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A comparative meta-analysis of the efficacy and tolerability of pregabalin versus placebo for the management of fibromyalgia in adults

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Abstract

Background
Fibromyalgia (FM) is a multifactorial condition of unknown aetiology. Although it is primarily characterised by chronic diffuse pain, it is also associated with a number of symptoms including: cognitive impairment, sleep problems, fatigue, anxiety and depression. FM patients frequently report of a reduced quality of life, and this often due to the inherent disability associated with these symptoms. Although there is currently no curative treatment for FM, the anti-convulsant drug pregabalin is one of a number of interventions employed to manage this condition.

Objectives
To assess the efficacy and tolerability of pregabalin for the management of FM in adults compared to a placebo.

Search methods
Electronic searches were performed using the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 1, 2017), MEDLINE accessed through PubMed (1966 to December 2016), and www.clinicaltrials.gov (website of the US National Institute of Health) to December 2016 for unpublished clinical trials. Additionally, searches were performed on the bibliographies of existing reviews to retrieve relevant articles.

Selection criteria
The studies included in this review investigated the efficacy and tolerability of pregabalin for the management of FM in adults. They were all full journal publications of randomised controlled trials (RCTs) which employed a double-blind experimental procedure and lasted for eight weeks or longer.

Data collection and analysis
The titles and abstracts of studies were individually scrutinised to determine their eligibility for inclusion. Studies which obviously did not satisfy the basic inclusion criteria (i.e. double-blind, RCT) were excluded outright. Full copies of potential studies were obtained and read in-depth to ascertain their eligibility for inclusion. The risk of bias was determined for each study using the criteria described in the

Cochrane Handbook for Systematic Reviews of Interventions [Higgins and Green 2011]. Data was then extracted and double-checked for accuracy prior to entry into Review Manager 5 [RevMan, 2014]

Main results

This review includes eight studies of both classical and enriched enrolment randomised withdrawal (EERW) design. Six studies of classical design (3812 participants) were included in this review. Participants were randomised at the start of the study to receive either: 150, 300, 450 or 600 mg daily pregabalin or placebo for 8 to 13 weeks. All studies used a placebo as the comparator. The studies had a low risk of bias with the exception of the last observation carried forward (LOCF) imputation for missing data which can overestimate or underestimate the magnitude of treatment effect. With regards to pain outcomes, pregabalin was more effective than placebo in reducing mean pain scores (SMD: -0.26; 95% CI; -0.34 to -0.19; P = <0.00001), as well as achieving both ≥30% (RR: 1.38; 95% CI; 1.23 to 1.55; P = 0.00001) and ≥50% reductions in pain intensity (RR: 1.61; 95% CI; 1.35 to 1.93; P = 0.00001); the numbers needed to treat for an additional beneficial (NNTB) outcome by pregabalin over placebo was ≈9 and ≈12 respectively. The overall effect of pregabalin in producing improvements to patient global impression of change (PGIC) was statistically significant (RR: 1.40; 95% CI; 1.25 to 1.58; P = 0.00001); the NNTB by pregabalin over placebo was ≈9. Pregabalin did not substantially reduce fatigue (SMD: -0.17; 95% CI; -0.25 to -0.09; P = <0.0001), anxiety (SMD: -0.13; 95% CI; -0.21 to -0.06; P = <0.0007), depression (SMD: -0.10; 95% CI; -0.18 to -0.02; P=0.01) or health related quality of life (SMD: 0.17; 95% CI; -0.26 to -0.09; P = <0.0001), but produced modest improvements to symptoms of sleep problems (SMD: -0.34; 95% CI; -0.42 to -0.27; P = <0.0001). The incidence of participant withdrawal was higher with pregabalin than placebo (RR: 1.75; 95% CI; 1.42 to 2.15; P = 0.00001); the numbers needed for an additional harmful outcome (NNTH) by pregabalin over placebo was ≈12. Somnolence and dizziness are two of the most common side-effect of pregabalin; both occurred more frequently following treatment with pregabalin as opposed to placebo; (RR: 3.89; 95% CI; 3.16 to 4.78; P = 0.00001) for dizziness and (RR: 3.42; 95% CI; 2.71 to 4.32; P = 0.00001) for somnolence. The NNTH by pregabalin over placebo was ≈3 for dizziness, and ≈7 for somnolence respectively. With regards to the incidence of serious adverse effects, there was no significant difference between pregabalin and placebo (RR: 1.06; 95% CI; 0.73 to 1.53; P = 0.31). Two studies (687 participants) of EERW design were included in this review. They were deemed as having a low risk of bias as there was no missing data and no imputation. The maintenance of therapeutic effect (MTR) was used as the primary efficacy outcome in this review. Of the participants whom entered the double-blind treatment phase, 39.8% of participants receiving pregabalin, and 20.9% of participants receiving placebo achieved MTR. The overall effect of pregabalin on achieving MTR was statistically significant (RR: 1.9; 95% CI; 1.5 to 2.4; P = 0.00001) and the NNTB by pregabalin over placebo was ≈5. As with the studies of classical design, the incidence of adverse effects was higher with pregabalin than placebo. 64.9% of participants experienced at least one adverse effect following treatment with pregabalin, as opposed to 48.7% of those receiving placebo. The overall effect of pregabalin in causing adverse effects was statistically significant (RR: 1.3; 95% CI; 1.2 to 1.5; P = 0.000028), and the NNTH by pregabalin over placebo was ≈6.

