	8.73 [0.52, 145.49]
Total (95% CI)		**765**		**266**	**100.0%**	**3.08 [1.01, 9.40]**
Total events	50		6			

Heterogeneity: $Tau^2 = 0.42$; $Chi^2 = 4.31$, $df = 3$ ($P = 0.23$); $I^2 = 30\%$

Test for overall effect: $Z = 1.97$ ($P = 0.05$)

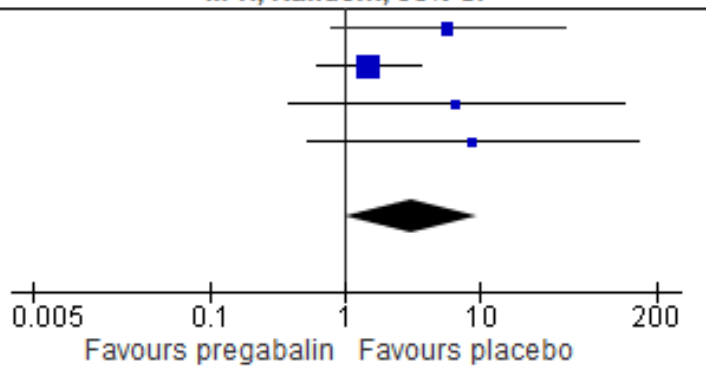


Figure S11: Effect of pregabalin on the risk of euphoria in patients with neuropathic pain

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Cardenas 2013	3	112	0	108	15.9%	6.75 [0.35, 129.20]
Lesser 2004	9	240	0	97	17.2%	7.73 [0.45, 131.46]
Rosenstock 2004	4	76	0	70	16.4%	8.30 [0.45, 151.41]
Simpson 2010	15	151	1	151	34.2%	15.00 [2.01, 112.13]
Stacey 2008	4	179	0	90	16.3%	4.55 [0.25, 83.59]
Total (95% CI)		**758**		**516**	**100.0%**	**8.80 [2.72, 28.54]**
Total events	35		1			

Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 4 (P = 0.97); I² = 0%

Test for overall effect: Z = 3.63 (P = 0.0003)

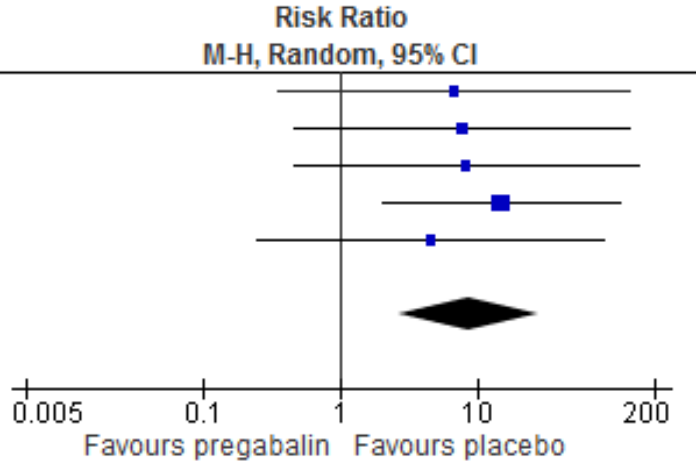


Figure S12: Effect of pregabalin on the risk of dry mouth in patients with neuropathic pain

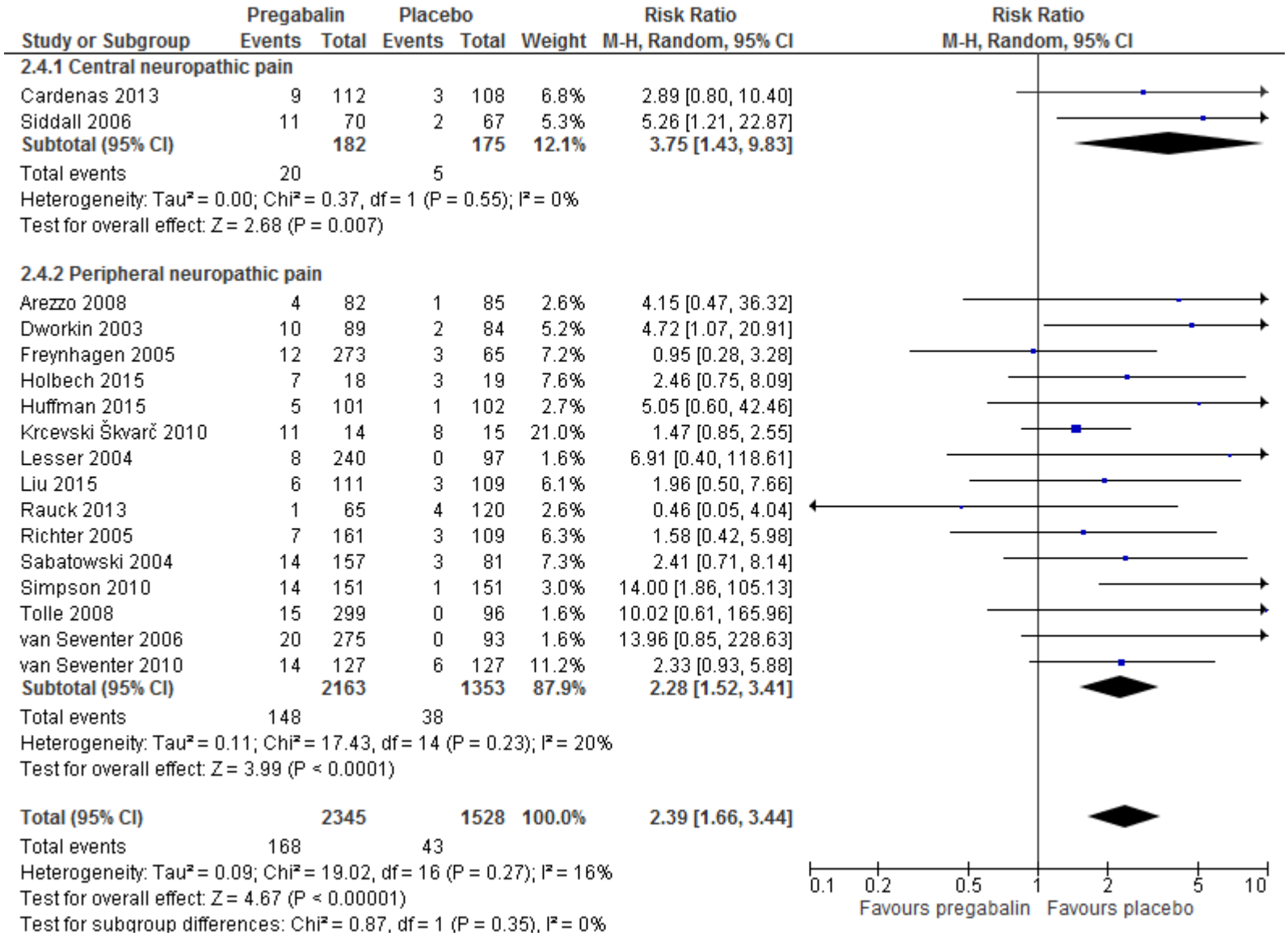


Figure S13: Effect of pregabalin on the risk of discontinuation due to adverse events

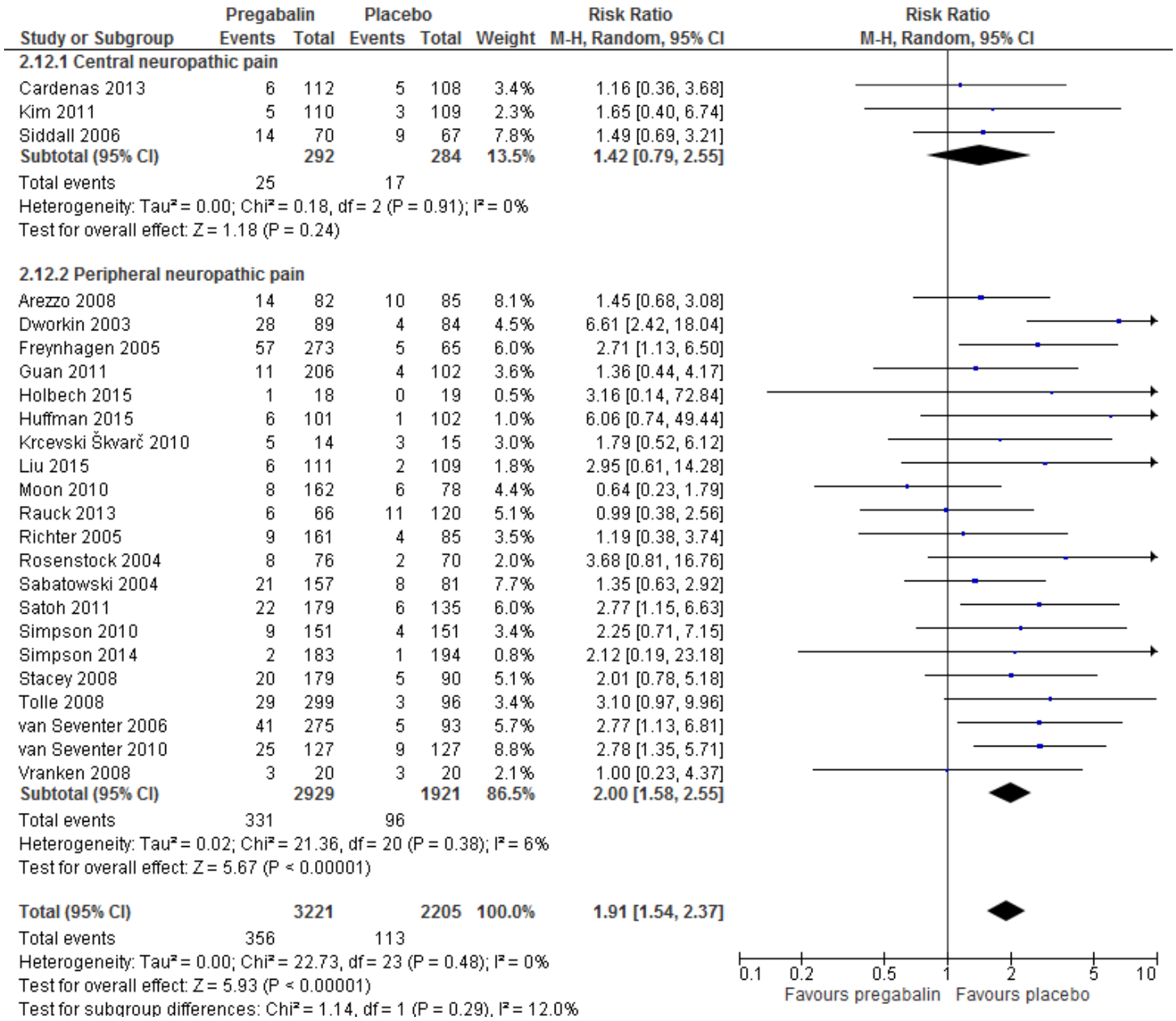


Figure S14: Effect of pregabalin on the risk of serious adverse events in patients with neuropathic pain

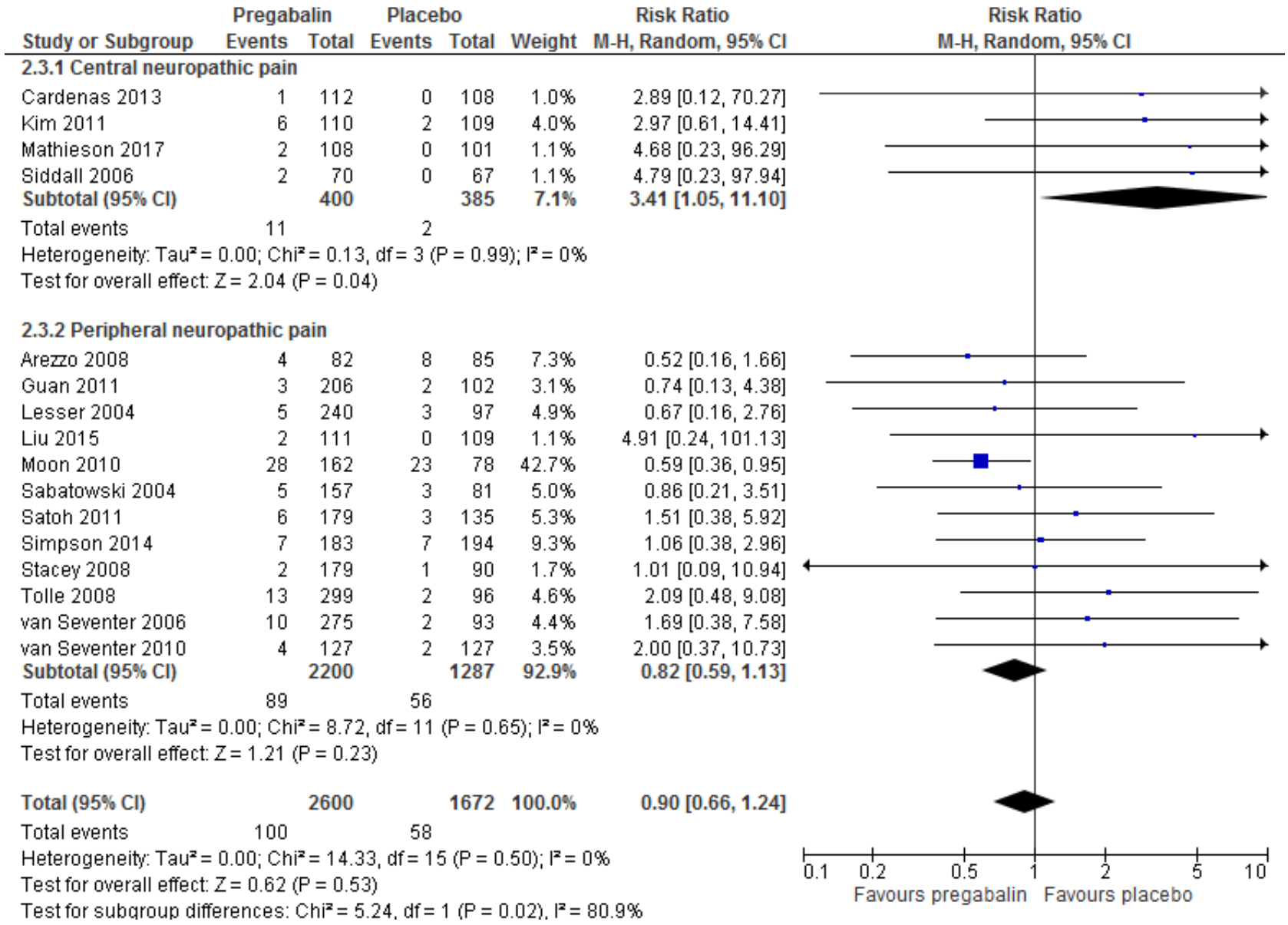


Figure S15: Effect of pregabalin on the sleep disturbance in patients with neuropathic pain

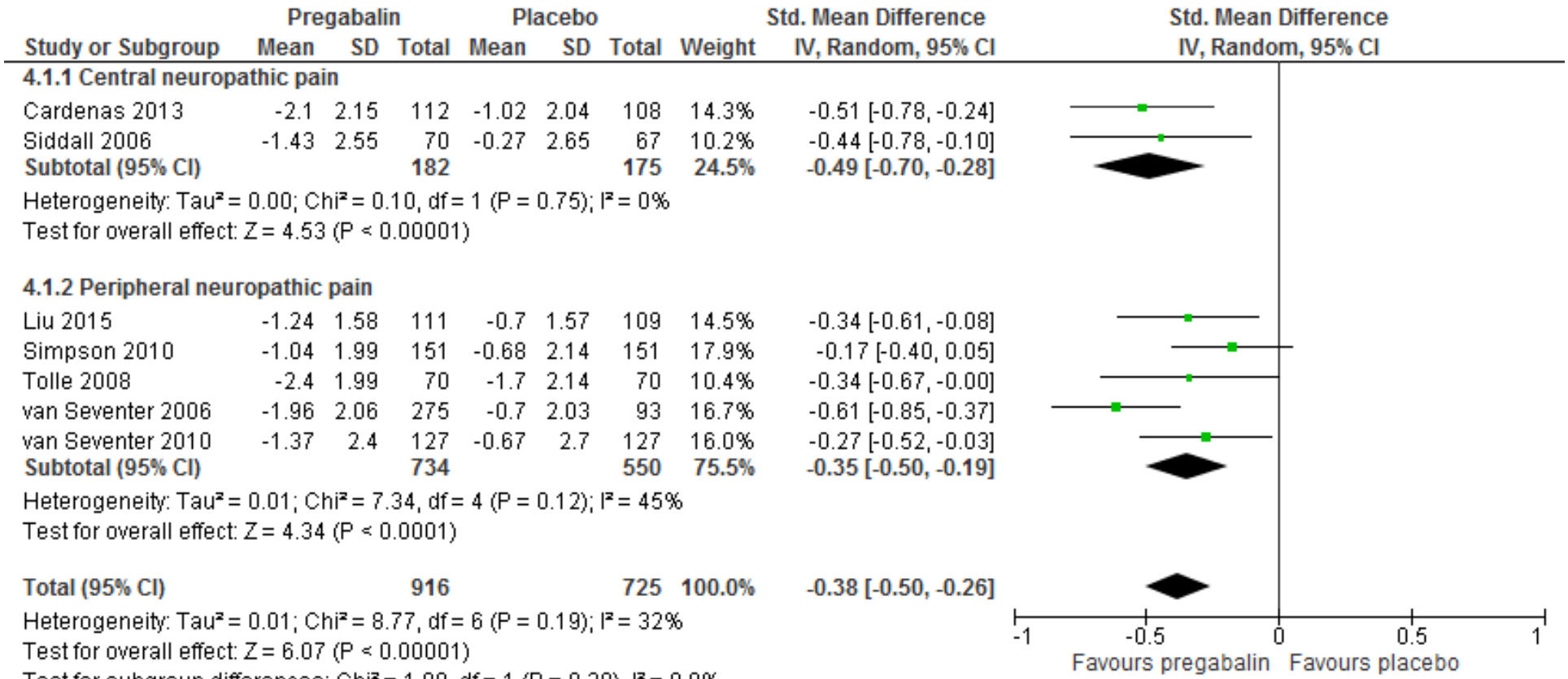


Figure S16: Effect of pregabalin on HADS-anxiety scores in patients with neuropathic pain

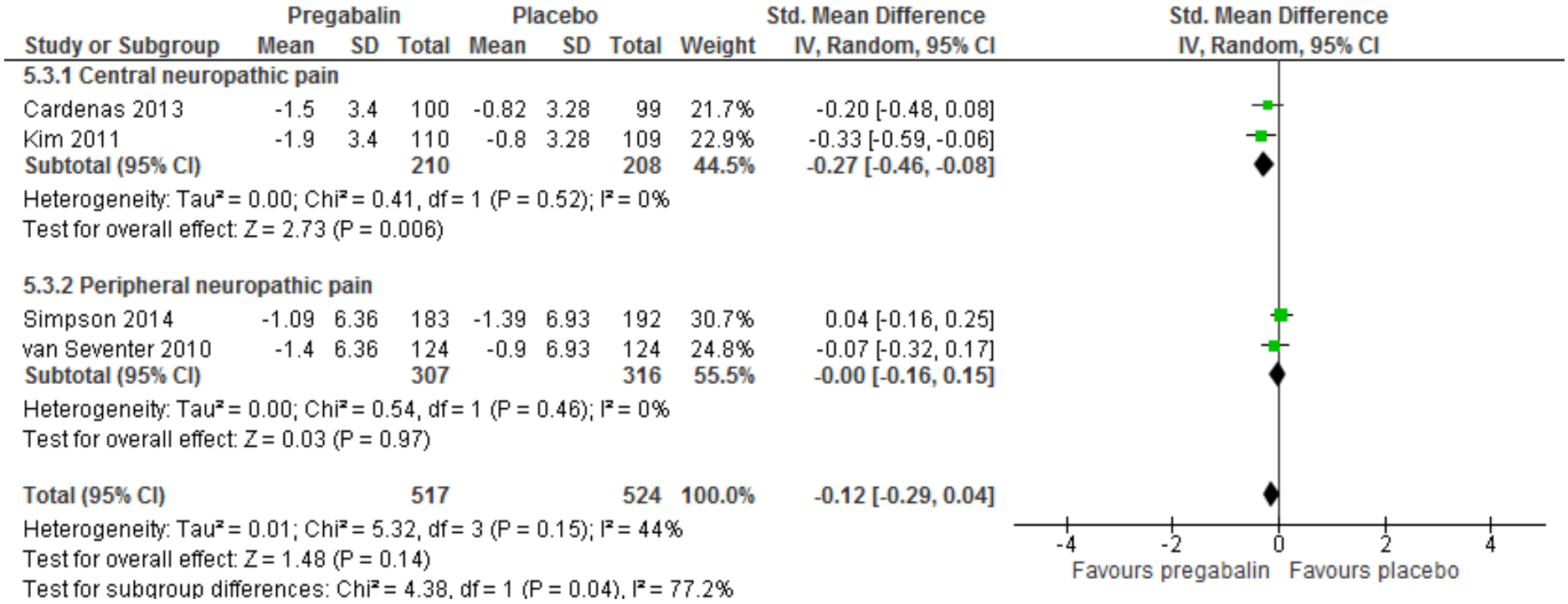
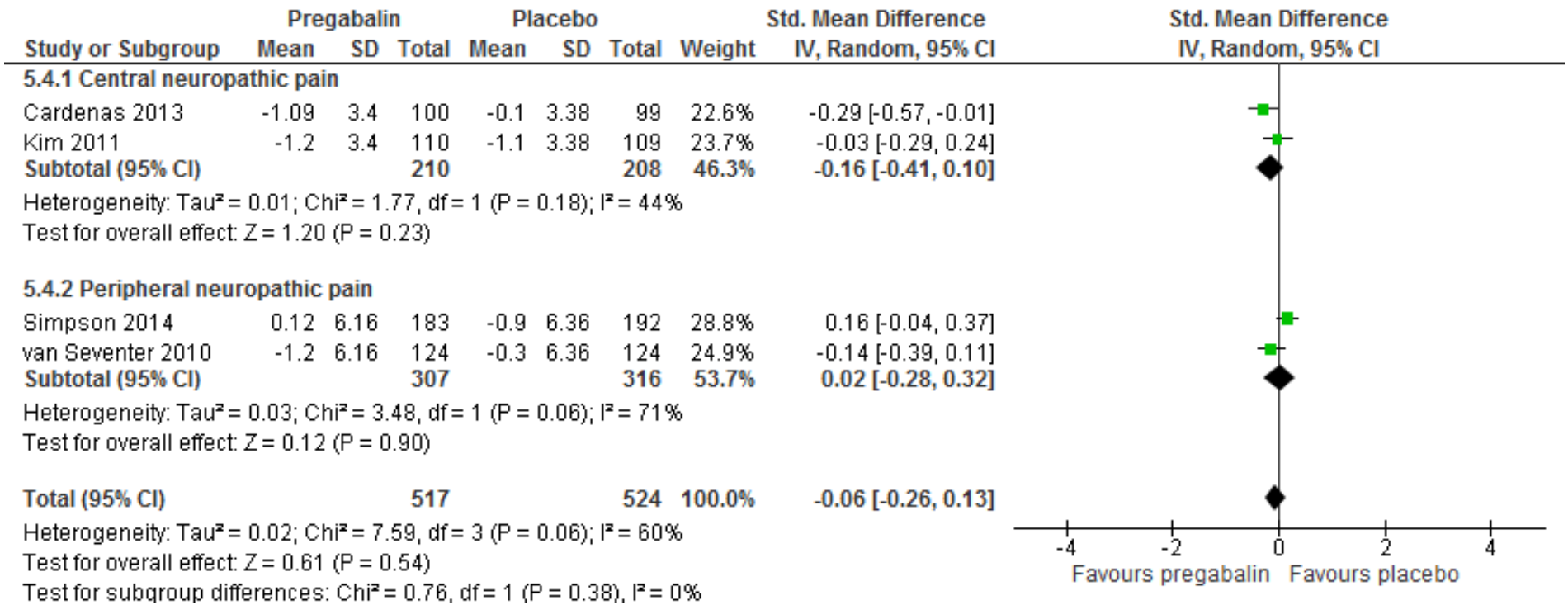


Figure S17: Effect of pregabalin on HADS-depression scores in patients with neuropathic pain



Appendix 1: Search strategy for identifying RCTs assessing the effects of pregabalin for management of neuropathic pain

MEDLINE

1. pain.mp. or Pain/

2. pain*.mp.

3. analgesia/

4. analges*.mp.

5. neuralgia/

6. 1 or 2 or 3 or 4 or 5

7. pregabalin/

8. clinical trials.mp. or Clinical Trial/

9. randomized clinical trial.mp.

10. controlled clinical trial.mp. or Controlled Clinical Trial/

11. double-blind trial.mp.

12. placebo.ab.

13. ((doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).ti,ab.

14. 8 or 9 or 10 or 11 or 12 or 13

15. 6 and 7 and 14

16. (animals not (animals and humans)).sh.

17. 15 not 16

EMBASE

1. pain/ or neuropathic pain/

2. analgesi*.mp.

3. 1 or 2

4. pregabalin.mp. or pregabalin/

5. controlled clinical trial/ or randomized clinical trial.mp.

6. double blind procedure/

7. placebo*.ab.

8. random*.ab.

9. ((doubl* or trebl* or tripl*) adj25 (blind* or mask*)).ab.

10. 5 or 6 or 7 or 8 or 9

11. 3 and 4 and 10

COCHRANE

#1	pain
#2	analgesia
#3	neuropathic pain
#4	neuralgia
#5	#1 or #2 or #3 or #4
#6	pregabalin
#7	lyrica
#8	#6 or #7
#9	randomized controlled trial.pt
#10	controlled controlled trial.pt
#11	randomized.ti,ab
#12	groups.ti,ab
#13	placebo.ti,ab
#14	#9 or #10 or #11 or #12 or #13
#15	#5 and #8 and #14

Appendix 2: List of excluded studies and reasons for exclusion

Study ID	Reference	Reason for exclusion
Al-Hihi 2017	Al-Hihi E, Badgett RG. In moderate-to-severe sciatica, pregabalin did not reduce leg pain intensity or improve quality of life. Annals of internal medicine. 2017; (2):[Jc4 p.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/558/CN-01394558/frame.html.	Not primary report of RCT
Anon 2010	Anonymous. Pregabalin effective in relieving post-traumatic peripheral neuropathic pain. Australian Journal of Pharmacy. 2010;91 (1086):82.	Not primary report of RCT
Baron 2008	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. European Journal of Pain. 2008;12(7):850-8.	Open label; also no placebo control
Baron 2010	Baron R, Freynhagen R, Tolle TR, Cloutier C, Leon T, Murphy TK, et al. The efficacy and safety of pregabalin in the treatment of neuropathic pain associated with chronic lumbosacral radiculopathy. Pain. 2010;150 (3):420-7.	Randomization based on response to interventions in run-in phase
Boyle 2012	Boyle J, Eriksson MEV, Gribble L, Gouni R, Johnsen S, Coppini DV, et al. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: Impact on pain, polysomnographic sleep, daytime functioning, and quality of life. Diabetes care. 2012;35 (12):2451-8.	No placebo control; only placebo run in

Calkins 2014	Calkins A, Shurman J, Jaros M, Kim R, Shang G. Peripheral edema and weight gain in adult patients with painful diabetic peripheral neuropathy (DPN) receiving gabapentin enacarbil (GEN) or pregabalin enrolled in a randomized phase 2 trial. Neurology Conference: 66th American Academy of Neurology Annual Meeting, AAN. 2014;82(10 SUPPL. 1).	Did not report neuropathic pain as an outcome
Cardenas 2012	Cardenas D, Nieshoff E, Suda K, Goto S, Kaneko T, Parsons B, et al. A 17-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center trial of pregabalin for the treatment of chronic central neuropathic pain after spinal cord injury. Journal of pain. 2012;Conference: 31st Annual Scientific Meeting of the American Pain Society. Honolulu, HI United States. Conference Publication: (var.pagings). 13 (4 SUPPL. 1):S62.	Duplicate of study already included in the review: Duplicate of Cardenas 2013
Cardenas 2013	Cardenas DD, Nieshoff E, Parsons B, Sanin L, Kaneko T, Suzuki M, et al. Assessment of neuropathic pain during a 17-week, double-blind, placebo-controlled, trial of pregabalin in patients with spinal cord injury. Regional Anesthesia and Pain Medicine Conference: 11th Annual ASRA Pain Medicine Meeting Miami, FL United States Conference Publication:. 2013;38(1).	Duplicate of study already included in the review: Duplicate of Cardenas 2013
De Andrade 2015	De Andrade DC, Teixeira MJ, Galhardoni R, Ferreira KASL, Malieno PB, Scisci N, et al. A phase III, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of pregabalin in the prevention and reduction of oxaliplatin-induced painful neuropathy (PreOx). Journal of Clinical Oncology Conference. 2015;33(15 SUPPL. 1).	Pain experienced during cancer chemotherapy

Duarte 2014	Duarte MAG, Cardenas-Soto K, Lem M, Castillo C, Gibbons C, Freeman R. Efficacy of pregabalin in the treatment of prediabetic neuropathic pain. Neurology Conference: 66th American Academy of Neurology Annual Meeting, AAN. 2014;82(10 SUPPL. 1).	No placebo control; evaluation in open-label run-in
Eerdekens 2016	Eerdekens M, Koch ED, Kok M, Sohns M, Forst T. Cebranopadol, a novel first-inclass analgesic: Efficacy, safety, tolerability in patients with pain due to diabetic peripheral neuropathy (U). Pain practice. 2016;Conference: 8th World Congress of the World Institute of Pain, WIP 2016. New York City, NY United States. Conference Publication: (var.pagings). 16 (SUPPL. 1):100.	Unclear how many participants were in each intervention arm
Freynhagen 2006	Freynhagen R, Busche P, Konrad C, Balkenohl M. [Effectiveness and time to onset of pregabalin in patients with neuropathic pain]. Der Schmerz. 2006;20(4):285-8.	Non-English study: Duplicate of Freynhagen 2005
Gabrani 2016	Gabrani A, Dobi D, Tomori S, Berberi F, Como A, Kapisyzi MR. Efectiveness of pregabalin compared with amytriptilin in acute Herpetic Neuralgia. Neurology Conference: 68th American Academy of Neurology Annual Meeting, AAN. 2016;86(16 SUPPL. 1).	Not a placebo-controlled study
Gilron 2011	Gilron I, Wajsbrot D, Therrien F, Lemay J. Pregabalin for peripheral neuropathic pain: a multicenter, enriched enrollment randomized withdrawal placebo-controlled trial. Clinical journal of pain. 2011;27(3):185-93.	Single-blinded Randomization to placebo/PGB occurred after a run in period of pre-gabalin?
Gonzalez-Duarte 2016	Gonzalez-Duarte A, Lem M, Diaz-Diaz E, Castillo C, Cardenas-Soto K. The Efficacy of Pregabalin in the Treatment of Prediabetic Neuropathic Pain. Clinical journal of pain. 2016;32(11):927-32.	Randomization based on response to interventions in run-in phase

Jenkins 2010	Jenkins T, Smart T, Hackman F, Cooke C, Tan K, Cheung R. Pregabalin in post-traumatic peripheral neuropathic pain: Efficient assessment of efficacy in a randomised, double-blind, placebo-controlled crossover study. European Journal of Pain Supplements. 2010;Conference: 3rd International Congress on Neuropathic Pain. Athens Greece. Conference Publication: (var.pagings). 4 (1):89.	Duplicate of study already excluded from the review: Jenkins 2012
Jenkins 2012	Jenkins TM, Smart TS, Hackman F, Cooke C, Tan KKC. Efficient assessment of efficacy in post-traumatic peripheral neuropathic pain patients: Pregabalin in a randomized, placebo-controlled, crossover study. Journal of pain research. 2012;5:243-50.	Phase I: proof of concept
Jensen-Dahm 2011	Jensen-Dahm C, Rowbotham MC, Reda H, Petersen KL. Effect of a single dose of pregabalin on herpes zoster pain. Trials [Electronic Resource]. 2011;12(55):28.	Phase 2
Kruszewski 2007	Kruszewski SP, Shane JA. Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. Neurology. 2007;68(24):2158-9.	Not primary report of RCT
Mishra 2012	Mishra S, Bhatnagar S, Goyal GN, Rana SPS, Upadhya SP. A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: a prospective randomized double-blind placebo-controlled study. American Journal of Hospice & Palliative Medicine. 2012;29(3):177-82.	Pain experienced during cancer chemotherapy

Morrison 2015	Morrison S, Parson H, Vinik AI. Pregabalin positively affects subjective pain, falls risk, and gait in persons with diabetic peripheral neuropathy. Diabetes. 2015;Conference: 75th Scientific Sessions of the American Diabetes Association. Boston, MA United States. Conference Publication: (var.pagings). 64 (SUPPL. 1):A164.	Cross-over trial that did not report data from first phase
Parsons 2013	Parsons B, Emir B. Examining the time-to-improvement of pain in patients with chronic neuropathic pain due to spinal cord injury. Journal of pain. 2013;Conference: 32nd Annual Scientific Meeting of the American Pain Society. New Orleans, LA United States. Conference Publication: (var.pagings). 14 (4 SUPPL. 1):S60.	Not primary report of RCT: report of 2 separate primary studies included in review
Parsons 2015	Parsons B, Emir B, Knapp L. Examining the Time to Improvement of Sleep Interference With Pregabalin in Patients With Painful Diabetic Peripheral Neuropathy and Postherpetic Neuralgia. American journal of therapeutics. 2015;22(4):257-68.	Not primary report of RCT
Parsons 2012	Parsons B, Nieshoff E, Cardenas D, Sanin L, Kaneko T, Suzuki M, et al. Weekly assessments of pain and sleep during a 17-week, double-blind, placebo-controlled trial of pregabalin for the treatment of chronic neuropathic pain after spinal cord injury. Neurology. 2012;Conference: 64th American Academy of Neurology Annual Meeting. New Orleans, LA United States. Conference Publication: (var.pagings). 79 (11):e88.	Duplicate of study already included in the review: Duplicate of Cardenas 2013

Parsons 2015 (Ann Neur)	Parsons B, Shang N, Yan P, Fan D. Efficacy and safety of pregabalin for postherpetic neuralgia in Chinese patients. Annals of Neurology. 2015;Conference: 140th Annual Meeting of the American Neurological Association, ANA 2015. Chicago, IL United States. Conference Publication: (var.pagings). 78 (SUPPL. 19):S92.	Duplicate of study already included in the review: Duplicate of Liu 2015
Puiu 2015	Puiu T, Kairys A, Pauer L, Schmidt-Wilcke T, Ichesco E, Hampson J, et al. Alterations in brain gray matter volume are associated with reduced evoked-pain connectivity following acute pregabalin administration. Neurology Conference: 67th American Academy of Neurology Annual Meeting, AAN. 2015;84(SUPPL. 14).	Included participants with fibromyalgia
Raskin 2014	Raskin P, Huffman C, Toth C, Asmus MJ, Messig M, Sanchez RJ, et al. Pregabalin in patients with inadequately treated painful diabetic peripheral neuropathy: a randomized withdrawal trial. Clinical journal of pain. 2014;30(5):379-90.	Randomization based on response to interventions in run-in phase
Satoh 2011	Satoh J, Yagihashi S, Baba M, Suzuki M, Arakawa A, Yoshiyama T. Efficacy and safety evaluation of pregabalin treatment over 52weeks in patients with diabetic neuropathic pain extended after a double-blind placebo-controlled trial. Journal of diabetes investigation. 2011;2 (6):457-63.	Open label; also no placebo control

van Seventer 2009	Van Seventer R, Murphy K, Temple J, McKenzie I, Serpell M, Toth C, et al. Pregabalin is effective in the treatment of posttraumatic peripheral neuropathic pain. Journal of pain. 2009;Conference: 28th Annual Scientific Meeting of the American Pain Society, APS. San Diego, CA United States. Conference Publication: (var.pagings). 10 (4 SUPPL. 1):S35.	Duplicate of study already included in the review: Van Seventer 2010
Vinik 2014- 1	Vinik A, Rosenstock J, Sharma U, Feins K, Hsu C, Merante D. Efficacy and safety of mirogabalin (DS-5565) for the treatment of diabetic peripheral neuropathic pain: A randomized, double-blind, placebo- and active comparator-controlled, adaptive proof-of-concept phase 2 study. Diabetes care. 2014;37 (12):3253-61.	Proof of concept study
Vinik 2014-2	Vinik A, Sharma U, Feins K, Hsu C, Merante D. Central nervous system safety and tolerability of DS-5565: A randomized, double-blind, placebo-and active comparator-controlled phase II study in diabetic peripheral neuropathic pain. Neurology Conference: 66th American Academy of Neurology Annual Meeting, AAN. 2014;82(10 SUPPL. 1).	Duplicate of study already excluded from the review (Vinik 2014-1)
Vinik 2014-3	Vinik A, Sharma U, Feins K, Hsu C, Merante D. DS-5565 for the treatment of diabetic peripheral neuropathic pain: Randomized, double-blind, placebo-and active comparator-controlled phase ii study. Neurology Conference: 66th American Academy of Neurology Annual Meeting, AAN. 2014;82(10 SUPPL. 1).	Duplicate of study already excluded from the review (Vinik 2014-1)

Vinik 2014-4	Vinik AI, Sharma U, Feins K, Hsu C, Merante D. Safety/tolerability profile of DS-5565: A new potent, specific alpha2-delta ligand for the treatment of diabetic peripheral neuro pathic pain. Diabetes. 2014;Conference: 74th Scientific Sessions of the American Diabetes Association. San Francisco, CA United States. Conference Publication: (var.pagings). 63 (SUPPL. 1):A298.	Duplicate of study already excluded from the review (Vinik 2014-1)
Vinik 2014-5	Vinik AI, Sharma U, Feins K, Hsu C, Merante D. A randomized, double-blind, placebo- and active comparator (pregabalin)-controlled phase II study of DS-5565 for the treatment of diabetic peripheral neuropathic pain. Diabetes. 2014;Conference: 74th Scientific Sessions of the American Diabetes Association. San Francisco, CA United States. Conference Publication: (var.pagings). 63 (SUPPL. 1):A294.	Duplicate of study already excluded from the review (Vinik 2014-1)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
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.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
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.	Suppl.
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.	5
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.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
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).	5
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.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
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.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
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).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
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.	7
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.	7
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).	7
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.	7-19
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-19
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7-19
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7-19
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).	20
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).	22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	24
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.	24

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(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Benefits and harms of pregabalin in the management of neuropathic pain: a rapid review and meta-analysis of randomized clinical trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023600.R1
Article Type:	Research
Date Submitted by the Author:	23-Aug-2018
Complete List of Authors:	Onakpoya, Igho; University of Oxford, Primary Care Health Sciences Thomas, Elizabeth; Bond University Faculty of Health Sciences and Medicine, Faculty of Health Sciences and Medicine Lee, Joseph; University of Oxford, Nuffield Department of Primary Care Health Sciences Goldacre, Ben; University of Oxford, Primary Care Health Sciences Heneghan, Carl; Oxford University, Primary Health Care
Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Nutrition and metabolism, Pharmacology and therapeutics
Keywords:	pregabalin, benefits, harms, systematic review, meta-analysis

Benefits and harms of pregabalin in the management of neuropathic pain: a rapid review and meta-analysis of randomized clinical trials

Igho J Onakpoya, research fellow[1], Elizabeth T Thomas, medical student[2], Joseph Lee, nihr in practice fellow[1], Ben Goldacre, senior clinical research fellow[1], Carl J Heneghan, director[1]

[1]University of Oxford, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Oxford, United Kingdom OX2 6GG

[2]Faculty of Health Sciences and Medicine, Bond University, 14 University Drive, Robina, Australia QLD 4226

Correspondence to IJ Onakpoya igho.onakpoya@phc.ox.ac.uk

ABSTRACT

Objective To assess the benefits and harms of pregabalin in the management of neuropathic pain

Design Rapid review and meta-analysis of phase III randomized placebo-controlled trials.

Participants Adults aged 18 and above with neuropathic pain defined according to the International Association for the Study of Pain (IASP) criteria.

Interventions Pregabalin or placebo.

Primary and secondary outcome measures Our primary outcomes were pain (as measured using validated scales) and adverse events. Our secondary outcomes were sleep disturbance, quality of life (QOL), patient global impression of change (PGIC), clinician global impression (CGI) scale, anxiety and depression scores, overall discontinuations and discontinuations because of adverse events.

Results We included 28 trials comprising 6087 participants. The neuropathic pain conditions studied were diabetic peripheral neuropathy, post-herpetic neuralgia, herpes zoster, sciatica (radicular pain), post-stroke pain and spinal cord injury-related pain. Patients who took pregabalin reported significant reductions in pain (numerical rating scale (NRS)) compared to placebo, SMD -0.49 (95% CI -0.66 to -0.32, P<0.00001); very low quality evidence. Pregabalin significantly reduced sleep interference scores (NRS) compared with placebo, SMD -0.38 (95% CI -0.50 to -0.26, P<0.00001) moderate quality evidence. Pregabalin significantly increased the risk of adverse events compared with placebo, RR 1.33 (95% CI 1.23 to 1.44, P<0.00001, low quality evidence). The risks of experiencing weight gain, somnolence, dizziness, peripheral oedema, fatigue, visual disturbances, ataxia, non-peripheral oedema, vertigo and euphoria were significantly increased with pregabalin. Pregabalin was significantly more likely than placebo to lead to discontinuation of the drug because of adverse events, RR 1.91 (95% CI 1.54 to 2.37, P<0.00001), low quality evidence.

Conclusion Pregabalin has beneficial effects on some symptoms of neuropathic pain. However, its use significantly increases the risk of a number of adverse events and discontinuation due to adverse events. The quality of the evidence from journal publications is low.

Strengths and limitations of the study

- We used the Cochrane criteria to assess the risk of bias.
- This is the first review that rates the quality of the evidence for each outcome assessed.
- The review may be prone to sampling bias, and we may have missed potentially eligible studies.
- We did not assess the extent to which different doses of pregabalin influenced the outcomes.

INTRODUCTION

Pregabalin is a gabapentinoid licensed for treatment of neurologic disorders. It is one of the earlier drugs approved by the United States Food and Drug Administration (FDA) (2004) for the treatment of painful diabetic neuropathy (PDN) and post-herpetic neuralgia (PHN).[1] Pregabalin is thought to exert its analgesic action through antagonistic activity at the voltage gated Ca2+ channels where it binds to the alpha-2-delta subunit.[1,2]

Prescriptions of pregabalin (and gabapentin) have markedly increased over the last few years. In the US, prescriptions for pregabalin rose from 39 million in 2012 to 64 million in 2016 (annual prescription costs increased from approximately $2 billion to $4.4 billion over the same period). [3] In the UK, pregabalin use increased 350% over a five year period between 2008 and 2013. [4] In England alone, there were over 6.2 million prescriptions of pregabalin across GP practices in 2017 costing about $440 million.[5]

Pregabalin is recommended as first-line pharmacologic agent for management of neuropathic pain[6]. There is, however, some evidence of increased mortality attributed pregabalin in the UK,[7] and this has led some authors to caution clinicians about the risk of harms when prescribing. [8] The risks are thought to be particularly acute for patients who use heroin and those who misuse gabapentinoids. Indeed, the UK government is soon to classify the drug as a class C controlled substance because of its abuse potential and increased reports of deaths attributed to its use.[9] Practicing clinicians have also recently called for the evidence for the effectiveness of pregabalin to be re-examined in the light of its potential to cause harms.[3,4]

Rapid reviews use accelerated methods to identify and synthesize the evidence from the literature in order to meet the needs of target audiences including policy makers, healthcare

professionals and patient groups.[10] The objective of this rapid review was therefore to evaluate the evidence for benefits and harms of pregabalin in the treatment of neuropathic pain in adults, using evidence from published randomized clinical trials (RCTs).

METHODS

We conducted electronic searches in the following databases: Medline, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL). We searched each database from inception till January 2018. No language restrictions were imposed. [See appendix 1 for a full search strategy]. We also hand searched the bibliography of eligible studies. [See appendix 2 for the full protocol].

We included phase III double-blinded placebo-controlled RCTs (efficacy studies) assessing the effects of pregabalin on neuropathic pain in adults aged 18 years and above. We included studies on neuropathic pain based on the definition of the International Association for the Study of Pain (IASP) definition.[11] These included trials on diabetic neuropathy, HIV-related neuropathy, lumbar radiculopathy, post-herpetic neuralgia, and chronic postsurgical pain. We included RCTs irrespective of study size and duration of intervention. If we included RCTs with a cross-over design, we used data from the first phase of the study. We excluded phase IV trials because they are typically unblinded. We also excluded studies that combined pregabalin with other types of pain intervention because the effects of such interventions would not be exclusively due to the actions of pregabalin; however, co-interventions used as rescue medication were allowed. Trials that randomized participants based on response to pregabalin therapy in the run-in phase were also excluded. Our main outcomes were pain (as measured using validated scales because such scales enhance the credibility of the measured outcomes[12]) and adverse events. Our secondary outcomes were sleep disturbance, quality of

life (QOL), patient global impression of change (PGIC), clinician global impression (CGI) scale, anxiety and depression, overall discontinuations and discontinuations because of adverse events.

The risk of bias for each included study was rated using the Cochrane criteria.[13] Two reviewers (IJO and ETT) independently screened abstracts and determined study eligibility. Disagreements were resolved through discussion. Three reviewers (IJO (8 studies), ETT (8 studies) and JL (10 studies)) independently extracted data according to pre-defined criteria into customized excel spreadsheets. The extracted data were independently verified by two reviewers (ETT and IJO). Any disagreements were resolved through discussion.. For each included study, we extracted data on study ID, settings, populations, interventions, outcomes and results.

Using the random effects model (Mantel-Haenszel) of the standard meta-analysis software (RevMan 5.3),[14] we computed standardized mean differences (SMDs) and 95% confidence intervals (CIs) for continuous outcomes and risk ratios with 95% CI for binary outcomes. We used pre- to post-intervention changes to assess intervention effects between pregabalin and placebo. Where studies reported data on change from baseline but did not report standard deviations (SDs), we imputed SDs (five studies) based on the SD of other studies included in the meta-analysis.[15] We used a value of P=0.05 as our threshold for statistical significance. We assessed heterogeneity using the I-squared statistic: values of 25%, 50% and 75% judged mild, moderate and substantial heterogeneity respectively. We investigated heterogeneity using subgroup (based on central or peripheral neuropathic pain) and sensitivity (based on study quality and/or duration) analyses. We used a funnel plot to assess publication bias.

One reviewer (ETT) entered the data on benefits on RevMan, and these were independently verified by a second reviewer (IJO). One reviewer (IJO) entered the data on harms onto RevMan, and these were independently verified by a second reviewer (ETT).. Using the GRADEpro software (version 3.6),[16] we rated the overall quality of the body of evidence for each outcome using the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE)[17] criteria which examines the following domains: study design; risk of bias; inconsistency; indirectness; and imprecision.

Patient public involvement

Because this was a rapid review, we did not enlist the services of patient representatives in this research.

RESULTS

Our searches identified 1349 non-duplicate citations, out of which 62 articles were considered eligible (Figure 1). We excluded 34 articles that did not fit our inclusion criteria. [See Appendix 3 for list of excluded studies and the reasons for exclusion]. In total, we included 28 studies[18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45] comprising 6087 participants (Table 1). The intervention duration was between three and 20 weeks (median 8 weeks) and all the trials were industry funded.

Twenty three studies examined the effectiveness of pregabalin in treatment of peripheral neuropathic pain including DPN, PHN and Herpes zoster (HZ) (Table 1). Five studies examined the effectiveness of pregabalin for treating central neuropathic pain including sciatica (radicular pain), post-stroke pain and spinal cord injury-related pain. Twenty five studies were conducted in two or more centres. Outcome measures for pain included

numerical rating scale (NRS), visual assessment scale (VAS), Short-Form McGill Pain Questionnaire visual assessment scale (SF-MPQ VAS), and SF-MPQ personal pain intensity (SF-MPQ PPI) index [see Table 1 for full characteristics of included studies]. The overall risk of bias in the included studies was moderate to high (Figures 2 and 3). This was mainly due to inadequate reporting of blinding procedures, selective outcome reporting and financial conflicts of interest amongst study authors. [See appendix 4 for the risk of bias judgements].