Author's conclusions

Pregabalin 300 to 600 mg daily has the potential to achieve substantial improvements the symptoms of FM, but this is generally observed in a minority of participants. Although its use can yield small improvements to the symptoms of pain and sleep problems, it is generally less effective in addressing the other symptoms of FM (i.e. fatigue, anxiety). Although the use of pregabalin is not associated with any serious adverse effects, participants typically experience adverse effects (i.e. somnolence and dizziness) more frequently than in the placebo group. Furthermore, the incidence of participant withdrawal due to adverse effects was higher in the pregabalin group. Generally speaking these observations did not follow a dose response relationship.

Plain language summary

Pregabalin versus placebo for the management of fibromyalgia in adults
Fibromyalgia (FM) is typically characterised by chronic diffuse pain, but is also associated with a number of symptoms including cognitive impairment, fatigue, sleep problems, anxiety and depression. There is currently no curative treatment for FM, and over-the-counter medication(s) are generally ineffective for the management of these symptoms. As a result, FM patients frequently report of a reduced quality of life; novel treatment options are therefore of growing interest to clinicians and patients alike.

Pregabalin is an anti-convulsant (anti-epileptic) drug which is used for the management of FM in certain parts of the world. Its use has been associated with marked reductions in pain intensity, as well as significant improvements to the associated symptoms of FM. However, it is not currently licenced for the treatment of FM in the United Kingdom (UK).

This review aimed to evaluate the efficacy and tolerability of pregabalin for the management of FM in adults, utilising evidence which was considered robust, and outcomes which were deemed clinically significant. Our results showed that pregabalin has the potential to substantially reduce pain intensity, as well as achieve significant improvements to sleep quality and the patients‟ quality of life. It was generally less effective in managing symptoms of anxiety, depression and fatigue. Common side effects of pregabalin include somnolence (inability to sleep) and dizziness, although its use is generally not associated with any serious side effects.

Background

Description of the condition

Fibromyalgia (FM) is a multifactorial condition characterised by chronic diffuse musculoskeletal pain, as well as a constellation of symptoms which can include: fatigue, sleep-disturbances, depression and varying degrees of cognitive impairment [Clauw, 2014; Rahman et al, 2014]. Patients frequently report of a reduced quality of life, and this is often due to the inherent disability [Bennett et al, 2007], loss of independence, and extensive use of medical care [Häuser et al, 2015] that is associated with the condition.