Pain

Twenty one studies provided adequate data on pain using the NRS or variants of it to allow meta-analysis. Meta-analysis showed a significant reduction in pain scores with pregabalin compared with placebo, SMD -0.49 (95% CI -0.66 to -0.32, P<0.00001, I^2=88%: Figure 4). Visual inspection of a funnel plot showed that the studies were almost symmetrically distributed around the mean difference for all trials (Figure S1); trim and fill analyses showed that the subsequent addition of studies with smaller sample sizes did not change the direction of effect. The effect was significant for peripheral neuropathic pain (P<0.00001), but not for central neuropathic pain (P=0.08; Appendix table 1). The overall quality of the evidence was very low (Summary of Findings (SoF) Table 1). Sensitivity analyses revealed similar direction of effects (Appendix Table 2). Four studies that measured pain using NRS did not provide adequate data for meta-analysis; three of these reported significant reductions in pain scores favouring pregabalin over placebo, while one reported no significant difference between groups (See Appendix Table 3).

Three studies measured pain using the VAS, and all showed significant reduction in pain scores favouring pregabalin over placebo (Appendix Table 3). Nine studies measured pain using SF-MPQ VAS, and all reported significant reduction in pain scores favouring

pregabalin over placebo. Four studies measured pain using SF-MPQ PPI index, and all reported significant reduction in pain scores favouring pregabalin over placebo.

Table 1: Main characteristics of RCTs assessing the effects of pregabalin in the management of central and peripheral neuropathic pain

Study ID	Design	Sample size	Duration	Setting	Population	Duration of neuropathic pain	Outcome measures	Interventions		
								Pregabalin	*Placebo*	*Co-interventions*
Arezzo 2008 [18]	Parallel-group	PGB 82; PLA 85	13 weeks	23 centres; USA	Men or women with T1DM or T2DM	≥3 months	**Primary:** Mean pain scores (MPS); proportion of responders; Adverse events≥3% **Secondary:** Sleep interference (11 point NRS), Present pain intensity (PPI) index; SF-MPQ VAS; CGIC; PGIC	600 mg/d Fixed	Not described	Aspirin (up to 325 mg/d for cardiac and stroke prophylaxis), acetaminophen (up to 4 g/d), SSRIs, and benzodiazepines such as lorazepam (dosed at bedtime with stable [>30 days] regimen for sleep problems) were allowed.
Cardenas 2013 [19]	Parallel-group	PGB 112; PLA 108	16 weeks	60 centres; Chile, China, Columbia, Czech Republic, Hong Kong, India, Japan, Phillipines, Russia, USA	Patients aged ≥18 years with C2-T12 complete/incomplete SCI	≥ 12 months	**Primary:** Duration-adjusted average change in pain (DAAC); **Secondary:** Change in mean pain score (from baseline to endpoint); Percentage of patients with >/=30% reduction in mean pain score at end point; PGIC scores at endpoint; change in mean pain-related sleep interference score; change from baseline in mean pain at each study week; change from baseline in pain-related sleep interference scores at each week; Medical Outcomes Study-Sleep Scale (MOS-SS); Hospital Anxiety and Depression scale scores (at baseline and endpoint)	150-600mg/d Flexible phase followed by maintenance phase	Matching grey capsule	Nonsteroidal anti-inflammatory drugs, cyclo-oxygenase-2 inhibitors, and acetaminophen (≤1.5 g/d in Japan, ≤4 g/d in all other countries) were permitted as rescue therapy. Antidepressants were permitted if the patient was on a stable dose within 30 days before the first visit.
Dworkin 2003 [20]	Parallel-group	PGB 89; PLA 84	8 weeks	29 centres; USA	Men or women ≥18 years old with post-herpetic neuralgia	≥3 months	**Primary:** Pain reduction in last 24 hours; Safety and adverse events **Secondary:** SF-MPQ at baseline, weeks 1,3,5,8; daily sleep interference score; MOS-SS; SF-36; PGIC; CGIC	300mg/d, 600mg/d Fixed	Identical in appearance; administered 1 capsule three times daily	Permitted medications included narcotic and non-narcotic analgesics, acetaminophen (not to exceed 4g/day), nonsteroidal anti-inflammatory drugs, aspirin, and antidepressants, including selective serotonin reuptake inhibitors (provided that dosing had been stable for at least 30 days before baseline)
Freynhagen 2005 [21]	Parallel-group	PGB 273; PLA 65	12 weeks	60 centres; 9 European countries that were not specified	Men or women ≥18 years old with primary diagnosis of painful DPN or post-herpetic neuralgia	≥3 months PHN, ≥6 months DPN	**Primary:** Mean Pain Score; adverse events; **Secondary:** daily sleep interference diary; MOS-SS; PGIC	150-600mg/d Flexible; 300mg/d, 600mg/d Fixed	Matching capsules; matching twice daily dosing schedule	SSRIs for treatment of depression, aspirin for myocardial infarction and stroke prophylaxis, short-acting benzodiazepines for insomnia, and paracetamol as rescue medication were allowable medications during the study period.
Guan 2011 [22]	Parallel-group	PGB 206; PLA 102	8 weeks	11 centres; China	Males or females 18-75 years with primary diagnosis of painful DPN or PHN	≥3 months PHN, ≥1 year, <5 years DPN	**Primary:** Mean Pain score (DPRS) during preceding 24h; DAAC score; **Secondary:** Daily sleep interference scale; SF-MPQ; PGIC; CGIC; Safety and adverse events	150-600mg/d Flexible	Flexible dose placebo in matching capsules; doses titrated using same regimen	NSAIDs and SSRIs allowed to be continued on stable dose
Holbech 2015 [23]	Cross-over	PGB 18; PLA 19	5 weeks	3 centres; Denmark	Males or females 20-85 years with polyneuropathy due to DPN	≥6 months	**Primary:** Total pain intensity on NRS; adverse events; **Secondary:** pain-related sleep disturbances; pain relief on 6-point verbal scale; **Other:** specific pain symptoms on the NRS; number of paracetamol tablets used as escape medication; SF-36 (health related QoL); Major Depression Inventory; QST tests	150mg/d, 300mg/d Fixed	Matched placebos of identical appearance to the 2 trial drugs were dosed similarly using double-dummy technique.	Up to 6 tablets of 500 mg paracetamol could be used daily as escape medication
Huffman 2015 [24]	Cross-over	PGB 101; PLA 102	6 weeks	36 centres; USA (25), Sweden (4), South Africa (4), Czech Republic (3)	Men or women ≥18 years old with painful DPN and with pain on walking	Not described	**Primary:** Numeric Rating Scale (NRS); DPN Pain on Walking (NRS); **Secondary:** 30%, 50% responders**;** Brief Pain Inventory-Short Form (BPI-sf); Daytime Total Activity Counts per Day; Steps per Day; Walk 12 questionnaire; Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) Total Quality of Life (TQOL) Score; Euro QoL-5 Dimensions (EQ-5D); Mean Sleep Interference Rating Score; HADS	150-300 mg/day Fixed	Matching placebo also administered in 3 divided doses	Not described

Kanodia 2011 [25]	Parallel-group	PGB 23; PLA 22	4 weeks	1 centre; India	Patients with acute herpes zoster presenting within 72 hours of onset	< 3 days	**Primary:** Pain on linear VAS; Adverse events	150mg/d Fixed	Not described	Oral acyclovir 800mg was given 5 times per day for 7 days
Kim 2011 [26]	Parallel-group	PGB 110; PLA 109	12 weeks	32 centres; Asia-Pacific	Males or females ≥18 years with diagnosis of central post-stroke pain	≥3 months	**Primary:** Mean pain score; **Secondary:** Daily sleep interference scale (DSIS); Weekly mean pain scores; proportion of 30%, 50% responders; quantitative assessment of Neuropathic pain (QANeP); Neuropathic Pain Symptom Inventory (NPSI); Weekly mean sleep interference scores; MOS-SS; HADS; SF-MPQ VAS- Part B; Euro Quality of Life (EQ-5D); PGIC; CGIC; Safety and tolerability	300,600mg/d Dose adjustment followed by fixed maintenance phase	Matching placebo	Stable medications for pain or insomnia if used normally >30 days before screening
Krcevski Skvarc 2010 [27]	Parallel-group	PGB 14; PLA 15	3 weeks	1 centre; Slovenia	Men or women 30-80 years with herpes zoster pain.		**Primary:** Assessment of pain severity (11 point Likert scale); Secondary: patients' ratings of the severity of allodynia, hyperalgesia, and burning, prickling and tingling sensations; rating of quality of sleep and physical activity; consumption of analgesics; occurrence of adverse events; SHN; PHN	150 or 300mg/d Fixed	Placebo also administered twice daily	Oxycodone, naproxen and/or tramadol, morphine, diclofenac
Lesser 2004 [28]	Parallel-group	PGB 240; PLA 97	5 weeks	45 centres; USA	Men or women ≥18 years old who were diagnosed with diabetes mellitus (type 1 or 2) and had distal symmetric sensorimotor polyneuropathy.	1-5 years	**Primary:** Pain (11-point NRS); **Secondary:** daily sleep interference diary; SF-MPQ; CGIC; PGIC; SF-36; POMS; **Safety outcomes**	75, 300, 600mg/d Fixed	Placebo administered three times daily	Acetaminophen and SSRIs permitted
Liu 2015 [29]	Parallel-group	PGB 112; PLA 110	8 weeks	22 centres; China	Male and female ethnically Chinese patients aged ≥ 18, diagnosed with post-herpetic neuralgia	Symptoms persisting ≥ 3 months after the healing of HZ lesions	**Primary:** Mean score of Daily Pain Rating Score; **Secondary:** Change from baseline on Pain VAS; Change from baseline on Present Pain Intensity (PPI) of the SF-MPQ; 30% pain responders at endpoint; change from baseline in weekly mean pain score; change from baseline in sleep interference score (11-point NRS); CGIC; PGIC; MOS-SS; Adverse events	150mg/d, 300mg/d Fixed	Matched placebo capsules on the same dosing schedule	Concomitant use of medications permitted except antidepressants, epileptics, analgesics or corticosteroids, skeletal muscle relaxants, mexelitine, and dextromethorphan as well as electrotherapy, transcutaneous electrical nerve stimulation, acupuncture, and neurosurgical therapy.
Mathieson 2017 [30]	Parallel-group	PGB 108; PLA 101	8 weeks	Number not specified; Australia	Patients with sciatica	≥1 week, <1 year	**Primary:** Average leg-pain intensity score over the course of previous 24 hours as assessed at 8 weeks and 52 weeks; **Secondary:** extent of disability (Roland Disability Questionnaire for sciatica); back pain intensity; global perceived effect; Quality of Life as measured on Short Form Health Survey 12; adverse events	150-600mg/d Flexible	Matching placebo capsules were packaged in white, opaque, sealed containers at a central pharmacy	Concomitant therapies included physical therapies as well as other analgesic medications (except for adjuvant analgesic agents), which would ideally be prescribed in accordance with the World Health Organization pain ladder. Trial clinicians were asked not to prescribe certain medicines (antiepileptic medications, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, topical lidocaine, and benzodiazepines) or to schedule interventional procedures.

Moon 2010 [31]	Parallel-group	PGB 162; PLA 78	10 weeks	Multicentre (number not specified); Korea	Korean patients aged 18 years with neuropathic pain (diabetic peripheral neuropathy, postherpetic neuralgia, or posttraumatic neuropathic pain)	Mean duration of pain pregabalin patients- 3 years, placebo patients 3.2 years	**Primary:** Endpoint mean DPRS score, Secondary: weekly mean DPRS score, duration adjusted average change (DAAC) of adjusted mean DPRS from baseline to endpoint, proportion of responders (whose scores reduced by 30% or 50%), Daily Sleep Interference Scale (DSIS), Euro Quality of Life assessment (EQ-5D): utility and VAS score; MOS-SS; HADS; PGIC; CGIC; **Tolerability evaluation** of adverse events and vital signs	150-600mg/d Flexible	Matching placebo capsules provided by Pfizer	Most patients were taking drug therapy at baseline, and the majority (83.8%) remained on concomitant drug therapy during the study, including one-third who received tricyclic antidepressants.
Rauck 2013 [32]	Parallel-group	PGB 56; PLA 112	20 weeks	85 centres; USA	Men or women ≥18 years old who were diagnosed with diabetes mellitus (type 1 or 2) and had pain attributed to DPN, defined as painful distal symmetric sensorimotor polyneuropathy.	≥6 months, <5 years	**Primary:** Change from baseline in pain intensity score (11 point PI-NRS); **Secondary:** Change from baseline in mean 24-hour average pain intensity score, daytime average pain intensity socre, nighttime average pain intensity score, current pain intensity score, daytime worst pain intensity score, nighttime worst pain intensity score, sleep interference score, and rescue analgesia consumption (mg); Neuropathic Pain Scale (NPS); SF-MPQ; pre- and post-50-foot (15 meter) walk pain scores; PGIC; CGIC; proportion of subjects achieving various levels of reduction in the 24-hour average pain intensity score; time to onset of sustained improvement in the 24-hour average pain intensity score; POMS; SF-36 health-related quality of life questionnaire; **Safety assessments**	300mg/d Fixed	Matching placebo in blister card	Acetaminophen, up to 3 g/day, was allowed as rescue medication for pain throughout the trial but was not allowed within 24 hours of any site visit for assessments.
Richter 2005 [33]	Parallel-group	PGB 161; PLA 85	6 weeks	Multicentre; not specified	Patients with diabetes and painful distal symmetrical sensorimotor polyneuropathy	1-5 years	**Primary:** Pain; Adverse events; **Secondary:** Pain characteristics (SF-MPQ, PPI); sleep interference (11 point NRS 0 to 10); health status (SF-36); psychologic state (POMS); global improvement (PGIC, CGIC)	150mg/d, 600mg/d Fixed	Matching dose and schedule	Aspirin (for prophylaxis of myocardial infarction and transient ischemic attacks), acetaminophen (3 g/day), and stable doses of serotonin reuptake inhibitors were allowed.
Rosenstock 2004 [34]	Parallel-group	PGB 76; PLA 70	8 weeks	25 centres	Men or women ≥18 years old with type 1 or 2 diabetes mellitus who reported symmetrical painful symptoms in distal extremities for a period of 1–5 years prior to study	1-5 years	**Primary:** Endpoint mean score **Secondary:** SF-MPQ-Sensory, affective and total score; daily sleep interference score; PGIC; CGIC; SF-36; Profile of Mood States (POMS); **Safety**	300mg/d Fixed	Lactose USP, 1 capsule three times daily	Acetaminophen (up to 4 g/day), aspirin (up to 325 mg/day for myocardial infarction or transient ischemic attack prophylaxis), and serotonin reuptake inhibitors provided no dose changes occurred within 30 days prior to randomization or during the study)
Sabatowski 2004 [35]	Parallel-group	PGB 157; PLA 81	8 weeks	53 centres; Europe, Australia	Men or women ≥18 years old with post-herpetic neuralgia	≥6 months	**Primary:** Endpoint mean score; **Secondary:** mean sleep interference scores, PGIC, CGIC, SF-36 health survey, Zung Self-Rating Depression Scale, VAS of the SF-MPQ, **Adverse events**	150mg/d, 300mg/d Fixed	Identical in appearance	Patients allowed to continue acetaminophen (up to 3 g/day), non-steroidal anti-inflammatory drugs, opioid or non-opioid analgesics, or antidepressants.
Satoh 2011 [36]	Parallel-group	PGB 179; PLA 90	13 weeks **intervention period	62 centres; Japan	Men or women ≥18 years old with diabetic peripheral neuropathy	≥ 1 year	**Primary:** Change from baseline in mean weekly pain score at week 13 using a 11 point NRS; **Secondary:** weekly mean pain scores, responder rates, SF-MPQ score, weekly mean sleep interference scores using 11-point NRS; MOS-Sleep Scale, SF-36, PGIC, CGIC, **Safety:** Adverse events.	300mg/d, 600mg/d Fixed	Not described, same schedule	Not described
Shabbir 2011 [37]	Parallel-group	PGB 70; PLA 70	6 weeks	2 centres; Mayo Hospital and Services Hospital, Lahore.	Men or women ≥18 years old with diabetic peripheral neuropathy	≥6 months	**Primary:** Reduction in pain (measured with NRS); responders who experienced 50% or more reduction in baseline pain score on NRS	150-600mg/d Flexible	Not described	Not described
Siddall 2006 [38]	Parallel-group	PGB 70; PLA 67	12 weeks	8 centres; Australia	Patients with central neuropathic pain in spinal cord injury	Persisted continuously for at least 3 months or with relapses and remission for at least 6 months	**Primary:** Endpoint mean pain scores, Sleep-interference scores, SF-MPQ Total, sensory and affective scores, from which VAS and PPI score was derived. MOS-sleep scale and HADS, PGIC; T**olerability and safety**	150-600mg/d Flexible	Placebo also administered twice daily	70% of patients taking other medications too: opiates, tricyclics, AEDs, NSAIDS/Cox2, Benzos, SSRI/SSNI, Muscle relaxants.
Simpson 2010 [39]	Parallel-group	PGB 151; PLA 151	14 weeks	44 centres; USA, Puerto Rico	Men or women ≥18 years old with painful HIV-DSP	≥ 3 months	**Primary:** Change from baseline in mean NPRS score; **Secondary:** change in sleep interference scores; MOS-Sleep Scale; PGIC; Pain- modified Brief Pain Inventory; Gracely Pain Scale (GPS); **Safety:** adverse events	150-600mg/d Flexible	Placebo also administered twice daily	Neurotoxic antiretroviral (ARV) drugs known to cause sensory neuropathy clinically similar to HIV-DSP must have been on stable doses for ≥3 months before screeningDoses of other pain medications had to be stable for ≥1 month before treatment and throughout the study.
Simpson 2014 [40]	Parallel-group	PGB 183; PLA 194	16 weeks	45 centres; South Africa, USA, India, Columbia, Thailand, Peru, Puerto Rico, Poland.	Men and women ≥18 years of age with HIV neuropathy	≥ 3 months	**Primary:** Change in Pain scores (NRS); **Secondary:** PGIC/CGIC; Brief Pain Symptom Inventory short form (BPI-sf);MOS-SS; Pain-related sleep interference and overall sleep disturbance (NRS-Sleep scale); Safety	150-600mg/d Flexible	Matching placebo delivered through system for randomization and drug dispensing	NSAIDs, if taken at stable dose for ≥4 weeks before study, antidepressants without efficacy for neuropathic pain if taken at stable dose for ≥30 days before study [SSRIs, bupropion, trazodone], nonbenzodiazepine hypnotics no more than

										once/week for sleep disturbance if clinically essential, rescue therapy of oral acetaminophen (max 3g/day), low dose (≤650mg/day) aspirin and stable antiretroviral treatment >8 weeks before study
Stacey 2008 [41]	Parallel-group	PGB 179; PLA 90	4 weeks	42 centres; United States, Germany, Italy, Spain, and United Kingdom	Men or women ≥ 18 years old with post-herpetic neuralgia	≥3 months	**Primary:** Pain reduction; time to onset of meaningful pain relief; **Secondary:** Daily sleep interference score; PGIC; VAS of the SF-MPQ; VAS anxiety; VAS allodynia; **Safety evaluation**	150-600mg/d Flexible dose; 300mg/d Fixed dose	Placebo also administered twice daily	Concomitant pain treatments permitted given that it must be stable for at least 30 days
Tolle 2008 [42]	Parallel-group	PGB 299; PLA 96	12 weeks	58 centres; Germany, Hungary, Poland, United Kingdom, Australia, and South Africa	Men or women ≥18 years old with painful symmetrical sensorimotor polyneuropathy due to diabetes	≥1 year	**Primary:** Pain reduction (according to 11-point NRS) from baseline; treatment responders; **Secondary:** PGIC; CGIC; EuroQoL Health Utilities Index; Daily pain-related sleep-interference scores; EQ-5D (VAS); **Safety evaluation**	150, 300, 300/600mg/d Fixed	Placebo also administered twice daily	SSRIs for depression or anxiety given in a stable dose for >30 days
Van Seventer 2006 [43]	Parallel-group	PGB 275; PLA 93	13 weeks	76 centres	Men or women ≥ 18 years old with post-herpetic neuralgia	>3 months	**Primary:** Endpoint mean pain scores; patients with ≥50% and ≥30% reduction in pain score from baseline; weekly mean pain scores; **Secondary:** endpoint mean sleep-interference scores, weekly mean sleep-interference scores, PGIC	150, 300, 600mg/d Fixed	Placebo also administered twice daily	non-narcotic analgesics, e.g., noramidopyrine and paracetamol, and stable regimens of opioids, anti-inflammatories, and antidepressants
Van Seventer 2010 [44]	Parallel-group	PGB 127; PLA 127	8 weeks	44 centres; Belgium, Canada, Denmark, Finland, Italy, Netherlands, Portugal, Romania, Sweden, Switzerland, United Kingdom	Men or women aged 18–80 with post- traumatic peripheral neuropathic pain	≥3 months	**Primary:** End-point mean pain score; **Secondary:** rating of extent to which pain interfered with sleep; MOS-SS;HADS; mBPI-sf; PGIC; **Tolerability and safety assessment**	150-600mg/d Flexible	Placebo also administered twice daily	NSAIDS, COX-2 inhibitors, opioid and non-opioid analgesics, anti-epileptic drugs, antidepressant medications, other concomitant medications if they had been stable for at least 1 month before the study and would remain stable throughout the study
Vranken 2008 [45]	Parallel-group	PGB 20; PLA 20	4 weeks	1 centre; Netherlands	Men and women ≥18 years old with central neuropathic pain	≥6 months	**Primary:** Pain intensity score (VAS); Mean endpoint pain score; Pain Disability Index (PDI); EQ-5D; Medical Outcomes Short-form Health Survey questionnaire 36 (SF36); **Safety**	150-600mg/d Flexible	Flexible dose placebo (1-4 capsules per day); matching capsules; on same dosing schedule	Adjuvant analgesics

ABBREVIATIONS: CGIC: Clinician global impression of change; DPN: Diabetic peripheral neuropathy; PGB: Pregabalin; PGIC: Patient global impression of change; PLA: Placebo; SF-MPQ PPI: Short-Form McGill Pain Questionnaire *personal pain intensity;* SF-MPQ VAS: Short-Form McGill Pain Questionnaire visual assessment scale; VAS: Visual assessment scale

Summary of Findings Table 1: Effect of pregabalin on NRS scores in patients with neuropathic pain

Patient or population: patients with neuropathic pain
Settings:
Intervention: Effect of pregabalin on pain

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Control**	Corresponding risk **Effect of pregabalin in pain**				
Mean Pain Score		The mean mean pain score in the intervention groups was **0.49 standard deviations lower** (0.66 to 0.32 lower)		5093 (21 studies)	⊕⊖⊖⊖ **very low**[1,2]	SMD -0.49 (-0.66 to -0.32)
Mean Pain Score - Central neuropathic pain (including sciatica (radicular pain))		The mean mean pain score - central neuropathic pain (including sciatica) in the intervention groups was **0.38 standard deviations lower** (0.8 lower to 0.04 higher)		785 (4 studies)	⊕⊖⊖⊖ **very low**[2,3,4]	SMD -0.38 (-0.8 to 0.04)
Mean Pain Score - Peripheral neuropathic pain (includes PDN, HZ & PHN)		The mean mean pain score - peripheral neuropathic pain (includes pdn, hz & phn) in the intervention groups was **0.52 standard deviations lower** (0.71 to 0.33 lower)		4308 (17 studies)	⊕⊖⊖⊖ **very low**[1,2]	SMD -0.52 (-0.71 to -0.33)

*The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **NRS:** Numerical rating scale; **SMD:** Standard mean deviation**; PDN:** Painful diabetic neuropathy; **HZ:** Herpes zoster; **PHN:** Post-herpetic neuralgia

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Inconsistency in allocation concealment and blinding, selective reporting, authors had financial ties to industry sponsor
[2] Substantial heterogeneity
[3] Industry-sponsored, selective reporting
[4] Wide confidence interval

Adverse events

Figure 5 shows that pregabalin was significantly more likely to cause adverse events compared with placebo, RR 1.33 (95% CI 1.23 to 1.44, P<0.00001, I^2=52%). This translates into an absolute effect of 145 (95% CI 101 to 194) more adverse events per 1000 treated. The overall quality of the evidence was low (SoF Table 2). Sensitivity analyses revealed similar direction of effects (Appendix Table 2). The risk of experiencing individual adverse events of weight gain, somnolence, dizziness, peripheral oedema, fatigue, visual disturbances, ataxia, non-peripheral oedema, dry mouth, vertigo and euphoria were significantly increased with pregabalin compared with placebo (see Appendix Table 1 and Figures S2 to S12). Pregabalin was also significantly more likely to cause discontinuation because of adverse events (RR 1.91, 95% CI 1.54 to 2.37, P<0.00001, I^2=0%); the quality of the evidence was low (SoF Table 2; Appendix Table 1; and Figure S13). Sensitivity analyses by study duration revealed similar direction of effects, but there was no significant difference with higher quality studies (Appendix Table 2).

There was no significant difference in the risk of serious adverse events (RR 0.9; 95% CI 0.66 to 1.24, P=0.50, I^2=0%; SoF Table 2; Appendix Table 1; and Figure S14); the quality of the evidence was moderate. Sensitivity analyses showed a significant effect in favour on pregabalin with three higher quality studies, but there was no difference based on study duration (Appendix Table 2). In total, six deaths were reported across four trials, five in pregabalin group and one in placebo: RR 0.86, 95% CI 0.18 to 4.06, P = 0.85, I^2=0%.

Summary of Findings Table 2: Effect of pregabalin on adverse events in patients with neuropathic pain

Patient or population: patients with Neuropathic pain
Settings:
Intervention: Effect of pregabalin on adverse events

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Effect of pregabalin on adverse events	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Number needed to harm (NNH)
Adverse events	**Study population**		**RR 1.33** (1.23 to 1.44)	4010 (19 studies)	⊕⊕⊖⊖ **low**[1,2]	6 (5 to 9)
	523 per 1000	**696 per 1000** (643 to 753)				
	Moderate					
	440 per 1000	**585 per 1000** (541 to 634)				
Discontinuations because of adverse events	**Study population**		**RR 1.91** (1.54 to 2.37)	5426 (24 studies)	⊕⊕⊖⊖ **low**[1,3]	22 (15 to 37)
	51 per 1000	**98 per 1000** (79 to 121)				
	Moderate					
	47 per 1000	**90 per 1000** (72 to 111)				
Serious adverse events	**Study population**		**RR 0.9** (0.66 to 1.24)	4272 (16 studies)	⊕⊕⊕⊖ **moderate**[1]	289 (-121 to 85)
	35 per 1000	**31 per 1000** (23 to 43)				
	Moderate					
	20 per 1000	**18 per 1000** (13 to 25)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Selective reporting, authors had financial ties to industry sponsor
[2] Moderate heterogeneity
[3] Wide confidence interval

Sleep disturbance

Twenty-one studies measured sleep interference using the NRS sleep interference scale or variants of it. Pregabalin significantly reduced sleep interference scores compared with placebo: SMD -0.38, 95% CI -0.50 to -0.26, P<0.00001, I^2=32%; the quality of the evidence was moderate (SoF Table 3; Appendix Table 1; and Figure S15). Fourteen studies reported sleep interference outcome measures with the NRS scale but did not provide adequate data for statistical pooling; 12 of these reported significant reductions in sleep interference scores favouring pregabalin over placebo, while two studies reported no significant difference between groups (Appendix Table 3). Seven studies measured sleep outcomes using the Medical Outcomes Study Sleep Scale (MOS-Sleep). We could not pool results from these studies because of insufficient data. All the studies reported significant improvements in sleep scores in favour of pregabalin over placebo (Appendix Table 3).

Quality of life (QOL)

Four studies assessed QOL using EQ-5D scores or variants of it. Two of these reported significant improvements with pregabalin compared with placebo, while the other two reported no significant differences between groups (Appendix Table 3).

Patient Global Impression of Change (PGIC)

Thirteen studies reported this outcome. Ten studies reported significant improvements in PGIC scores with pregabalin compared with placebo, while three studies found no significant differences between groups (Appendix Table 3). We could not pool results from these studies because insufficient data were published.

Summary of Findings Table 3: Effect of pregabalin on sleep scores in patients with neuropathic pain

Patient or population: patients with Neuropathic pain
Settings:
Intervention: Effect of pregabalin on sleep

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Control**	Corresponding risk **Effect of pregabalin on sleep**				
Sleep interference		The mean sleep interference in the intervention groups was **0.38 standard deviations lower** (0.5 to 0.26 lower)		1641 (7 studies)	⊕⊕⊕⊖ **moderate**[1]	SMD -0.38 (-0.5 to -0.26)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **SMD:** Standardized mean difference

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Selective reporting, authors had financial ties to industry sponsor

Clinician Global Impression of Change

Six studies reported this outcome; four of these reported significant improvements with pregabalin compared with placebo, while two found no significant differences between groups (Appendix Table 3).

Anxiety and depression scores

Four studies were pooled for this outcome. There was no significant difference in HADS-Anxiety scores between groups: SMD -0.12, 95% CI -0.29 to 0.04, P=0.14, I^2=44%; the quality of the evidence was moderate (SoF Table 4; Figure S16). There was also no significant difference in HADS-Depression scores between groups: SMD -0.06, 95% CI -0.26 to 0.13, P=0.54, I^2=60%; the quality of the evidence was low (SoF Table 4; Appendix Table 1 and Figure S17). One study[42] that did not provide sufficient data for statistical pooling reported significant improvement in the HADS-Anxiety scores in favour of pregabalin, but no significant difference in HADS-depression scores between groups (Appendix Table 1). One study[41] measured anxiety using the VAS anxiety scale and reported significant improvements in QOL scores with fixed- and flexible-dose pregabalin compared with placebo (P=0.03 and P=0.02 respectively.

Overall discontinuations

In total, there were 1,203 drop-outs (approximately 20%) in the 28 trials (n=5972) that reported the data (Appendix Table 1). There was no significant difference in overall discontinuation rates between groups, RR 1.09 (95% CI 0.93 to 1.28, P=0.29, I^2=51%).

Summary of Findings Table 4: Effect of pregabalin on anxiety and depression scores in patients with neuropathic pain

Patient or population: patients with Neuropathic pain
Settings:
Intervention: Effect of pregabalin on anxiety and depression

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Control**	Corresponding risk **Effect of pregabalin on anxiety and depression**				
HADS-Anxiety		The mean hads-anxiety in the intervention groups was **0.12 standard deviations lower** (0.29 lower to 0.04 higher)		1041 (4 studies)	⊕⊕⊕⊖ **moderate**[1]	SMD -0.12 (-0.29 to 0.04)
HADS-Depression		The mean hads-depression in the intervention groups was **0.06 standard deviations lower** (0.26 lower to 0.13 higher)		1041 (4 studies)	⊕⊕⊖⊖ **low**[1,2]	SMD -0.06 (-0.26 to 0.13)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **HADS:** Hospital anxiety and depression scale; **SMD:** Standardized mean difference

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Selective reporting, authors had financial ties to industry sponsor
[2] Moderate heterogeneity

DISCUSSION

Summary of the evidence

The evidence from published RCTs suggests that pregabalin reduces pain in patients with neuropathic pain. The effect is statistically significant in peripheral neuropathic pain, but not with central neuropathic pain. Pregabalin significantly increases the risk of adverse events including weight gain, somnolence, dizziness, dry mouth, peripheral oedema, fatigue, visual disturbances, ataxia, non-peripheral oedema, vertigo and euphoria. Pregabalin significantly reduces sleep interference scores compared with placebo. There was insufficient evidence to assess an effect on quality of life. The evidence for PGIC and CGIC scores was mixed among studies that reported these outcomes and there were no significant effects on HADS anxiety and depression scores compared with placebo. There were five deaths in the pregabalin arms and one in the placebo, but insufficient power to detect an overall effect.

Comparison with the existing literature

We have identified several published reviews assessing the effectiveness of pregabalin the management of neuropathic pain, and our results are partly consistent with these. Zhang et al[46] and Wang et al[47] showed that pregabalin was more efficacious than placebo for treatment of DPN-associated pain and PHN-associated pain respectively; however, the two reviews did not base their results on changes from baseline between groups. Semel et al[48] and Freeman et al[49] also concluded that pregabalin was more effective than placebo for neuropathic pain; however, both reviews did not account for the quality of the included primary studies. Finnerup et al[50] concluded that there was modest evidence supporting the use of pregabalin for treatment of neuropathic pain; although the authors used GRADE criteria to assess the strength of recommendation, they did not report the quality of the evidence. In an overview of Cochrane reviews, Wiffen et al[51] concluded that there was clinical trial evidence

supporting the use of pregabalin for treatment of some aspects of neuropathic pan; however, the authors did not rate the quality of the evidence for the outcomes reported.

Two reviews[52,53] that examined the safety profile of pregabalin concluded that pregabalin use was significantly more associated with adverse events than placebo; however, both reviews did not rate the quality of the evidence for the outcomes reported.

Comparison with existing guidelines

We identified several guidelines that recommend the use of pregabalin for treatment of neuropathic pain, and some of their specifications are consistent with our results. For instance, the European Federation of Neurological Societies (EFNS) guideline[54] based on data from comparative studies recommended pregabalin as first line treatment for neuropathic pain; however, the guidance assessed only the level, but not the quality, of the evidence; and also notes that there are too few large scale comparative studies to make definite conclusions about the benefits and harms. Similarly, the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitationn guidance[55] recommends pregabalin as first line treatment based on levels (and not quality) of the evidence; however, they guidance recommends that clinical trials of longer duration should be conducted. The Canadian Pain Society (CPS) guidance[56] recommends pregabalin as first-line treatment for neuropathic pain, but acknowledges that paucity of longer-duration trials limit the conclusions that can be drawn about its benefits and harms on the long-term.

Strengths and limitations

This rapid review has limitations due to its streamlined methods and search strategy. Firstly, the rapid review methodology employed could have introduced selective outcome reporting bias; nevertheless, most of the outcomes reported in this review have been listed as outcomes of interest to be considered when designing trials of neuropathic pain interventions.[57] There is a risk that our review may be prone to sampling bias, and that we may have missed potentially eligible studies, which could have been identified by searching clinical trials registries and grey literature. However, we comprehensively searched the literature, and used standard criteria to assess the risk of bias and rate the quality of the evidence. It has also been reported that generally the conclusions of rapid reviews and full reviews do not greatly differ[58]; and enhanced rapid reviews where data is independently checked by a second reviewer could help policy makers with quicker access to the evidence base.[59] This review therefore provides the most up to date comprehensive summary of the available literature, as it accounts for study quality and reports clinically meaningful patient outcomes. We did not assess the extent to which different doses of pregabalin influenced the outcomes assessed; in addition, the benefits and harms of pregabalin were not analyzed according to specific neuropathic pain conditions; only two subgroups (central and peripheral neuropathic pain) were assessed.

Implications for research

The quality of the included studies examining efficacy of pregabalin for pain was rated as low or very low according to the GRADE framework. This highlights the need for larger, robust, high-quality clinical trials to be conducted, with particular attention paid to minimizing selective reporting of outcomes. Concerns about selective reporting could be mitigated if drug manufacturers enabled access to clinical study reports (CSRs), especially as

industry-sponsored trials are likely to skew reports in favour of benefits over harms.[60,61] This would allow for a more comprehensive assessment of the benefits and harms of pregabalin. Of note, all the included trials were industry-sponsored, and an overwhelming majority of the authors of the include studies had financial ties to the pharmaceutical industry. Of note, the results of the only published charity-funded phase IV placebo-controlled trial that assessed the effectiveness of pregabalin in management of neuropathic (radicular) pain contrast our meta-analysis results – there was no significant difference in pain scores between groups.[62] Independent and publicly funded trials assessing the benefits and harms of pregabalin should be conducted. Only a few studies assessed the effect of pregabalin in improving quality of life, anxiety and depression and CGIC. Future trials should further assess the role of pregabalin for these outcomes. Studies investigating the type of neuropathic pain pregabalin relieves (e.g. stimulus-dependent pain such as hyperalgesia or allodynia), or spontaneous pain could be an area of consideration for future research.

That the median duration of intervention was nine weeks suggests that the intermediate to longer term benefits of pregabalin for neuropathic pain are unproven. Indeed in real life clinical care, it has been reported that the initial benefits seen with use of the drug in patients with neuropathic pain were no longer apparent after 6 to 12 months of therapy.[63] Therefore, RCTs that are adequately powered, and with longer durations of interventions are desirable. The finding of 5 deaths among 891 participants on pregabalin, vs 1 death among 320 participants on placebo, is somewhat concerning. Given the low frequency of this outcome (coupled with the short trial durations), RCTs are unlikely to be informative; we suggest pharmacoepidemiological studies in routinely collected electronic health records and spontaneous reporting databases to assess the impact of pregabalin on mortality.

Implications for clinical practice

Very low-to-moderate quality evidence suggests that pregabalin improves some symptoms of neuropathic pain. However, it significantly increases the risk of adverse events including somnolence, oedema, visual disturbances, ataxia, vertigo and euphoria. Pregabalin also increases the risk of drug discontinuation because of adverse events. Clinicians should be cautious about prescribing pregabalin, and should consider whether its benefits outweigh potential harms in individual patients.

Conclusions

The evidence from RCTs in journal publications suggests that pregabalin has beneficial effects on some symptoms of neuropathic pain. However, its use significantly increases the risk of adverse events and discontinuation due to adverse events. The quality of the evidence from journal publications is overall low, and the duration of trials is short. Greater transparency in the reporting of outcomes is advocated; independent and publicly funded trials assessing the effects of pregabalin in neuropathic pain should be encouraged. Allowing researchers access to full CSRs of pregabalin trials should be a priority for drug companies and regulators.

Acknowledgement

IJO, BG and CJH are part of the Evidence Synthesis Working Group. The Evidence Synthesis Working Group is funded by the National Institute for Health Research School for Primary Care Research (NIHR SPCR) [ProjectNumber 390]. JL is supported by an NIHR In Practice Fellowship. The views expressed are those of the author(s) and not necessarily those of the NIHR, the NHS or the Department of Health.

Funding

None

Data sharing statement

No additional data available

Authors' Contribution

IJO was involved with devising the review methods, conducting electronic searches, screening of abstracts, data extraction, data analysis and interpretation, and co-drafting of the review. ETT was involved with devising the review methods, screening of abstracts, data extraction, data analysis and interpretation, and co-drafting of the review. JL was involved with data extraction, data analysis and interpretation, and co-drafting of the review. BG was involved with devising the review methods, data analysis and interpretation, and co-drafting of the review. CJH was involved with devising the review methods, data analysis and interpretation, and co-drafting of the review.

Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). CJH has received expenses and fees for his media work. He has received expenses from the WHO, FDA, and holds grant funding from the NIHR, the NIHR School of Primary Care Research, The Wellcome Trust and the WHO. He has received financial remuneration from an asbestos case. He has also received income from the publication of a series of toolkit books published by Blackwells. On occasion, he receives expenses for teaching EBM and is also paid for his GP work in NHS out of hours. CEBM jointly runs the EvidenceLive

Conference with the BMJ and the Overdiagnosis Conference with some international partners which are based on a non-profit making model. BG receives funding from the Laura and John Arnold Foundation and reports personal fees from intermittent additional personal income from speaking and writing for lay audiences on problems in science and medicine including regulatory shortcomings. IJO, ETT and JL have no interests to disclose.

Transparency declaration

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Figure legends

Figure 1: Flow chart showing the process for inclusion of RCTs assessing the effects of pregabalin in the management of neuropathic pain

Figure 2: Graphical representation of the risk of bias in RCTs assessing the effects of pregabalin in the management of neuropathic pain

Figure 3: Risk of bias summary for RCTs assessing the effects of pregabalin in the management of neuropathic pain

Figure 4: Effect of pregabalin on pain scores in patients with neuropathic pain

Figure 5: Effect of pregabalin on the risk of adverse events in patients with neuropathic pain

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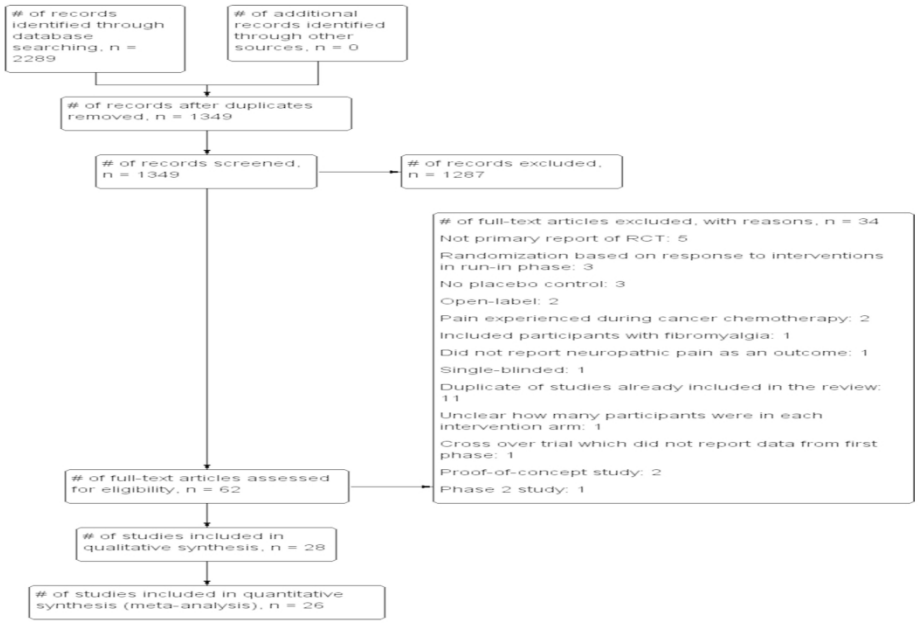

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Figure 2: Graphical representation of the risk of bias in RCTs assessing the effects of pregabalin in the management of neuropathic pain

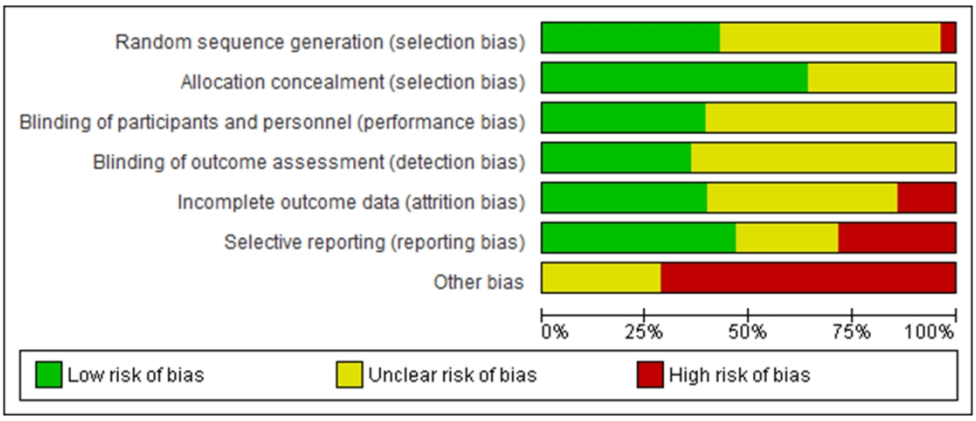

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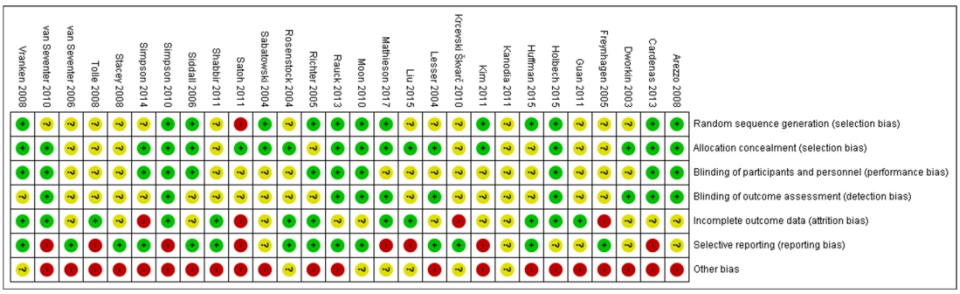
Figure 3: Risk of bias summary for RCTs assessing the effects of pregabalin in the management of neuropathic pain



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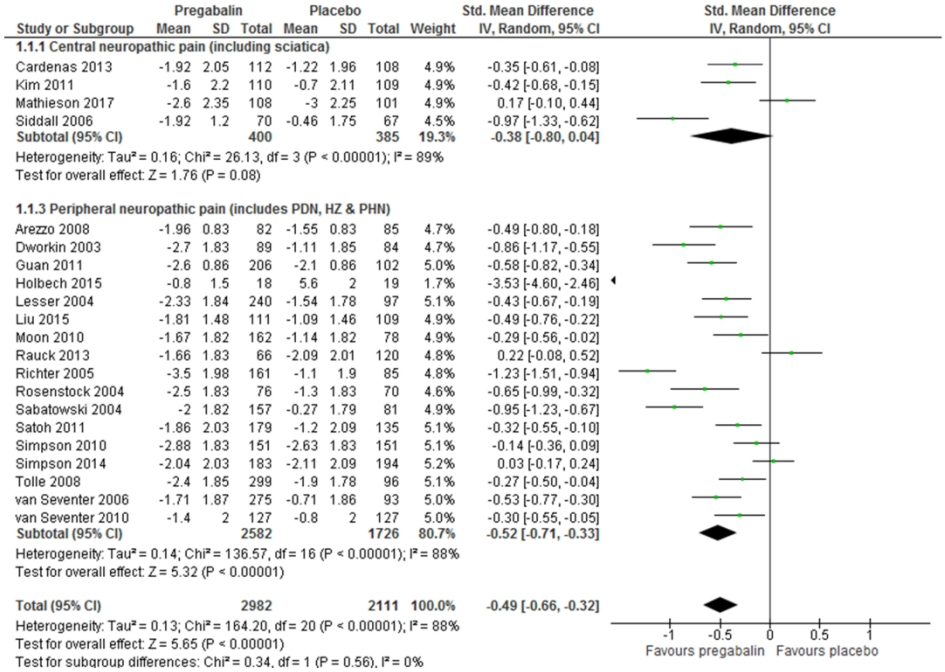

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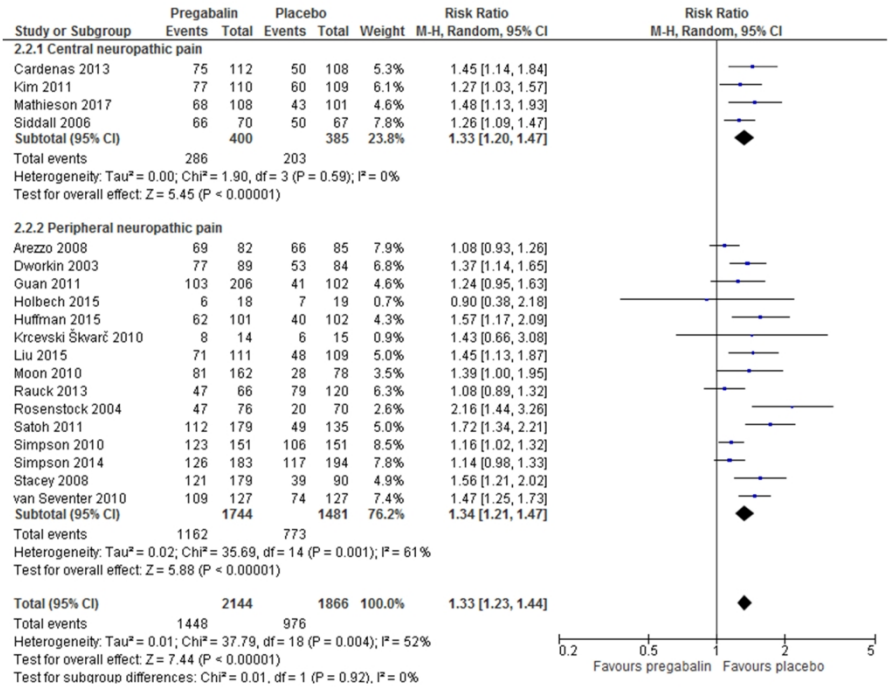
Figure 5: Effect of pregabalin on the risk of adverse events in patients with neuropathic pain



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Appendix Table 1: Benefits and harms of pregabalin in the management of neuropathic pain