The definitive aetiology and pathogenesis of FM remains unknown, although there appears to be a significant degree of variation in its cause and consequence [Clauw et al, 2014] [Rahman et al, 2014]. Due to this in part, the classification of FM is debated, with some rheumatologists considering it to be a specific pain disorder or pain sensitivity syndrome [Clauw, 2014; Yunus, 2008], whereas others coin it a functional somatic syndrome or somatoform disorder [Hauser and Henningsen, 2014].

As described by Sommer et al. [2012], the factors which may predispose, trigger or exacerbate the symptoms of FM are varied, and can include: depression, psychosocial stress (i.e. work and family conflicts), physical stress (i.e. infection, surgery, accidents), genetics, physical and/or sexual abuse experienced in childhood, sleep problems, and other lifestyle choices such as smoking or physical

inactivity (as reviewed by Bellato et al, 2012]). To complicate matters further, comorbidities such as depression and post-traumatic stress disorder (PTSD) are known to worsen symptoms [Lange and Petermann, 2010; Wolfe et al, 2013], suggesting that the condition may perpetuate as a vicious cycle in the absence of appropriate intervention.

Pathophysiological changes which may underlie the development of FM have been described, although their roles in this process are considered speculative [Clauw et al, 2014; Rahman et al, 2014; Sommer et al, 2012]. For example, following the observation that the concentrations of neuroendocrine transmitters (i.e. serotonin, cortisol, substance P and growth hormone) were altered in patients with FM, it was postulated that the dysregulation of the autonomic and/or neuroendocrine system may underlie the pathogenesis of FM [Jahan et al, 2012]. Other possible explanations include alterations to sensory processing in the brain (i.e. due to central sensitisation) [Woolf, 2011], attenuated reactivity of the hypothalamus-pituitary adrenal axis [Ross et al, 2010], and alterations to the balance of anti-inflammatory: pro-inflammatory cytokines [Wallace et al, 2014].

At present, there is no diagnostic test for FM. Although routine laboratory investigations may be considered to support in diagnosis, they are generally avoided unless there is sufficient cause to do so (i.e. swollen joints and suspected rheumatoid arthritis). Instead, a differential diagnosis is established by the individual assessment of a patient's symptoms [Wolfe et al, 2011] using the criteria set by the American College of Rheumatology (ACR) [Wolfe et al, 2010]. This typically involves a discussion between patient and doctor regarding symptoms and their severity, which is then recorded and translated into a score to ascertain the degree of „fibromyalgia-ness" [Wolfe et al, 2010]. Prior to this, the ACR (1990) classification criteria was used, which defined FM as "widespread pain lasting for longer than three months" with "mild or greater" tenderness observed following palpitation at 11 or more of the 18 specified „tender points" (i.e. the sub-occipital muscle insertions) [Wolfe et al, 1990]. The reasons for this change included the fact that clinicians rarely (or inaccurately) performed tender point examination, and there was no comprehensive assessment of symptoms other than pain [Wolfe et al, 2010]. Although a physical examination is no longer required, it is still recommended to identify other possible causes for the patient's symptoms.

It is not uncommon for multiple diagnoses to be made to capture the full spectrum of symptoms. This is due to the considerable overlap between the symptoms of FM and other conditions such as neuropathic pain (20-35% overlap) [Koroschetz et al, 2011]. Subsequently, the ACR (1990) and (2010) diagnostic criteria are often employed in conjunction [Wolfe et al, 1990; 2010].