Outcome	Overall analysis	Subgroup analyses		Test for subgroup differences
		Central neuropathic pain	*Peripheral neuropathic pain*	
Mean change in pain scores - NRS	(n = 5093): SMD -0.49 (-0.66 to -0.32, P < 0.00001, I^2=88%	(n = 785): SMD -0.38 (-0.80 to 0.04), P = 0.08, I^2=89%	(n = 4308): SMD -0.52 (-0.71 to -0.33), P < 0.00001, I^2=88%	P = 0.56, I^2=0%
Mean change in sleep interference scores - NRS	(n = 1641): SMD -0.38 (-0.50 to -0.26, P < 0.00001, I^2=32%	(n = 357): SMD -0.49 (-0.70 to -0.28), P < 0.00001, I^2=0%	(n = 1284): SMD -0.35 (-0.50 to -0.19), P < 0.0001, I^2=45%	P = 0.30, I^2=8%
Mean change in HADS-anxiety scores	(n = 1041): SMD -0.12 (-0.29 to 0.04, P = 0.14, I^2=44%	(n = 418): SMD -0.27 (-0.46 to -0.08, P = 0.006, I^2=0%	(n = 623): SMD -0.00 (-0.16 to 0.15, P = 0.97, I^2=0%	P = 0.04, I^2=77.2%
Mean change in HADS-depression scores	(n = 1041): SMD -0.06 (-0.26 to 0.13, P = 0.54, I^2=60%	(n = 418): SMD -0.16 (-0.41 to 0.10, P = 0.23, I^2=44%	(n = 623): SMD 0.02 (-0.28 to 0.32, P = 0.90, I^2=71%	P = 0.38, I^2=8%
Overall adverse events	(n = 4010): RR 1.33 (1.23 to 1.44), P < 0.00001, I^2=52%	(n = 489): RR 1.33 (1.20 to 1.47), P < 0.00001, I^2=0%	(n = 3225): RR 1.34 (1.21 to 1.47), P < 0.00001, I^2=61%	P = 0.92, I^2=0%
Adverse event: weight gain	(n = 3636): RR 4.58, (2.88 to 7.28), P < 0.00001, I^2=0%	(n = 428): RR 3.77 (0.94 to 15.08), P = 0.06, I^2=0%	(n = 3636): RR 4.69 (2.87 to 7.68), P < 0.00001, I^2=0%	P = 0.77, I^2=0%
Adverse event: somnolence	(n = 5695): RR 2.84, (2.36 to 3.42), P < 0.00001, I^2=0%	(n = 785): RR 3.18 (2.16 to 4.68), P < 0.00001, I^2=0%	(n = 4910): RR 2.74 (2.22 to 3.40), P < 0.00001, I^2=1%	P = 0.51, I^2=0%
Adverse event: dizziness	(n = 5732): RR 2.94 (2.30 to 3.74), P < 0.00001, I^2=63%	(n = 785): RR 3.38 (2.46 to 4.63), P < 0.00001, I^2=0%	(n = 4947): RR 2.89 (2.17 to 3.85), P < 0.00001, I^2=67%	P = 0.48, I^2=0%
Adverse event: peripheral edema	(n = 5001): RR 2.63 (1.86 to 3.73), P < 0.00001, I^2=41%	(n = 439): RR 3.90 (1.63 to 9.36), P = 0.002, I^2=0%	(n = 4562): RR 2.53 (1.74 to 3.68), P < 0.00001, I^2=44%	P = 0.37, I^2=0%
Adverse event: fatigue*	(n = 3958): RR 1.83 (1.32 to 2.54), P = 0.0003, I^2=14%	N/A	N/A	N/A
Adverse event: visual disturbance	(n = 2814): RR 2.50 (1.53 to 4.09), P = 0.0003, I^2=6%	(n = 566): RR 4.05 (1.27 to 12.91), P = 0.02, I^2=0%	(n = 2248): RR 2.36 (1.32 to 4.22), P = 0.004, I^2=16%	P = 0.42, I^2=0%
Adverse event: ataxia**	(n = 1045): RR 5.49 (1.84 to 16.36), P = 0.002, I^2=0%	N/A	N/A	N/A
Adverse event: dry mouth	(n = 3873): RR 2.39 (1.66 to 3.44), P < 0.0001, I^2=16%	(n = 357): RR 3.75 (1.43 to 9.83), P = 0.007, I^2=0%	(n = 3516): RR 2.28 (1.52 to 3.41), P < 0.0001, I^2=20%	P = 0.35, I^2=0%
Adverse event: non-peripheral edema	(n = 2337): RR 3.51 (1.93 to 6.40), P < 0.0001, I^2=0%	(n = 785): RR 3.82 (1.65 to 8.85), P = 0.002, I^2=0%	(n = 1552): RR 3.70 (1.36 to 10.06), P = 0.01, I^2=19%	P = 0.96, I^2=0%
Adverse event: vertigo**	(n = 1031): RR 3.08 (1.01 to 9.40), P = 0.05, I^2=30%	N/A	N/A	N/A
Adverse event: euphoria*	(n = 1274): RR 8.80 (2.72 to 28.54), P = 0.0003, I^2=0%	N/A	N/A	N/A
Discontinuation due to adverse events	(n = 5426): RR 1.91 (1.54 to 2.37), P < 0.00001, I^2=0%	(n = 576): RR 1.42 (0.79 to 2.55), P = 0.24, I^2=0%	(n = 4850): RR 2.00 (1.58 to 2.55), P < 0.00001, I^2=6%	P = 0.29, I^2=12%

Abbreviations: HADS: Hospital anxiety depression scale; NRS: Numerical rating scale; RR: Risk ratio; SMD: Standardized mean difference

*only one RCT on central neuropathic pain reported adequate data
**all RCTs were in patients with peripheral neuropathic pain

Appendix Table 2: Sensitivity analyses by study quality and duration in clinical trials assessing the benefits and harms of pregabalin in neuropathic pain

Outcome	Sensitivity analysis based on higher quality studies*	Sensitivity analysis based on shorter duration of intervention**	Sensitivity analysis based on longer duration of intervention***
Pain	5 studies (n = 932): SMD -0.56 (-1.07 to -0.05; P = 0.03; I^2=92%)	10 studies (n = 2408): SMD -0.68 (-0.96 to -0.40; P < 0.00001; I^2=90%)	10 studies (n = 2685): SMD -0.31 (-0.49 to -0.13; P = 0.0006; I^2=79%)
Adverse events	6 studies (n = 1152): RR 1.17 (1.06 to 1.29; P = 0.002; I^2=23%)	11 studies (n = 2088): RR 1.46 (1.34 to 1.58; P < 0.00001; I^2=0%)	8 studies (n = 1922): RR 1.23 (1.12 to 1.35; P < 0.0001; I^2=55%)
Serious adverse events	3 studies (n = 627): RR 0.59 (0.38 to 0.92; P = 0.02; I^2=0%)	8 studies (n = 2088): RR 0.72 (0.49 to 1.07; P = 0.11; I^2=0%)	7 studies (n = 1674): RR 0.93 (0.55 to 1.59; P = 0.79; I^2=26%)
Discontinuation due to adverse events	6 studies (n = 1152): RR 1.22 (0.79 to 1.87; P = 0.37; I^2=0%)	13 studies (n = 2403): RR 1.95 (1.34 to 2.84; P = 0.0005; I^2=27%)	11 studies (n = 3023): RR 1.88 (1.40 to 2.53; P < 0.0001; I^2=0%)

*studies that adequately reported randomization and blinding procedures

**Studies duration lasting less than 12 weeks

***Studies duration lasting at least 12 weeks

Appendix Table 3: Main results* of RCTs assessing the benefits and harms of pregabalin in the management of neuropathic pain

		Pain			Sleep Disturbance				
Study ID	**NRS**	**VAS Score**	**SF-MPQ VAS**	**SF-MPQ PPI**	**Sleep Interference Scores**	**MOS-Sleep**	**Quality of Life (EQ-5D)**	**PGIC**	**CGIC**
Arezzo 2008			Significantly favoured PGB over PLA (MD -11.06, 95% CI, -18.89 to -3.22; P = 0.006)					Significant improvement with PGB compared to PLA, P= 0.002	
Cardenas 2013						Significant improvement with PGB over PLA on domains of sleep disturbance, awaken short of breath, sleep quantity, and optimal seep subscales (P<0.05)		PGIC reported as binary outcome; significantly improved with PGB compared with PLA, P<0.001	Significant improvement in the PGB arm (P= 0.0294)
Dworkin 2003			Significantly favoured PGB over PLA (MD -17.62, 95% CI, -25.37 to -9.86; P = 0.0001		Significantly favoured PGB over PLA (MD -1.58, 95% CI, -2.19 to -0.97; P = 0.0001)	Significantly favoured PGB over PLA (MD -9.80, 95% CI, -14.49 to -5.11; P = 0.0001)		Significantly improved with PGB versus PLA, P = 0.001	
Freynhagen 2005	Both flexible- and fixed-dose PGB significantly reduced endpoint mean pain score versus PLA (P=0.002 and P<0.001 respectively)				Significantly improved at endpoint in each PGB treatment group over PLA (P<0.001)	Significantly favoured PGB over PLA (P<0.05)			
Guan 2011			Significantly improved with PGB vs PLA LSMD -6.56, 95% CI -11.65 to -1.47, P=0.012		Significantly improved with PGB vs PLA: LSMD -0.5, 95% CI -0.93 to -0.07, P=0.023				
Holbech 2015					Significantly improved with PGB vs PLA LSMD -0.55, 95% CI -0.93 to -0.17, P=0.004				
Huffmann 2015	Significant treatment difference favouring PGB over PLA for DPN pain (P=0.034) and DPN pain on walking (P=0.001)							Significant improvements with PGB compared to PLA (P=0.002)	
Kanodia 2011		Significantly improved with PGB compared to PLA: MD -21, 95% CI: -23.8 to -18.2; P = 0.004)							
Kim 2011					Significantly favoured PGB over PLA (P<0.05)	Significant improvement with PGB over PLA in sleep quantity (P=0.03), sleep adequacy (P=0.13), snoring (P=0.39), and reduced the sleep problems index (P=0.049)	No significant difference between groups at endpoint, MD 0 (95% CI -0.1, 0,1) P= 0.566	No significant difference between groups at endpoint, -0.2 (95% CI -0.5, 0.1) P=0.144	Significant improvement of in PGB group vs PLA: MD -0.3 (95% CI -0.6, 0) (P=0.049)
Krcevski Skvarč 2010	No significant difference between groups, P values not reported								
Lesser 2004					Significantly favoured PGB over PLA (P=0.0001)				
Liu 2015			Significant decrease with PGB compared with PLA: MD -8.18, 95% CI: -11.99 to -4.37; P<0.0001)	Significant decrease in with PGB compared with PLA: MD -0.37, 95% CI: -0.58 to -0.16; P=0.0007).		Significantly greater improvements with PGB in subscales of sleep disturbance (P=0.0039) and quantity of sleep (P=0.0035) compared with PLA		Significantly improved with PGB versus PLA: LSMD -0.49 95% CI -0.72 to -0.27, P<0.0001	Significant improvement with PGB versus PLA, LSMD -0.62 95% (CI -0.86, -0.39), P<0.0001
Mathieson 2017									
Moon 2010					Significantly favoured PGB over PLA: LSMD -0.51 (95% CI, -0.96 to -0.07; P = 0.024)	Significantly greater improvements with PGB in subscales of sleep disturbance (P=0.0034) and quantity of sleep (P=0.018) compared with PLA	No significant differences in endpoint scores of EQ-5D utility score least squares means 0.03, 95% CI -0.04, 0.09 P= 0.429, or EQ-5D VAS at endpoint LSMD 3.50 (95% CI -1.18, 8.18) P= 0.142	No statistically significant difference between groups	No statistically significant difference between groups
Rauck 2013					No significant difference between groups: MD 0.11 (95% CI -0.60 to 0.82)				
Richter 2005			Significantly favoured PGB 600mg/day over PLA (MD -14.67, 95% CI, -21.92 to -7.41; P = 0.0002). No significant	Significantly favoured PGB 600mg/day over PLA (MD -0.66, 95% CI, -0.97 to -0.35; P = 0.0002). No significant difference	Significantly favoured PGB over PLA: LSMD -1.152; 95% CI -1.752 to -0.551; P=0.0004				

			difference between PGB 150mg/day and PLA (MD -4.78, 95% CI, -12.20 to -2.64; P = 0.20)	between PGB 150 mg/day and PLA (MD -0.17, 95% CI, -0.49 to 0.14; P = 0.28)					
Rosenstock 2004			Significantly favoured PGB over PLA (MD -16.19, 95% CI, -24.52 to -7.86; P = 0.0002)	Significantly favoured PGB over PLA (MD -0.37, 95% CI, -0.72 to -0.02; P = 0.036)	Significantly favoured PGB over PLA: LSMD -1.54, 95% CI -2.28 to -0.80, P=0.0001				
Sabatowski 2004					Significantly favoured PGB over PLA: LSMD -1.11, 95% CI -1.71 to -0.51, P=0.0003 for 150 mg/day; LSMD -1.43, 95% CI -2.04 to -0.82, P=0.0001 for 300 mg/day				
Satoh 2011			Significantly favoured PGB 300 mg/day and 600 mg/day over PLA (P < 0.05)		Significantly improved in the 300 and 600 mg/ day PGB groups compared with PLA (P < 0.0001 and P = 0.0273 respectively)				
Shabbir 2011	Significant improvement in pain of DPN was observed in patients receiving PGB (48.1%) and compared to those receiving PLA (10.5%), P values not reported								
Siddall 2006			Significantly favoured PGB over PLA (MD -17.6, 95% CI, -25.2 to -10.0; P<0.001)	Significantly favoured PGB over PLA (MD -0.66, 95% CI, -0.99 to -0.32; P<0.001)					
Simpson 2010								Significant self-reported improvement favouring PGB over PLA: 82.8% vs 66.7% (P= 0.008)	
Simpson 2014					No significant difference between groups: LSMD 0.04, 95% CI 0.43 to 0.35, P =0.840			No significant differences between groups: (P=0.505)	No significant differences between groups (P=0.427)
Stacey 2008		Significant improvement in VAS allodynia scores with PGB compared to PLA (flexible-dose: MD -14.4 mm [P<0 .0001] and fixed-dose, MD -8.98 mm [P =0.0075])	Significant improvement in with PGB compared to PLA (flexible-dose: MD -16.33 mm [P<0 .0001] and fixed-dose, MD -11.97 mm [P =0 .0008])		Significant improvements with flexible- and fixed-dose PGB. Results of between-group differences not reported		Fixed or flexible dose PGB demonstrated significant improvement in VAS anxiety scores over PLA (fixed-dose, 19.95, P = 0.025, and flexible-dose, -17.81; P= 0.024)	Patients treated with any PGB treatment regimen were significantly more likely to rate themselves as minimally, much, or very much improved on the PGIC at end point compared with PLA	
Tolle 2008							Significant improvements in utility scores for 150, 300, 600mg/day respectively compared to PLA, all P ≤ 0.0263	Significant improvement with 600 mg/day PGB versus PLA in subjects reporting “improved” or “much improved” (50.5% vs 33.3%, P = 0.02)	Significant superiority of PGB 600 mg/day over PLA (P= 0.009)
Van Seventer 2006						Significant improvement in MOS sleep scale problems with PGB compared with PLA MD – 7.54, 95% CI -11.52 to -3.56, P<0.001		Patients in the 150 mg/day (P = 0.02) and 600 mg/day (P = 0.003) groups were more likely to report global improvement than those in the PLA group	
Van Seventer 2010								Significant improvement in favour of PGB over PLA (P = 0.006)	
Vranken 2008		Significant decrease in with PGB compared with PLA: MD 2.18, 95% CI: 0.57 to 3.80; P = 0.01)					Statistically significant improvement for both the EQ-5D utility score (p<0.001) and EQ-5D VAS score with PGB compared to PLA (P<0.001)		

ABBREVIATIONS: CGIC: Clinician global impression of change; LSMD: Least square mean difference; MD: Mean difference; MOS-Sleep: Medical Outcomes Study Sleep Scale; NRS: numerical rating scale; PGB: Pregabalin; PGIC: Patient global impression of change; PLA: Placebo; SF-MPQ PPI: Short-Form McGill Pain Questionnaire personal pain intensity; SF-MPQ VAS: Short-Form McGill Pain Questionnaire visual assessment scale; VAS: Visual assessment scale

*These outcome results have been presented narratively because there was inadequate data to pool results across studies

Figure S1: Funnel plot for publication bias in RCTs assessing the effect of pregabalin in neuropathic pain. The broken line represents the mean difference for all trials.

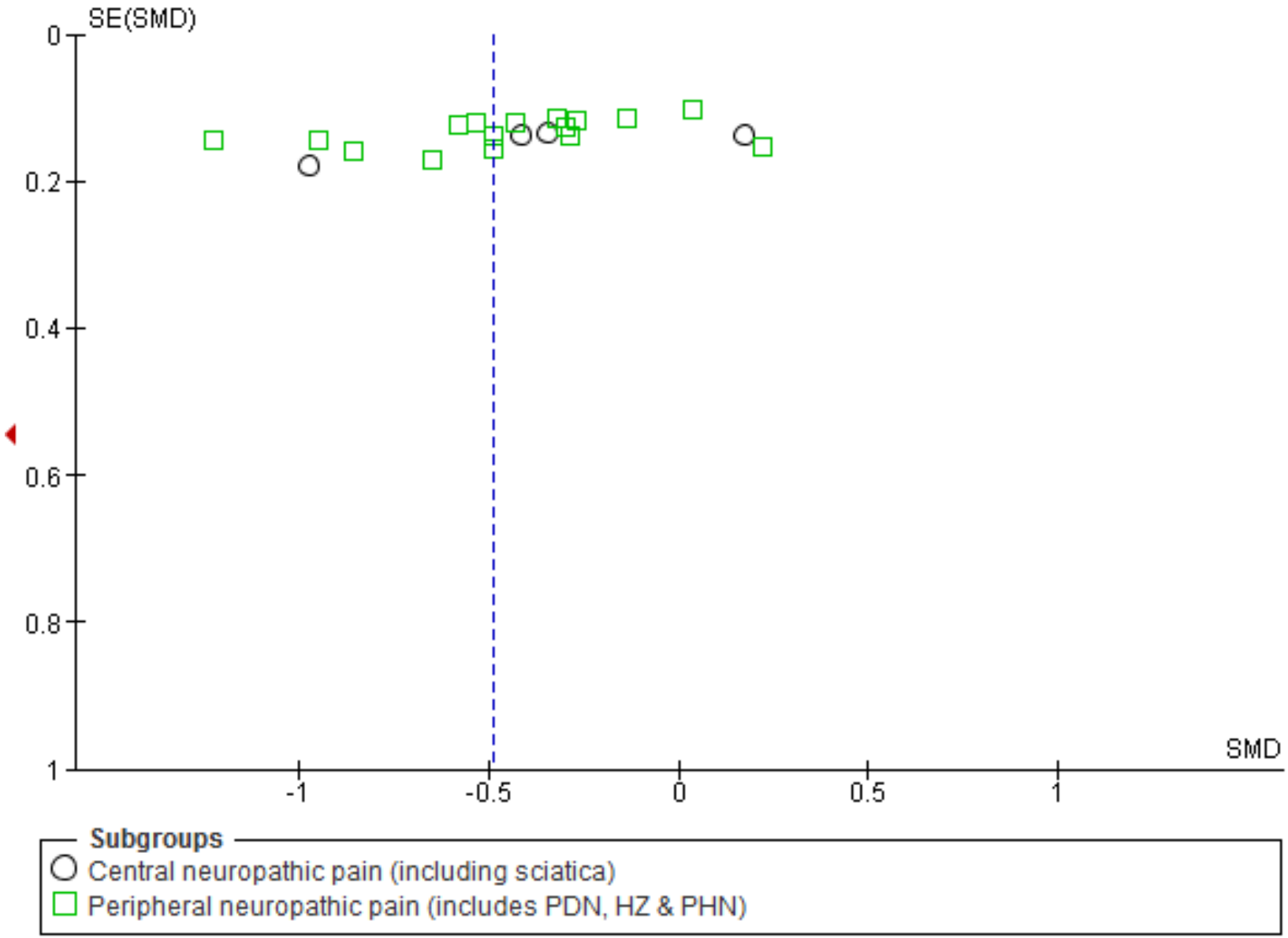


Figure S2: Effect of pregabalin on the risk of weight gain in patients with neuropathic pain

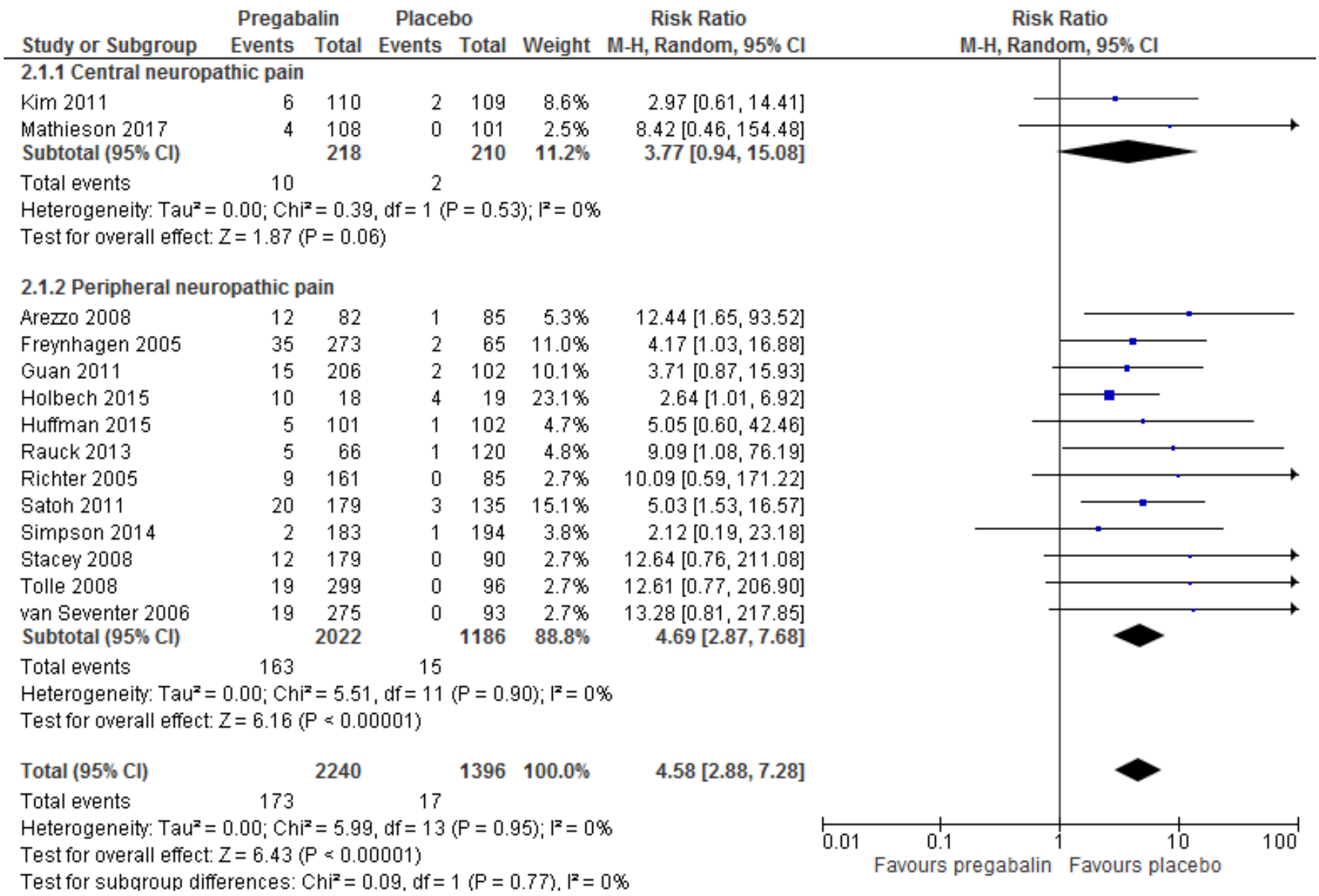


Figure S3: Effect of pregabalin on the risk of somnolence in patients with neuropathic pain

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 Central neuropathic pain						
Cardenas 2013	37	112	14	108	11.2%	2.55 [1.46, 4.44]
Kim 2011	24	110	5	109	4.0%	4.76 [1.88, 12.01]
Mathieson 2017	9	108	4	101	2.6%	2.10 [0.67, 6.62]
Siddall 2006	29	70	6	67	5.2%	4.63 [2.05, 10.43]
Subtotal (95% CI)		**400**		**385**	**23.1%**	**3.18 [2.16, 4.68]**
Total events	99		29			
Heterogeneity: Tau² = 0.00; Chi² = 2.68, df = 3 (P = 0.44); I² = 0%						
Test for overall effect: Z = 5.87 (P < 0.00001)						
2.5.2 Peripheral neuropathic pain						
Arezzo 2008	11	82	5	85	3.4%	2.28 [0.83, 6.28]
Dworkin 2003	22	89	6	84	4.8%	3.46 [1.48, 8.11]
Freynhagen 2005	32	273	0	65	0.4%	15.66 [0.97, 252.40]
Guan 2011	16	206	3	102	2.4%	2.64 [0.79, 8.86]
Huffman 2015	12	101	4	102	2.9%	3.03 [1.01, 9.08]
Krcevski Škvarč 2010	9	14	4	15	4.0%	2.41 [0.96, 6.08]
Lesser 2004	44	240	4	97	3.5%	4.45 [1.64, 12.04]
Liu 2015	6	111	5	109	2.6%	1.18 [0.37, 3.75]
Rauck 2013	9	66	5	120	3.1%	3.27 [1.14, 9.36]
Richter 2005	22	161	3	85	2.5%	3.87 [1.19, 12.57]
Rosenstock 2004	15	76	2	70	1.7%	6.91 [1.64, 29.13]
Sabatowski 2004	30	157	6	81	5.0%	2.58 [1.12, 5.94]
Satoh 2011	46	179	11	135	9.0%	3.15 [1.70, 5.86]
Simpson 2010	35	151	13	151	9.8%	2.69 [1.48, 4.88]
Simpson 2014	13	183	4	194	2.8%	3.45 [1.14, 10.37]
Stacey 2008	27	179	2	90	1.7%	6.79 [1.65, 27.91]
Tolle 2008	17	299	1	96	0.9%	5.46 [0.74, 40.48]
van Seventer 2006	42	275	4	93	3.5%	3.55 [1.31, 9.64]
van Seventer 2010	20	127	8	127	5.7%	2.50 [1.14, 5.47]
Vranken 2008	9	20	9	20	7.4%	1.00 [0.50, 1.98]
Subtotal (95% CI)		**2989**		**1921**	**76.9%**	**2.74 [2.22, 3.40]**
Total events	437		99			
Heterogeneity: Tau² = 0.00; Chi² = 19.24, df = 19 (P = 0.44); I² = 1%						
Test for overall effect: Z = 9.25 (P < 0.00001)						
Total (95% CI)		**3389**		**2306**	**100.0%**	**2.84 [2.36, 3.42]**
Total events	536		128			
Heterogeneity: Tau² = 0.00; Chi² = 22.21, df = 23 (P = 0.51); I² = 0%						
Test for overall effect: Z = 10.99 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.43, df = 1 (P = 0.51), I² = 0%						

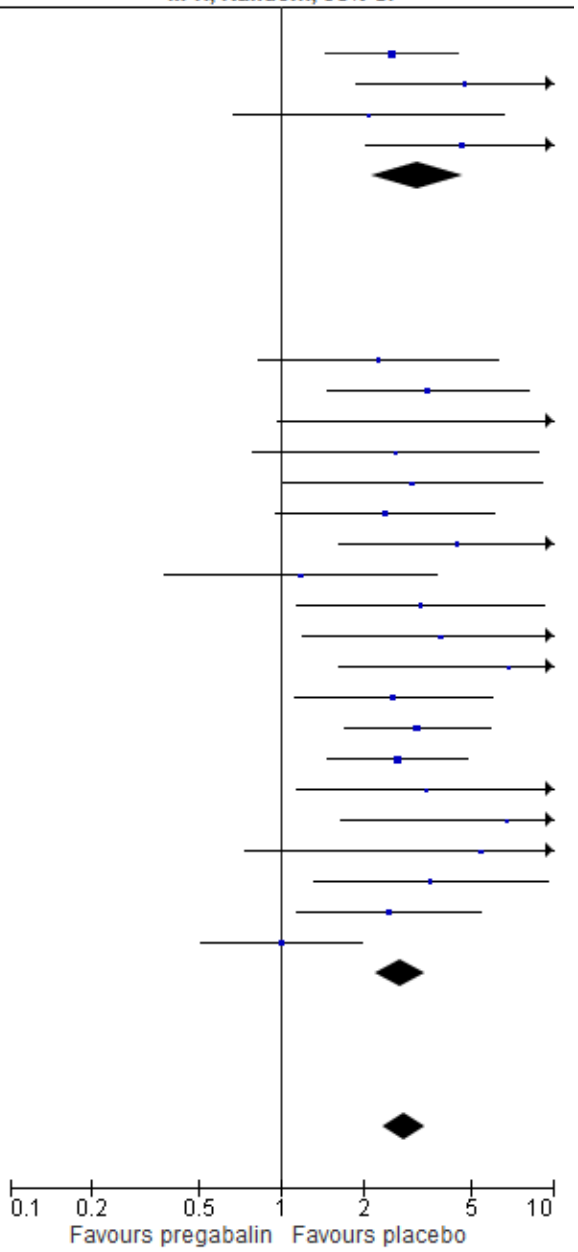


Figure S4: Effect of pregabalin on the risk of dizziness in patients with neuropathic pain

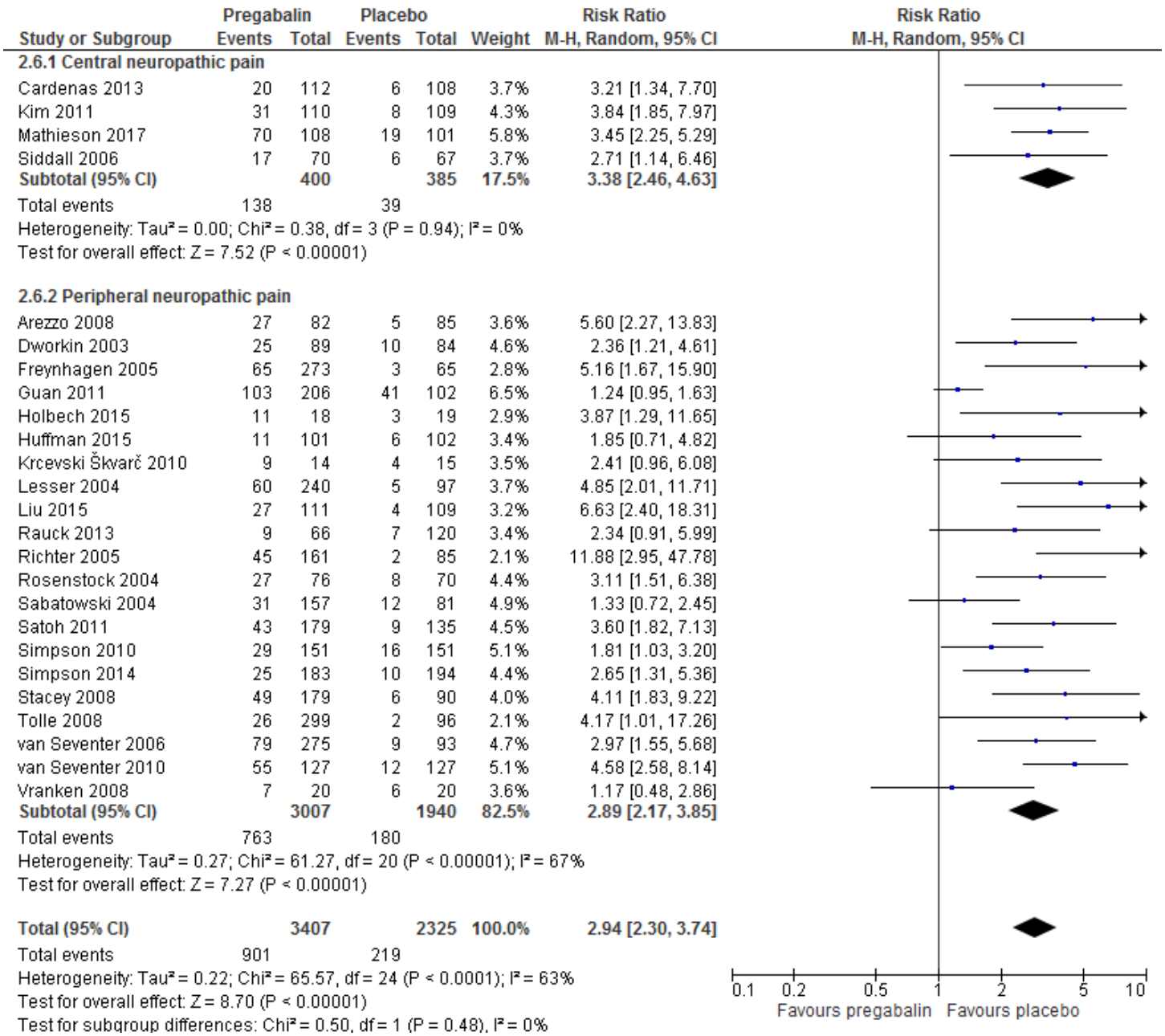


Figure S5: Effect of pregabalin on the risk of peripheral edema in patients with neuropathic pain

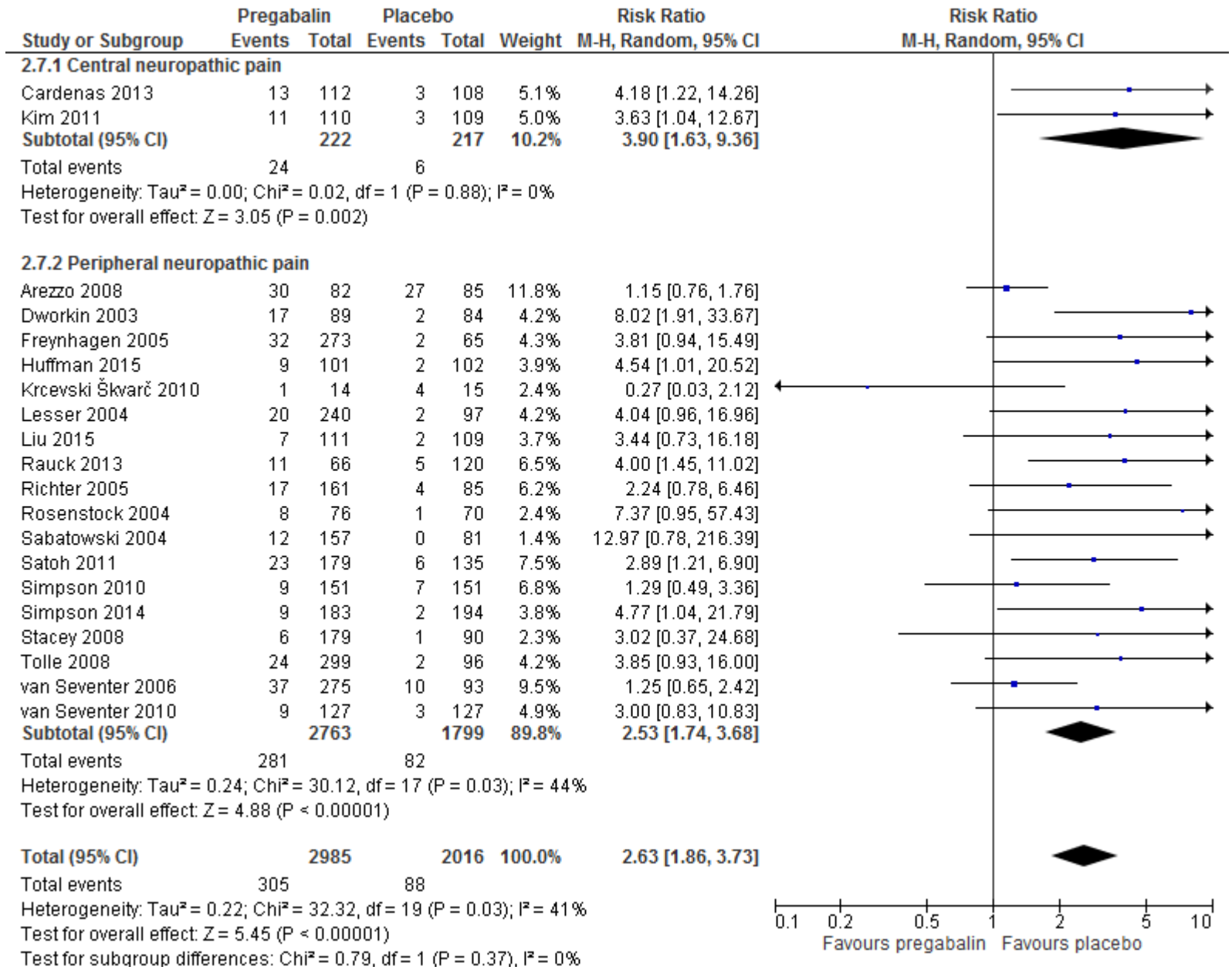


Figure S6: Effect of pregabalin on the risk of fatigue including asthenia in patients with neuropathic pain

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Arezzo 2008	8	82	1	82	2.4%	8.00 [1.02, 62.53]
Cardenas 2013	8	112	1	108	2.4%	7.71 [0.98, 60.65]
Freynhagen 2005	21	273	0	65	1.3%	10.36 [0.64, 168.79]
Guan 2011	23	206	7	102	11.9%	1.63 [0.72, 3.66]
Holbech 2015	7	18	3	19	6.5%	2.46 [0.75, 8.09]
Huffman 2015	11	101	3	102	6.0%	3.70 [1.06, 12.88]
Krcevski Škvarč 2010	8	14	8	15	15.9%	1.07 [0.56, 2.06]
Lesser 2004	13	240	3	97	6.1%	1.75 [0.51, 6.01]
Liu 2015	5	111	1	109	2.2%	4.91 [0.58, 41.35]
Rauck 2013	4	66	3	120	4.5%	2.42 [0.56, 10.51]
Richter 2005	13	161	3	85	6.1%	2.29 [0.67, 7.81]
Rosenstock 2004	3	76	2	70	3.2%	1.38 [0.24, 8.03]
Sabatowski 2004	7	157	4	81	6.4%	0.90 [0.27, 2.99]
Stacey 2008	13	179	1	90	2.5%	6.54 [0.87, 49.18]
Tolle 2008	10	299	0	96	1.3%	6.79 [0.40, 114.81]
van Seventer 2006	12	275	5	93	8.4%	0.81 [0.29, 2.24]
van Seventer 2010	15	127	10	127	13.0%	1.50 [0.70, 3.21]
Total (95% CI)		**2497**		**1461**	**100.0%**	**1.83 [1.32, 2.54]**
Total events	181		55			

Heterogeneity: Tau² = 0.06; Chi² = 18.63, df = 16 (P = 0.29); I² = 14%

Test for overall effect: Z = 3.62 (P = 0.0003)

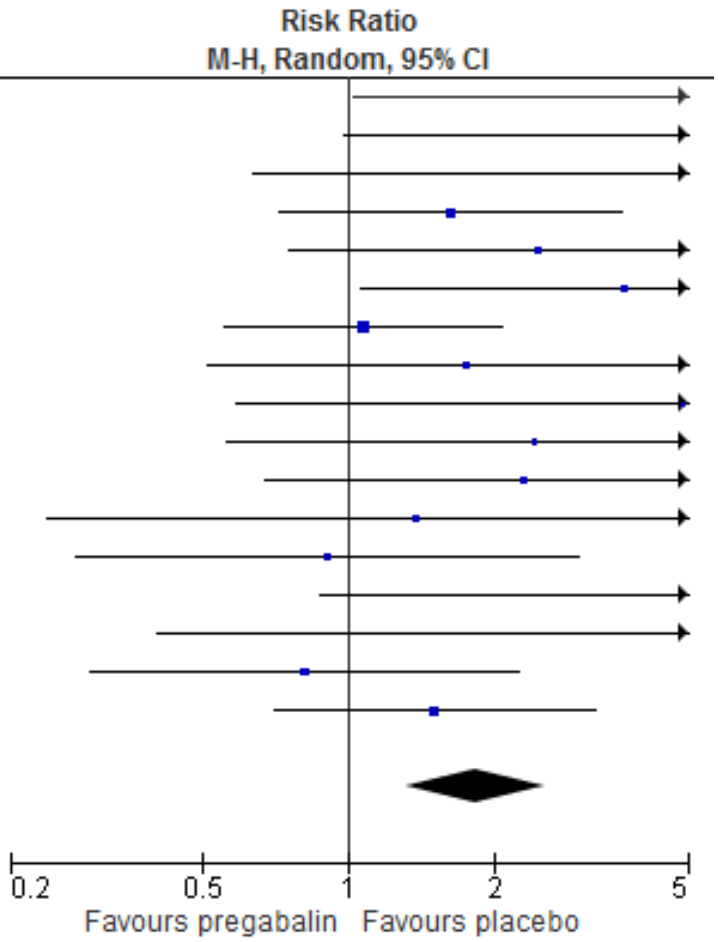
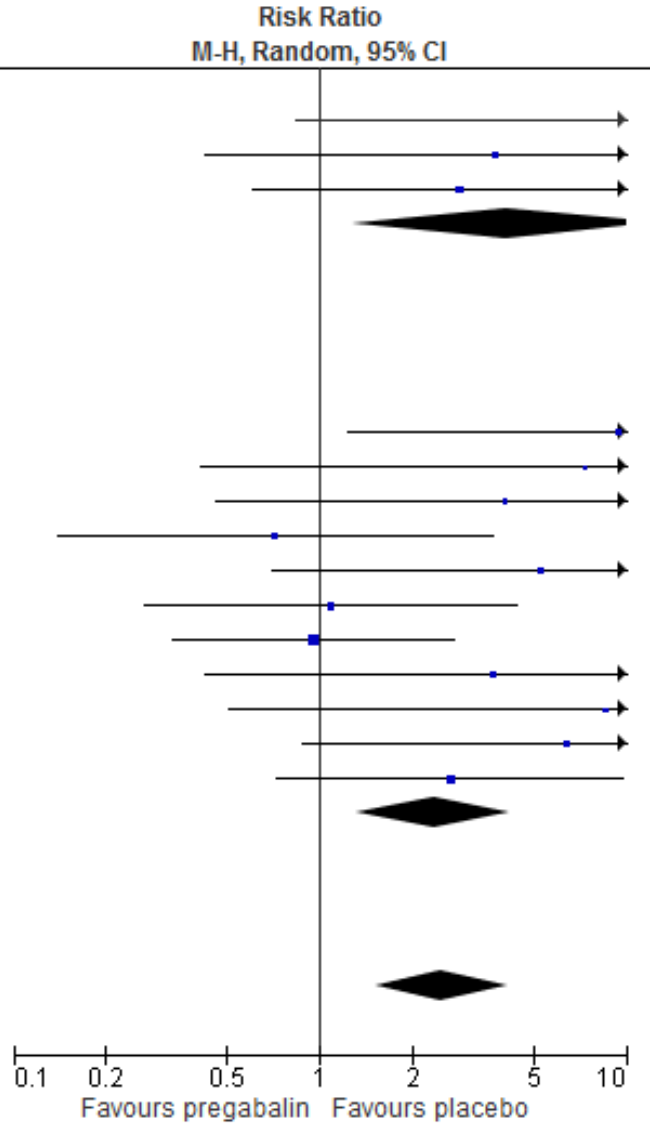


Figure S7: Effect of pregabalin on the risk of visual disturbances* in patients with neuropathic pain

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.8.1 Central neuropathic pain						
Cardenas 2013	7	112	0	108	2.9%	14.47 [0.84, 250.29]
Mathieson 2017	4	108	1	101	4.9%	3.74 [0.43, 32.91]
Siddall 2006	6	70	2	67	9.1%	2.87 [0.60, 13.73]
Subtotal (95% CI)		**290**		**276**	**17.0%**	**4.05 [1.27, 12.91]**
Total events	17		3			
Heterogeneity: Tau² = 0.00; Chi² = 1.03, df = 2 (P = 0.60); I² = 0%						
Test for overall effect: Z = 2.36 (P = 0.02)						
2.8.2 Peripheral neuropathic pain						
Dworkin 2003	10	89	1	84	5.6%	9.44 [1.23, 72.14]
Holbech 2015	3	18	0	19	2.8%	7.37 [0.41, 133.37]
Huffman 2015	4	101	1	102	4.9%	4.04 [0.46, 35.52]
Krcevski Škvarč 2010	2	14	3	15	8.4%	0.71 [0.14, 3.66]
Lesser 2004	13	240	1	97	5.7%	5.25 [0.70, 39.62]
Rauck 2013	3	66	5	120	11.2%	1.09 [0.27, 4.42]
Richter 2005	9	161	5	85	18.1%	0.95 [0.33, 2.75]
Rosenstock 2004	4	76	1	70	5.0%	3.68 [0.42, 32.17]
Stacey 2008	8	179	0	90	2.9%	8.59 [0.50, 147.25]
van Seventer 2006	19	275	1	93	5.8%	6.43 [0.87, 47.34]
van Seventer 2010	8	127	3	127	12.7%	2.67 [0.72, 9.82]
Subtotal (95% CI)		**1346**		**902**	**83.0%**	**2.36 [1.32, 4.22]**
Total events	83		21			
Heterogeneity: Tau² = 0.16; Chi² = 11.95, df = 10 (P = 0.29); I² = 16%						
Test for overall effect: Z = 2.90 (P = 0.004)						
Total (95% CI)		**1636**		**1178**	**100.0%**	**2.50 [1.53, 4.09]**
Total events	100		24			
Heterogeneity: Tau² = 0.06; Chi² = 13.90, df = 13 (P = 0.38); I² = 6%						
Test for overall effect: Z = 3.64 (P = 0.0003)						
Test for subgroup differences: Chi² = 0.66, df = 1 (P = 0.42), I² = 0%						



*includes blurring of vision and amblyopia

Figure S8: Effect of pregabalin on the risk of ataxia in patients with neuropathic pain

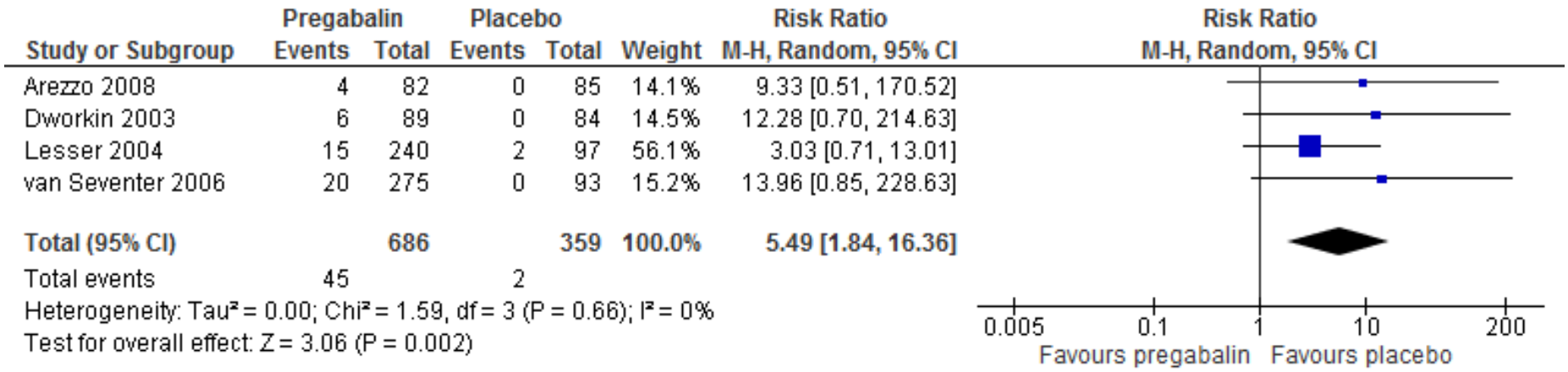


Figure S9: Effect of pregabalin on the risk of non-peripheral edema in patients with neuropathic pain

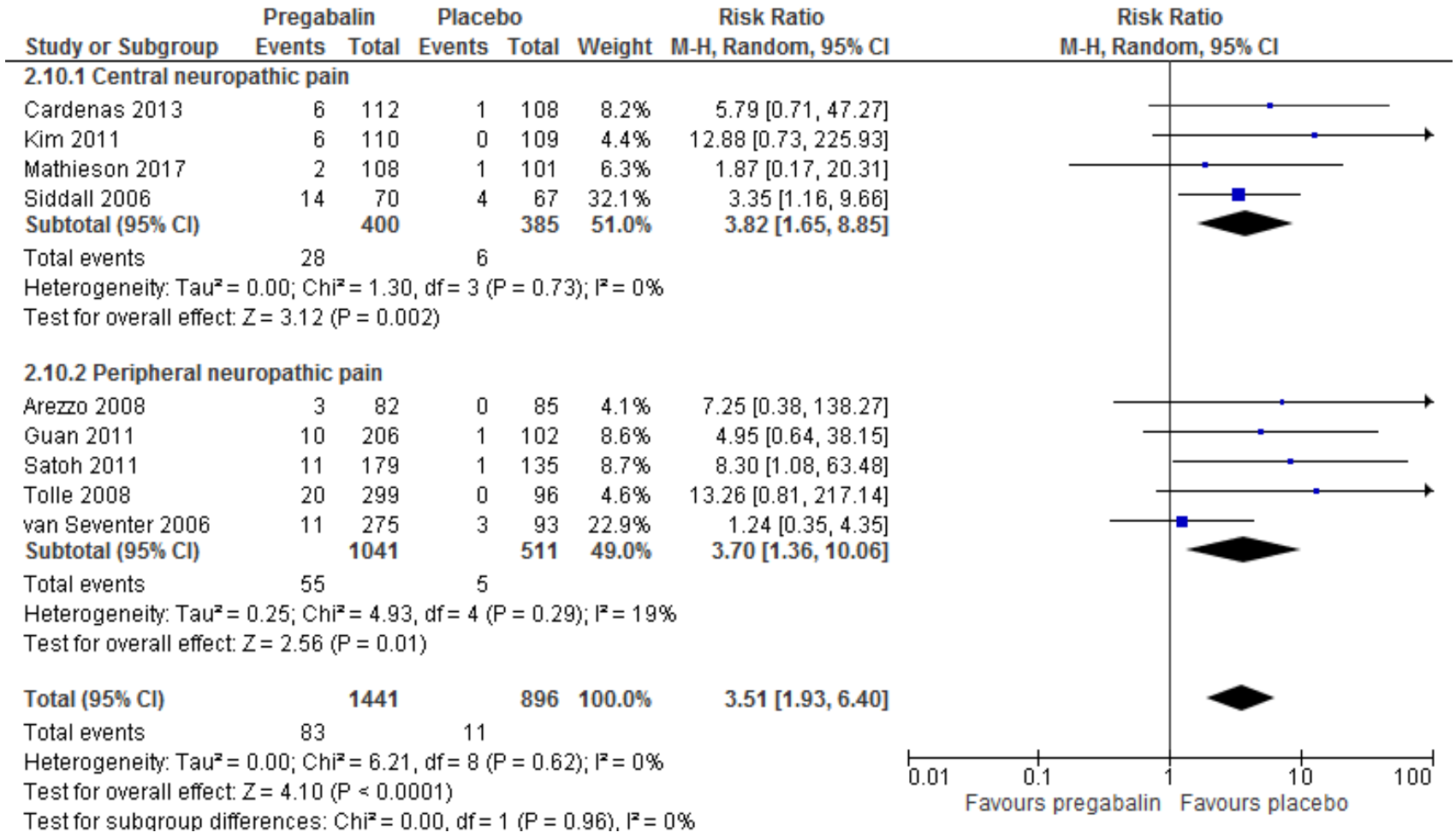


Figure S10: Effect of pregabalin on the risk of vertigo in patients with neuropathic pain

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Freynhagen 2005	24	273	1	65	22.5%	5.71 [0.79, 41.47]
Krcevski Škvarč 2010	7	14	5	15	51.8%	1.50 [0.62, 3.64]
Stacey 2008	6	179	0	90	12.7%	6.57 [0.37, 115.38]
Tolle 2008	13	299	0	96	13.1%	8.73 [0.52, 145.49]
Total (95% CI)		**765**		**266**	**100.0%**	**3.08 [1.01, 9.40]**
Total events	50		6			

Heterogeneity: Tau² = 0.42; Chi² = 4.31, df = 3 (P = 0.23); I² = 30%

Test for overall effect: Z = 1.97 (P = 0.05)

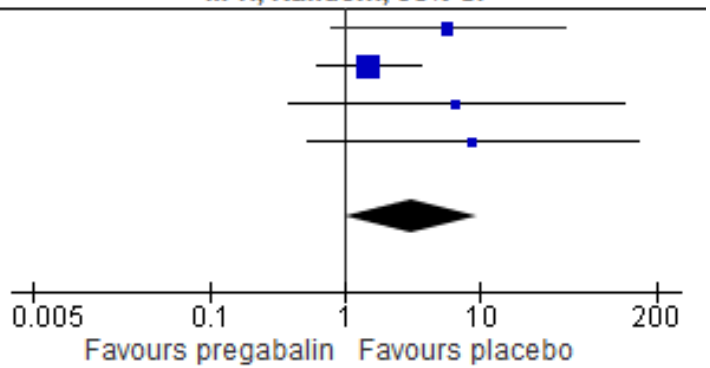


Figure S11: Effect of pregabalin on the risk of euphoria in patients with neuropathic pain

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Cardenas 2013	3	112	0	108	15.9%	6.75 [0.35, 129.20]
Lesser 2004	9	240	0	97	17.2%	7.73 [0.45, 131.46]
Rosenstock 2004	4	76	0	70	16.4%	8.30 [0.45, 151.41]
Simpson 2010	15	151	1	151	34.2%	15.00 [2.01, 112.13]
Stacey 2008	4	179	0	90	16.3%	4.55 [0.25, 83.59]
Total (95% CI)		**758**		**516**	**100.0%**	**8.80 [2.72, 28.54]**
Total events	35		1			

Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 4 (P = 0.97); I² = 0%

Test for overall effect: Z = 3.63 (P = 0.0003)

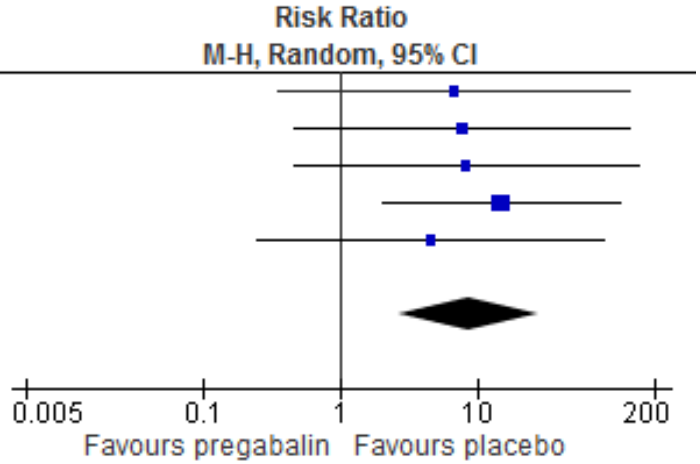


Figure S12: Effect of pregabalin on the risk of dry mouth in patients with neuropathic pain

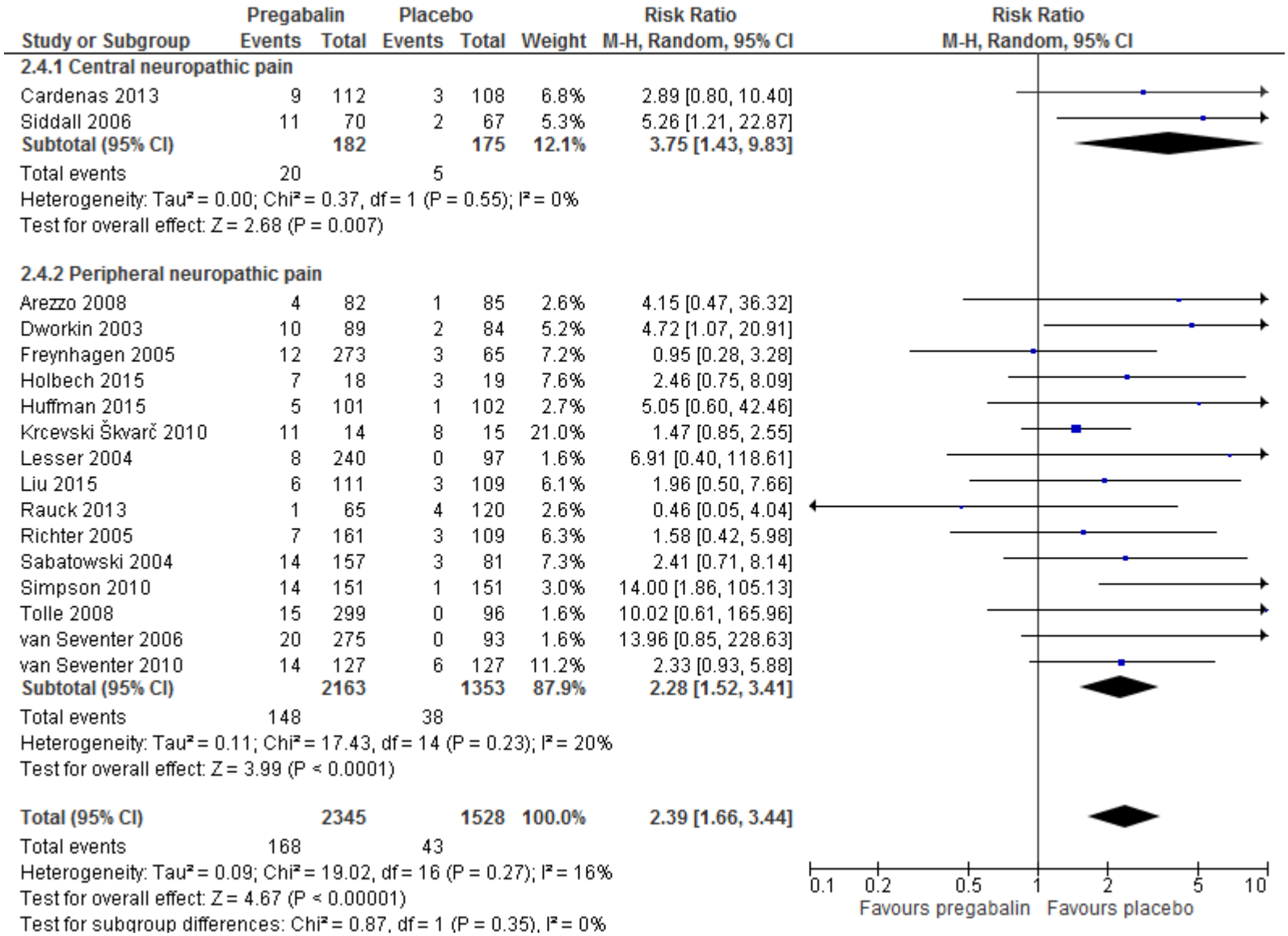


Figure S13: Effect of pregabalin on the risk of discontinuation due to adverse events

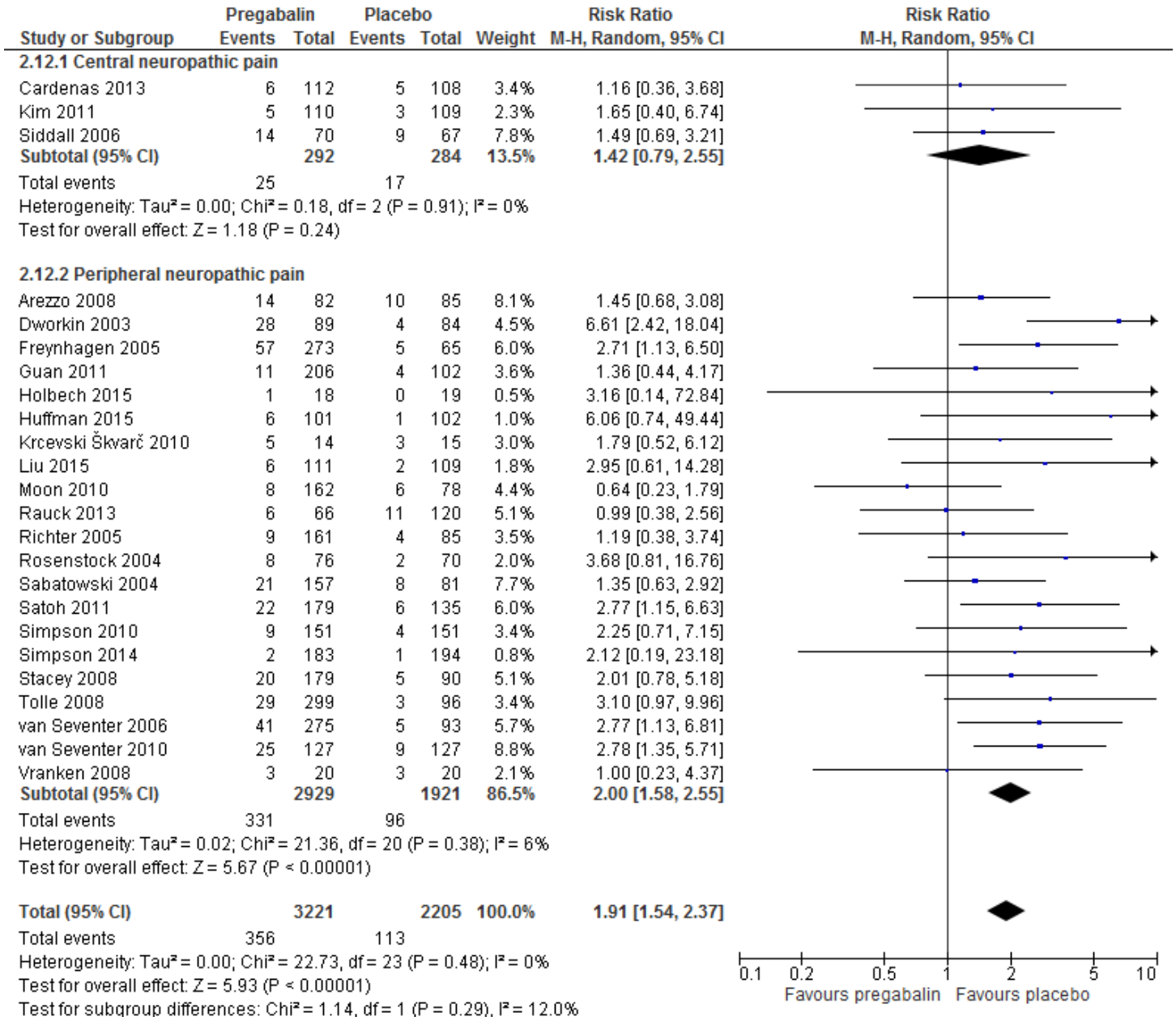


Figure S14: Effect of pregabalin on the risk of serious adverse events in patients with neuropathic pain

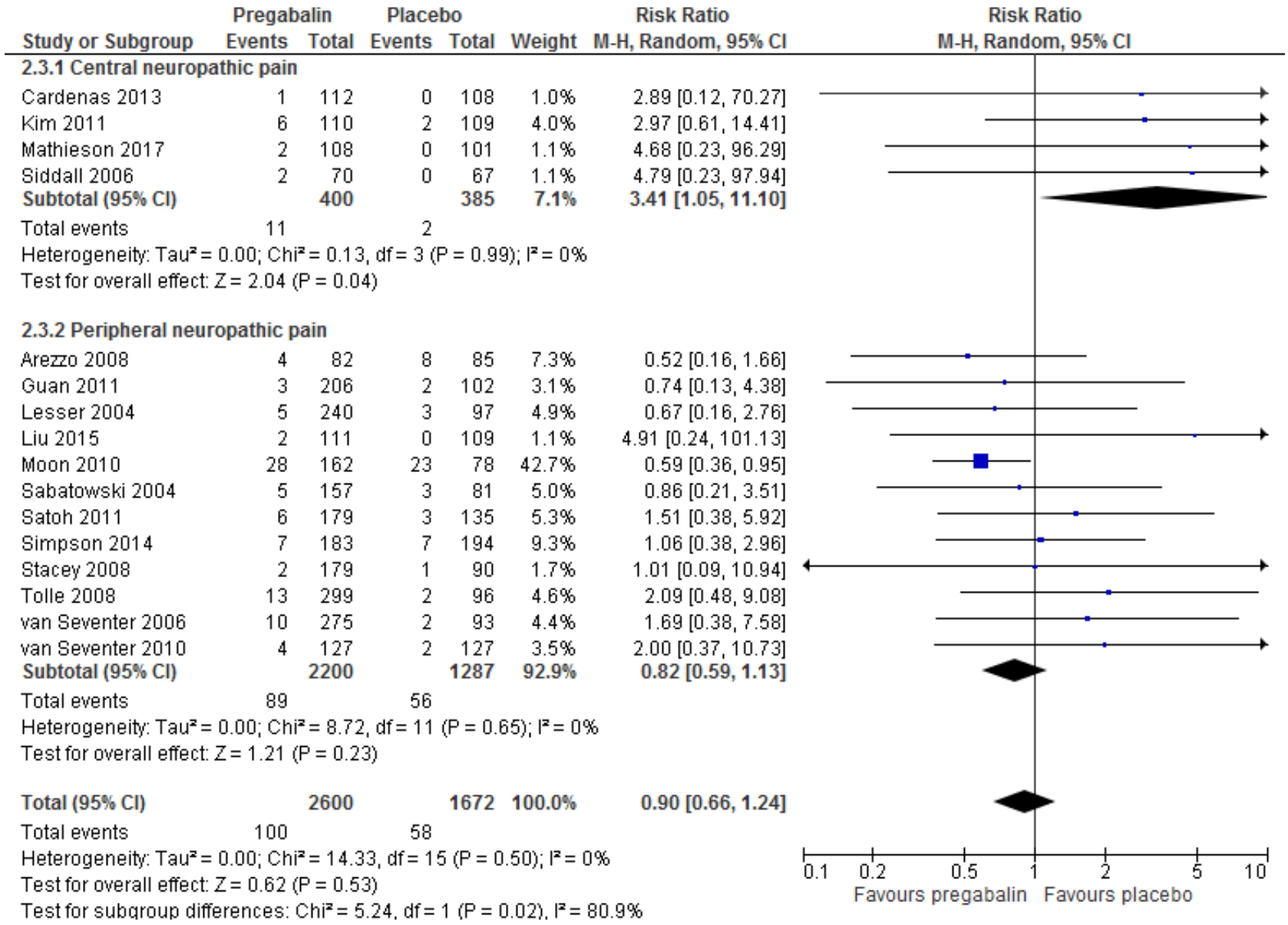


Figure S15: Effect of pregabalin on the sleep disturbance in patients with neuropathic pain

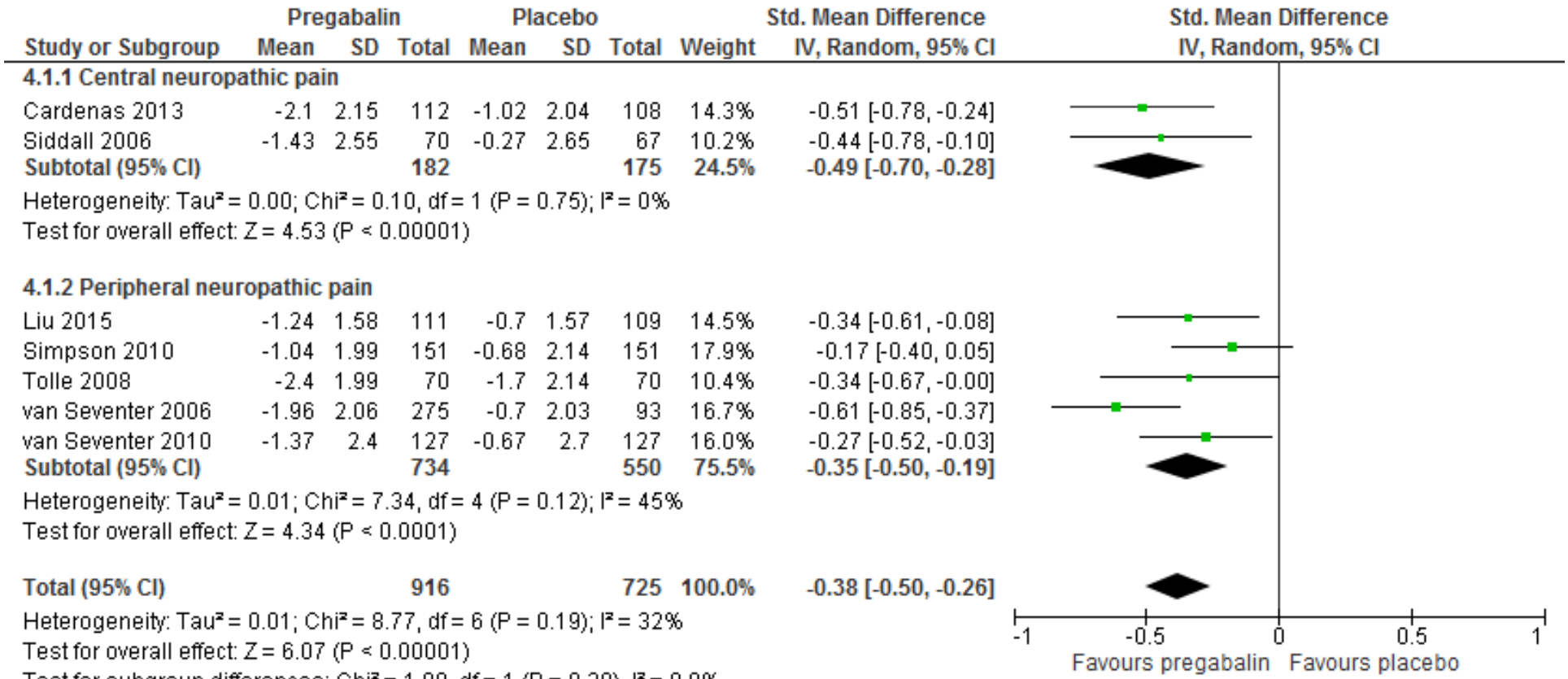


Figure S16: Effect of pregabalin on HADS-anxiety scores in patients with neuropathic pain

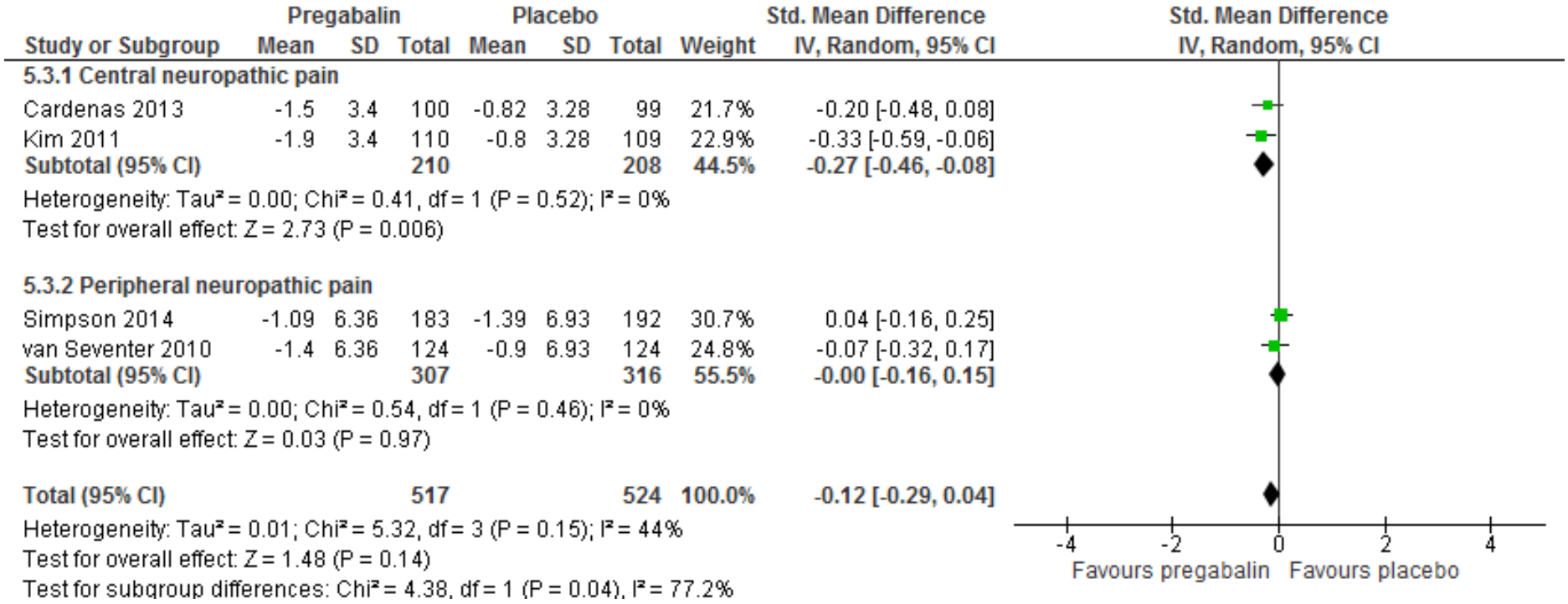
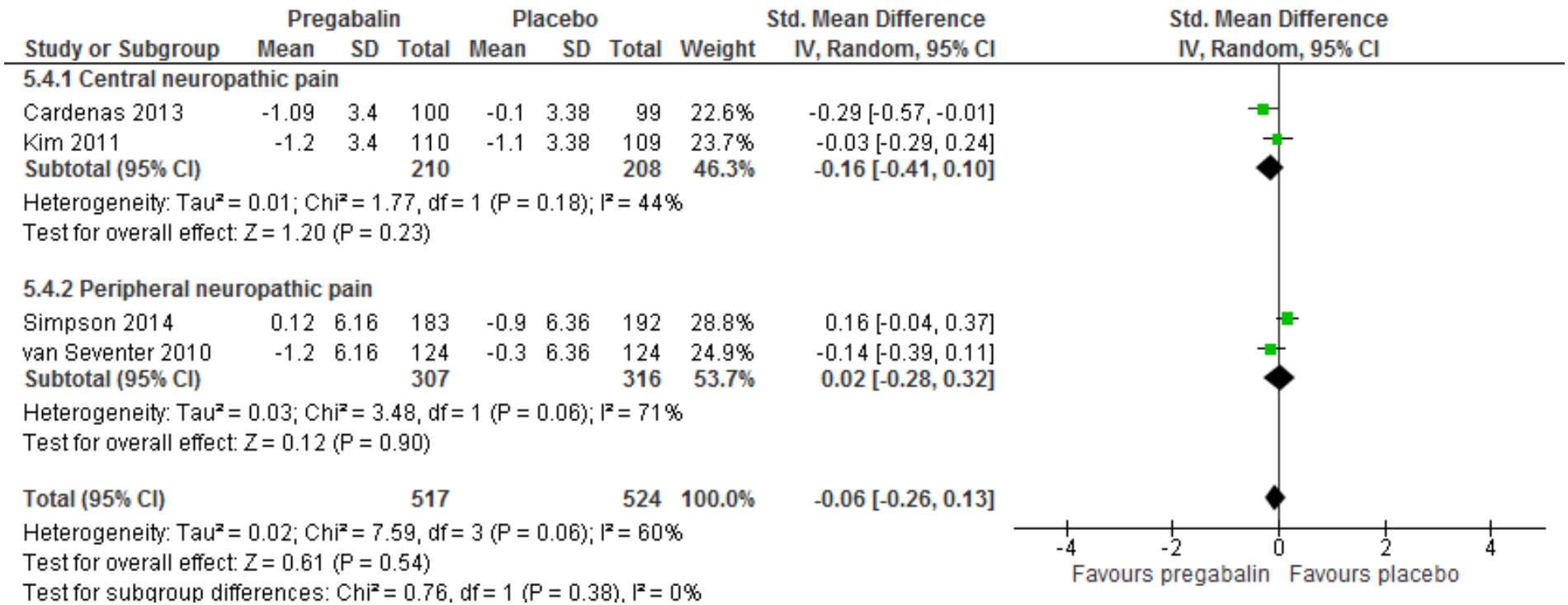


Figure S17: Effect of pregabalin on HADS-depression scores in patients with neuropathic pain



Appendix 1: Search strategy for identifying RCTs assessing the effects of pregabalin for management of neuropathic pain

MEDLINE

1. pain.mp. or Pain/

2. pain*.mp.

3. analgesia/

4. analges*.mp.

5. neuralgia/

6. 1 or 2 or 3 or 4 or 5

7. pregabalin/

8. clinical trials.mp. or Clinical Trial/

9. randomized clinical trial.mp.

10. controlled clinical trial.mp. or Controlled Clinical Trial/

11. double-blind trial.mp.

12. placebo.ab.

13. ((doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).ti,ab.

14. 8 or 9 or 10 or 11 or 12 or 13

15. 6 and 7 and 14

16. (animals not (animals and humans)).sh.

17. 15 not 16

EMBASE

1. pain/ or neuropathic pain/

2. analgesi*.mp.

3. 1 or 2

4. pregabalin.mp. or pregabalin/

5. controlled clinical trial/ or randomized clinical trial.mp.

6. double blind procedure/

7. placebo*.ab.

8. random*.ab.

9. ((doubl* or trebl* or tripl*) adj25 (blind* or mask*)).ab.

10. 5 or 6 or 7 or 8 or 9

11. 3 and 4 and 10

COCHRANE

#1	pain
#2	analgesia
#3	neuropathic pain
#4	neuralgia
#5	#1 or #2 or #3 or #4
#6	pregabalin
#7	lyrica
#8	#6 or #7
#9	randomized controlled trial.pt
#10	controlled controlled trial.pt
#11	randomized.ti,ab
#12	groups.ti,ab
#13	placebo.ti,ab
#14	#9 or #10 or #11 or #12 or #13
#15	#5 and #8 and #14

Appendix 2: Systematic review protocol

Benefits and harms of pregabalin in the management of neuropathic pain: a rapid systematic review and meta-analysis of randomized clinical trials

Igho J Onakpoya
University of Oxford, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, Oxford, United Kingdom

Elizabeth T Thomas
Faculty of Health Sciences and Medicine, Bond University, Australia

Joseph Lee
University of Oxford, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, Oxford, United Kingdom

Ben Goldacre
University of Oxford, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, Oxford, United Kingdom

Carl J Heneghan
University of Oxford, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, Oxford, United Kingdom

Corresponding author: Igho Onakpoya, University of Oxford, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Oxford United Kingdom OX2 6GG. Email: igho.onakpoya@phc.ox.ac.uk.

BACKGROUND

Pregabalin is a gabapentinoid licensed for treatment of neurologic disorders. It is one of the earlier drugs approved by the FDA (2004) for the treatment of painful diabetic neuropathy (PDN) and post-herpetic neuralgia (PHN) [1]. Pregabalin is thought to exert its analgesic action through antagonistic activity at the voltage gated Ca2+ channels where it binds to the alpha-2-delta subunit [1,2].

Prescriptions of pregabalin (and gabapentin) have markedly increased over the last few years. In the US, prescriptions for pregabalin rose from 39 million in 2012 to 64 million in 2016 *versus* (spend increased from approximately $2 billion to $4.4 billion over the same period [3]. In the UK, pregabalin use increased 350% over a five year period between 2008 and 2013 [4]. In England alone, there were over 6.2 million prescriptions of pregabalin across GP practices in 2017 costing about $440 million [5].

There is, however, some evidence of increased mortality attributed pregabalin in the UK [6], and this has led some authors to caution clinicians about the risk of harms when prescribing [7]. The risks are thought to be particularly acute for patients who use heroin and those who misuse gabapentinoids. Indeed, the UK government is soon to classify the drug as a class C controlled substance because of its abuse potential and increased reports of deaths attributed to its use [8]. Practicing clinicians have also recently called for the evidence for the effectiveness of pregabalin to be re-examined in the light of its potential to cause harms [3,4].

OBJECTIVES

To rapidly evaluate the evidence for benefits and harms of pregabalin in the treatment of neuropathic pain in adults, using evidence from published randomized clinical trials (RCTs).

METHODS

Search strategy

We will conduct electronic searches in the following databases:

- Medline;
- Embase; and
- The Cochrane Central Register of Clinical Trials

Each database will be searched from inception till January 2018. No language restrictions will be imposed. We will also hand search the bibliography of eligible studies. Two review authors will independently assess the eligibility of studies for inclusion. Any disagreements were resolved through discussion.

Types of studies

We will include phase III double-blinded placebo-controlled RCTs assessing the effects of pregabalin on neuropathic pain aged 18 years and above. We will include studies on neuropathic pain based on the definition of the International Association for the Study of Pain (IASP) definition [9]. These include trials on diabetic neuropathy, HIV-related neuropathy, lumbar radiculopathy, post-herpetic neuralgia, and chronic postsurgical pain. We will include RCTs irrespective of study size and duration. If we include RCTs with a cross-over design, we will use data from only the first phase of the study. We will exclude phase IV trials because they are typically unblinded. We will also exclude studies that combine pregabalin with other types of intervention; however, co-interventions will be allowed. Trials that randomized participants based on response to pregabalin therapy in the run-in phase will also be excluded.

Outcomes

Primary outcomes

- Pain (as measured using validated scales)

- Adverse events

Secondary outcomes

- Sleep disturbance;
- Quality of life (QOL);
- Patient global impression of change (PGIC);
- Clinician global impression (CGI);
- Overall discontinuations; and
- Discontinuations because of adverse events.

Risk of bias assessment

We will assess the risk of bias for each included study using Cochrane criteria [10] which examines the following domains:

- Method of randomisation;
- Concealment of allocation;
- Blinding of participants and personnel;
- Blinding of outcome assessment;
- Incomplete outcome data;
- Selective reporting;
- Other bias (e.g. industry funding, conflicts of interest, etc).

Two review authors will independently assess the risk of bias. Any disagreements will be resolved through discussion.

Data extraction:

We will use a customized excel spreadsheet to extract relevant data from included studies. Data to be extracted will include:

- Study ID (first author, publication year, journal, country)

- Participants (numbers, medical condition, demographics, etc.)
- Intervention (type of intervention and duration)
- Results (primary and secondary outcome measures, effect size, adverse events)
- Sources of funding

Five review authors will independently extracted the data. Any disagreements were resolved through discussion.

Data analyses:

We will compute standardized mean differences (SMDs) and 95% confidence intervals (CIs) for continuous outcomes and risk ratios with 95% CI for binary outcomes. We will use the random effects model (Mantel-Haenszel) of the standard meta-analysis software (RevMan 5.3) [11] for meta-analysis. For continuous outcomes, pre- to post-intervention changes will be used to compute the data. When two or more pregabalin arms are present, the arms will be combined to create single pair-wise comparisons [12]. If we are unable to statistically combine the data, the results will be presented in a narrative format. If $\geq$ 10 studies are available for statistical pooling, we will use a funnel plot to test for publication bias. Two review authors will independently enter the data onto RevMan, and will also independently cross-check each other's entry.

Subgroup analysis and investigation of heterogeneity

We will assess heterogeneity using the I-squared statistic: values of 25%, 50% and 75% will represent mild, moderate and substantial heterogeneity respectively. We will conduct subgroup analyses based on the predominant pathway for neuropathic pain - central or peripheral neuropathic pain. We will conduct sensitivity based on study quality (studies that adequately report randomization and blinding procedures) and intervention duration (shorter or longer duration of therapy). We will visually inspect funnel plots to determine publication bias.

Rating the quality of the evidence

We will use the GRADEpro software (version 3.6) [13] to rate the overall quality of the body of evidence for each outcome based on the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) [14] criteria which examines the following domains:

- Study design;
- Risk of bias;
- Inconsistency;
- Indirectness; and
- Imprecision.

The overall quality of the body of the evidence will rated from high to very low as follows:

- High - Further research is very unlikely to change our confidence in the estimate of effect
- Moderate - Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
- Low - Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- Very low - We are very uncertain about the estimate

We will use Summary of findings (SOF) tables to present these results.

Patient public involvement

Because this is a rapid review, we will not enlist the services of patient representatives.

Sources of funding

None

Conflicts of interest

None

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3 Goodman CW, Brett AS. Gabapentin and Pregabalin for Pain - Is Increased Prescribing a Cause for Concern? N Engl J Med. 2017 Aug 3;377(5):411-414.

4 Spence D. Bad medicine: gabapentin and pregabalin. BMJ. 2013 Nov 8;347:f6747. doi: 10.1136/bmj.f6747.

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7 Morrison EE, Sandilands EA, Webb DJ. Gabapentin and pregabalin: do the benefits outweigh the harms? J R Coll Physicians Edinb 2017; 47: 310–3

8 Iacobucci G. UK government to reclassify pregabalin and gabapentin after rise in deaths. BMJ. 2017 Sep 25;358:j4441. doi: 10.1136/bmj.j4441.

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10 Higgins JP, Altman DG, Gøtzsche PC, . The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Br Med J 2011; 343: d5928–d5928

11 Review Manager (RevMan) (Computer program). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011

12 Cochrane Handbook of Systematic Reviews. How to include multiple groups from one study. Chapter 16 (Section 5.4). http://handbook.cochrane.org/chapter_16/16_5_4_how_to_include_multiple_groups_from_one_study.htm [Accessed 20 June 2016]

13 GRADEpro. Computer program on www.gradepro.org. Version 3.6. McMaster University, 2014.

14 GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ 2004; 328(7454): 1490.

Appendix 3: List of excluded studies and reasons for exclusion

Study ID	Reference	Reason for exclusion
Al-Hihi 2017	Al-Hihi E, Badgett RG. In moderate-to-severe sciatica, pregabalin did not reduce leg pain intensity or improve quality of life. Annals of internal medicine. 2017; (2):[Jc4 p.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/558/CN-01394558/frame.html.	Not primary report of RCT
Anon 2010	Anonymous. Pregabalin effective in relieving post-traumatic peripheral neuropathic pain. Australian Journal of Pharmacy. 2010;91 (1086):82.	Not primary report of RCT
Baron 2008	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. European Journal of Pain. 2008;12(7):850-8.	Open label; also no placebo control
Baron 2010	Baron R, Freynhagen R, Tolle TR, Cloutier C, Leon T, Murphy TK, et al. The efficacy and safety of pregabalin in the treatment of neuropathic pain associated with chronic lumbosacral radiculopathy. Pain. 2010;150 (3):420-7.	Randomization based on response to interventions in run-in phase
Boyle 2012	Boyle J, Eriksson MEV, Gribble L, Gouni R, Johnsen S, Coppini DV, et al. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: Impact on pain, polysomnographic sleep, daytime functioning, and quality of life. Diabetes care. 2012;35 (12):2451-8.	No placebo control; only placebo run in

Calkins 2014	Calkins A, Shurman J, Jaros M, Kim R, Shang G. Peripheral edema and weight gain in adult patients with painful diabetic peripheral neuropathy (DPN) receiving gabapentin enacarbil (GEN) or pregabalin enrolled in a randomized phase 2 trial. Neurology Conference: 66th American Academy of Neurology Annual Meeting, AAN. 2014;82(10 SUPPL. 1).	Did not report neuropathic pain as an outcome
Cardenas 2012	Cardenas D, Nieshoff E, Suda K, Goto S, Kaneko T, Parsons B, et al. A 17-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center trial of pregabalin for the treatment of chronic central neuropathic pain after spinal cord injury. Journal of pain. 2012;Conference: 31st Annual Scientific Meeting of the American Pain Society. Honolulu, HI United States. Conference Publication: (var.pagings). 13 (4 SUPPL. 1):S62.	Duplicate of study already included in the review: Duplicate of Cardenas 2013
Cardenas 2013	Cardenas DD, Nieshoff E, Parsons B, Sanin L, Kaneko T, Suzuki M, et al. Assessment of neuropathic pain during a 17-week, double-blind, placebo-controlled, trial of pregabalin in patients with spinal cord injury. Regional Anesthesia and Pain Medicine Conference: 11th Annual ASRA Pain Medicine Meeting Miami, FL United States Conference Publication:. 2013;38(1).	Duplicate of study already included in the review: Duplicate of Cardenas 2013
De Andrade 2015	De Andrade DC, Teixeira MJ, Galhardoni R, Ferreira KASL, Malieno PB, Scisci N, et al. A phase III, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of pregabalin in the prevention and reduction of oxaliplatin-induced painful neuropathy (PreOx). Journal of Clinical Oncology Conference. 2015;33(15 SUPPL. 1).	Pain experienced during cancer chemotherapy

Duarte 2014	Duarte MAG, Cardenas-Soto K, Lem M, Castillo C, Gibbons C, Freeman R. Efficacy of pregabalin in the treatment of prediabetic neuropathic pain. Neurology Conference: 66th American Academy of Neurology Annual Meeting, AAN. 2014;82(10 SUPPL. 1).	No placebo control; evaluation in open-label run-in
Eerdekens 2016	Eerdekens M, Koch ED, Kok M, Sohns M, Forst T. Cebranopadol, a novel first-inclass analgesic: Efficacy, safety, tolerability in patients with pain due to diabetic peripheral neuropathy (U). Pain practice. 2016;Conference: 8th World Congress of the World Institute of Pain, WIP 2016. New York City, NY United States. Conference Publication: (var.pagings). 16 (SUPPL. 1):100.	Unclear how many participants were in each intervention arm
Freynhagen 2006	Freynhagen R, Busche P, Konrad C, Balkenohl M. [Effectiveness and time to onset of pregabalin in patients with neuropathic pain]. Der Schmerz. 2006;20(4):285-8.	Non-English study: Duplicate of Freynhagen 2005
Gabrani 2016	Gabrani A, Dobi D, Tomori S, Berberi F, Como A, Kapisyzi MR. Efectiveness of pregabalin compared with amytriptilin in acute Herpetic Neuralgia. Neurology Conference: 68th American Academy of Neurology Annual Meeting, AAN. 2016;86(16 SUPPL. 1).	Not a placebo-controlled study
Gilron 2011	Gilron I, Wajsbrot D, Therrien F, Lemay J. Pregabalin for peripheral neuropathic pain: a multicenter, enriched enrollment randomized withdrawal placebo-controlled trial. Clinical journal of pain. 2011;27(3):185-93.	Single-blinded Randomization to placebo/PGB occurred after a run in period of pre-gabalin?
Gonzalez-Duarte 2016	Gonzalez-Duarte A, Lem M, Diaz-Diaz E, Castillo C, Cardenas-Soto K. The Efficacy of Pregabalin in the Treatment of Prediabetic Neuropathic Pain. Clinical journal of pain. 2016;32(11):927-32.	Randomization based on response to interventions in run-in phase

Jenkins 2010	Jenkins T, Smart T, Hackman F, Cooke C, Tan K, Cheung R. Pregabalin in post-traumatic peripheral neuropathic pain: Efficient assessment of efficacy in a randomised, double-blind, placebo-controlled crossover study. European Journal of Pain Supplements. 2010;Conference: 3rd International Congress on Neuropathic Pain. Athens Greece. Conference Publication: (var.pagings). 4 (1):89.	Duplicate of study already excluded from the review: Jenkins 2012
Jenkins 2012	Jenkins TM, Smart TS, Hackman F, Cooke C, Tan KKC. Efficient assessment of efficacy in post-traumatic peripheral neuropathic pain patients: Pregabalin in a randomized, placebo-controlled, crossover study. Journal of pain research. 2012;5:243-50.	Phase I: proof of concept
Jensen-Dahm 2011	Jensen-Dahm C, Rowbotham MC, Reda H, Petersen KL. Effect of a single dose of pregabalin on herpes zoster pain. Trials [Electronic Resource]. 2011;12(55):28.	Phase 2
Kruszewski 2007	Kruszewski SP, Shane JA. Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. Neurology. 2007;68(24):2158-9.	Not primary report of RCT
Mishra 2012	Mishra S, Bhatnagar S, Goyal GN, Rana SPS, Upadhya SP. A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: a prospective randomized double-blind placebo-controlled study. American Journal of Hospice & Palliative Medicine. 2012;29(3):177-82.	Pain experienced during cancer chemotherapy

Morrison 2015	Morrison S, Parson H, Vinik AI. Pregabalin positively affects subjective pain, falls risk, and gait in persons with diabetic peripheral neuropathy. Diabetes. 2015;Conference: 75th Scientific Sessions of the American Diabetes Association. Boston, MA United States. Conference Publication: (var.pagings). 64 (SUPPL. 1):A164.	Cross-over trial that did not report data from first phase
Parsons 2013	Parsons B, Emir B. Examining the time-to-improvement of pain in patients with chronic neuropathic pain due to spinal cord injury. Journal of pain. 2013;Conference: 32nd Annual Scientific Meeting of the American Pain Society. New Orleans, LA United States. Conference Publication: (var.pagings). 14 (4 SUPPL. 1):S60.	Not primary report of RCT: report of 2 separate primary studies included in review
Parsons 2015	Parsons B, Emir B, Knapp L. Examining the Time to Improvement of Sleep Interference With Pregabalin in Patients With Painful Diabetic Peripheral Neuropathy and Postherpetic Neuralgia. American journal of therapeutics. 2015;22(4):257-68.	Not primary report of RCT
Parsons 2012	Parsons B, Nieshoff E, Cardenas D, Sanin L, Kaneko T, Suzuki M, et al. Weekly assessments of pain and sleep during a 17-week, double-blind, placebo-controlled trial of pregabalin for the treatment of chronic neuropathic pain after spinal cord injury. Neurology. 2012;Conference: 64th American Academy of Neurology Annual Meeting. New Orleans, LA United States. Conference Publication: (var.pagings). 79 (11):e88.	Duplicate of study already included in the review: Duplicate of Cardenas 2013

Parsons 2015 (Ann Neur)	Parsons B, Shang N, Yan P, Fan D. Efficacy and safety of pregabalin for postherpetic neuralgia in Chinese patients. Annals of Neurology. 2015;Conference: 140th Annual Meeting of the American Neurological Association, ANA 2015. Chicago, IL United States. Conference Publication: (var.pagings). 78 (SUPPL. 19):S92.	Duplicate of study already included in the review: Duplicate of Liu 2015
Puiu 2015	Puiu T, Kairys A, Pauer L, Schmidt-Wilcke T, Ichesco E, Hampson J, et al. Alterations in brain gray matter volume are associated with reduced evoked-pain connectivity following acute pregabalin administration. Neurology Conference: 67th American Academy of Neurology Annual Meeting, AAN. 2015;84(SUPPL. 14).	Included participants with fibromyalgia
Raskin 2014	Raskin P, Huffman C, Toth C, Asmus MJ, Messig M, Sanchez RJ, et al. Pregabalin in patients with inadequately treated painful diabetic peripheral neuropathy: a randomized withdrawal trial. Clinical journal of pain. 2014;30(5):379-90.	Randomization based on response to interventions in run-in phase
Satoh 2011	Satoh J, Yagihashi S, Baba M, Suzuki M, Arakawa A, Yoshiyama T. Efficacy and safety evaluation of pregabalin treatment over 52weeks in patients with diabetic neuropathic pain extended after a double-blind placebo-controlled trial. Journal of diabetes investigation. 2011;2 (6):457-63.	Open label; also no placebo control

van Seventer 2009	Van Seventer R, Murphy K, Temple J, McKenzie I, Serpell M, Toth C, et al. Pregabalin is effective in the treatment of posttraumatic peripheral neuropathic pain. Journal of pain. 2009;Conference: 28th Annual Scientific Meeting of the American Pain Society, APS. San Diego, CA United States. Conference Publication: (var.pagings). 10 (4 SUPPL. 1):S35.	Duplicate of study already included in the review: Van Seventer 2010
Vinik 2014- 1	Vinik A, Rosenstock J, Sharma U, Feins K, Hsu C, Merante D. Efficacy and safety of mirogabalin (DS-5565) for the treatment of diabetic peripheral neuropathic pain: A randomized, double-blind, placebo- and active comparator-controlled, adaptive proof-of-concept phase 2 study. Diabetes care. 2014;37 (12):3253-61.	Proof of concept study
Vinik 2014-2	Vinik A, Sharma U, Feins K, Hsu C, Merante D. Central nervous system safety and tolerability of DS-5565: A randomized, double-blind, placebo-and active comparator-controlled phase II study in diabetic peripheral neuropathic pain. Neurology Conference: 66th American Academy of Neurology Annual Meeting, AAN. 2014;82(10 SUPPL. 1).	Duplicate of study already excluded from the review (Vinik 2014-1)
Vinik 2014-3	Vinik A, Sharma U, Feins K, Hsu C, Merante D. DS-5565 for the treatment of diabetic peripheral neuropathic pain: Randomized, double-blind, placebo-and active comparator-controlled phase ii study. Neurology Conference: 66th American Academy of Neurology Annual Meeting, AAN. 2014;82(10 SUPPL. 1).	Duplicate of study already excluded from the review (Vinik 2014-1)

Vinik 2014-4	Vinik AI, Sharma U, Feins K, Hsu C, Merante D. Safety/tolerability profile of DS-5565: A new potent, specific alpha2-delta ligand for the treatment of diabetic peripheral neuro pathic pain. Diabetes. 2014;Conference: 74th Scientific Sessions of the American Diabetes Association. San Francisco, CA United States. Conference Publication: (var.pagings). 63 (SUPPL. 1):A298.	Duplicate of study already excluded from the review (Vinik 2014-1)
Vinik 2014-5	Vinik AI, Sharma U, Feins K, Hsu C, Merante D. A randomized, double-blind, placebo- and active comparator (pregabalin)-controlled phase II study of DS-5565 for the treatment of diabetic peripheral neuropathic pain. Diabetes. 2014;Conference: 74th Scientific Sessions of the American Diabetes Association. San Francisco, CA United States. Conference Publication: (var.pagings). 63 (SUPPL. 1):A294.	Duplicate of study already excluded from the review (Vinik 2014-1)

Appendix 4: Risk of bias judgements for included studies

Arezzo 2008

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random code
Allocation concealment (selection bias)	Low risk	Number-coded study medications to the study sites were assigned using an interactive voice-response system
Blinding of participants and personnel (performance bias)	Low risk	Blinding was maintained by dispensing pregabalin and placebo in identical capsules
Blinding of outcome assessment (detection bias)	Low risk	The sponsor, members of the study site, and the patients were unaware of the treatment assignment
Incomplete outcome data (attrition bias)	Unclear risk	Reasons for attrition reported; however, drop-out rates were 34.1% for pregabalin and 28.1% for placebo
Selective reporting (reporting bias)	Unclear risk	Outcomes reported as specified in methods. BOCF results also reported for pain scores. However, MD and SD for baseline and end-points were not reported separately, and some outcomes were reported at other time points other than at 13 weeks.
Other bias	High risk	All investigators had financial ties to the sponsor

Cardenas 2013

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Low risk	Interactive response technology system (via phone or internet) provided a unique identification number for each patient
Blinding of participants and personnel (performance bias)	Low risk	Both placebo and pregabalin were in the form of gray capsules
Blinding of outcome assessment (detection bias)	Low risk	Treatment allocation was concealed from patient and investigator
Incomplete outcome data (attrition bias)	Unclear risk	Acceptable dropout 15.7% placebo, 17% PGB. Reasons for dropout explained. ITT analysis (and modified ITT analysis) performed
Selective reporting (reporting bias)	High risk	Following pre-specified outcomes from protocol not reported in study: Modified Brief Pain Inventory Interference Scale; Quantitative Assessment of Neuropathic Pain (QANeP) 6 outcomes; NPSI (9 outcomes)
Other bias	High risk	All the investigators had financial ties to the study sponsor

Dworkin 2003

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequential randomization schedule generated with block size of four. Unclear how this schedule was generated
Allocation concealment (selection bias)	Low risk	Study medication was packaged and labeled with sequential randomization numbers
Blinding of participants and personnel (performance bias)	Unclear risk	Placebo capsules were identical in appearance to pregabalin; however also states that blinding could have been broken in emergency situations
Blinding of outcome assessment (detection bias)	Low risk	Blind maintained until after the study was completed and all decisions regarding data evaluability had been made
Incomplete outcome data (attrition bias)	Unclear risk	Uneven numbers of drop outs- PGB 35%, placebo 12%. Reasons provided- mostly due to adverse events
Selective reporting (reporting bias)	Unclear risk	29 patients had possibly important variations from the protocol and details of this are specified. Secondary outcome of CGIC- mentioned in results that clinicians assessments of global change closely parallelled patients' assessments however no figures given
Other bias	High risk	All the investigators had financial ties to the study sponsor

Freynhagen 2005

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Unclear risk	All patients received active medication or matching placebo capsules. Double blinded. However, unclear whether they were identical in appearance and taste
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	High risk	High rates of dropout: PGB flexible dose 35%, PGB fixed dose 38%, 46%. Reasons provided (mostly due to adverse events for PGB, lack of efficacy for Placebo).
Selective reporting (reporting bias)	Low risk	Outcomes specified in methods match those found in results.
Other bias	High risk	All study investigators had financial ties to the study sponsor

Guan 2011

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Unclear risk	Double blinded- however insufficient information to determine whether blind could have been broken
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Low risk	Low numbers of dropout due to adverse events (3% PGB, 5% Placebo), however no information on total numbers of dropout (or other reasons for dropout)
Selective reporting (reporting bias)	Unclear risk	The weekly mean pain DPRS score was listed as a secondary efficacy outcome in protocol, but included in the primary outcomes in publication. Also, final report introduced DAAC (Duration-adjusted average change score) as a primary outcome
Other bias	High risk	All study investigators had financial ties to the study sponsor

Holbech 2015

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Low risk	Randomization plan was generated by a person at a pharmacy not otherwise involved in the trial; Sealed, opaque envelopes used in emergency situations.
Blinding of participants and personnel (performance bias)	Low risk	Double-blinded (patients, investigators and all other staff). Identical tablets.
Blinding of outcome assessment (detection bias)	Low risk	Patients, investigators, and all other staff involved in the conduct of the trial were blinded to individual treatment assignments for the duration of the study.
Incomplete outcome data (attrition bias)	Low risk	Acceptable numbers of drop out (5% placebo, 17% pregabalin). Reasons provided (withdrawn consent, adverse events)
Selective reporting (reporting bias)	Unclear risk	All but 2 of the secondary outcomes in the protocol have been omitted and re-analysed as "expoloratory" outcomes in the final analysis.
Other bias	High risk	Majority of trial investigators had financial ties to the study sponsor

Huffman 2015

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated codes
Allocation concealment (selection bias)	Unclear risk	Not decribed
Blinding of participants and personnel (performance bias)	Unclear risk	Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	Drop-out rates notsignificantly different between groups. Reasons for drop-outs specified
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified in protocol
Other bias	High risk	All authors have, or have had financial ties to pharmaceutical industry

Kanodia 2011

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Unclear risk	States that it is a double blind trial, but there are no details of how this was performed (or who was blinded).
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Unclear risk	No details given about whether there was attrition or explanation.
Selective reporting (reporting bias)	Unclear risk	Pre-specified outcomes in methods match those found in results. Poor reporting of outcomes from each intervention group
Other bias	Unclear risk	Very small sample size

Kim 2011

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated schedule
Allocation concealment (selection bias)	Low risk	Centralised telerandomisation system (IMPALA)
Blinding of participants and personnel (performance bias)	Unclear risk	Matching placebo; double-blinded; unclear whether dientical in appearance
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Unclear risk	Acceptable rates of drop out (15% pregabalin, 17% placebo). Reasons for discontinuation provided. ITT analysis performed
Selective reporting (reporting bias)	High risk	Daily Sleep interference scale (DSIS) omited as a secondary outcome.
Other bias	High risk	All study authors except one had financial ties to the study sponsor

Krcevski Škvarč 2010

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	High risk	High rates of attrition (64% pregabalin, 40% placebo). Reasons for study discontinuation provided. ITT analysis performed and reported.
Selective reporting (reporting bias)	Low risk	Outcomes specified in the methods match those reported in the results
Other bias	Unclear risk	Some differences in baseline characteristics; proportion taking antiviral therapy higher in pregabalin group, differences in distribution of zoster and severirty of rash. The study authors had no competing interests

Lesser 2004

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information as to how it was generated
Allocation concealment (selection bias)	Low risk	Code was maintained by the Clinical Pharmacy Operations department, with no access by other individuals or departments. Medication was shipped to the sites in blocks in unit-dose trays. Each patient was assigned the next sequential random number
Blinding of participants and personnel (performance bias)	Unclear risk	Each patient took one small and two larger capsules, with the proper mix of active medication and placebo, for each dose to achieve double-blinding. Does not specify that the active intervention and placebo were identical
Blinding of outcome assessment (detection bias)	Low risk	Blinding was maintained until all decisions regarding data evaluability were made
Incomplete outcome data (attrition bias)	Unclear risk	Low drop out rates (8% placebo, 11% PGB). Only states that 18/35 dropouts were due to adverse events.
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes in methods match those found in results.
Other bias	High risk	Baseline characteristics: more people in placebo group taking antidiabetic medication (insulin) compared to PGB group. More T1DM and T2DM in placebo group. The study authors had financial ties to the sponsor.

Liu 2015

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Low risk	Interactive voice response system
Blinding of participants and personnel (performance bias)	Unclear risk	Placebo was matched to pregabalin. Not specified whether active and placebo pills were identical in appearance
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information.
Incomplete outcome data (attrition bias)	Low risk	Acceptable drop out rates (12% pregabalin, 16% placebo). Reasons for withdrawal provided. ITT analysis performed.
Selective reporting (reporting bias)	High risk	Omitted pre-specified secondary outcomes relating to the HADS Anxiety and Depression score.
Other bias	Unclear risk	Two authors had financial ties to the study sponsor

Mathieson 2017

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-derived random-number sequence
Allocation concealment (selection bias)	Low risk	Packaged in white, opaque, sealed containers
Blinding of participants and personnel (performance bias)	Unclear risk	Pregabalin capsules and matching placebo capsules. Unclear whether they were identical in appearance
Blinding of outcome assessment (detection bias)	Low risk	Some outcomes were assessed by means of telephone contact with the patients by trained trial researchers, but reports that all the research staff, statisticians, trial clinicians, and patients were unaware of the trial-group assignments during recruitment, data collection, and analysis.
Incomplete outcome data (attrition bias)	Low risk	Acceptable number of drop outs (16% pregabalin, 14% placebo). Reasons provided. ITT analysis performed (although it did not include 2 randomised patients).
Selective reporting (reporting bias)	High risk	The primary outcome was measured at fewer time points than was specified in the protocol which specified pain intensity would be measured at baseline then weeks 2,4,8,12,26 and 52. Study reported pain only at weeks 8, 52. All other outcomes remained the same as pre-specified.
Other bias	Unclear risk	Some differences in baseline characteristics, such as sex, dermatomal pain, neurologic deficit, clinically suspected level of spine associated with leg pain, and PainDETECT scores. Three authors had financial ties to the pharmaceutical industry

Moon 2010

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized tele-randomization system
Allocation concealment (selection bias)	Low risk	Central web–telephone software
Blinding of participants and personnel (performance bias)	Low risk	Mentions double-blinded; "pregabalin and matching placebo"
Blinding of outcome assessment (detection bias)	Low risk	Study report does not specify, although protocol states that the outcome assessors were blinded.
Incomplete outcome data (attrition bias)	Unclear risk	Uneven numbers of drop out (14.8% pregabalin, 20.5% placebo), however reasons for drop out provided. ITT analysis performed and reported.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes in protocol reported.
Other bias	Unclear risk	The authors fail to declare whether they had financial ties to Pfizer.

Rauck 2013

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Low risk	Drug containers of identical appearance
Blinding of participants and personnel (performance bias)	Low risk	PGB was provided with identical-inappearance placebo capsules to ensure blinding of subjects and investigators. All tablets were provided by an unblinded, third-party pharmacist.
Blinding of outcome assessment (detection bias)	Low risk	Study does not provide sufficient information, although trial protocol does state that the outcome assessors were blinded.
Incomplete outcome data (attrition bias)	Unclear risk	Reasons for dropout reported although attrition rates were 29% for pregabalin and 25% for placebo.
Selective reporting (reporting bias)	Low risk	Reports all pre-specified outcomes from the protocol.
Other bias	High risk	The authors had financial ties to the sponsor

Richter 2005

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer generated sequence
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Low risk	Study capsules were identical (doses were also matched to size of tablets for both pregabalin and placebo)
Blinding of outcome assessment (detection bias)	Unclear risk	Blind was maintained until completion of study and data evaluability determination however does not specify whether outcome assessors or other investigators were blinded.
Incomplete outcome data (attrition bias)	Low risk	Acceptable attrition rates (15% placebo, 5% PGB 150mg/d, 12% PGB 600mg/d [overall 9% pregabalin]). Reasons for drop out provided.
Selective reporting (reporting bias)	Low risk	Outcomes specified in the Methods match those reported in the results.
Other bias	High risk	Two-thirds of the authors had financial ties to the study sponsor

Rosenstock 2004

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequential randomization numbers according to a randomization schedule designed to attain an even distribution between pregabalin and placebo. Unclear how this sequence was generated.
Allocation concealment (selection bias)	Low risk	Study medication was packaged and labeled with sequential randomization numbers.
Blinding of participants and personnel (performance bias)	Unclear risk	All medications were packaged in blinded fashion. Not specified whether the active intervention and placebo were identical in appearance
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Low risk	Acceptable attrition rates (14% pregabalin, 11% placebo). Reasons for withdrawal provided. ITT analysis performed.
Selective reporting (reporting bias)	Low risk	Outcomes specified in the Methods match those reported in the results.
Other bias	Unclear risk	The authors did not state whether they had any competing interests

Sabatowski 2004

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated code
Allocation concealment (selection bias)	Low risk	Study medication was packaged and labeled with sequential randomisation numbers
Blinding of participants and personnel (performance bias)	Unclear risk	All medications were blinded and taken orally. Placebo capsules were identical in appearance to capsules containing active drug. However, an investigator could break the randomisation code and, thus, the blind for a patient if a medical emergency occurred.
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Unclear risk	Reasons for dropout provided, however unequal attrition rates across the groups (12.3% PGB 150mg/d, 21.1% PGB 300mg/d, Overall PGB 16.6%, 24.7% Placebo). Both ITT and PPA reported but ITT value used in abstract.
Selective reporting (reporting bias)	Unclear risk	Results of CGIC are not reported, just states that it shows a "statistically significant improvement".
Other bias	High risk	Majority of the investigators had financial ties to the study sponsor

Satoh 2011

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Allocation based on the results of a laboratory test (CrCl)
Allocation concealment (selection bias)	Low risk	Centrally organised using a validated web-based system.
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	High risk	Unequal dropout across the groups (11.8% placebo, 14.7% 300 mg/day PGB, 28.9% in the 600 mg/day PGB). All reasons for attrition were not provided.
Selective reporting (reporting bias)	High risk	Secondary outcome added in published study: patient impression of subjective symptoms (including numbness, pain and paraesthesia) which showed favourable results for pregabalin.
Other bias	High risk	All authors had financial ties to the study sponsor

Shabbir 2011

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Low risk	Appears to be no attrition from either of the randomised groups.
Selective reporting (reporting bias)	Low risk	Outcomes specified in the methods match those reported in the results.
Other bias	High risk	Baseline characteristics table not provided to compare across the intervention arms. Pregabalin was administered twice daily; daily frequency of placebo administration not specified. The authors did not state whether they had any competing interests

Siddall 2006

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Study medication was packaged and labeled with sequential randomization numbers according to the randomization schedule
Blinding of participants and personnel (performance bias)	Low risk	Medication was blinded by using capsules of identical size, color, taste, and smell for placebo and pregabalin
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Unclear risk	High (and uneven) attrition rates: pregabalin 30%, placebo 45%. Reasons for withdrawal provided. ITT analysis results reported.
Selective reporting (reporting bias)	Low risk	Outcomes specified in the Methods match those reported in the results.
Other bias	High risk	All trial investigators had financial ties to the study sponsor

Simpson 2010

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Low risk	Central computerized telerandomization system, ensured that investigators remained blinded to treatment assignments during the study
Blinding of participants and personnel (performance bias)	Low risk	Study drug and placebo were identical in appearance in order to preserve blinding.
Blinding of outcome assessment (detection bias)	Low risk	Study does not provide sufficient information, although trial protocol does state that the outcome assessors were blinded.
Incomplete outcome data (attrition bias)	Low risk	Similar rates of attrition (21% pregabalin, 19% placebo). Reasons for drop out provided, however not all randomised patients are included in the ITT analysis.
Selective reporting (reporting bias)	High risk	Prespecified outcomes (assessing QANeP) omitted in final study. Safety outcomes not prespecified in protocol added to final study.
Other bias	High risk	All trial investigators had, or have had finantial ties to the study sponsor

Simpson 2014

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Computer generated "pseudorandom" code
Allocation concealment (selection bias)	Low risk	Automated telerandomization system.
Blinding of participants and personnel (performance bias)	Low risk	Patients were randomised in a double blind fashion through study sponsors sysetm for randomization and dispensing.
Blinding of outcome assessment (detection bias)	Unclear risk	Participants, investigators and study sponsor personnel were blinded to interventions after treatment assignment, but unclear whether this includes outcome assessors.
Incomplete outcome data (attrition bias)	High risk	Reasons provided for drop outs though there is a high attrition rate (31% pregabalin, 31% placebo).
Selective reporting (reporting bias)	Low risk	Outcomes specified in the protocol match those reported in the study.
Other bias	High risk	Study prematurely terminated by Pfizer following unfavourable results. All trial investigators had finantial ties to the study sponsor

Stacey 2008

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information; reports double-blinded but unclear who is blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Unclear risk	Rates of attrition are not comparable across the groups (5.5% flexible dose PGB, 20.5% fixed dose PGB, 16.7% Placebo). Reasons for drop out provided.
Selective reporting (reporting bias)	Low risk	Outcomes specified in the methods match those reported in the results.
Other bias	High risk	All authors had financial ties to the study sponsor

Tolle 2008

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Low risk	Similar attrition rates across the groups (Placebo 17.7%, PGB 150mg/d 17.2%, PGB 300mg/d 20.2%, PGB 300/600mg/d 22.8%). Reasons for withdrawal provided. ITT analysis performed and reported.
Selective reporting (reporting bias)	High risk	EuroQoL Health Utilities Index not reported in final results (although mentioned in the abstract and methods).
Other bias	High risk	All authors had financial ties to the study sponsor

van Seventer 2006

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information although states double-blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Unclear risk	High attrition rates across the groups (36.6% placebo, 29.9% PGB 150mg/d, 36.7% PGB 300mg/d, 36.6% PGB 300/600mg/d). Reasons for withdrawal provided. ITT analysis performed.
Selective reporting (reporting bias)	Low risk	Outcomes specified in the methods match those reported in the results.
Other bias	High risk	All study authors had financial ties to the study sponsor

van Seventer 2010

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Low risk	An Interactive Voice Recognition System was used.
Blinding of participants and personnel (performance bias)	Low risk	Medication was blinded by using capsules of identical size, color, taste and smell for placebo, and pregabalin.
Blinding of outcome assessment (detection bias)	Low risk	Trial protocol specifies that outcome assessor was blinded.
Incomplete outcome data (attrition bias)	Low risk	Reasons for discontinuation provided, attrition rates comparable across the groups- 24.4% for pregabalin, 22.8% for placebo. ITT analysis performed (although excluded one patient from each group due to lack of post-baseline data).
Selective reporting (reporting bias)	High risk	Protocol specified CGIC a secondary outcome however this was omitted in published report. Other omitted outcomes include Pain Treatment Satisfaction Scale (PTSS)- Impact of current pain medication, satisfaction with current pain medication, medication characteristics, efficacy; Neuropathic Pain Symptom Inventory total intensity score, Medical Outcome Study Cognitive Subscale (reasoning, concentration, confusion, memory, attention, thinking); Davidson Trauma scale (severity, frequency, total score).
Other bias	High risk	All study authors had financial ties to the study sponsor

Vranken 2008

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized according to the automated assignment system
Allocation concealment (selection bias)	Low risk	Hospital pharmacist prepared identical, coded medication bottles containing identical capsules of pregabalin or placebo. Unclear if pharmacist was otherwise involved in the study or third party.
Blinding of participants and personnel (performance bias)	Low risk	Coded medication bottle was supplied by hospital pharmacist to the blinded treating physician. Medication bottle contained identical capsules.
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Low risk	Reasonable rates of attrition (15% pregabalin, 20% of placebo). Reasons for discontinuation provided.
Selective reporting (reporting bias)	Low risk	Outcomes specified in the methods match those reported in the results.
Other bias	Unclear risk	Some differences in baseline characteristics including site of pain and concomitant therapies. The authors did not report whether they had any competing interests

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
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.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
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.	Suppl.
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.	5
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.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
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).	5
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.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
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.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
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).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
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.	7
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.	7
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).	7
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.	7-19
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-19
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7-19
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7-19
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).	20
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).	22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	24
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.	24

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(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

Benefits and harms of pregabalin in the management of neuropathic pain: a rapid review and meta-analysis of randomized clinical trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-023600.R2
Article Type:	Research
Date Submitted by the Author:	19-Nov-2018
Complete List of Authors:	Onakpoya, Igho; University of Oxford, Primary Care Health Sciences Thomas, Elizabeth; Bond University Faculty of Health Sciences and Medicine, Faculty of Health Sciences and Medicine Lee, Joseph; University of Oxford, Nuffield Department of Primary Care Health Sciences Goldacre, Ben; University of Oxford, Primary Care Health Sciences Heneghan, Carl; Oxford University, Primary Health Care
Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Nutrition and metabolism, Pharmacology and therapeutics
Keywords:	pregabalin, benefits, harms, systematic review, meta-analysis

Benefits and harms of pregabalin in the management of neuropathic pain: a rapid review and meta-analysis of randomized clinical trials

Igho J Onakpoya, research fellow[1], Elizabeth T Thomas, medical student[2], Joseph Lee, nihr in practice fellow[1], Ben Goldacre, senior clinical research fellow[1], Carl J Heneghan, director[1]

[1]University of Oxford, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Oxford, United Kingdom OX2 6GG

[2]Faculty of Health Sciences and Medicine, Bond University, 14 University Drive, Robina, Australia QLD 4226

Correspondence to IJ Onakpoya igho.onakpoya@phc.ox.ac.uk

ABSTRACT

Objective To assess the benefits and harms of pregabalin in the management of neuropathic pain

Design Rapid review and meta-analysis of phase III randomized placebo-controlled trials.

Participants Adults aged 18 and above with neuropathic pain defined according to the International Association for the Study of Pain (IASP) criteria.

Interventions Pregabalin or placebo.

Primary and secondary outcome measures Our primary outcomes were pain (as measured using validated scales) and adverse events. Our secondary outcomes were sleep disturbance, quality of life (QOL), patient global impression of change (PGIC), clinician global impression (CGI) scale, anxiety and depression scores, overall discontinuations and discontinuations because of adverse events.

Results We included 28 trials comprising 6087 participants. The neuropathic pain conditions studied were diabetic peripheral neuropathy, post-herpetic neuralgia, herpes zoster, sciatica (radicular pain), post-stroke pain and spinal cord injury-related pain. Patients who took pregabalin reported significant reductions in pain (numerical rating scale (NRS)) compared to placebo, SMD -0.49 (95% CI -0.66 to -0.32, P<0.00001); very low quality evidence. Pregabalin significantly reduced sleep interference scores (NRS) compared with placebo, SMD -0.38 (95% CI -0.50 to -0.26, P<0.00001) moderate quality evidence. Pregabalin significantly increased the risk of adverse events compared with placebo, RR 1.33 (95% CI 1.23 to 1.44, P<0.00001, low quality evidence). The risks of experiencing weight gain, somnolence, dizziness, peripheral oedema, fatigue, visual disturbances, ataxia, non-peripheral oedema, vertigo and euphoria were significantly increased with pregabalin. Pregabalin was significantly more likely than placebo to lead to discontinuation of the drug because of adverse events, RR 1.91 (95% CI 1.54 to 2.37, P<0.00001), low quality evidence.

Conclusion Pregabalin has beneficial effects on some symptoms of neuropathic pain. However, its use significantly increases the risk of a number of adverse events and discontinuation due to adverse events. The quality of the evidence from journal publications is low.

Strengths and limitations of the study

- We used the Cochrane criteria to assess the risk of bias.
- This is the first review that rates the quality of the evidence for each outcome assessed.
- The review may be prone to sampling bias, and we may have missed potentially eligible studies.
- We did not assess the extent to which different doses of pregabalin influenced the outcomes.

INTRODUCTION

Pregabalin is a gabapentinoid licensed for treatment of neurologic disorders. It is one of the earlier drugs approved by the United States Food and Drug Administration (FDA) (2004) for the treatment of painful diabetic neuropathy (PDN) and post-herpetic neuralgia (PHN).[1] Pregabalin is thought to exert its analgesic action through antagonistic activity at the voltage gated Ca2+ channels where it binds to the alpha-2-delta subunit.[1,2]

Prescriptions of pregabalin (and gabapentin) have markedly increased over the last few years. In the US, prescriptions for pregabalin rose from 39 million in 2012 to 64 million in 2016 (annual prescription costs increased from approximately $2 billion to $4.4 billion over the same period). [3] In the UK, pregabalin use increased 350% over a five year period between 2008 and 2013. [4] In England alone, there were over 6.2 million prescriptions of pregabalin across GP practices in 2017 costing about $440 million.[5]

Pregabalin is recommended as first-line pharmacologic agent for management of neuropathic pain[6]. There is, however, some evidence of increased mortality attributed to pregabalin in the UK,[7] and this has led some authors to caution clinicians about the risk of harms when prescribing. [8] The risks are thought to be particularly acute for patients who use heroin and those who misuse gabapentinoids. Indeed, the UK government is soon to classify the drug as a class C controlled substance because of its abuse potential and increased reports of deaths attributed to its use.[9] Practicing clinicians have also recently called for the evidence for the effectiveness of pregabalin to be re-examined in the light of its potential to cause harms.[3,4]

Rapid reviews use accelerated methods to identify and synthesize the evidence from the literature in order to meet the needs of target audiences including policy makers, healthcare

professionals and patient groups.[10] The objective of this rapid review was therefore to evaluate the evidence for benefits and harms of pregabalin in the treatment of neuropathic pain in adults, using evidence from published randomized clinical trials (RCTs).

METHODS

We conducted electronic searches in the following databases: Medline, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL). We searched each database from inception till January 2018. No language restrictions were imposed. [See appendix 1 for a full search strategy]. We also hand searched the bibliography of eligible studies. [See appendix 2 for the full protocol].

We included phase III double-blinded placebo-controlled RCTs (efficacy studies) assessing the effects of pregabalin on neuropathic pain in adults aged 18 years and above. We included studies based on the definition of the International Association for the Study of Pain (IASP) definition.[11] These included trials on diabetic neuropathy, HIV-related neuropathy, lumbar radiculopathy, post-herpetic neuralgia, and chronic postsurgical pain. We included RCTs irrespective of study size and duration of intervention. If we included RCTs with a cross-over design, we used data from the first phase of the study. We excluded phase IV trials because they are typically unblinded. We also excluded studies that combined pregabalin with other types of pain intervention because the effects of such interventions would not be exclusively due to the actions of pregabalin; however, co-interventions used as rescue medication were allowed. Trials that randomized participants based on response to pregabalin therapy in the run-in phase were also excluded. Our main outcomes were pain (as measured using validated scales because such scales enhance the credibility of the measured outcomes[12]) and adverse events. Our secondary outcomes were sleep disturbance, quality of life (QOL), patient global

impression of change (PGIC), clinician global impression (CGI) scale, anxiety and depression, overall discontinuations and discontinuations because of adverse events.

The risk of bias for each included study was rated using the Cochrane criteria.[13] Two reviewers (IJO and ETT) independently screened abstracts and determined study eligibility. Disagreements were resolved through discussion. Three reviewers (IJO (8 studies), ETT (8 studies) and JL (10 studies)) independently extracted data according to pre-defined criteria into customized excel spreadsheets. The extracted data were independently verified by two reviewers (ETT and IJO). Any disagreements were resolved through discussion. For each included study, we extracted data on study ID, settings, populations, interventions, outcomes and results.

Using the random effects model (Mantel-Haenszel) of the standard meta-analysis software (RevMan 5.3),[14] we computed standardized mean differences (SMDs) and 95% confidence intervals (CIs) for continuous outcomes and risk ratios with 95% CI for binary outcomes. We used pre- to post-intervention changes to assess intervention effects between pregabalin and placebo. Where studies reported data on change from baseline but did not report standard deviations (SDs), we imputed SDs (five studies) based on the SD of other studies included in the meta-analysis.[15] We used a value of P=0.05 as our threshold for statistical significance. We assessed heterogeneity using the I-squared statistic: values of 25%, 50% and 75% judged mild, moderate and substantial heterogeneity respectively. We investigated heterogeneity using subgroup (based on central or peripheral neuropathic pain) and sensitivity (based on study quality and/or duration) analyses. We used a funnel plot to assess publication bias.

One reviewer (ETT) entered the data on benefits on RevMan, and these were independently verified by a second reviewer (IJO). One reviewer (IJO) entered the data on harms onto RevMan, and these were independently verified by a second reviewer (ETT). Using the GRADEpro software (version 3.6),[16] we rated the overall quality of the body of evidence for each outcome using the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE)[17] criteria which examines the following domains: study design; risk of bias; inconsistency; indirectness; and imprecision.

Patient public involvement

Because this was a rapid review, we did not enlist the services of patient representatives in this research.

RESULTS

Our searches identified 1349 non-duplicate citations, out of which 62 articles were considered eligible (Figure 1). We excluded 34 articles that did not fit our inclusion criteria. [See Appendix 3 for list of excluded studies and the reasons for exclusion]. In total, we included 28 studies[18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45] comprising 6087 participants (Table 1). The intervention duration was between three and 20 weeks (median 8 weeks) and all the trials were industry funded.

Twenty three studies examined the effectiveness of pregabalin in treatment of peripheral neuropathic pain including DPN, PHN and Herpes zoster (HZ) (Table 1). Five studies examined the effectiveness of pregabalin for treating central neuropathic pain including sciatica (radicular pain), post-stroke pain and spinal cord injury-related pain. Twenty five studies were conducted in two or more centres. Outcome measures for pain included

numerical rating scale (NRS), visual assessment scale (VAS), Short-Form McGill Pain Questionnaire visual assessment scale (SF-MPQ VAS), and SF-MPQ personal pain intensity (SF-MPQ PPI) index [see Table 1 for full characteristics of included studies]. The overall risk of bias in the included studies was moderate to high (Figures 2 and 3). This was mainly due to inadequate reporting of blinding procedures, selective outcome reporting and financial conflicts of interest amongst study authors. [See appendix 4 for the risk of bias judgements].

Pain

Twenty one studies provided adequate data on pain using the NRS or variants of it to allow meta-analysis. Meta-analysis showed a significant reduction in pain scores with pregabalin compared with placebo, SMD -0.49 (95% CI -0.66 to -0.32, P<0.00001, I^2=88%: Figure 4). Visual inspection of a funnel plot showed that the studies were almost symmetrically distributed around the mean difference for all trials (Figure S1); trim and fill analyses showed that the subsequent addition of studies with smaller sample sizes did not change the direction of effect. The effect was significant for peripheral neuropathic pain (P<0.00001), but not for central neuropathic pain (P=0.08; Appendix table 1). The overall quality of the evidence was very low (Summary of Findings (SoF) Table 1). Sensitivity analyses revealed similar direction of effects (Appendix Table 2). Four studies that measured pain using NRS did not provide adequate data for meta-analysis; three of these reported significant reductions in pain scores favouring pregabalin over placebo, while one reported no significant difference between groups (See Appendix Table 3).

Three studies measured pain using the VAS, and all showed significant reduction in pain scores favouring pregabalin over placebo (Appendix Table 3). Nine studies measured pain using SF-MPQ VAS, and all reported significant reduction in pain scores favouring

pregabalin over placebo. Four studies measured pain using SF-MPQ PPI index, and all reported significant reduction in pain scores favouring pregabalin over placebo.

Table 1: Main characteristics of RCTs assessing the effects of pregabalin in the management of central and peripheral neuropathic pain

Study ID	Design	Sample size	Duration	Setting	Population	Duration of neuropathic pain	Outcome measures	Interventions		
								Pregabalin	*Placebo*	*Co-interventions*
Arezzo 2008 [18]	Parallel-group	PGB 82; PLA 85	13 weeks	23 centres; USA	Men or women with T1DM or T2DM	≥3 months	**Primary:** Mean pain scores (MPS); proportion of responders; Adverse events≥3% **Secondary:** Sleep interference (11 point NRS), Present pain intensity (PPI) index; SF-MPQ VAS; CGIC; PGIC	600 mg/d Fixed	Not described	Aspirin (up to 325 mg/d for cardiac and stroke prophylaxis), acetaminophen (up to 4 g/d), SSRIs, and benzodiazepines such as lorazepam (dosed at bedtime with stable [>30 days] regimen for sleep problems) were allowed.
Cardenas 2013 [19]	Parallel-group	PGB 112; PLA 108	16 weeks	60 centres; Chile, China, Columbia, Czech Republic, Hong Kong, India, Japan, Philippines, Russia, USA	Patients aged ≥18 years with C2-T12 complete/incomplete SCI	≥ 12 months	**Primary:** Duration-adjusted average change in pain (DAAC); **Secondary:** Change in mean pain score (from baseline to endpoint); Percentage of patients with >/=30% reduction in mean pain score at end point; PGIC scores at endpoint; change in mean pain-related sleep interference score; change from baseline in mean pain at each study week; change from baseline in pain-related sleep interference scores at each week; Medical Outcomes Study-Sleep Scale (MOS-SS); Hospital Anxiety and Depression scale scores (at baseline and endpoint)	150-600mg/d Flexible phase followed by maintenance phase	Matching grey capsule	Nonsteroidal anti-inflammatory drugs, cyclo-oxygenase-2 inhibitors, and acetaminophen (≤1.5 g/d in Japan, ≤4 g/d in all other countries) were permitted as rescue therapy. Antidepressants were permitted if the patient was on a stable dose within 30 days before the first visit.
Dworkin 2003 [20]	Parallel-group	PGB 89; PLA 84	8 weeks	29 centres; USA	Men or women ≥18 years old with post-herpetic neuralgia	≥3 months	**Primary:** Pain reduction in last 24 hours; Safety and adverse events **Secondary:** SF-MPQ at baseline, weeks 1,3,5,8; daily sleep interference score; MOS-SS; SF-36; PGIC; CGIC	300mg/d, 600mg/d Fixed	Identical in appearance; administered 1 capsule three times daily	Permitted medications included narcotic and non-narcotic analgesics, acetaminophen (not to exceed 4g/day), nonsteroidal anti-inflammatory drugs, aspirin, and antidepressants, including selective serotonin reuptake inhibitors (provided that dosing had been stable for at least 30 days before baseline)
Freynhagen 2005 [21]	Parallel-group	PGB 273; PLA 65	12 weeks	60 centres; 9 European countries that were not specified	Men or women ≥18 years old with primary diagnosis of painful DPN or post-herpetic neuralgia	≥3 months PHN, ≥6 months DPN	**Primary:** Mean Pain Score; adverse events; **Secondary:** daily sleep interference diary; MOS-SS; PGIC	150-600mg/d Flexible; 300mg/d, 600mg/d Fixed	Matching capsules; matching twice daily dosing schedule	SSRIs for treatment of depression, aspirin for myocardial infarction and stroke prophylaxis, short-acting benzodiazepines for insomnia, and paracetamol as rescue medication were allowable medications during the study period.
Guan 2011 [22]	Parallel-group	PGB 206; PLA 102	8 weeks	11 centres; China	Males or females 18-75 years with primary diagnosis of painful DPN or PHN	≥3 months PHN, ≥1 year, <5 years DPN	**Primary:** Mean Pain score (DPRS) during preceding 24h; DAAC score; **Secondary:** Daily sleep interference scale; SF-MPQ; PGIC; CGIC; Safety and adverse events	150-600mg/d Flexible	Flexible dose placebo in matching capsules; doses titrated using same regimen	NSAIDs and SSRIs allowed to be continued on stable dose
Holbech 2015 [23]	Cross-over	PGB 18; PLA 19	5 weeks	3 centres; Denmark	Males or females 20-85 years with polyneuropathy due to DPN	≥6 months	**Primary:** Total pain intensity on NRS; adverse events; **Secondary:** pain-related sleep disturbances; pain relief on 6-point verbal scale; **Other:** specific pain symptoms on the NRS; number of paracetamol tablets used as escape medication; SF-36 (health related QoL); Major Depression Inventory; QST tests	150mg/d, 300mg/d Fixed	Matched placebos of identical appearance to the 2 trial drugs were dosed similarly using double-dummy technique.	Up to 6 tablets of 500 mg paracetamol could be used daily as escape medication
Huffman 2015 [24]	Cross-over	PGB 101; PLA 102	6 weeks	36 centres; USA (25), Sweden (4), South Africa (4), Czech Republic (3)	Men or women ≥18 years old with painful DPN and with pain on walking	Not described	**Primary:** Numeric Rating Scale (NRS); DPN Pain on Walking (NRS); **Secondary:** 30%, 50% responders**;** Brief Pain Inventory-Short Form (BPI-sf); Daytime Total Activity Counts per Day; Steps per Day; Walk 12 questionnaire; Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) Total Quality of Life (TQOL) Score; Euro QoL-5 Dimensions (EQ-5D); Mean Sleep Interference Rating Score; HADS	150-300 mg/day Fixed	Matching placebo also administered in 3 divided doses	Not described

Kanodia 2011 [25]	Parallel-group	PGB 23; PLA 22	4 weeks	1 centre; India	Patients with acute herpes zoster presenting within 72 hours of onset	< 3 days	**Primary:** Pain on linear VAS; Adverse events	150mg/d Fixed	Not described	Oral acyclovir 800mg was given 5 times per day for 7 days
Kim 2011 [26]	Parallel-group	PGB 110; PLA 109	12 weeks	32 centres; Asia-Pacific	Males or females ≥18 years with diagnosis of central post-stroke pain	≥3 months	**Primary:** Mean pain score; **Secondary:** Daily sleep interference scale (DSIS); Weekly mean pain scores; proportion of 30%, 50% responders; quantitative assessment of Neuropathic pain (QANeP); Neuropathic Pain Symptom Inventory (NPSI); Weekly mean sleep interference scores; MOS-SS; HADS; SF-MPQ VAS- Part B; Euro Quality of Life (EQ-5D); PGIC; CGIC; Safety and tolerability	300,600mg/d Dose adjustment followed by fixed maintenance phase	Matching placebo	Stable medications for pain or insomnia if used normally >30 days before screening
Krcevski Skvarc 2010 [27]	Parallel-group	PGB 14; PLA 15	3 weeks	1 centre; Slovenia	Men or women 30-80 years with herpes zoster pain.		**Primary:** Assessment of pain severity (11 point Likert scale); Secondary: patients' ratings of the severity of allodynia, hyperalgesia, and burning, prickling and tingling sensations; rating of quality of sleep and physical activity; consumption of analgesics; occurrence of adverse events; SHN; PHN	150 or 300mg/d Fixed	Placebo also administered twice daily	Oxycodone, naproxen and/or tramadol, morphine, diclofenac
Lesser 2004 [28]	Parallel-group	PGB 240; PLA 97	5 weeks	45 centres; USA	Men or women ≥18 years old who were diagnosed with diabetes mellitus (type 1 or 2) and had distal symmetric sensorimotor polyneuropathy.	1-5 years	**Primary:** Pain (11-point NRS); **Secondary:** daily sleep interference diary; SF-MPQ; CGIC; PGIC; SF-36; POMS; **Safety outcomes**	75, 300, 600mg/d Fixed	Placebo administered three times daily	Acetaminophen and SSRIs permitted
Liu 2015 [29]	Parallel-group	PGB 112; PLA 110	8 weeks	22 centres; China	Male and female ethnically Chinese patients aged ≥ 18, diagnosed with post-herpetic neuralgia	Symptoms persisting ≥ 3 months after the healing of HZ lesions	**Primary:** Mean score of Daily Pain Rating Score; **Secondary:** Change from baseline on Pain VAS; Change from baseline on Present Pain Intensity (PPI) of the SF-MPQ; 30% pain responders at endpoint; change from baseline in weekly mean pain score; change from baseline in sleep interference score (11-point NRS); CGIC; PGIC; MOS-SS; Adverse events	150mg/d, 300mg/d Fixed	Matched placebo capsules on the same dosing schedule	Concomitant use of medications permitted except antidepressants, epileptics, analgesics or corticosteroids, skeletal muscle relaxants, mexelitine, and dextromethorphan as well as electrotherapy, transcutaneous electrical nerve stimulation, acupuncture, and neurosurgical therapy.
Mathieson 2017 [30]	Parallel-group	PGB 108; PLA 101	8 weeks	Number not specified; Australia	Patients with sciatica	≥1 week, <1 year	**Primary:** Average leg-pain intensity score over the course of previous 24 hours as assessed at 8 weeks and 52 weeks; **Secondary:** extent of disability (Roland Disability Questionnaire for sciatica); back pain intensity; global perceived effect; Quality of Life as measured on Short Form Health Survey 12; adverse events	150-600mg/d Flexible	Matching placebo capsules were packaged in white, opaque, sealed containers at a central pharmacy	Concomitant therapies included physical therapies as well as other analgesic medications (except for adjuvant analgesic agents), which would ideally be prescribed in accordance with the World Health Organization pain ladder. Trial clinicians were asked not to prescribe certain medicines (antiepileptic medications, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, topical lidocaine, and benzodiazepines) or to schedule interventional procedures.

Moon 2010 [31]	Parallel-group	PGB 162; PLA 78	10 weeks	Multicentre (number not specified); Korea	Korean patients aged 18 years with neuropathic pain (diabetic peripheral neuropathy, postherpetic neuralgia, or posttraumatic neuropathic pain)	Mean duration of pain pregabalin patients- 3 years, placebo patients 3.2 years	**Primary:** Endpoint mean DPRS score, Secondary: weekly mean DPRS score, duration adjusted average change (DAAC) of adjusted mean DPRS from baseline to endpoint, proportion of responders (whose scores reduced by 30% or 50%), Daily Sleep Interference Scale (DSIS), Euro Quality of Life assessment (EQ-5D): utility and VAS score; MOS-SS; HADS; PGIC; CGIC; **Tolerability evaluation** of adverse events and vital signs	150-600mg/d Flexible	Matching placebo capsules provided by Pfizer	Most patients were taking drug therapy at baseline, and the majority (83.8%) remained on concomitant drug therapy during the study, including one-third who received tricyclic antidepressants.
Rauck 2013 [32]	Parallel-group	PGB 56; PLA 112	20 weeks	85 centres; USA	Men or women ≥18 years old who were diagnosed with diabetes mellitus (type 1 or 2) and had pain attributed to DPN, defined as painful distal symmetric sensorimotor polyneuropathy.	≥6 months, <5 years	**Primary:** Change from baseline in pain intensity score (11 point PI-NRS); **Secondary:** Change from baseline in mean 24-hour average pain intensity score, daytime average pain intensity score, nighttime average pain intensity score, current pain intensity score, daytime worst pain intensity score, nighttime worst pain intensity score, sleep interference score, and rescue analgesia consumption (mg); Neuropathic Pain Scale (NPS); SF-MPQ; pre- and post-50-foot (15 meter) walk pain scores; PGIC; CGIC; proportion of subjects achieving various levels of reduction in the 24-hour average pain intensity score; time to onset of sustained improvement in the 24-hour average pain intensity score; POMS; SF-36 health-related quality of life questionnaire; **Safety assessments**	300mg/d Fixed	Matching placebo in blister card	Acetaminophen, up to 3 g/day, was allowed as rescue medication for pain throughout the trial but was not allowed within 24 hours of any site visit for assessments.
Richter 2005 [33]	Parallel-group	PGB 161; PLA 85	6 weeks	Multicentre; not specified	Patients with diabetes and painful distal symmetrical sensorimotor polyneuropathy	1-5 years	**Primary:** Pain; Adverse events; **Secondary:** Pain characteristics (SF-MPQ, PPI); sleep interference (11 point NRS 0 to 10); health status (SF-36); psychologic state (POMS); global improvement (PGIC, CGIC)	150mg/d, 600mg/d Fixed	Matching dose and schedule	Aspirin (for prophylaxis of myocardial infarction and transient ischemic attacks), acetaminophen (3 g/day), and stable doses of serotonin reuptake inhibitors were allowed.
Rosenstock 2004 [34]	Parallel-group	PGB 76; PLA 70	8 weeks	25 centres	Men or women ≥18 years old with type 1 or 2 diabetes mellitus who reported symmetrical painful symptoms in distal extremities for a period of 1–5 years prior to study	1-5 years	**Primary:** Endpoint mean score **Secondary:** SF-MPQ-Sensory, affective and total score; daily sleep interference score; PGIC; CGIC; SF-36; Profile of Mood States (POMS); **Safety**	300mg/d Fixed	Lactose USP, 1 capsule three times daily	Acetaminophen (up to 4 g/day), aspirin (up to 325 mg/day for myocardial infarction or transient ischemic attack prophylaxis), and serotonin reuptake inhibitors provided no dose changes occurred within 30 days prior to randomization or during the study)
Sabatowski 2004 [35]	Parallel-group	PGB 157; PLA 81	8 weeks	53 centres; Europe, Australia	Men or women ≥18 years old with post-herpetic neuralgia	≥6 months	**Primary:** Endpoint mean score; **Secondary:** mean sleep interference scores, PGIC, CGIC, SF-36 health survey, Zung Self-Rating Depression Scale, VAS of the SF-MPQ, **Adverse events**	150mg/d, 300mg/d Fixed	Identical in appearance	Patients allowed to continue acetaminophen (up to 3 g/day), non-steroidal anti-inflammatory drugs, opioid or non-opioid analgesics, or antidepressants.
Satoh 2011 [36]	Parallel-group	PGB 179; PLA 90	13 weeks **intervention period	62 centres; Japan	Men or women ≥18 years old with diabetic peripheral neuropathy	≥ 1 year	**Primary:** Change from baseline in mean weekly pain score at week 13 using a 11 point NRS; **Secondary:** weekly mean pain scores, responder rates, SF-MPQ score, weekly mean sleep interference scores using 11-point NRS; MOS-Sleep Scale, SF-36, PGIC, CGIC, **Safety:** Adverse events.	300mg/d, 600mg/d Fixed	Not described, same schedule	Not described
Shabbir 2011 [37]	Parallel-group	PGB 70; PLA 70	6 weeks	2 centres; Mayo Hospital and Services Hospital, Lahore.	Men or women ≥18 years old with diabetic peripheral neuropathy	≥6 months	**Primary:** Reduction in pain (measured with NRS); responders who experienced 50% or more reduction in baseline pain score on NRS	150-600mg/d Flexible	Not described	Not described
Siddall 2006 [38]	Parallel-group	PGB 70; PLA 67	12 weeks	8 centres; Australia	Patients with central neuropathic pain in spinal cord injury	Persisted continuously for at least 3 months or with relapses and remission for at least 6 months	**Primary:** Endpoint mean pain scores, Sleep-interference scores, SF-MPQ Total, sensory and affective scores, from which VAS and PPI score was derived. MOS-sleep scale and HADS, PGIC; T**olerability and safety**	150-600mg/d Flexible	Placebo also administered twice daily	70% of patients taking other medications too: opiates, tricyclics, AEDs, NSAIDS/Cox2, Benzos, SSRI/SSNI, Muscle relaxants.
Simpson 2010 [39]	Parallel-group	PGB 151; PLA 151	14 weeks	44 centres; USA, Puerto Rico	Men or women ≥18 years old with painful HIV-DSP	≥ 3 months	**Primary:** Change from baseline in mean NPRS score; **Secondary:** change in sleep interference scores; MOS-Sleep Scale; PGIC; Pain- modified Brief Pain Inventory; Gracely Pain Scale (GPS); **Safety:** adverse events	150-600mg/d Flexible	Placebo also administered twice daily	Neurotoxic antiretroviral (ARV) drugs known to cause sensory neuropathy clinically similar to HIV-DSP must have been on stable doses for ≥3 months before screening. Doses of other pain medications had to be stable for ≥1 month before treatment and throughout the study.
Simpson 2014 [40]	Parallel-group	PGB 183; PLA 194	16 weeks	45 centres; South Africa, USA, India, Columbia, Thailand, Peru, Puerto Rico, Poland.	Men and women ≥18 years of age with HIV neuropathy	≥ 3 months	**Primary:** Change in Pain scores (NRS); **Secondary:** PGIC/CGIC; Brief Pain Symptom Inventory short form (BPI-sf);MOS-SS; Pain-related sleep interference and overall sleep disturbance (NRS-Sleep scale); Safety	150-600mg/d Flexible	Matching placebo delivered through system for randomization and drug dispensing	NSAIDs, if taken at stable dose for ≥4 weeks before study, antidepressants without efficacy for neuropathic pain if taken at stable dose for ≥30 days before study [SSRIs, bupropion, trazodone], nonbenzodiazepine hypnotics no more than

										once/week for sleep disturbance if clinically essential, rescue therapy of oral acetaminophen (max 3g/day), low dose (≤650mg/day) aspirin and stable antiretroviral treatment >8 weeks before study
Stacey 2008 [41]	Parallel-group	PGB 179; PLA 90	4 weeks	42 centres; United States, Germany, Italy, Spain, and United Kingdom	Men or women ≥ 18 years old with post-herpetic neuralgia	≥3 months	**Primary:** Pain reduction; time to onset of meaningful pain relief; **Secondary:** Daily sleep interference score; PGIC; VAS of the SF-MPQ; VAS anxiety; VAS allodynia; **Safety evaluation**	150-600mg/d Flexible dose; 300mg/d Fixed dose	Placebo also administered twice daily	Concomitant pain treatments permitted given that it must be stable for at least 30 days
Tolle 2008 [42]	Parallel-group	PGB 299; PLA 96	12 weeks	58 centres; Germany, Hungary, Poland, United Kingdom, Australia, and South Africa	Men or women ≥18 years old with painful symmetrical sensorimotor polyneuropathy due to diabetes	≥1 year	**Primary:** Pain reduction (according to 11-point NRS) from baseline; treatment responders; **Secondary:** PGIC; CGIC; EuroQoL Health Utilities Index; Daily pain-related sleep-interference scores; EQ-5D (VAS); **Safety evaluation**	150, 300, 300/600mg/d Fixed	Placebo also administered twice daily	SSRIs for depression or anxiety given in a stable dose for >30 days
Van Seventer 2006 [43]	Parallel-group	PGB 275; PLA 93	13 weeks	76 centres	Men or women ≥ 18 years old with post-herpetic neuralgia	>3 months	**Primary:** Endpoint mean pain scores; patients with ≥50% and ≥30% reduction in pain score from baseline; weekly mean pain scores; **Secondary:** endpoint mean sleep-interference scores, weekly mean sleep-interference scores, PGIC	150, 300, 600mg/d Fixed	Placebo also administered twice daily	non-narcotic analgesics, e.g., noramidopyrine and paracetamol, and stable regimens of opioids, anti-inflammatories, and antidepressants
Van Seventer 2010 [44]	Parallel-group	PGB 127; PLA 127	8 weeks	44 centres; Belgium, Canada, Denmark, Finland, Italy, Netherlands, Portugal, Romania, Sweden, Switzerland, United Kingdom	Men or women aged 18–80 with post- traumatic peripheral neuropathic pain	≥3 months	**Primary:** End-point mean pain score; **Secondary:** rating of extent to which pain interfered with sleep; MOS-SS;HADS; mBPI-sf; PGIC; **Tolerability and safety assessment**	150-600mg/d Flexible	Placebo also administered twice daily	NSAIDS, COX-2 inhibitors, opioid and non-opioid analgesics, anti-epileptic drugs, antidepressant medications, other concomitant medications if they had been stable for at least 1 month before the study and would remain stable throughout the study
Vranken 2008 [45]	Parallel-group	PGB 20; PLA 20	4 weeks	1 centre; Netherlands	Men and women ≥18 years old with central neuropathic pain	≥6 months	**Primary:** Pain intensity score (VAS); Mean endpoint pain score; Pain Disability Index (PDI); EQ-5D; Medical Outcomes Short-form Health Survey questionnaire 36 (SF36); **Safety**	150-600mg/d Flexible	Flexible dose placebo (1-4 capsules per day); matching capsules; on same dosing schedule	Adjuvant analgesics

ABBREVIATIONS: CGIC: Clinician global impression of change; DPN: Diabetic peripheral neuropathy; PGB: Pregabalin; PGIC: Patient global impression of change; PLA: Placebo; SF-MPQ PPI: Short-Form McGill Pain Questionnaire *personal pain intensity;* SF-MPQ VAS: Short-Form McGill Pain Questionnaire visual assessment scale; VAS: Visual assessment scale

Summary of Findings Table 1: Effect of pregabalin on NRS scores in patients with neuropathic pain

Patient or population: patients with neuropathic pain
Settings:
Intervention: Effect of pregabalin on pain

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	**Effect of pregabalin in pain**				
Mean Pain Score		The mean pain score in the intervention groups was **0.49 standard deviations lower** (0.66 to 0.32 lower)		5093 (21 studies)	⊕⊖⊖⊖ **very low**[1,2]	SMD -0.49 (-0.66 to -0.32)
Mean Pain Score - Central neuropathic pain (including sciatica (radicular pain))		The mean mean pain score - central neuropathic pain (including sciatica) in the intervention groups was **0.38 standard deviations lower** (0.8 lower to 0.04 higher)		785 (4 studies)	⊕⊖⊖⊖ **very low**[2,3,4]	SMD -0.38 (-0.8 to 0.04)
Mean Pain Score - Peripheral neuropathic pain (includes PDN, HZ & PHN)		The mean mean pain score - peripheral neuropathic pain (includes pdn, hz & phn) in the intervention groups was **0.52 standard deviations lower** (0.71 to 0.33 lower)		4308 (17 studies)	⊕⊖⊖⊖ **very low**[1,2]	SMD -0.52 (-0.71 to -0.33)

*The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **NRS:** Numerical rating scale; **SMD:** Standard mean deviation**; PDN:** Painful diabetic neuropathy; **HZ:** Herpes zoster; **PHN:** Post-herpetic neuralgia

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Inconsistency in allocation concealment and blinding, selective reporting, authors had financial ties to industry sponsor
[2] Substantial heterogeneity
[3] Industry-sponsored, selective reporting
[4] Wide confidence interval

Adverse events

Figure 5 shows that pregabalin was significantly more likely to cause adverse events compared with placebo, RR 1.33 (95% CI 1.23 to 1.44, P<0.00001, I^2=52%). This translates into an absolute effect of 145 (95% CI 101 to 194) more adverse events per 1000 treated. The overall quality of the evidence was low (SoF Table 2). Sensitivity analyses revealed similar direction of effects (Appendix Table 2). The risk of experiencing individual adverse events of weight gain, somnolence, dizziness, peripheral oedema, fatigue, visual disturbances, ataxia, non-peripheral oedema, dry mouth, vertigo and euphoria were significantly increased with pregabalin compared with placebo (see Appendix Table 1 and Figures S2 to S12). Pregabalin was also significantly more likely to cause discontinuation because of adverse events (RR 1.91, 95% CI 1.54 to 2.37, P<0.00001, I^2=0%); the quality of the evidence was low (SoF Table 2; Appendix Table 1; and Figure S13). Sensitivity analyses by study duration revealed similar direction of effects, but there was no significant difference with higher quality studies (Appendix Table 2).

There was no significant difference in the risk of serious adverse events (RR 0.9; 95% CI 0.66 to 1.24, P=0.50, I^2=0%; SoF Table 2; Appendix Table 1; and Figure S14); the quality of the evidence was moderate. Sensitivity analyses showed a significant effect in favour on pregabalin with three higher quality studies, but there was no difference based on study duration (Appendix Table 2). In total, six deaths were reported across four trials, five in pregabalin group and one in placebo: RR 0.86, 95% CI 0.18 to 4.06, P = 0.85, I^2=0%.

Summary of Findings Table 2: Effect of pregabalin on adverse events in patients with neuropathic pain

Patient or population: patients with Neuropathic pain
Settings:
Intervention: Effect of pregabalin on adverse events

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Effect of pregabalin on adverse events	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Number needed to harm (NNH)
Adverse events	**Study population**		**RR 1.33** (1.23 to 1.44)	4010 (19 studies)	⊕⊕⊖⊖ **low**[1,2]	6 (5 to 9)
	523 per 1000	**696 per 1000** (643 to 753)				
	Moderate					
	440 per 1000	**585 per 1000** (541 to 634)				
Discontinuations because of adverse events	**Study population**		**RR 1.91** (1.54 to 2.37)	5426 (24 studies)	⊕⊕⊖⊖ **low**[1,3]	22 (15 to 37)
	51 per 1000	**98 per 1000** (79 to 121)				
	Moderate					
	47 per 1000	**90 per 1000** (72 to 111)				
Serious adverse events	**Study population**		**RR 0.9** (0.66 to 1.24)	4272 (16 studies)	⊕⊕⊕⊖ **moderate**[1]	289 (-121 to 85)
	35 per 1000	**31 per 1000** (23 to 43)				
	Moderate					
	20 per 1000	**18 per 1000** (13 to 25)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Selective reporting, authors had financial ties to industry sponsor
[2] Moderate heterogeneity
[3] Wide confidence interval

Sleep disturbance

Twenty-one studies measured sleep interference using the NRS sleep interference scale or variants of it. Pregabalin significantly reduced sleep interference scores compared with placebo: SMD -0.38, 95% CI -0.50 to -0.26, P<0.00001, I^2=32%; the quality of the evidence was moderate (SoF Table 3; Appendix Table 1; and Figure S15). Fourteen studies reported sleep interference outcome measures with the NRS scale but did not provide adequate data for statistical pooling; 12 of these reported significant reductions in sleep interference scores favouring pregabalin over placebo, while two studies reported no significant difference between groups (Appendix Table 3). Seven studies measured sleep outcomes using the Medical Outcomes Study Sleep Scale (MOS-Sleep). We could not pool results from these studies because of insufficient data. All the studies reported significant improvements in sleep scores in favour of pregabalin over placebo (Appendix Table 3).

Quality of life (QOL)

Four studies assessed QOL using EQ-5D scores or variants of it. Two of these reported significant improvements with pregabalin compared with placebo, while the other two reported no significant differences between groups (Appendix Table 3).

Patient Global Impression of Change (PGIC)

Thirteen studies reported this outcome. Ten studies reported significant improvements in PGIC scores with pregabalin compared with placebo, while three studies found no significant differences between groups (Appendix Table 3). We could not pool results from these studies because insufficient data were published.

Summary of Findings Table 3: Effect of pregabalin on sleep scores in patients with neuropathic pain

Patient or population: patients with Neuropathic pain
Settings:
Intervention: Effect of pregabalin on sleep

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Effect of pregabalin on sleep				
Sleep interference		The mean sleep interference in the intervention groups was **0.38 standard deviations lower** (0.5 to 0.26 lower)		1641 (7 studies)	⊕⊕⊕⊖ **moderate**[1]	SMD -0.38 (-0.5 to -0.26)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **SMD:** Standardized mean difference

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Selective reporting, authors had financial ties to industry sponsor

Clinician Global Impression of Change

Six studies reported this outcome; four of these reported significant improvements with pregabalin compared with placebo, while two found no significant differences between groups (Appendix Table 3).

Anxiety and depression scores

Four studies were pooled for this outcome. There was no significant difference in HADS-Anxiety scores between groups: SMD -0.12, 95% CI -0.29 to 0.04, P=0.14, I^2=44%; the quality of the evidence was moderate (SoF Table 4; Figure S16). There was also no significant difference in HADS-Depression scores between groups: SMD -0.06, 95% CI -0.26 to 0.13, P=0.54, I^2=60%; the quality of the evidence was low (SoF Table 4; Appendix Table 1 and Figure S17). One study[42] that did not provide sufficient data for statistical pooling reported significant improvement in the HADS-Anxiety scores in favour of pregabalin, but no significant difference in HADS-depression scores between groups (Appendix Table 1). One study[41] measured anxiety using the VAS anxiety scale and reported significant improvements in QOL scores with fixed- and flexible-dose pregabalin compared with placebo (P=0.03 and P=0.02 respectively.

Overall discontinuations

In total, there were 1,203 drop-outs (approximately 20%) in the 28 trials (n=5972) that reported the data (Appendix Table 1). There was no significant difference in overall discontinuation rates between groups, RR 1.09 (95% CI 0.93 to 1.28, P=0.29, I^2=51%).

Summary of Findings Table 4: Effect of pregabalin on anxiety and depression scores in patients with neuropathic pain

Patient or population: patients with Neuropathic pain
Settings:
Intervention: Effect of pregabalin on anxiety and depression

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	**Effect of pregabalin on anxiety and depression**				
HADS-Anxiety		The mean hads-anxiety in the intervention groups was **0.12 standard deviations lower** (0.29 lower to 0.04 higher)		1041 (4 studies)	⊕⊕⊕⊖ **moderate**[1]	SMD -0.12 (-0.29 to 0.04)
HADS-Depression		The mean hads-depression in the intervention groups was **0.06 standard deviations lower** (0.26 lower to 0.13 higher)		1041 (4 studies)	⊕⊕⊖⊖ **low**[1,2]	SMD -0.06 (-0.26 to 0.13)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **HADS:** Hospital anxiety and depression scale; **SMD:** Standardized mean difference

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Selective reporting, authors had financial ties to industry sponsor
[2] Moderate heterogeneity

DISCUSSION

Summary of the evidence

The evidence from published RCTs suggests that pregabalin reduces pain in patients with neuropathic pain. The effect is statistically significant in peripheral neuropathic pain, but not with central neuropathic pain. Pregabalin significantly increases the risk of adverse events including weight gain, somnolence, dizziness, dry mouth, peripheral oedema, fatigue, visual disturbances, ataxia, non-peripheral oedema, vertigo and euphoria. Pregabalin significantly reduces sleep interference scores compared with placebo. There was insufficient evidence to assess an effect on quality of life. The evidence for PGIC and CGIC scores was mixed among studies that reported these outcomes and there were no significant effects on HADS anxiety and depression scores compared with placebo. There were five deaths in the pregabalin arms and one in the placebo, but insufficient power to detect an overall effect.

Comparison with the existing literature

We have identified several published reviews assessing the effectiveness of pregabalin the management of neuropathic pain, and our results are partly consistent with these. Zhang et al[46] and Wang et al[47] showed that pregabalin was more efficacious than placebo for treatment of DPN-associated pain and PHN-associated pain respectively; however, the two reviews did not base their results on changes from baseline between groups. Semel et al[48] and Freeman et al[49] also concluded that pregabalin was more effective than placebo for neuropathic pain; however, both reviews did not account for the quality of the included primary studies. Finnerup et al[50] concluded that there was modest evidence supporting the use of pregabalin for treatment of neuropathic pain; although the authors used GRADE criteria to assess the strength of recommendation, they did not report the quality of the evidence. In an overview of Cochrane reviews, Wiffen et al[51] concluded that there was clinical trial evidence

supporting the use of pregabalin for treatment of some aspects of neuropathic pan; however, the authors did not rate the quality of the evidence for the outcomes reported.

Two reviews[52,53] that examined the safety profile of pregabalin concluded that pregabalin use was significantly more associated with adverse events than placebo; however, both reviews did not rate the quality of the evidence for the outcomes reported.

Comparison with existing guidelines

We identified several guidelines that recommend the use of pregabalin for treatment of neuropathic pain, and some of their specifications are consistent with our results. For instance, the European Federation of Neurological Societies (EFNS) guideline[54] based on data from comparative studies recommended pregabalin as first line treatment for neuropathic pain; however, the guidance assessed only the level, but not the quality, of the evidence; and also notes that there are too few large scale comparative studies to make definite conclusions about the benefits and harms. Similarly, the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitationn guidance[55] recommends pregabalin as first line treatment based on levels (and not quality) of the evidence; however, they guidance recommends that clinical trials of longer duration should be conducted. The Canadian Pain Society (CPS) guidance[56] recommends pregabalin as first-line treatment for neuropathic pain, but acknowledges that paucity of longer-duration trials limit the conclusions that can be drawn about its benefits and harms on the long-term.

Strengths and limitations

This rapid review has limitations due to its streamlined methods and search strategy. Firstly, the rapid review methodology employed could have introduced selective outcome reporting bias; nevertheless, most of the outcomes reported in this review have been listed as outcomes of interest to be considered when designing trials of neuropathic pain interventions.[57] There is a risk that our review may be prone to sampling bias, and that we may have missed potentially eligible studies, which could have been identified by searching clinical trials registries and grey literature. However, we comprehensively searched the literature, and used standard criteria to assess the risk of bias and rate the quality of the evidence. It has also been reported that generally the conclusions of rapid reviews and full reviews do not greatly differ[58]; and enhanced rapid reviews where data is independently checked by a second reviewer could help policy makers with quicker access to the evidence base.[59] This review therefore provides the most up to date comprehensive summary of the available literature, as it accounts for study quality and reports clinically meaningful patient outcomes. We did not assess the extent to which different doses of pregabalin influenced the outcomes assessed; in addition, the benefits and harms of pregabalin were not analyzed according to specific neuropathic pain conditions; only two subgroups (central and peripheral neuropathic pain) were assessed.

Implications for research

The quality of the included studies examining efficacy of pregabalin for pain was rated as low or very low according to the GRADE framework. This highlights the need for larger, robust, high-quality clinical trials to be conducted, with particular attention paid to minimizing selective reporting of outcomes. Concerns about selective reporting could be mitigated if drug manufacturers enabled access to clinical study reports (CSRs), especially as

industry-sponsored trials are likely to skew reports in favour of benefits over harms.[60,61] This would allow for a more comprehensive assessment of the benefits and harms of pregabalin. Of note, all the included trials were industry-sponsored, and an overwhelming majority of the authors of the include studies had financial ties to the pharmaceutical industry. Of note, the results of the only published charity-funded phase IV placebo-controlled trial that assessed the effectiveness of pregabalin in management of neuropathic (radicular) pain contrast our meta-analysis results – there was no significant difference in pain scores between groups.[62] Independent and publicly funded trials assessing the benefits and harms of pregabalin should be conducted. Only a few studies assessed the effect of pregabalin in improving quality of life, anxiety and depression and CGIC. Future trials should further assess the role of pregabalin for these outcomes. Studies investigating the type of neuropathic pain pregabalin relieves (e.g. stimulus-dependent pain such as hyperalgesia or allodynia), or spontaneous pain could be an area of consideration for future research.

That the median duration of intervention was nine weeks suggests that the intermediate to longer term benefits of pregabalin for neuropathic pain are unproven. Indeed in real life clinical care, it has been reported that the initial benefits seen with use of the drug in patients with neuropathic pain were no longer apparent after 6 to 12 months of therapy.[63] Therefore, RCTs that are adequately powered, and with longer durations of interventions are desirable. The finding of 5 deaths among 891 participants on pregabalin, vs 1 death among 320 participants on placebo, is somewhat concerning. Given the low frequency of this outcome (coupled with the short trial durations), RCTs are unlikely to be informative; we suggest pharmacoepidemiological studies in routinely collected electronic health records and spontaneous reporting databases to assess the impact of pregabalin on mortality.

Implications for clinical practice

Very low-to-moderate quality evidence suggests that pregabalin improves some symptoms of neuropathic pain. However, it significantly increases the risk of adverse events including somnolence, oedema, visual disturbances, ataxia, vertigo and euphoria. Pregabalin also increases the risk of drug discontinuation because of adverse events. Clinicians should be cautious about prescribing pregabalin, and should consider whether its benefits outweigh potential harms in individual patients.

Conclusions

The evidence from RCTs in journal publications suggests that pregabalin has beneficial effects on some symptoms of neuropathic pain. However, its use significantly increases the risk of adverse events and discontinuation due to adverse events. The quality of the evidence from journal publications is overall low, and the duration of trials is short. Greater transparency in the reporting of outcomes is advocated; independent and publicly funded trials assessing the effects of pregabalin in neuropathic pain should be encouraged. Allowing researchers access to full CSRs of pregabalin trials should be a priority for drug companies and regulators.

Acknowledgement

IJO, BG and CJH are part of the Evidence Synthesis Working Group. The Evidence Synthesis Working Group is funded by the National Institute for Health Research School for Primary Care Research (NIHR SPCR) [ProjectNumber 390]. JL is supported by an NIHR In Practice Fellowship. The views expressed are those of the author(s) and not necessarily those of the NIHR, the NHS or the Department of Health.

Funding

None

Data sharing statement

No additional data available

Authors' Contribution

IJO was involved with devising the review methods, conducting electronic searches, screening of abstracts, data extraction, data analysis and interpretation, and co-drafting of the review. ETT was involved with devising the review methods, screening of abstracts, data extraction, data analysis and interpretation, and co-drafting of the review. JL was involved with data extraction, data analysis and interpretation, and co-drafting of the review. BG was involved with devising the review methods, data analysis and interpretation, and co-drafting of the review. CJH was involved with devising the review methods, data analysis and interpretation, and co-drafting of the review.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). CJH has received expenses and fees for his media work. He has received expenses from the WHO, FDA, and holds grant funding from the NIHR, the NIHR School of Primary Care Research, The Wellcome Trust and the WHO. He has received financial remuneration from an asbestos case. He has also received income from the publication of a series of toolkit books published by Blackwells. On occasion, he receives expenses for teaching EBM and is also paid for his GP work in NHS out of hours. CEBM jointly runs the EvidenceLive

Conference with the BMJ and the Overdiagnosis Conference with some international partners which are based on a non-profit making model. BG receives funding from the Laura and John Arnold Foundation and reports personal fees from intermittent additional personal income from speaking and writing for lay audiences on problems in science and medicine including regulatory shortcomings. IJO, ETT and JL have no interests to disclose.

Transparency declaration

The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Figure legends

Figure 1: Flow chart showing the process for inclusion of RCTs assessing the effects of pregabalin in the management of neuropathic pain

Figure 2: Graphical representation of the risk of bias in RCTs assessing the effects of pregabalin in the management of neuropathic pain

Figure 3: Risk of bias summary for RCTs assessing the effects of pregabalin in the management of neuropathic pain

Figure 4: Effect of pregabalin on pain scores in patients with neuropathic pain

Figure 5: Effect of pregabalin on the risk of adverse events in patients with neuropathic pain

Figure 1: Flow chart showing the process for inclusion of RCTs assessing the effects of pregabalin in the management of neuropathic pain

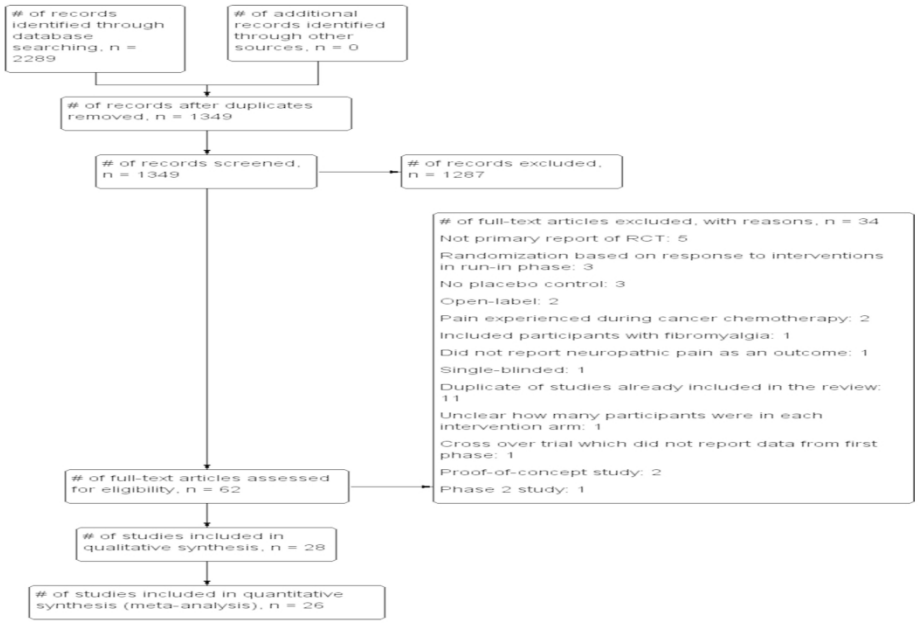

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Figure 2: Graphical representation of the risk of bias in RCTs assessing the effects of pregabalin in the management of neuropathic pain

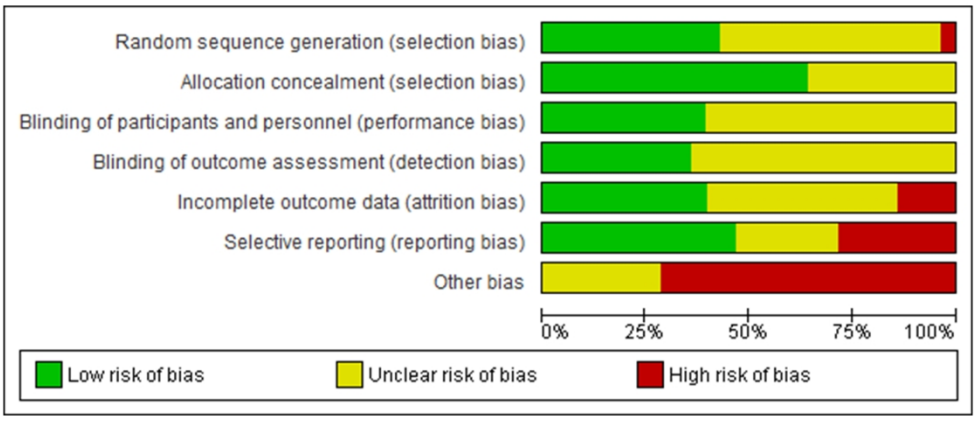

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Figure 3: Risk of bias summary for RCTs assessing the effects of pregabalin in the management of neuropathic pain

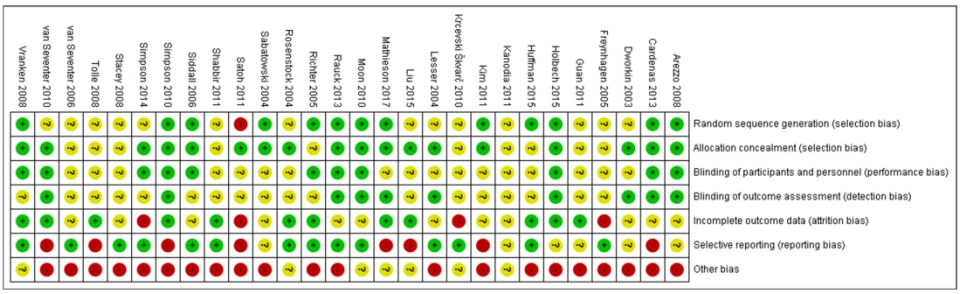

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Figure 4: Effect of pregabalin on pain scores in patients with neuropathic pain

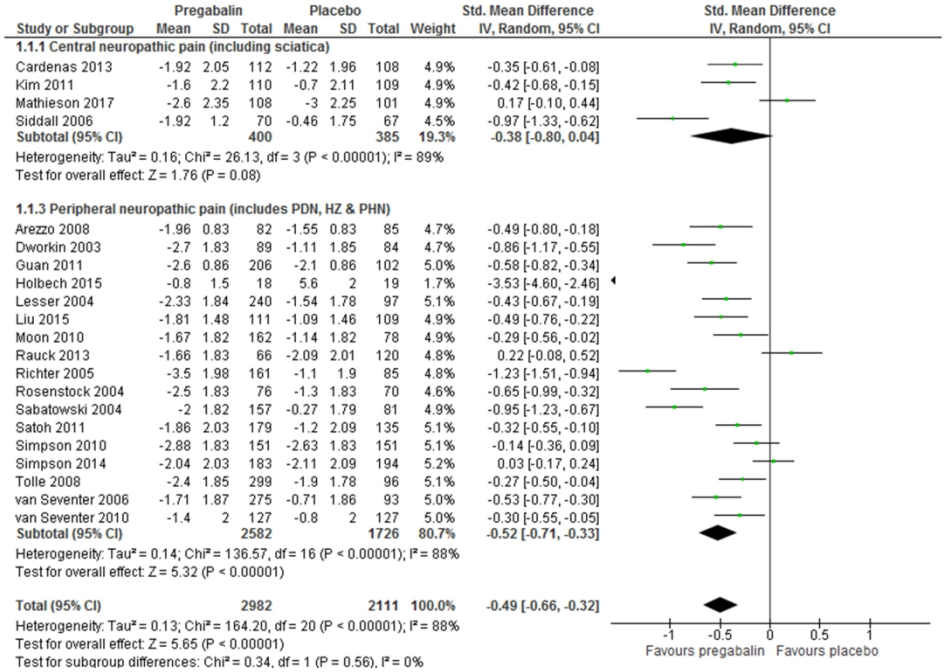

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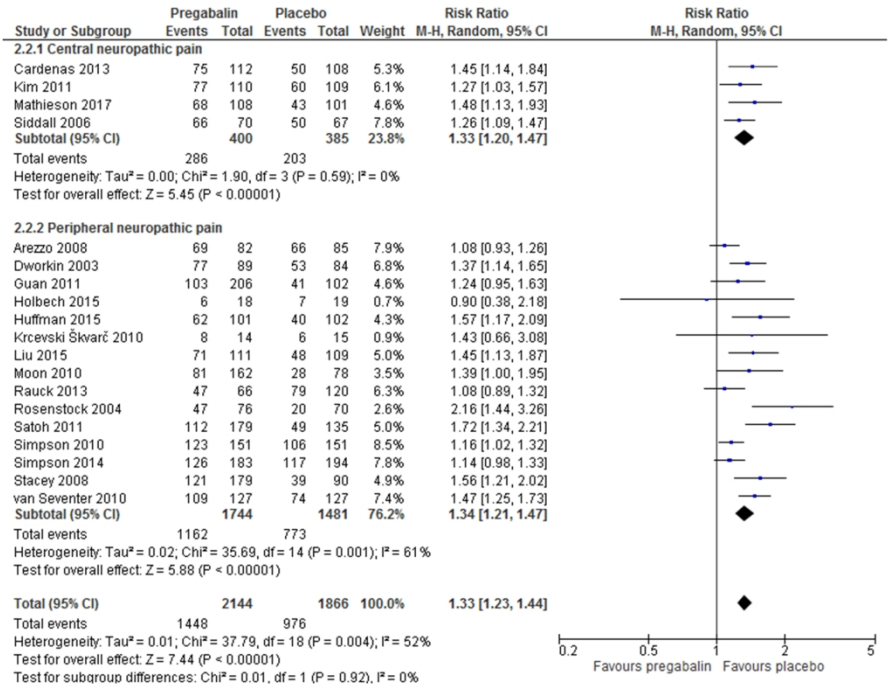
Figure 5: Effect of pregabalin on the risk of adverse events in patients with neuropathic pain



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Appendix 1: Search strategy for identifying RCTs assessing the effects of pregabalin for management of neuropathic pain

MEDLINE

1. pain.mp. or Pain/

2. pain*.mp.

3. analgesia/

4. analges*.mp.

5. neuralgia/

6. 1 or 2 or 3 or 4 or 5

7. pregabalin/

8. clinical trials.mp. or Clinical Trial/

9. randomized clinical trial.mp.

10. controlled clinical trial.mp. or Controlled Clinical Trial/

11. double-blind trial.mp.

12. placebo.ab.

13. ((doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).ti,ab.

14. 8 or 9 or 10 or 11 or 12 or 13

15. 6 and 7 and 14

16. (animals not (animals and humans)).sh.

17. 15 not 16

EMBASE

1. pain/ or neuropathic pain/

2. analgesi*.mp.

3. 1 or 2

4. pregabalin.mp. or pregabalin/

5. controlled clinical trial/ or randomized clinical trial.mp.

6. double blind procedure/

7. placebo*.ab.

8. random*.ab.

9. ((doubl* or trebl* or tripl*) adj25 (blind* or mask*)).ab.

10. 5 or 6 or 7 or 8 or 9

11. 3 and 4 and 10

COCHRANE

#1	pain
#2	analgesia
#3	neuropathic pain
#4	neuralgia
#5	#1 or #2 or #3 or #4
#6	pregabalin
#7	lyrica
#8	#6 or #7
#9	randomized controlled trial.pt
#10	controlled controlled trial.pt
#11	randomized.ti,ab
#12	groups.ti,ab
#13	placebo.ti,ab
#14	#9 or #10 or #11 or #12 or #13
#15	#5 and #8 and #14

Appendix 2: Systematic review protocol

Benefits and harms of pregabalin in the management of neuropathic pain: a rapid systematic review and meta-analysis of randomized clinical trials

Igho J Onakpoya

University of Oxford, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, Oxford, United Kingdom

Elizabeth T Thomas

Faculty of Health Sciences and Medicine, Bond University, Australia

Joseph Lee

University of Oxford, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, Oxford, United Kingdom

Ben Goldacre

University of Oxford, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, Oxford, United Kingdom

Carl J Heneghan

University of Oxford, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, Oxford, United Kingdom

Corresponding author: Igho Onakpoya, University of Oxford, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Oxford United Kingdom OX2 6GG. Email: igho.onakpoya@phc.ox.ac.uk.

BACKGROUND

Pregabalin is a gabapentinoid licensed for treatment of neurologic disorders. It is one of the earlier drugs approved by the FDA (2004) for the treatment of painful diabetic neuropathy (PDN) and post-herpetic neuralgia (PHN) [1]. Pregabalin is thought to exert its analgesic action through antagonistic activity at the voltage gated Ca2+ channels where it binds to the alpha-2-delta subunit [1,2].

Prescriptions of pregabalin (and gabapentin) have markedly increased over the last few years. In the US, prescriptions for pregabalin rose from 39 million in 2012 to 64 million in 2016 *versus* (spend increased from approximately $2 billion to $4.4 billion over the same period [3]. In the UK, pregabalin use increased 350% over a five year period between 2008 and 2013 [4]. In England alone, there were over 6.2 million prescriptions of pregabalin across GP practices in 2017 costing about $440 million [5].

There is, however, some evidence of increased mortality attributed pregabalin in the UK [6], and this has led some authors to caution clinicians about the risk of harms when prescribing [7]. The risks are thought to be particularly acute for patients who use heroin and those who misuse gabapentinoids. Indeed, the UK government is soon to classify the drug as a class C controlled substance because of its abuse potential and increased reports of deaths attributed to its use [8]. Practicing clinicians have also recently called for the evidence for the effectiveness of pregabalin to be re-examined in the light of its potential to cause harms [3,4].

OBJECTIVES

To rapidly evaluate the evidence for benefits and harms of pregabalin in the treatment of neuropathic pain in adults, using evidence from published randomized clinical trials (RCTs).

METHODS

Search strategy

We will conduct electronic searches in the following databases:

- Medline;
- Embase; and
- The Cochrane Central Register of Clinical Trials

Each database will be searched from inception till January 2018. No language restrictions will be imposed. We will also hand search the bibliography of eligible studies. Two review authors will independently assess the eligibility of studies for inclusion. Any disagreements will be resolved through discussion.

Types of studies

We will include phase III double-blinded placebo-controlled RCTs assessing the effects of pregabalin on neuropathic pain aged 18 years and above. We will include studies on neuropathic pain based on the definition of the International Association for the Study of Pain (IASP) definition [9]. These include trials on diabetic neuropathy, HIV-related neuropathy, lumbar radiculopathy, post-herpetic neuralgia, and chronic postsurgical pain. We will include RCTs irrespective of study size and duration. If we include RCTs with a cross-over design, we will use data from only the first phase of the study. We will exclude phase IV trials because they are typically unblinded. We will also exclude studies that combine pregabalin with other types of intervention; however, co-interventions will be allowed. Trials that randomized participants based on response to pregabalin therapy in the run-in phase will also be excluded.

Outcomes

Primary outcomes

- Pain (as measured using validated scales)

- Adverse events

Secondary outcomes

- Sleep disturbance;
- Quality of life (QOL);
- Patient global impression of change (PGIC);
- Clinician global impression (CGI);
- Overall discontinuations; and
- Discontinuations because of adverse events.

Risk of bias assessment

We will assess the risk of bias for each included study using Cochrane criteria [10] which examines the following domains:

- Method of randomisation;
- Concealment of allocation;
- Blinding of participants and personnel;
- Blinding of outcome assessment;
- Incomplete outcome data;
- Selective reporting;
- Other bias (e.g. industry funding, conflicts of interest, etc).

Two review authors will independently assess the risk of bias. Any disagreements will be resolved through discussion.

Data extraction:

We will use a customized excel spreadsheet to extract relevant data from included studies. Data to be extracted will include:

- Study ID (first author, publication year, journal, country)

- Participants (numbers, medical condition, demographics, etc.)
- Intervention (type of intervention and duration)
- Results (primary and secondary outcome measures, effect size, adverse events)
- Sources of funding

Five review authors will independently extracted the data. Any disagreements will be resolved through discussion.

Data analyses:

We will compute standardized mean differences (SMDs) and 95% confidence intervals (CIs) for continuous outcomes and risk ratios with 95% CI for binary outcomes. We will use the random effects model (Mantel-Haenszel) of the standard meta-analysis software (RevMan 5.3) [11] for meta-analysis. For continuous outcomes, pre- to post-intervention changes will be used to compute the data. When two or more pregabalin arms are present, the arms will be combined to create single pair-wise comparisons [12]. If we are unable to statistically combine the data, the results will be presented in a narrative format. If $\geq$ 10 studies are available for statistical pooling, we will use a funnel plot to test for publication bias. Two review authors will independently enter the data onto RevMan, and will also independently cross-check each other's entry.

Subgroup analysis and investigation of heterogeneity

We will assess heterogeneity using the I-squared statistic: values of 25%, 50% and 75% will represent mild, moderate and substantial heterogeneity respectively. We will conduct subgroup analyses based on the predominant pathway for neuropathic pain - central or peripheral neuropathic pain. We will conduct sensitivity based on study quality (studies that adequately report randomization and blinding procedures) and intervention duration (shorter or longer duration of therapy). We will visually inspect funnel plots to determine publication bias.

Rating the quality of the evidence

We will use the GRADEpro software (version 3.6) [13] to rate the overall quality of the body of evidence for each outcome based on the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) [14] criteria which examines the following domains:

- Study design;
- Risk of bias;
- Inconsistency;
- Indirectness; and
- Imprecision.

The overall quality of the body of the evidence will rated from high to very low as follows:

- High - Further research is very unlikely to change our confidence in the estimate of effect
- Moderate - Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
- Low - Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- Very low - We are very uncertain about the estimate

We will use Summary of findings (SOF) tables to present these results.

Patient public involvement

Because this is a rapid review, we will not enlist the services of patient representatives.

Sources of funding

None

Conflicts of interest

None

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Appendix 3: List of excluded studies and reasons for exclusion

Study ID	Reference	Reason for exclusion
Al-Hihi 2017	Al-Hihi E, Badgett RG. In moderate-to-severe sciatica, pregabalin did not reduce leg pain intensity or improve quality of life. Annals of internal medicine. 2017; (2):[Jc4 p.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/558/CN-01394558/frame.html.	Not primary report of RCT
Anon 2010	Anonymous. Pregabalin effective in relieving post-traumatic peripheral neuropathic pain. Australian Journal of Pharmacy. 2010;91 (1086):82.	Not primary report of RCT
Baron 2008	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. European Journal of Pain. 2008;12(7):850-8.	Open label; also no placebo control
Baron 2010	Baron R, Freynhagen R, Tolle TR, Cloutier C, Leon T, Murphy TK, et al. The efficacy and safety of pregabalin in the treatment of neuropathic pain associated with chronic lumbosacral radiculopathy. Pain. 2010;150 (3):420-7.	Randomization based on response to interventions in run-in phase
Boyle 2012	Boyle J, Eriksson MEV, Gribble L, Gouni R, Johnsen S, Coppini DV, et al. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: Impact on pain, polysomnographic sleep, daytime functioning, and quality of life. Diabetes care. 2012;35 (12):2451-8.	No placebo control; only placebo run in

Calkins 2014	Calkins A, Shurman J, Jaros M, Kim R, Shang G. Peripheral edema and weight gain in adult patients with painful diabetic peripheral neuropathy (DPN) receiving gabapentin enacarbil (GEN) or pregabalin enrolled in a randomized phase 2 trial. Neurology Conference: 66th American Academy of Neurology Annual Meeting, AAN. 2014;82(10 SUPPL. 1).	Did not report neuropathic pain as an outcome
Cardenas 2012	Cardenas D, Nieshoff E, Suda K, Goto S, Kaneko T, Parsons B, et al. A 17-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center trial of pregabalin for the treatment of chronic central neuropathic pain after spinal cord injury. Journal of pain. 2012;Conference: 31st Annual Scientific Meeting of the American Pain Society. Honolulu, HI United States. Conference Publication: (var.pagings). 13 (4 SUPPL. 1):S62.	Duplicate of study already included in the review: Duplicate of Cardenas 2013
Cardenas 2013	Cardenas DD, Nieshoff E, Parsons B, Sanin L, Kaneko T, Suzuki M, et al. Assessment of neuropathic pain during a 17-week, double-blind, placebo-controlled, trial of pregabalin in patients with spinal cord injury. Regional Anesthesia and Pain Medicine Conference: 11th Annual ASRA Pain Medicine Meeting Miami, FL United States Conference Publication:. 2013;38(1).	Duplicate of study already included in the review: Duplicate of Cardenas 2013
De Andrade 2015	De Andrade DC, Teixeira MJ, Galhardoni R, Ferreira KASL, Malieno PB, Scisci N, et al. A phase III, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of pregabalin in the prevention and reduction of oxaliplatin-induced painful neuropathy (PreOx). Journal of Clinical Oncology Conference. 2015;33(15 SUPPL. 1).	Pain experienced during cancer chemotherapy

Duarte 2014	Duarte MAG, Cardenas-Soto K, Lem M, Castillo C, Gibbons C, Freeman R. Efficacy of pregabalin in the treatment of prediabetic neuropathic pain. Neurology Conference: 66th American Academy of Neurology Annual Meeting, AAN. 2014;82(10 SUPPL. 1).	No placebo control; evaluation in open-label run-in
Eerdekens 2016	Eerdekens M, Koch ED, Kok M, Sohns M, Forst T. Cebranopadol, a novel first-inclass analgesic: Efficacy, safety, tolerability in patients with pain due to diabetic peripheral neuropathy (U). Pain practice. 2016;Conference: 8th World Congress of the World Institute of Pain, WIP 2016. New York City, NY United States. Conference Publication: (var.pagings). 16 (SUPPL. 1):100.	Unclear how many participants were in each intervention arm
Freynhagen 2006	Freynhagen R, Busche P, Konrad C, Balkenohl M. [Effectiveness and time to onset of pregabalin in patients with neuropathic pain]. Der Schmerz. 2006;20(4):285-8.	Non-English study: Duplicate of Freynhagen 2005
Gabrani 2016	Gabrani A, Dobi D, Tomori S, Berberi F, Como A, Kapisyzi MR. Efectiveness of pregabalin compared with amytriptilin in acute Herpetic Neuralgia. Neurology Conference: 68th American Academy of Neurology Annual Meeting, AAN. 2016;86(16 SUPPL. 1).	Not a placebo-controlled study
Gilron 2011	Gilron I, Wajsbrot D, Therrien F, Lemay J. Pregabalin for peripheral neuropathic pain: a multicenter, enriched enrollment randomized withdrawal placebo-controlled trial. Clinical journal of pain. 2011;27(3):185-93.	Single-blinded Randomization to placebo/PGB occurred after a run in period of pre-gabalin?
Gonzalez-Duarte 2016	Gonzalez-Duarte A, Lem M, Diaz-Diaz E, Castillo C, Cardenas-Soto K. The Efficacy of Pregabalin in the Treatment of Prediabetic Neuropathic Pain. Clinical journal of pain. 2016;32(11):927-32.	Randomization based on response to interventions in run-in phase

Jenkins 2010	Jenkins T, Smart T, Hackman F, Cooke C, Tan K, Cheung R. Pregabalin in post-traumatic peripheral neuropathic pain: Efficient assessment of efficacy in a randomised, double-blind, placebo-controlled crossover study. European Journal of Pain Supplements. 2010;Conference: 3rd International Congress on Neuropathic Pain. Athens Greece. Conference Publication: (var.pagings). 4 (1):89.	Duplicate of study already excluded from the review: Jenkins 2012
Jenkins 2012	Jenkins TM, Smart TS, Hackman F, Cooke C, Tan KKC. Efficient assessment of efficacy in post-traumatic peripheral neuropathic pain patients: Pregabalin in a randomized, placebo-controlled, crossover study. Journal of pain research. 2012;5:243-50.	Phase I: proof of concept
Jensen-Dahm 2011	Jensen-Dahm C, Rowbotham MC, Reda H, Petersen KL. Effect of a single dose of pregabalin on herpes zoster pain. Trials [Electronic Resource]. 2011;12(55):28.	Phase 2
Kruszewski 2007	Kruszewski SP, Shane JA. Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. Neurology. 2007;68(24):2158-9.	Not primary report of RCT
Mishra 2012	Mishra S, Bhatnagar S, Goyal GN, Rana SPS, Upadhya SP. A comparative efficacy of amitriptyline, gabapentin, and pregabalin in neuropathic cancer pain: a prospective randomized double-blind placebo-controlled study. American Journal of Hospice & Palliative Medicine. 2012;29(3):177-82.	Pain experienced during cancer chemotherapy

Morrison 2015	Morrison S, Parson H, Vinik AI. Pregabalin positively affects subjective pain, falls risk, and gait in persons with diabetic peripheral neuropathy. Diabetes. 2015;Conference: 75th Scientific Sessions of the American Diabetes Association. Boston, MA United States. Conference Publication: (var.pagings). 64 (SUPPL. 1):A164.	Cross-over trial that did not report data from first phase
Parsons 2013	Parsons B, Emir B. Examining the time-to-improvement of pain in patients with chronic neuropathic pain due to spinal cord injury. Journal of pain. 2013;Conference: 32nd Annual Scientific Meeting of the American Pain Society. New Orleans, LA United States. Conference Publication: (var.pagings). 14 (4 SUPPL. 1):S60.	Not primary report of RCT: report of 2 separate primary studies included in review
Parsons 2015	Parsons B, Emir B, Knapp L. Examining the Time to Improvement of Sleep Interference With Pregabalin in Patients With Painful Diabetic Peripheral Neuropathy and Postherpetic Neuralgia. American journal of therapeutics. 2015;22(4):257-68.	Not primary report of RCT
Parsons 2012	Parsons B, Nieshoff E, Cardenas D, Sanin L, Kaneko T, Suzuki M, et al. Weekly assessments of pain and sleep during a 17-week, double-blind, placebo-controlled trial of pregabalin for the treatment of chronic neuropathic pain after spinal cord injury. Neurology. 2012;Conference: 64th American Academy of Neurology Annual Meeting. New Orleans, LA United States. Conference Publication: (var.pagings). 79 (11):e88.	Duplicate of study already included in the review: Duplicate of Cardenas 2013

Parsons 2015 (Ann Neur)	Parsons B, Shang N, Yan P, Fan D. Efficacy and safety of pregabalin for postherpetic neuralgia in Chinese patients. Annals of Neurology. 2015;Conference: 140th Annual Meeting of the American Neurological Association, ANA 2015. Chicago, IL United States. Conference Publication: (var.pagings). 78 (SUPPL. 19):S92.	Duplicate of study already included in the review: Duplicate of Liu 2015
Puiu 2015	Puiu T, Kairys A, Pauer L, Schmidt-Wilcke T, Ichesco E, Hampson J, et al. Alterations in brain gray matter volume are associated with reduced evoked-pain connectivity following acute pregabalin administration. Neurology Conference: 67th American Academy of Neurology Annual Meeting, AAN. 2015;84(SUPPL. 14).	Included participants with fibromyalgia
Raskin 2014	Raskin P, Huffman C, Toth C, Asmus MJ, Messig M, Sanchez RJ, et al. Pregabalin in patients with inadequately treated painful diabetic peripheral neuropathy: a randomized withdrawal trial. Clinical journal of pain. 2014;30(5):379-90.	Randomization based on response to interventions in run-in phase
Satoh 2011	Satoh J, Yagihashi S, Baba M, Suzuki M, Arakawa A, Yoshiyama T. Efficacy and safety evaluation of pregabalin treatment over 52weeks in patients with diabetic neuropathic pain extended after a double-blind placebo-controlled trial. Journal of diabetes investigation. 2011;2 (6):457-63.	Open label; also no placebo control

van Seventer 2009	Van Seventer R, Murphy K, Temple J, McKenzie I, Serpell M, Toth C, et al. Pregabalin is effective in the treatment of posttraumatic peripheral neuropathic pain. Journal of pain. 2009;Conference: 28th Annual Scientific Meeting of the American Pain Society, APS. San Diego, CA United States. Conference Publication: (var.pagings). 10 (4 SUPPL. 1):S35.	Duplicate of study already included in the review: Van Seventer 2010
Vinik 2014- 1	Vinik A, Rosenstock J, Sharma U, Feins K, Hsu C, Merante D. Efficacy and safety of mirogabalin (DS-5565) for the treatment of diabetic peripheral neuropathic pain: A randomized, double-blind, placebo- and active comparator-controlled, adaptive proof-of-concept phase 2 study. Diabetes care. 2014;37 (12):3253-61.	Proof of concept study
Vinik 2014-2	Vinik A, Sharma U, Feins K, Hsu C, Merante D. Central nervous system safety and tolerability of DS-5565: A randomized, double-blind, placebo-and active comparator-controlled phase II study in diabetic peripheral neuropathic pain. Neurology Conference: 66th American Academy of Neurology Annual Meeting, AAN. 2014;82(10 SUPPL. 1).	Duplicate of study already excluded from the review (Vinik 2014-1)
Vinik 2014-3	Vinik A, Sharma U, Feins K, Hsu C, Merante D. DS-5565 for the treatment of diabetic peripheral neuropathic pain: Randomized, double-blind, placebo-and active comparator-controlled phase ii study. Neurology Conference: 66th American Academy of Neurology Annual Meeting, AAN. 2014;82(10 SUPPL. 1).	Duplicate of study already excluded from the review (Vinik 2014-1)

Vinik 2014-4	Vinik AI, Sharma U, Feins K, Hsu C, Merante D. Safety/tolerability profile of DS-5565: A new potent, specific alpha2-delta ligand for the treatment of diabetic peripheral neuro pathic pain. Diabetes. 2014;Conference: 74th Scientific Sessions of the American Diabetes Association. San Francisco, CA United States. Conference Publication: (var.pagings). 63 (SUPPL. 1):A298.	Duplicate of study already excluded from the review (Vinik 2014-1)
Vinik 2014-5	Vinik AI, Sharma U, Feins K, Hsu C, Merante D. A randomized, double-blind, placebo- and active comparator (pregabalin)-controlled phase II study of DS-5565 for the treatment of diabetic peripheral neuropathic pain. Diabetes. 2014;Conference: 74th Scientific Sessions of the American Diabetes Association. San Francisco, CA United States. Conference Publication: (var.pagings). 63 (SUPPL. 1):A294.	Duplicate of study already excluded from the review (Vinik 2014-1)

Appendix 4: Risk of bias judgements for included studies

Arezzo 2008

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random code
Allocation concealment (selection bias)	Low risk	Number-coded study medications to the study sites were assigned using an interactive voice-response system
Blinding of participants and personnel (performance bias)	Low risk	Blinding was maintained by dispensing pregabalin and placebo in identical capsules
Blinding of outcome assessment (detection bias)	Low risk	The sponsor, members of the study site, and the patients were unaware of the treatment assignment
Incomplete outcome data (attrition bias)	Unclear risk	Reasons for attrition reported; however, drop-out rates were 34.1% for pregabalin and 28.1% for placebo
Selective reporting (reporting bias)	Unclear risk	Outcomes reported as specified in methods. BOCF results also reported for pain scores. However, MD and SD for baseline and end-points were not reported separately, and some outcomes were reported at other time points other than at 13 weeks.
Other bias	High risk	All investigators had financial ties to the sponsor

Cardenas 2013

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Low risk	Interactive response technology system (via phone or internet) provided a unique identification number for each patient
Blinding of participants and personnel (performance bias)	Low risk	Both placebo and pregabalin were in the form of gray capsules
Blinding of outcome assessment (detection bias)	Low risk	Treatment allocation was concealed from patient and investigator
Incomplete outcome data (attrition bias)	Unclear risk	Acceptable dropout 15.7% placebo, 17% PGB. Reasons for dropout explained. ITT analysis (and modified ITT analysis) performed
Selective reporting (reporting bias)	High risk	Following pre-specified outcomes from protocol not reported in study: Modified Brief Pain Inventory Interference Scale; Quantitative Assessment of Neuropathic Pain (QANeP) 6 outcomes; NPSI (9 outcomes)
Other bias	High risk	All the investigators had financial ties to the study sponsor

Dworkin 2003

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequential randomization schedule generated with block size of four. Unclear how this schedule was generated
Allocation concealment (selection bias)	Low risk	Study medication was packaged and labeled with sequential randomization numbers
Blinding of participants and personnel (performance bias)	Unclear risk	Placebo capsules were identical in appearance to pregabalin; however also states that blinding could have been broken in emergency situations
Blinding of outcome assessment (detection bias)	Low risk	Blind maintained until after the study was completed and all decisions regarding data evaluability had been made
Incomplete outcome data (attrition bias)	Unclear risk	Uneven numbers of drop outs- PGB 35%, placebo 12%. Reasons provided- mostly due to adverse events
Selective reporting (reporting bias)	Unclear risk	29 patients had possibly important variations from the protocol and details of this are specified. Secondary outcome of CGIC- mentioned in results that clinicians assessments of global change closely parallelled patients' assessments however no figures given
Other bias	High risk	All the investigators had financial ties to the study sponsor

Freynhagen 2005

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Unclear risk	All patients received active medication or matching placebo capsules. Double blinded. However, unclear whether they were identical in appearance and taste
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	High risk	High rates of dropout: PGB flexible dose 35%, PGB fixed dose 38%, 46%. Reasons provided (mostly due to adverse events for PGB, lack of efficacy for Placebo).
Selective reporting (reporting bias)	Low risk	Outcomes specified in methods match those found in results.
Other bias	High risk	All study investigators had financial ties to the study sponsor

Guan 2011

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Unclear risk	Double blinded- however insufficient information to determine whether blind could have been broken
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Low risk	Low numbers of dropout due to adverse events (3% PGB, 5% Placebo), however no information on total numbers of dropout (or other reasons for dropout)
Selective reporting (reporting bias)	Unclear risk	The weekly mean pain DPRS score was listed as a secondary efficacy outcome in protocol, but included in the primary outcomes in publication. Also, final report introduced DAAC (Duration-adjusted average change score) as a primary outcome
Other bias	High risk	All study investigators had financial ties to the study sponsor

Holbech 2015

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Low risk	Randomization plan was generated by a person at a pharmacy not otherwise involved in the trial; Sealed, opaque envelopes used in emergency situations.
Blinding of participants and personnel (performance bias)	Low risk	Double-blinded (patients, investigators and all other staff). Identical tablets.
Blinding of outcome assessment (detection bias)	Low risk	Patients, investigators, and all other staff involved in the conduct of the trial were blinded to individual treatment assignments for the duration of the study.
Incomplete outcome data (attrition bias)	Low risk	Acceptable numbers of drop out (5% placebo, 17% pregabalin). Reasons provided (withdrawn consent, adverse events)
Selective reporting (reporting bias)	Unclear risk	All but 2 of the secondary outcomes in the protocol have been omitted and re-analysed as "expoloratory" outcomes in the final analysis.
Other bias	High risk	Majority of trial investigators had financial ties to the study sponsor

Huffman 2015

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated codes
Allocation concealment (selection bias)	Unclear risk	Not decribed
Blinding of participants and personnel (performance bias)	Unclear risk	Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	Drop-out rates notsignificantly different between groups. Reasons for drop-outs specified
Selective reporting (reporting bias)	Low risk	Outcomes reported as specified in protocol
Other bias	High risk	All authors have, or have had financial ties to pharmaceutical industry

Kanodia 2011

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Unclear risk	States that it is a double blind trial, but there are no details of how this was performed (or who was blinded).
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Unclear risk	No details given about whether there was attrition or explanation.
Selective reporting (reporting bias)	Unclear risk	Pre-specified outcomes in methods match those found in results. Poor reporting of outcomes from each intervention group
Other bias	Unclear risk	Very small sample size

Kim 2011

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated schedule
Allocation concealment (selection bias)	Low risk	Centralised telerandomisation system (IMPALA)
Blinding of participants and personnel (performance bias)	Unclear risk	Matching placebo; double-blinded; unclear whether dientical in appearance
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Unclear risk	Acceptable rates of drop out (15% pregabalin, 17% placebo). Reasons for discontinuation provided. ITT analysis performed
Selective reporting (reporting bias)	High risk	Daily Sleep interference scale (DSIS) omited as a secondary outcome.
Other bias	High risk	All study authors except one had financial ties to the study sponsor

Krcevski Škvarč 2010

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	High risk	High rates of attrition (64% pregabalin, 40% placebo). Reasons for study discontinuation provided. ITT analysis performed and reported.
Selective reporting (reporting bias)	Low risk	Outcomes specified in the methods match those reported in the results
Other bias	Unclear risk	Some differences in baseline characteristics; proportion taking antiviral therapy higher in pregabalin group, differences in distribution of zoster and severirty of rash. The study authors had no competing interests

Lesser 2004

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information as to how it was generated
Allocation concealment (selection bias)	Low risk	Code was maintained by the Clinical Pharmacy Operations department, with no access by other individuals or departments. Medication was shipped to the sites in blocks in unit-dose trays. Each patient was assigned the next sequential random number
Blinding of participants and personnel (performance bias)	Unclear risk	Each patient took one small and two larger capsules, with the proper mix of active medication and placebo, for each dose to achieve double-blinding. Does not specify that the active intervention and placebo were identical
Blinding of outcome assessment (detection bias)	Low risk	Blinding was maintained until all decisions regarding data evaluability were made
Incomplete outcome data (attrition bias)	Unclear risk	Low drop out rates (8% placebo, 11% PGB). Only states that 18/35 dropouts were due to adverse events.
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes in methods match those found in results.
Other bias	High risk	Baseline characteristics: more people in placebo group taking antidiabetic medication (insulin) compared to PGB group. More T1DM and T2DM in placebo group. The study authors had financial ties to the sponsor.

Liu 2015

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Low risk	Interactive voice response system
Blinding of participants and personnel (performance bias)	Unclear risk	Placebo was matched to pregabalin. Not specified whether active and placebo pills were identical in appearance
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information.
Incomplete outcome data (attrition bias)	Low risk	Acceptable drop out rates (12% pregabalin, 16% placebo). Reasons for withdrawal provided. ITT analysis performed.
Selective reporting (reporting bias)	High risk	Omitted pre-specified secondary outcomes relating to the HADS Anxiety and Depression score.
Other bias	Unclear risk	Two authors had financial ties to the study sponsor

Mathieson 2017

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-derived random-number sequence
Allocation concealment (selection bias)	Low risk	Packaged in white, opaque, sealed containers
Blinding of participants and personnel (performance bias)	Unclear risk	Pregabalin capsules and matching placebo capsules. Unclear whether they were identical in appearance
Blinding of outcome assessment (detection bias)	Low risk	Some outcomes were assessed by means of telephone contact with the patients by trained trial researchers, but reports that all the research staff, statisticians, trial clinicians, and patients were unaware of the trial-group assignments during recruitment, data collection, and analysis.
Incomplete outcome data (attrition bias)	Low risk	Acceptable number of drop outs (16% pregabalin, 14% placebo). Reasons provided. ITT analysis performed (although it did not include 2 randomised patients).
Selective reporting (reporting bias)	High risk	The primary outcome was measured at fewer time points than was specified in the protocol which specified pain intensity would be measured at baseline then weeks 2,4,8,12,26 and 52. Study reported pain only at weeks 8, 52. All other outcomes remained the same as pre-specified.
Other bias	Unclear risk	Some differences in baseline characteristics, such as sex, dermatomal pain, neurologic deficit, clinically suspected level of spine associated with leg pain, and PainDETECT scores. Three authors had financial ties to the pharmaceutical industry

Moon 2010

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized tele-randomization system
Allocation concealment (selection bias)	Low risk	Central web–telephone software
Blinding of participants and personnel (performance bias)	Low risk	Mentions double-blinded; "pregabalin and matching placebo"
Blinding of outcome assessment (detection bias)	Low risk	Study report does not specify, although protocol states that the outcome assessors were blinded.
Incomplete outcome data (attrition bias)	Unclear risk	Uneven numbers of drop out (14.8% pregabalin, 20.5% placebo), however reasons for drop out provided. ITT analysis performed and reported.
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes in protocol reported.
Other bias	Unclear risk	The authors fail to declare whether they had financial ties to Pfizer.

Rauck 2013

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Low risk	Drug containers of identical appearance
Blinding of participants and personnel (performance bias)	Low risk	PGB was provided with identical-inappearance placebo capsules to ensure blinding of subjects and investigators. All tablets were provided by an unblinded, third-party pharmacist.
Blinding of outcome assessment (detection bias)	Low risk	Study does not provide sufficient information, although trial protocol does state that the outcome assessors were blinded.
Incomplete outcome data (attrition bias)	Unclear risk	Reasons for dropout reported although attrition rates were 29% for pregabalin and 25% for placebo.
Selective reporting (reporting bias)	Low risk	Reports all pre-specified outcomes from the protocol.
Other bias	High risk	The authors had financial ties to the sponsor

Richter 2005

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer generated sequence
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Low risk	Study capsules were identical (doses were also matched to size of tablets for both pregabalin and placebo)
Blinding of outcome assessment (detection bias)	Unclear risk	Blind was maintained until completion of study and data evaluability determination however does not specify whether outcome assessors or other investigators were blinded.
Incomplete outcome data (attrition bias)	Low risk	Acceptable attrition rates (15% placebo, 5% PGB 150mg/d, 12% PGB 600mg/d [overall 9% pregabalin]). Reasons for drop out provided.
Selective reporting (reporting bias)	Low risk	Outcomes specified in the Methods match those reported in the results.
Other bias	High risk	Two-thirds of the authors had financial ties to the study sponsor

Rosenstock 2004

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequential randomization numbers according to a randomization schedule designed to attain an even distribution between pregabalin and placebo. Unclear how this sequence was generated.
Allocation concealment (selection bias)	Low risk	Study medication was packaged and labeled with sequential randomization numbers.
Blinding of participants and personnel (performance bias)	Unclear risk	All medications were packaged in blinded fashion. Not specified whether the active intervention and placebo were identical in appearance
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Low risk	Acceptable attrition rates (14% pregabalin, 11% placebo). Reasons for withdrawal provided. ITT analysis performed.
Selective reporting (reporting bias)	Low risk	Outcomes specified in the Methods match those reported in the results.
Other bias	Unclear risk	The authors did not state whether they had any competing interests

Sabatowski 2004

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated code
Allocation concealment (selection bias)	Low risk	Study medication was packaged and labeled with sequential randomisation numbers
Blinding of participants and personnel (performance bias)	Unclear risk	All medications were blinded and taken orally. Placebo capsules were identical in appearance to capsules containing active drug. However, an investigator could break the randomisation code and, thus, the blind for a patient if a medical emergency occurred.
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Unclear risk	Reasons for dropout provided, however unequal attrition rates across the groups (12.3% PGB 150mg/d, 21.1% PGB 300mg/d, Overall PGB 16.6%, 24.7% Placebo). Both ITT and PPA reported but ITT value used in abstract.
Selective reporting (reporting bias)	Unclear risk	Results of CGIC are not reported, just states that it shows a "statistically significant improvement".
Other bias	High risk	Majority of the investigators had financial ties to the study sponsor

Satoh 2011

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Allocation based on the results of a laboratory test (CrCl)
Allocation concealment (selection bias)	Low risk	Centrally organised using a validated web-based system.
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	High risk	Unequal dropout across the groups (11.8% placebo, 14.7% 300 mg/day PGB, 28.9% in the 600 mg/day PGB). All reasons for attrition were not provided.
Selective reporting (reporting bias)	High risk	Secondary outcome added in published study: patient impression of subjective symptoms (including numbness, pain and paraesthesia) which showed favourable results for pregabalin.
Other bias	High risk	All authors had financial ties to the study sponsor

Shabbir 2011

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Low risk	Appears to be no attrition from either of the randomised groups.
Selective reporting (reporting bias)	Low risk	Outcomes specified in the methods match those reported in the results.
Other bias	High risk	Baseline characteristics table not provided to compare across the intervention arms. Pregabalin was administered twice daily; daily frequency of placebo administration not specified. The authors did not state whether they had any competing interests

Siddall 2006

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Study medication was packaged and labeled with sequential randomization numbers according to the randomization schedule
Blinding of participants and personnel (performance bias)	Low risk	Medication was blinded by using capsules of identical size, color, taste, and smell for placebo and pregabalin
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Unclear risk	High (and uneven) attrition rates: pregabalin 30%, placebo 45%. Reasons for withdrawal provided. ITT analysis results reported.
Selective reporting (reporting bias)	Low risk	Outcomes specified in the Methods match those reported in the results.
Other bias	High risk	All trial investigators had financial ties to the study sponsor

Simpson 2010

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Low risk	Central computerized telerandomization system, ensured that investigators remained blinded to treatment assignments during the study
Blinding of participants and personnel (performance bias)	Low risk	Study drug and placebo were identical in appearance in order to preserve blinding.
Blinding of outcome assessment (detection bias)	Low risk	Study does not provide sufficient information, although trial protocol does state that the outcome assessors were blinded.
Incomplete outcome data (attrition bias)	Low risk	Similar rates of attrition (21% pregabalin, 19% placebo). Reasons for drop out provided, however not all randomised patients are included in the ITT analysis.
Selective reporting (reporting bias)	High risk	Prespecified outcomes (assessing QANeP) omitted in final study. Safety outcomes not prespecified in protocol added to final study.
Other bias	High risk	All trial investigators had, or have had finantial ties to the study sponsor

Simpson 2014

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Computer generated "pseudorandom" code
Allocation concealment (selection bias)	Low risk	Automated telerandomization system.
Blinding of participants and personnel (performance bias)	Low risk	Patients were randomised in a double blind fashion through study sponsors sysetm for randomization and dispensing.
Blinding of outcome assessment (detection bias)	Unclear risk	Participants, investigators and study sponsor personnel were blinded to interventions after treatment assignment, but unclear whether this includes outcome assessors.
Incomplete outcome data (attrition bias)	High risk	Reasons provided for drop outs though there is a high attrition rate (31% pregabalin, 31% placebo).
Selective reporting (reporting bias)	Low risk	Outcomes specified in the protocol match those reported in the study.
Other bias	High risk	Study prematurely terminated by Pfizer following unfavourable results. All trial investigators had finantial ties to the study sponsor

Stacey 2008

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information; reports double-blinded but unclear who is blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Unclear risk	Rates of attrition are not comparable across the groups (5.5% flexible dose PGB, 20.5% fixed dose PGB, 16.7% Placebo). Reasons for drop out provided.
Selective reporting (reporting bias)	Low risk	Outcomes specified in the methods match those reported in the results.
Other bias	High risk	All authors had financial ties to the study sponsor

Tolle 2008

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Low risk	Similar attrition rates across the groups (Placebo 17.7%, PGB 150mg/d 17.2%, PGB 300mg/d 20.2%, PGB 300/600mg/d 22.8%). Reasons for withdrawal provided. ITT analysis performed and reported.
Selective reporting (reporting bias)	High risk	EuroQoL Health Utilities Index not reported in final results (although mentioned in the abstract and methods).
Other bias	High risk	All authors had financial ties to the study sponsor

van Seventer 2006

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information although states double-blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Unclear risk	High attrition rates across the groups (36.6% placebo, 29.9% PGB 150mg/d, 36.7% PGB 300mg/d, 36.6% PGB 300/600mg/d). Reasons for withdrawal provided. ITT analysis performed.
Selective reporting (reporting bias)	Low risk	Outcomes specified in the methods match those reported in the results.
Other bias	High risk	All study authors had financial ties to the study sponsor

van Seventer 2010

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Low risk	An Interactive Voice Recognition System was used.
Blinding of participants and personnel (performance bias)	Low risk	Medication was blinded by using capsules of identical size, color, taste and smell for placebo, and pregabalin.
Blinding of outcome assessment (detection bias)	Low risk	Trial protocol specifies that outcome assessor was blinded.
Incomplete outcome data (attrition bias)	Low risk	Reasons for discontinuation provided, attrition rates comparable across the groups- 24.4% for pregabalin, 22.8% for placebo. ITT analysis performed (although excluded one patient from each group due to lack of post-baseline data).
Selective reporting (reporting bias)	High risk	Protocol specified CGIC a secondary outcome however this was omitted in published report. Other omitted outcomes include Pain Treatment Satisfaction Scale (PTSS)- Impact of current pain medication, satisfaction with current pain medication, medication characteristics, efficacy; Neuropathic Pain Symptom Inventory total intensity score, Medical Outcome Study Cognitive Subscale (reasoning, concentration, confusion, memory, attention, thinking); Davidson Trauma scale (severity, frequency, total score).
Other bias	High risk	All study authors had financial ties to the study sponsor

Vranken 2008

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized according to the automated assignment system
Allocation concealment (selection bias)	Low risk	Hospital pharmacist prepared identical, coded medication bottles containing identical capsules of pregabalin or placebo. Unclear if pharmacist was otherwise involved in the study or third party.
Blinding of participants and personnel (performance bias)	Low risk	Coded medication bottle was supplied by hospital pharmacist to the blinded treating physician. Medication bottle contained identical capsules.
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information
Incomplete outcome data (attrition bias)	Low risk	Reasonable rates of attrition (15% pregabalin, 20% of placebo). Reasons for discontinuation provided.
Selective reporting (reporting bias)	Low risk	Outcomes specified in the methods match those reported in the results.
Other bias	Unclear risk	Some differences in baseline characteristics including site of pain and concomitant therapies. The authors did not report whether they had any competing interests

Appendix Table 1: Benefits and harms of pregabalin in the management of neuropathic pain

Outcome	Overall analysis	Subgroup analyses		Test for subgroup differences
		Central neuropathic pain	*Peripheral neuropathic pain*	
Mean change in pain scores - NRS	(n = 5093): SMD -0.49 (-0.66 to -0.32, P < 0.00001, I^2=88%	(n = 785): SMD -0.38 (-0.80 to 0.04), P = 0.08, I^2=89%	(n = 4308): SMD -0.52 (-0.71 to -0.33), P < 0.00001, I^2=88%	P = 0.56, I^2=0%
Mean change in sleep interference scores - NRS	(n = 1641): SMD -0.38 (-0.50 to -0.26, P < 0.00001, I^2=32%	(n = 357): SMD -0.49 (-0.70 to -0.28), P < 0.00001, I^2=0%	(n = 1284): SMD -0.35 (-0.50 to -0.19), P < 0.0001, I^2=45%	P = 0.30, I^2=8%
Mean change in HADS-anxiety scores	(n = 1041): SMD -0.12 (-0.29 to 0.04, P = 0.14, I^2=44%	(n = 418): SMD -0.27 (-0.46 to -0.08, P = 0.006, I^2=0%	(n = 623): SMD -0.00 (-0.16 to 0.15, P = 0.97, I^2=0%	P = 0.04, I^2=77.2%
Mean change in HADS-depression scores	(n = 1041): SMD -0.06 (-0.26 to 0.13, P = 0.54, I^2=60%	(n = 418): SMD -0.16 (-0.41 to 0.10, P = 0.23, I^2=44%	(n = 623): SMD 0.02 (-0.28 to 0.32, P = 0.90, I^2=71%	P = 0.38, I^2=8%
Overall adverse events	(n = 4010): RR 1.33 (1.23 to 1.44), P < 0.00001, I^2=52%	(n = 489): RR 1.33 (1.20 to 1.47), P < 0.00001, I^2=0%	(n = 3225): RR 1.34 (1.21 to 1.47), P < 0.00001, I^2=61%	P = 0.92, I^2=0%
Adverse event: weight gain	(n = 3636): RR 4.58, (2.88 to 7.28), P < 0.00001, I^2=0%	(n = 428): RR 3.77 (0.94 to 15.08), P = 0.06, I^2=0%	(n = 3636): RR 4.69 (2.87 to 7.68), P < 0.00001, I^2=0%	P = 0.77, I^2=0%
Adverse event: somnolence	(n = 5695): RR 2.84, (2.36 to 3.42), P < 0.00001, I^2=0%	(n = 785): RR 3.18 (2.16 to 4.68), P < 0.00001, I^2=0%	(n = 4910): RR 2.74 (2.22 to 3.40), P < 0.00001, I^2=1%	P = 0.51, I^2=0%
Adverse event: dizziness	(n = 5732): RR 2.94 (2.30 to 3.74), P < 0.00001, I^2=63%	(n = 785): RR 3.38 (2.46 to 4.63), P < 0.00001, I^2=0%	(n = 4947): RR 2.89 (2.17 to 3.85), P < 0.00001, I^2=67%	P = 0.48, I^2=0%
Adverse event: peripheral edema	(n = 5001): RR 2.63 (1.86 to 3.73), P < 0.00001, I^2=41%	(n = 439): RR 3.90 (1.63 to 9.36), P = 0.002, I^2=0%	(n = 4562): RR 2.53 (1.74 to 3.68), P < 0.00001, I^2=44%	P = 0.37, I^2=0%
Adverse event: fatigue*	(n = 3958): RR 1.83 (1.32 to 2.54), P = 0.0003, I^2=14%	N/A	N/A	N/A
Adverse event: visual disturbance	(n = 2814): RR 2.50 (1.53 to 4.09), P = 0.0003, I^2=6%	(n = 566): RR 4.05 (1.27 to 12.91), P = 0.02, I^2=0%	(n = 2248): RR 2.36 (1.32 to 4.22), P = 0.004, I^2=16%	P = 0.42, I^2=0%
Adverse event: ataxia**	(n = 1045): RR 5.49 (1.84 to 16.36), P = 0.002, I^2=0%	N/A	N/A	N/A
Adverse event: dry mouth	(n = 3873): RR 2.39 (1.66 to 3.44), P < 0.0001, I^2=16%	(n = 357): RR 3.75 (1.43 to 9.83), P = 0.007, I^2=0%	(n = 3516): RR 2.28 (1.52 to 3.41), P < 0.0001, I^2=20%	P = 0.35, I^2=0%
Adverse event: non-peripheral edema	(n = 2337): RR 3.51 (1.93 to 6.40), P < 0.0001, I^2=0%	(n = 785): RR 3.82 (1.65 to 8.85), P = 0.002, I^2=0%	(n = 1552): RR 3.70 (1.36 to 10.06), P = 0.01, I^2=19%	P = 0.96, I^2=0%
Adverse event: vertigo**	(n = 1031): RR 3.08 (1.01 to 9.40), P = 0.05, I^2=30%	N/A	N/A	N/A
Adverse event: euphoria*	(n = 1274): RR 8.80 (2.72 to 28.54), P = 0.0003, I^2=0%	N/A	N/A	N/A
Discontinuation due to adverse events	(n = 5426): RR 1.91 (1.54 to 2.37), P < 0.00001, I^2=0%	(n = 576): RR 1.42 (0.79 to 2.55), P = 0.24, I^2=0%	(n = 4850): RR 2.00 (1.58 to 2.55), P < 0.00001, I^2=6%	P = 0.29, I^2=12%

Abbreviations: HADS: Hospital anxiety depression scale; NRS: Numerical rating scale; RR: Risk ratio; SMD: Standardized mean difference

*only one RCT on central neuropathic pain reported adequate data
**all RCTs were in patients with peripheral neuropathic pain

Appendix Table 2: Sensitivity analyses by study quality and duration in clinical trials assessing the benefits and harms of pregabalin in neuropathic pain

Outcome	Sensitivity analysis based on higher quality studies*	Sensitivity analysis based on shorter duration of intervention**	Sensitivity analysis based on longer duration of intervention***
Pain	5 studies (n = 932): SMD -0.56 (-1.07 to -0.05; P = 0.03; I^2=92%)	10 studies (n = 2408): SMD -0.68 (-0.96 to -0.40; P < 0.00001; I^2=90%)	10 studies (n = 2685): SMD -0.31 (-0.49 to -0.13; P = 0.0006; I^2=79%)
Adverse events	6 studies (n = 1152): RR 1.17 (1.06 to 1.29; P = 0.002; I^2=23%)	11 studies (n = 2088): RR 1.46 (1.34 to 1.58; P < 0.00001; I^2=0%)	8 studies (n = 1922): RR 1.23 (1.12 to 1.35; P < 0.0001; I^2=55%)
Serious adverse events	3 studies (n = 627): RR 0.59 (0.38 to 0.92; P = 0.02; I^2=0%)	8 studies (n = 2088): RR 0.72 (0.49 to 1.07; P = 0.11; I^2=0%)	7 studies (n = 1674): RR 0.93 (0.55 to 1.59; P = 0.79; I^2=26%)
Discontinuation due to adverse events	6 studies (n = 1152): RR 1.22 (0.79 to 1.87; P = 0.37; I^2=0%)	13 studies (n = 2403): RR 1.95 (1.34 to 2.84; P = 0.0005; I^2=27%)	11 studies (n = 3023): RR 1.88 (1.40 to 2.53; P < 0.0001; I^2=0%)

*studies that adequately reported randomization and blinding procedures

**Studies duration lasting less than 12 weeks

***Studies duration lasting at least 12 weeks

Appendix Table 3: Main results* of RCTs assessing the benefits and harms of pregabalin in the management of neuropathic pain

		Pain			Sleep Disturbance				
Study ID	**NRS**	**VAS Score**	**SF-MPQ VAS**	**SF-MPQ PPI**	**Sleep Interference Scores**	**MOS-Sleep**	**Quality of Life (EQ-5D)**	**PGIC**	**CGIC**
Arezzo 2008			Significantly favoured PGB over PLA (MD -11.06, 95% CI, -18.89 to -3.22; P = 0.006)					Significant improvement with PGB compared to PLA, P= 0.002	
Cardenas 2013						Significant improvement with PGB over PLA on domains of sleep disturbance, awaken short of breath, sleep quantity, and optimal seep subscales (P<0.05)		PGIC reported as binary outcome; significantly improved with PGB compared with PLA, P<0.001	Significant improvement in the PGB arm (P= 0.0294)
Dworkin 2003			Significantly favoured PGB over PLA (MD -17.62, 95% CI, -25.37 to -9.86; P = 0.0001		Significantly favoured PGB over PLA (MD -1.58, 95% CI, -2.19 to -0.97; P = 0.0001)	Significantly favoured PGB over PLA (MD -9.80, 95% CI, -14.49 to -5.11; P = 0.0001)		Significantly improved with PGB versus PLA, P = 0.001	
Freynhagen 2005	Both flexible- and fixed-dose PGB significantly reduced endpoint mean pain score versus PLA (P=0.002 and P<0.001 respectively)				Significantly improved at endpoint in each PGB treatment group over PLA (P<0.001)	Significantly favoured PGB over PLA (P<0.05)			
Guan 2011			Significantly improved with PGB vs PLA LSMD -6.56, 95% CI -11.65 to -1.47, P=0.012		Significantly improved with PGB vs PLA: LSMD -0.5, 95% CI -0.93 to -0.07, P=0.023				
Holbech 2015					Significantly improved with PGB vs PLA LSMD -0.55, 95% CI -0.93 to -0.17, P=0.004				
Huffmann 2015	Significant treatment difference favouring PGB over PLA for DPN pain (P=0.034) and DPN pain on walking (P=0.001)							Significant improvements with PGB compared to PLA (P=0.002)	
Kanodia 2011		Significantly improved with PGB compared to PLA: MD -21, 95% CI: -23.8 to -18.2; P = 0.004)							
Kim 2011					Significantly favoured PGB over PLA (P<0.05)	Significant improvement with PGB over PLA in sleep quantity (P=0.03), sleep adequacy (P=0.13), snoring (P=0.39), and reduced the sleep problems index (P=0.049)	No significant difference between groups at endpoint, MD 0 (95% CI -0.1, 0,1) P= 0.566	No significant difference between groups at endpoint, -0.2 (95% CI -0.5, 0.1) P=0.144	Significant improvement of in PGB group vs PLA: MD -0.3 (95% CI -0.6, 0) (P=0.049)
Krcevski Skvarč 2010	No significant difference between groups, P values not reported								
Lesser 2004					Significantly favoured PGB over PLA (P=0.0001)				
Liu 2015			Significant decrease with PGB compared with PLA: MD -8.18, 95% CI: -11.99 to -4.37; P<0.0001)	Significant decrease in with PGB compared with PLA: MD -0.37, 95% CI: -0.58 to -0.16; P=0.0007).		Significantly greater improvements with PGB in subscales of sleep disturbance (P=0.0039) and quantity of sleep (P=0.0035) compared with PLA		Significantly improved with PGB versus PLA: LSMD -0.49 95% CI -0.72 to -0.27, P<0.0001	Significant improvement with PGB versus PLA, LSMD -0.62 95% (CI -0.86, -0.39), P<0.0001
Mathieson 2017									
Moon 2010					Significantly favoured PGB over PLA: LSMD -0.51 (95% CI, -0.96 to -0.07; P = 0.024)	Significantly greater improvements with PGB in subscales of sleep disturbance (P=0.0034) and quantity of sleep (P=0.018) compared with PLA	No significant differences in endpoint scores of EQ-5D utility score least squares means 0.03, 95% CI -0.04, 0.09 P= 0.429, or EQ-5D VAS at endpoint LSMD 3.50 (95% CI -1.18, 8.18) P= 0.142	No statistically significant difference between groups	No statistically significant difference between groups
Rauck 2013					No significant difference between groups: MD 0.11 (95% CI -0.60 to 0.82)				
Richter 2005			Significantly favoured PGB 600mg/day over PLA (MD -14.67, 95% CI, -21.92 to -7.41; P = 0.0002). No significant	Significantly favoured PGB 600mg/day over PLA (MD -0.66, 95% CI, -0.97 to -0.35; P = 0.0002). No significant difference	Significantly favoured PGB over PLA: LSMD -1.152; 95% CI -1.752 to -0.551; P=0.0004				

			difference between PGB 150mg/day and PLA (MD -4.78, 95% CI, -12.20 to -2.64; P = 0.20)	between PGB 150 mg/day and PLA (MD -0.17, 95% CI, -0.49 to 0.14; P = 0.28)					
Rosenstock 2004			Significantly favoured PGB over PLA (MD -16.19, 95% CI, -24.52 to -7.86; P = 0.0002)	Significantly favoured PGB over PLA (MD -0.37, 95% CI, -0.72 to -0.02; P = 0.036)	Significantly favoured PGB over PLA: LSMD -1.54, 95% CI -2.28 to -0.80, P=0.0001				
Sabatowski 2004					Significantly favoured PGB over PLA: LSMD -1.11, 95% CI -1.71 to -0.51, P=0.0003 for 150 mg/day; LSMD -1.43, 95% CI -2.04 to -0.82, P=0.0001 for 300 mg/day				
Satoh 2011			Significantly favoured PGB 300 mg/day and 600 mg/day over PLA (P < 0.05)		Significantly improved in the 300 and 600 mg/ day PGB groups compared with PLA (P < 0.0001 and P = 0.0273 respectively)				
Shabbir 2011	Significant improvement in pain of DPN was observed in patients receiving PGB (48.1%) and compared to those receiving PLA (10.5%), P values not reported								
Siddall 2006			Significantly favoured PGB over PLA (MD -17.6, 95% CI, -25.2 to -10.0; P<0.001)	Significantly favoured PGB over PLA (MD -0.66, 95% CI, -0.99 to -0.32; P<0.001)					
Simpson 2010								Significant self-reported improvement favouring PGB over PLA: 82.8% vs 66.7% (P= 0.008)	
Simpson 2014					No significant difference between groups: LSMD 0.04, 95% CI 0.43 to 0.35, P =0.840			No significant differences between groups: (P=0.505)	No significant differences between groups (P=0.427)
Stacey 2008		Significant improvement in VAS allodynia scores with PGB compared to PLA (flexible-dose: MD -14.4 mm [P<0 .0001] and fixed-dose, MD -8.98 mm [P =0.0075])	Significant improvement in with PGB compared to PLA (flexible-dose: MD -16.33 mm [P<0 .0001] and fixed-dose, MD -11.97 mm [P =0 .0008])		Significant improvements with flexible- and fixed-dose PGB. Results of between-group differences not reported		Fixed or flexible dose PGB demonstrated significant improvement in VAS anxiety scores over PLA (fixed-dose, 19.95, P = 0.025, and flexible-dose, -17.81; P= 0.024)	Patients treated with any PGB treatment regimen were significantly more likely to rate themselves as minimally, much, or very much improved on the PGIC at end point compared with PLA	
Tolle 2008							Significant improvements in utility scores for 150, 300, 600mg/day respectively compared to PLA, all P ≤ 0.0263	Significant improvement with 600 mg/day PGB versus PLA in subjects reporting “improved” or “much improved” (50.5% vs 33.3%, P = 0.02)	Significant superiority of PGB 600 mg/day over PLA (P= 0.009)
Van Seventer 2006						Significant improvement in MOS sleep scale problems with PGB compared with PLA MD – 7.54, 95% CI -11.52 to -3.56, P<0.001		Patients in the 150 mg/day (P = 0.02) and 600 mg/day (P = 0.003) groups were more likely to report global improvement than those in the PLA group	
Van Seventer 2010								Significant improvement in favour of PGB over PLA (P = 0.006)	
Vranken 2008		Significant decrease in with PGB compared with PLA: MD 2.18, 95% CI: 0.57 to 3.80; P = 0.01)					Statistically significant improvement for both the EQ-5D utility score (p<0.001) and EQ-5D VAS score with PGB compared to PLA (P<0.001)		

ABBREVIATIONS: CGIC: Clinician global impression of change; LSMD: Least square mean difference; MD: Mean difference; MOS-Sleep: Medical Outcomes Study Sleep Scale; NRS: numerical rating scale; PGB: Pregabalin; PGIC: Patient global impression of change; PLA: Placebo; SF-MPQ PPI: Short-Form McGill Pain Questionnaire personal pain intensity; SF-MPQ VAS: Short-Form McGill Pain Questionnaire visual assessment scale; VAS: Visual assessment scale

*These outcome results have been presented narratively because there was inadequate data to pool results across studies

Figure S1: Funnel plot for publication bias in RCTs assessing the effect of pregabalin in neuropathic pain. The broken line represents the mean difference for all trials.

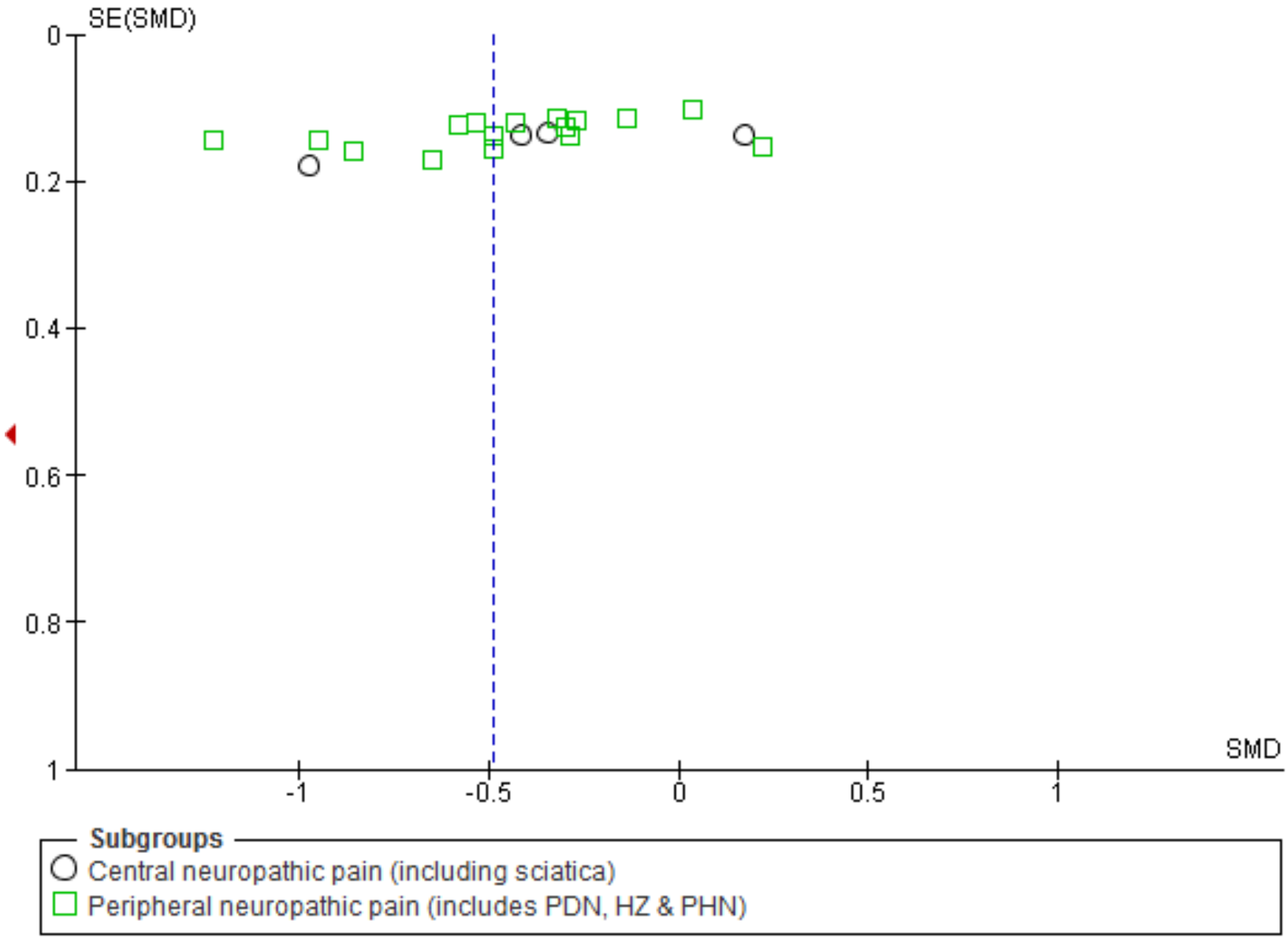


Figure S2: Effect of pregabalin on the risk of weight gain in patients with neuropathic pain

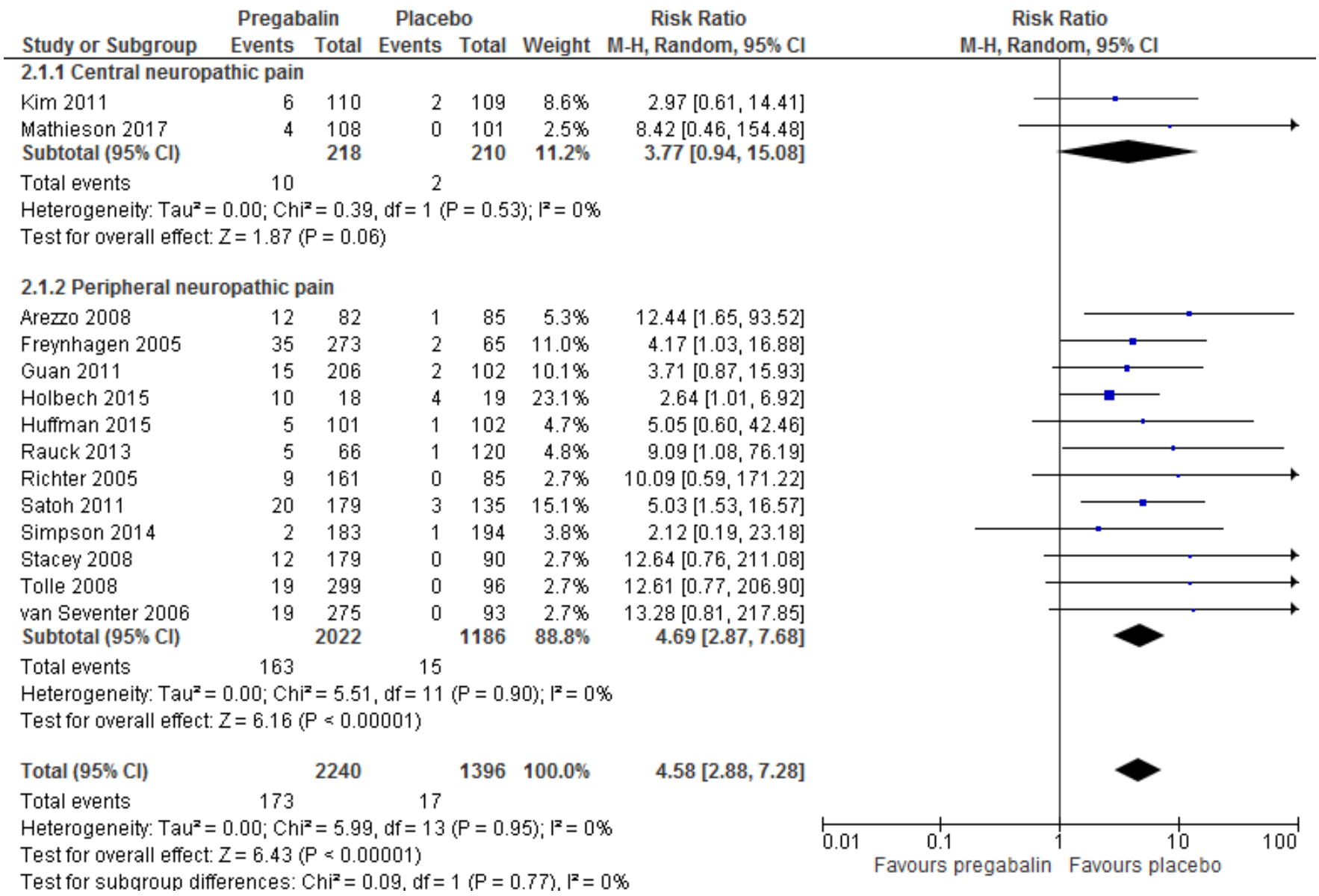


Figure S3: Effect of pregabalin on the risk of somnolence in patients with neuropathic pain

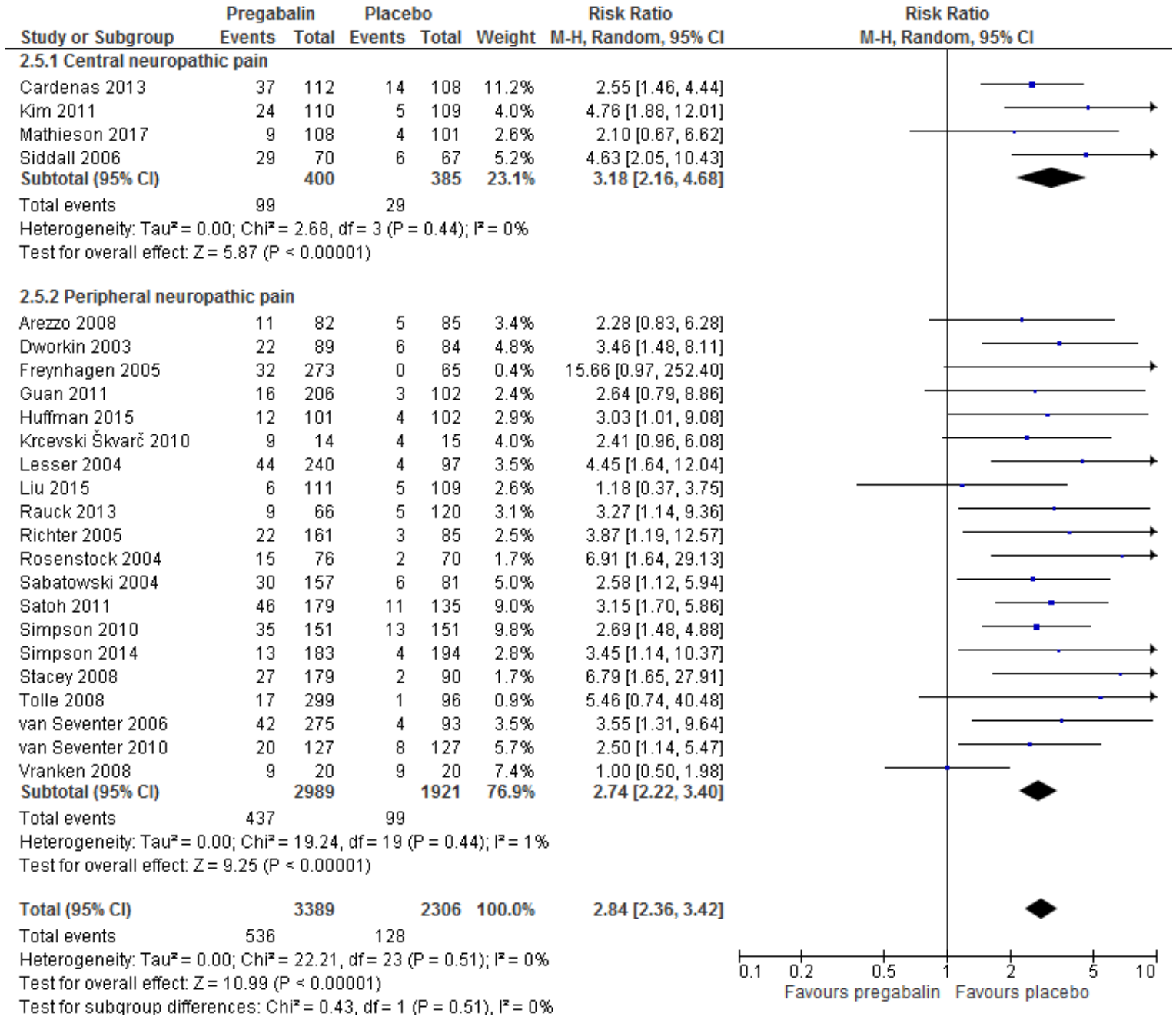


Figure S4: Effect of pregabalin on the risk of dizziness in patients with neuropathic pain

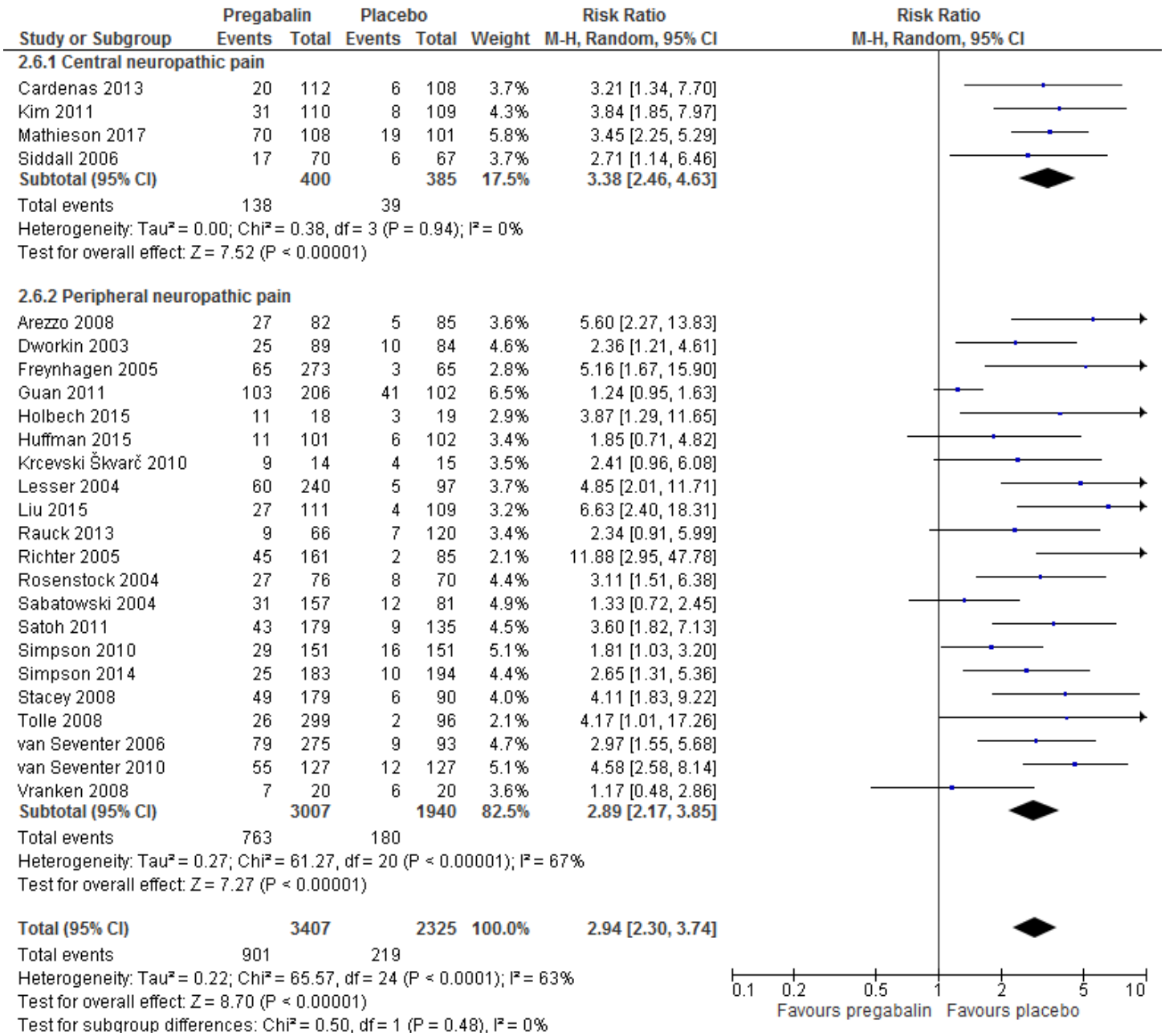


Figure S5: Effect of pregabalin on the risk of peripheral edema in patients with neuropathic pain

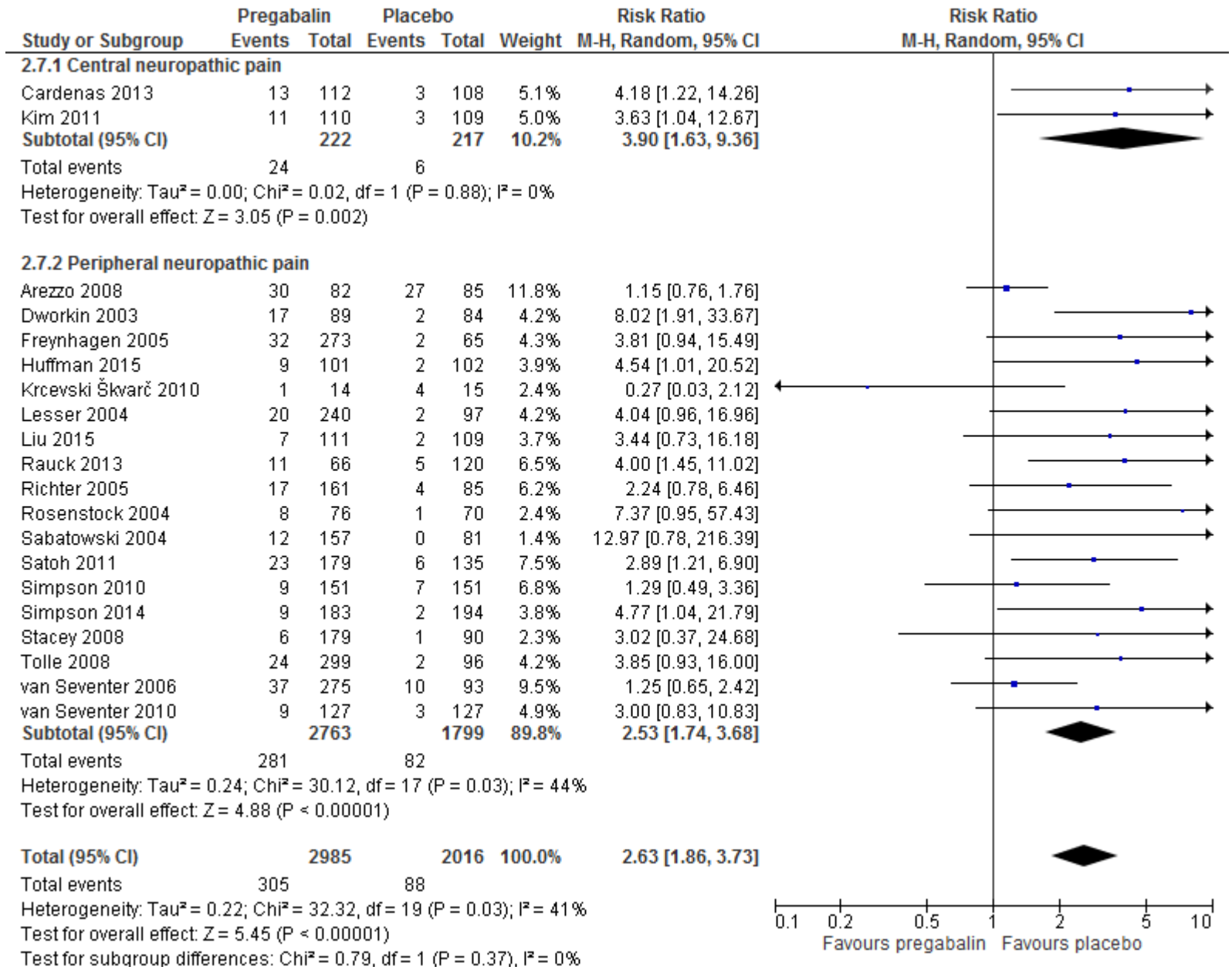


Figure S6: Effect of pregabalin on the risk of fatigue including asthenia in patients with neuropathic pain

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Arezzo 2008	8	82	1	82	2.4%	8.00 [1.02, 62.53]
Cardenas 2013	8	112	1	108	2.4%	7.71 [0.98, 60.65]
Freynhagen 2005	21	273	0	65	1.3%	10.36 [0.64, 168.79]
Guan 2011	23	206	7	102	11.9%	1.63 [0.72, 3.66]
Holbech 2015	7	18	3	19	6.5%	2.46 [0.75, 8.09]
Huffman 2015	11	101	3	102	6.0%	3.70 [1.06, 12.88]
Krcevski Škvarč 2010	8	14	8	15	15.9%	1.07 [0.56, 2.06]
Lesser 2004	13	240	3	97	6.1%	1.75 [0.51, 6.01]
Liu 2015	5	111	1	109	2.2%	4.91 [0.58, 41.35]
Rauck 2013	4	66	3	120	4.5%	2.42 [0.56, 10.51]
Richter 2005	13	161	3	85	6.1%	2.29 [0.67, 7.81]
Rosenstock 2004	3	76	2	70	3.2%	1.38 [0.24, 8.03]
Sabatowski 2004	7	157	4	81	6.4%	0.90 [0.27, 2.99]
Stacey 2008	13	179	1	90	2.5%	6.54 [0.87, 49.18]
Tolle 2008	10	299	0	96	1.3%	6.79 [0.40, 114.81]
van Seventer 2006	12	275	5	93	8.4%	0.81 [0.29, 2.24]
van Seventer 2010	15	127	10	127	13.0%	1.50 [0.70, 3.21]
Total (95% CI)		**2497**		**1461**	**100.0%**	**1.83 [1.32, 2.54]**
Total events	181		55			

Heterogeneity: Tau² = 0.06; Chi² = 18.63, df = 16 (P = 0.29); I² = 14%

Test for overall effect: Z = 3.62 (P = 0.0003)

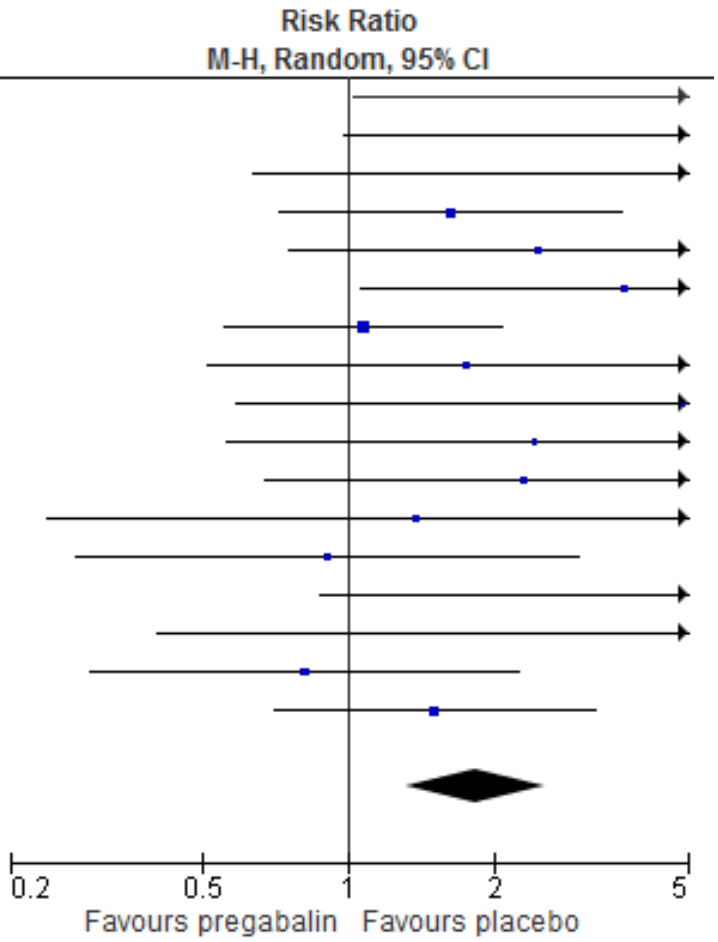
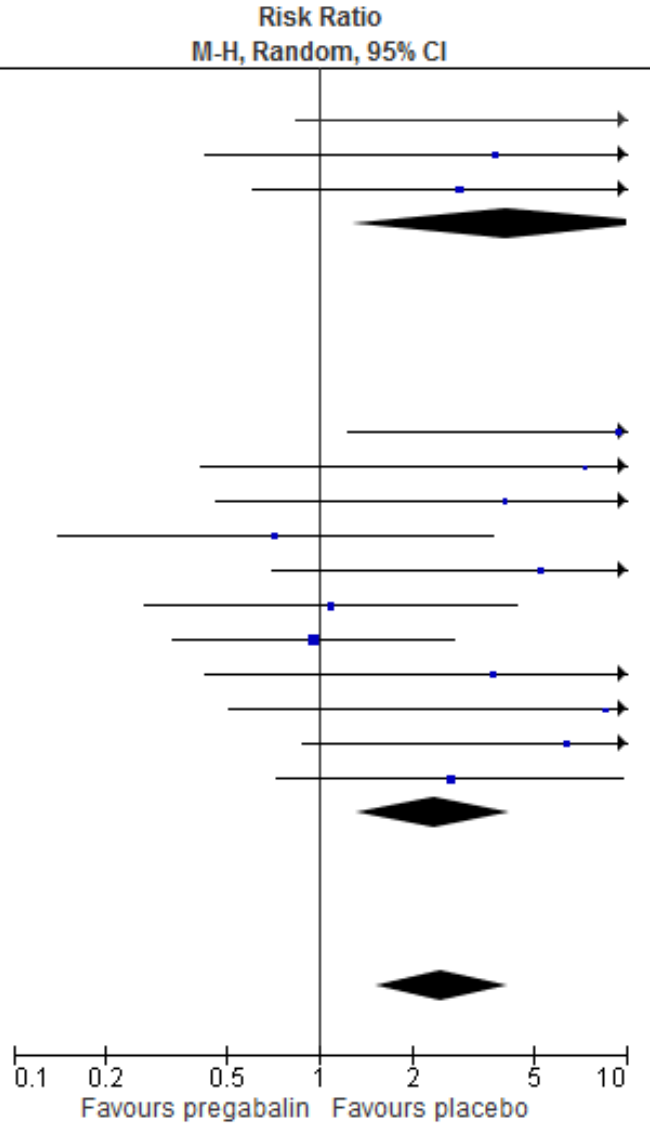


Figure S7: Effect of pregabalin on the risk of visual disturbances* in patients with neuropathic pain

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.8.1 Central neuropathic pain						
Cardenas 2013	7	112	0	108	2.9%	14.47 [0.84, 250.29]
Mathieson 2017	4	108	1	101	4.9%	3.74 [0.43, 32.91]
Siddall 2006	6	70	2	67	9.1%	2.87 [0.60, 13.73]
Subtotal (95% CI)		**290**		**276**	**17.0%**	**4.05 [1.27, 12.91]**
Total events	17		3			
Heterogeneity: Tau² = 0.00; Chi² = 1.03, df = 2 (P = 0.60); I² = 0%						
Test for overall effect: Z = 2.36 (P = 0.02)						
2.8.2 Peripheral neuropathic pain						
Dworkin 2003	10	89	1	84	5.6%	9.44 [1.23, 72.14]
Holbech 2015	3	18	0	19	2.8%	7.37 [0.41, 133.37]
Huffman 2015	4	101	1	102	4.9%	4.04 [0.46, 35.52]
Krcevski Škvarč 2010	2	14	3	15	8.4%	0.71 [0.14, 3.66]
Lesser 2004	13	240	1	97	5.7%	5.25 [0.70, 39.62]
Rauck 2013	3	66	5	120	11.2%	1.09 [0.27, 4.42]
Richter 2005	9	161	5	85	18.1%	0.95 [0.33, 2.75]
Rosenstock 2004	4	76	1	70	5.0%	3.68 [0.42, 32.17]
Stacey 2008	8	179	0	90	2.9%	8.59 [0.50, 147.25]
van Seventer 2006	19	275	1	93	5.8%	6.43 [0.87, 47.34]
van Seventer 2010	8	127	3	127	12.7%	2.67 [0.72, 9.82]
Subtotal (95% CI)		**1346**		**902**	**83.0%**	**2.36 [1.32, 4.22]**
Total events	83		21			
Heterogeneity: Tau² = 0.16; Chi² = 11.95, df = 10 (P = 0.29); I² = 16%						
Test for overall effect: Z = 2.90 (P = 0.004)						
Total (95% CI)		**1636**		**1178**	**100.0%**	**2.50 [1.53, 4.09]**
Total events	100		24			
Heterogeneity: Tau² = 0.06; Chi² = 13.90, df = 13 (P = 0.38); I² = 6%						
Test for overall effect: Z = 3.64 (P = 0.0003)						
Test for subgroup differences: Chi² = 0.66, df = 1 (P = 0.42), I² = 0%						



*includes blurring of vision and amblyopia

Figure S8: Effect of pregabalin on the risk of ataxia in patients with neuropathic pain

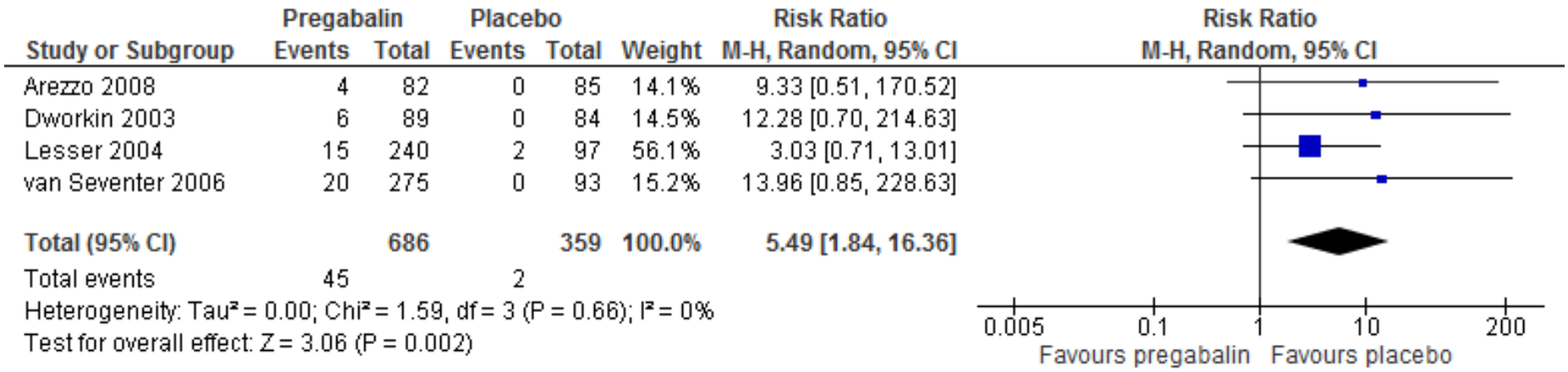


Figure S9: Effect of pregabalin on the risk of non-peripheral edema in patients with neuropathic pain

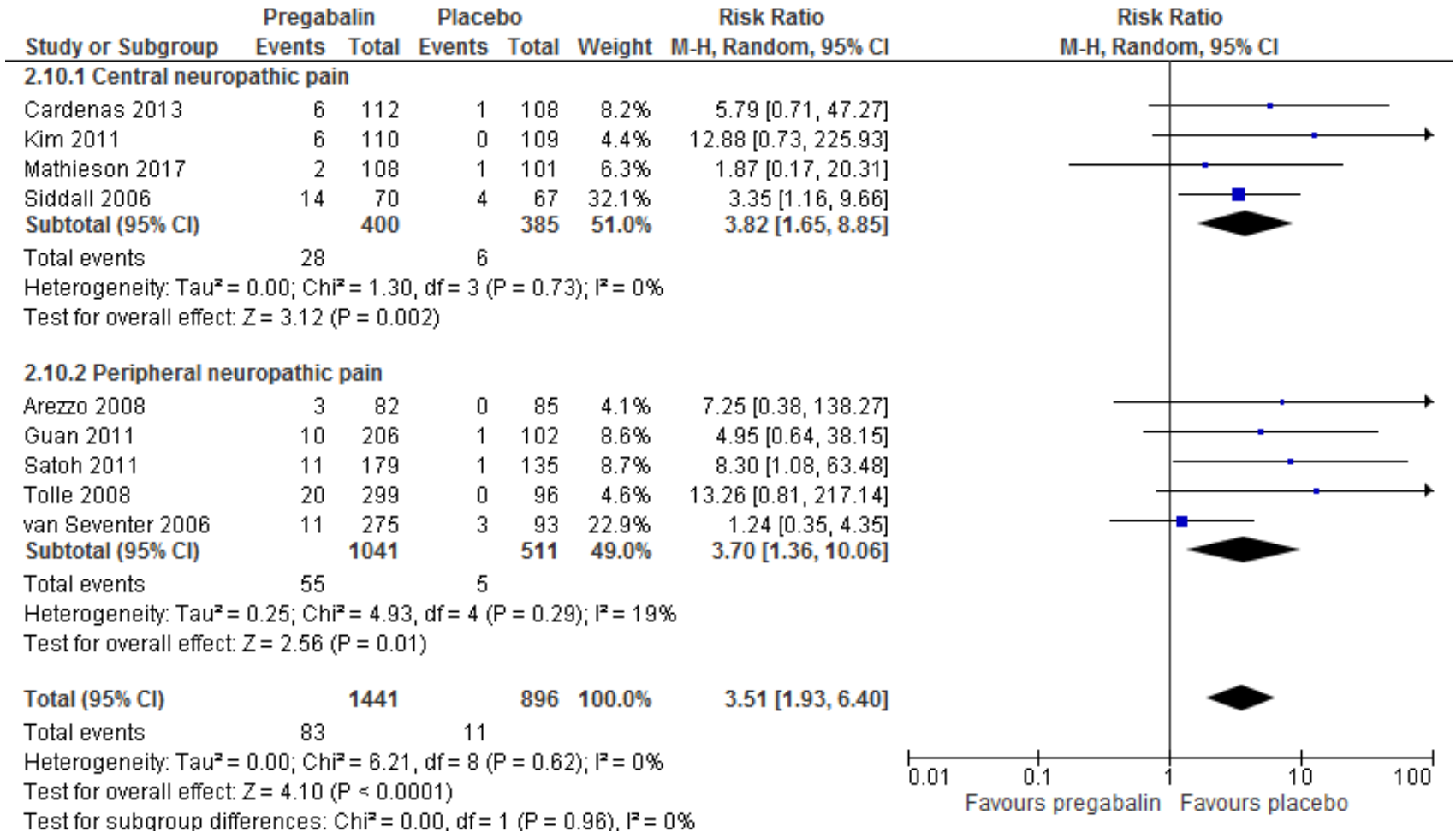


Figure S10: Effect of pregabalin on the risk of vertigo in patients with neuropathic pain

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Freynhagen 2005	24	273	1	65	22.5%	5.71 [0.79, 41.47]
Krcevski Škvarč 2010	7	14	5	15	51.8%	1.50 [0.62, 3.64]
Stacey 2008	6	179	0	90	12.7%	6.57 [0.37, 115.38]
Tolle 2008	13	299	0	96	13.1%	8.73 [0.52, 145.49]
Total (95% CI)		**765**		**266**	**100.0%**	**3.08 [1.01, 9.40]**
Total events	50		6			

Heterogeneity: Tau² = 0.42; Chi² = 4.31, df = 3 (P = 0.23); I² = 30%

Test for overall effect: Z = 1.97 (P = 0.05)

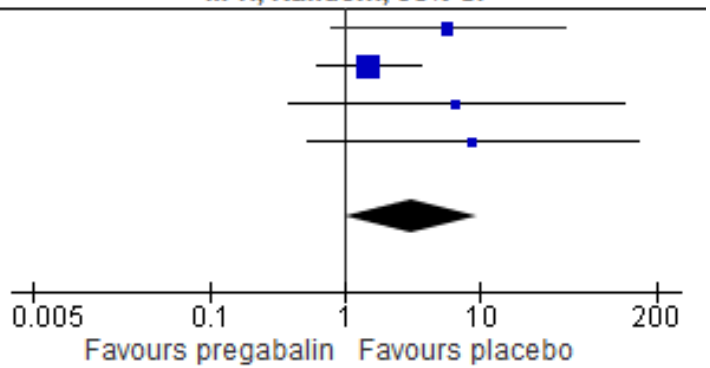


Figure S11: Effect of pregabalin on the risk of euphoria in patients with neuropathic pain

Study or Subgroup	Pregabalin Events	Pregabalin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Cardenas 2013	3	112	0	108	15.9%	6.75 [0.35, 129.20]
Lesser 2004	9	240	0	97	17.2%	7.73 [0.45, 131.46]
Rosenstock 2004	4	76	0	70	16.4%	8.30 [0.45, 151.41]
Simpson 2010	15	151	1	151	34.2%	15.00 [2.01, 112.13]
Stacey 2008	4	179	0	90	16.3%	4.55 [0.25, 83.59]
Total (95% CI)		**758**		**516**	**100.0%**	**8.80 [2.72, 28.54]**
Total events	35		1			

Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 4 (P = 0.97); I² = 0%

Test for overall effect: Z = 3.63 (P = 0.0003)

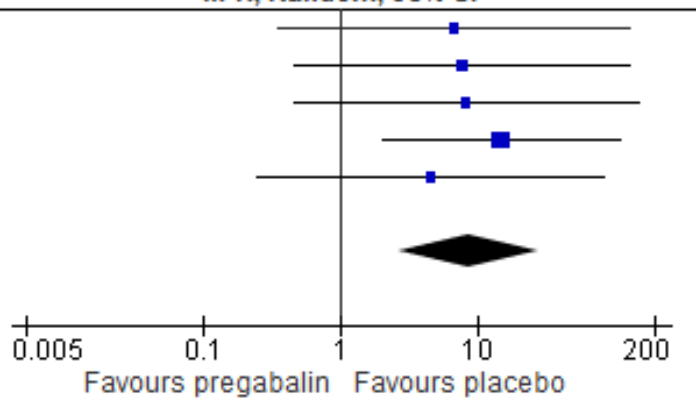


Figure S12: Effect of pregabalin on the risk of dry mouth in patients with neuropathic pain

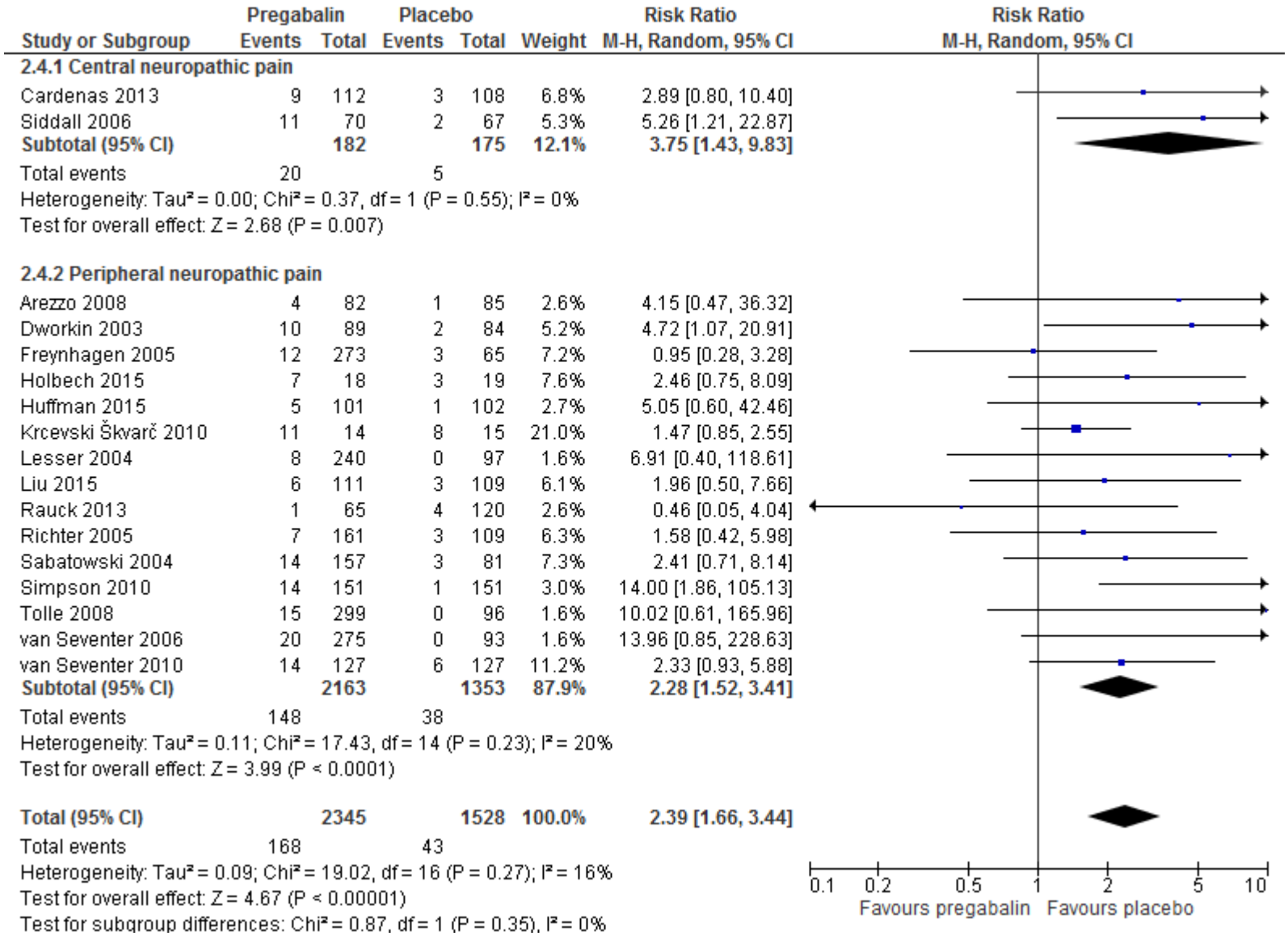


Figure S13: Effect of pregabalin on the risk of discontinuation due to adverse events

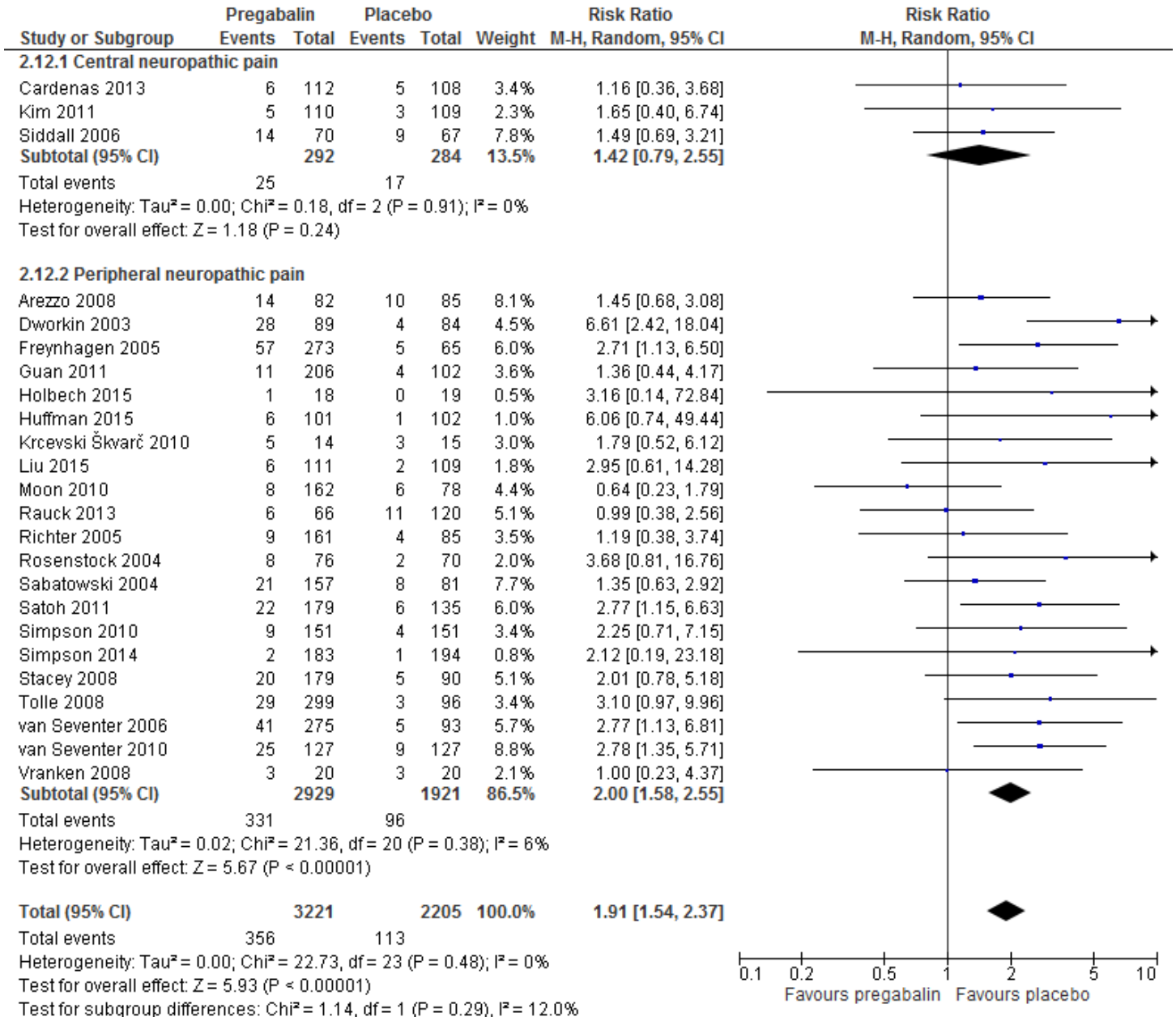


Figure S14: Effect of pregabalin on the risk of serious adverse events in patients with neuropathic pain

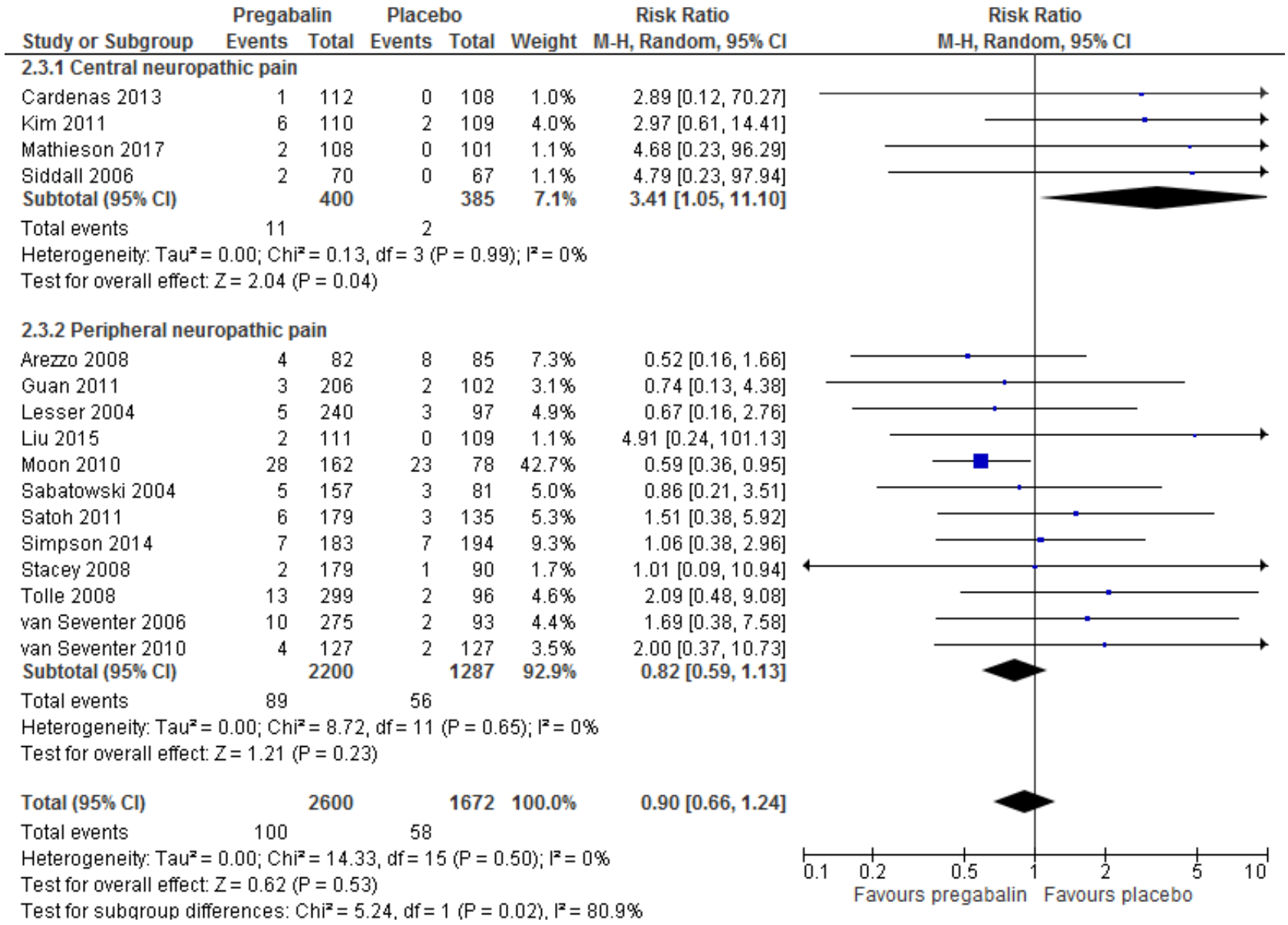


Figure S15: Effect of pregabalin on the sleep disturbance in patients with neuropathic pain

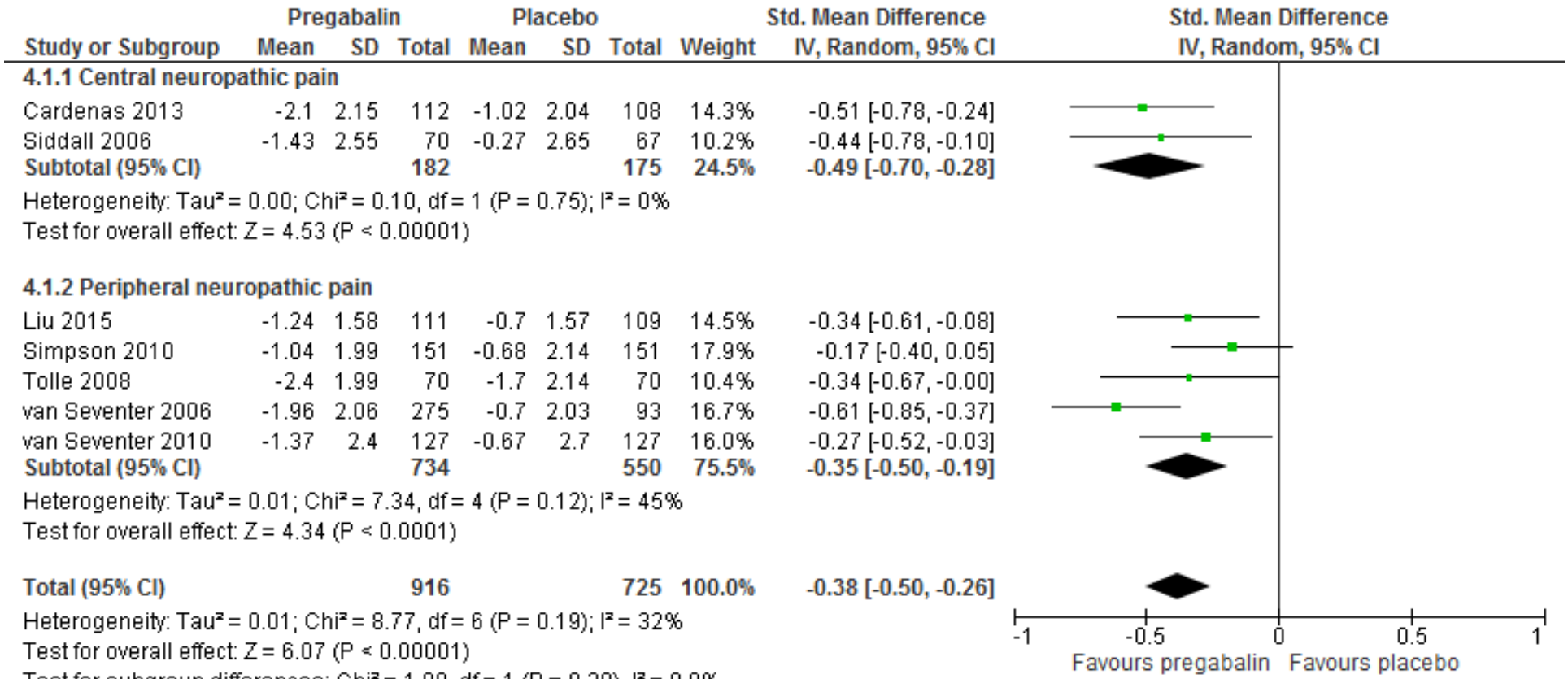


Figure S16: Effect of pregabalin on HADS-anxiety scores in patients with neuropathic pain

Study or Subgroup	Pregabalin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
5.3.1 Central neuropathic pain								
Cardenas 2013	-1.5	3.4	100	-0.82	3.28	99	21.7%	-0.20 [-0.48, 0.08]
Kim 2011	-1.9	3.4	110	-0.8	3.28	109	22.9%	-0.33 [-0.59, -0.06]
Subtotal (95% CI)			**210**			**208**	**44.5%**	**-0.27 [-0.46, -0.08]**
Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%								
Test for overall effect: Z = 2.73 (P = 0.006)								
5.3.2 Peripheral neuropathic pain								
Simpson 2014	-1.09	6.36	183	-1.39	6.93	192	30.7%	0.04 [-0.16, 0.25]
van Seventer 2010	-1.4	6.36	124	-0.9	6.93	124	24.8%	-0.07 [-0.32, 0.17]
Subtotal (95% CI)			**307**			**316**	**55.5%**	**-0.00 [-0.16, 0.15]**
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 1 (P = 0.46); I² = 0%								
Test for overall effect: Z = 0.03 (P = 0.97)								
Total (95% CI)			**517**			**524**	**100.0%**	**-0.12 [-0.29, 0.04]**
Heterogeneity: Tau² = 0.01; Chi² = 5.32, df = 3 (P = 0.15); I² = 44%								
Test for overall effect: Z = 1.48 (P = 0.14)								
Test for subgroup differences: Chi² = 4.38, df = 1 (P = 0.04), I² = 77.2%								

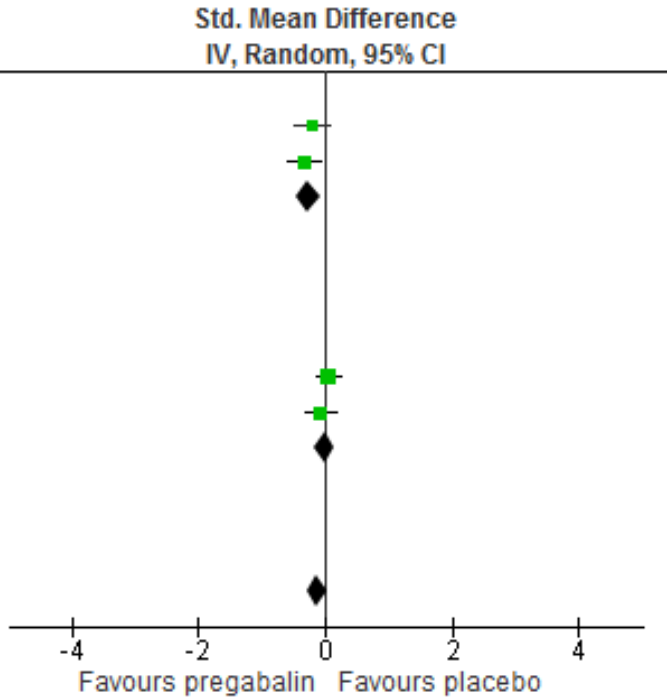
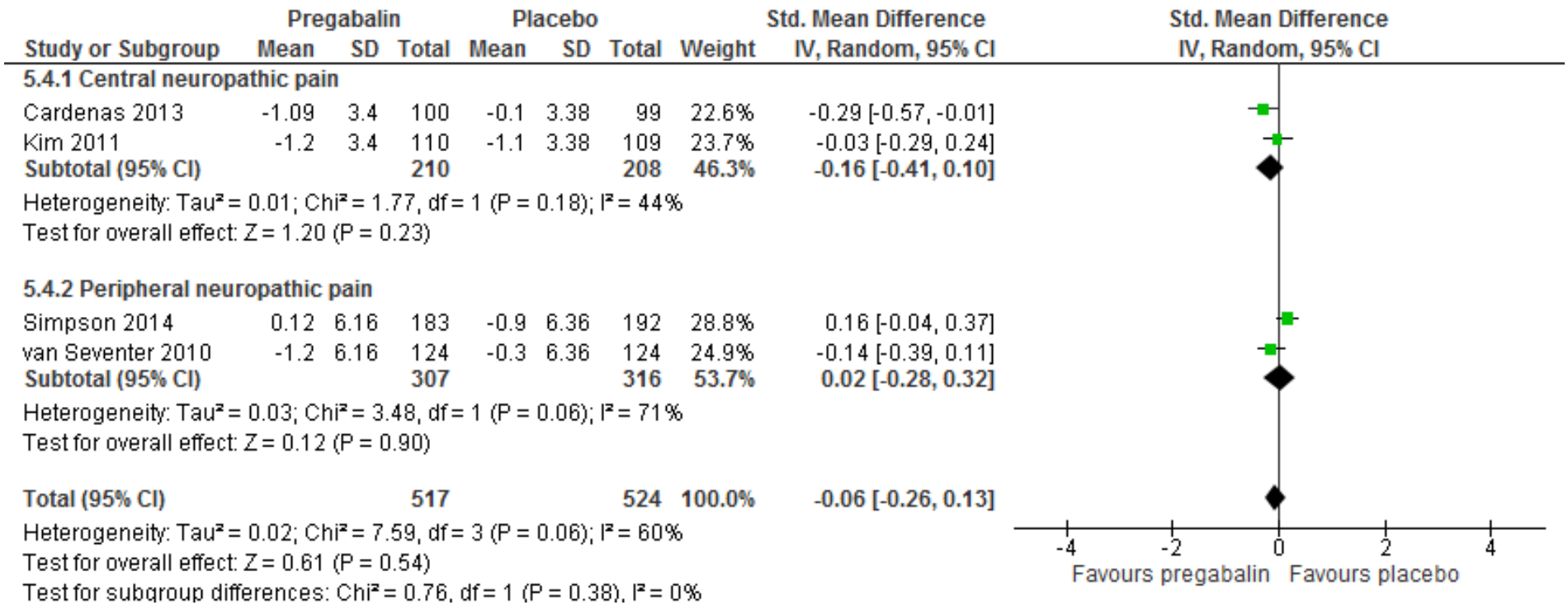


Figure S17: Effect of pregabalin on HADS-depression scores in patients with neuropathic pain



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
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.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
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.	Suppl.
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.	5
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.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
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).	5
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.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
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.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
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).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
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.	7
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.	7
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).	7
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.	7-19
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-19
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7-19
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7-19
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).	20
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).	22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	24
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.	24

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(6): e1000097. doi:10.1371/journal.pmed1000097

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