Today the prevalence of FM is estimated at approximately 2-3% of the general population [Branco et al, 2010; Wolfe et al, 2013], although this may vary between geographic populations [Queiroz et al, 2013] and is likely be higher due to misdiagnosis or under-diagnosis [Wolfe et al, 2013]. FM has typically been considered a female dominated condition, but following the introduction of the ACR (2010) classification criteria the proportion of female to male sufferers was estimated to have changed from ≈8:1 to ≈2:1 [Derry et al, 2016]. It is thought that this was a

result of men having fewer „tender points‟ than women do [Leresche et al, 2011], meaning they were often underdiagnosed using the ACR (1990) tender-point examination. This new value is more consistent with other chronic pain conditions [Vincent et al, 2013] and thought to be a better representation of FM sufferers in the present day.

Generally speaking the management of FM requires a multi-disciplinary approach, with pharmacological interventions being combined with physical and/or cognitive therapy [Okifuji and Hare, 2013]. As there is no universally effective treatment for all FM patients, a multi-pronged approach is employed to manage patients on an individual basis. Pharmacological interventions include: conventional analgesics, anti-depressants (i.e. serotonin-noradrenaline reuptake inhibitors) [Lunn et al, 2014; Wolfe et al, 2013], tricyclic agents (i.e. amitriptyline) [Moore et al, 2015] and anticonvulsants like pregabalin [Derry et al, 2016; Okifuji and Hare, 2013].

Description of the intervention

Pregabalin is a successor to gabapentin and was introduced as an anti-convulsive agent for patients with epilepsy in 2004. In the United Kingdom (UK), pregabalin is approved for the treatment of peripheral and central neuropathic pain, epilepsy and generalised anxiety disorder; however, it is not currently licensed for the treatment of FM. Pregabalin was first licenced for the treatment of FM in 2007, and is currently used in the USA, Canada, and a number of countries in South America, the Middle East, and Asia. Guidance from the National Institute for Health and Care Excellence (NICE) suggests that treatment with pregabalin should be initiated at a relatively low dose of 150 mg daily. This is generally split into 2-3 divided doses and may be increased after 3-7 days to 300mg daily, or to a maximum of 600mg daily after a further 7 days. Generally speaking this depends on the individual’s response and tolerability to pregabalin, and is left to the discretion of the patient-practitioner.

How the intervention might work

Pregabalin is broadly defined as a gamma-aminobutyric acid (GABA)-analogue, but its mechanism of action is not thought to involve direct interaction with the GABAreceptor [Bhusal et al, 2016; Taylor et al, 2007]. This is because pregabalin was shown to be pharmacologically inactive at GABA radio-ligand binding sites; and the observation that the action of pregabalin was not diminished following co-administration with GABA-receptor antagonists/agonists [Taylor et al, 2007].

The accepted model explaining pregabalins' mechanism of action is thought to involve two different and possibly inter-dependent pathways: - the interaction with presynaptic voltage-gated calcium ion channels, and the subsequent activation of postsynaptic N-methyl-D-aspartate (NMDA) receptors [Bhusal et al, 2016]. Pregabalin binds with high affinity to the α-2-δ subunits of the type 1 voltage-gated calcium channels found on the presynaptic neurones to induce an allosteric change between the calcium channel and proteins of the synaptic vesicle (i.e. syntaxin). Ultimately, this reduces the ability of vesicles to fuse and release neurotransmitters (i.e. glutamate, noradrenaline and substance P) into the synaptic cleft [Bhusal et al, 2016; Taylor et al, 2007], conferring the anti-epileptic, analgesic and anxiolytic effects of pregabalin [Bhusal et al, 2016].

Why is it important to do this review?
FM is foremost characterised by chronic diffuse pain. At present, the proportion of patients with chronic pain who achieve significant pain relief following treatment is only estimated at ≈30-50% [Moore et al, 2013]; this value is likely to be even lower for patients with FM [Wiffen et al, 2013]. That being said, patients who do achieve significant pain relief can experience substantial improvements to their quality of life, as well as marked improvements to comorbid symptoms such as fatigue. [Moore et al, 2010].

This review aimed to collate reliable and robust evidence regarding the efficacy and tolerability of pregabalin for the management of FM. Unlike other reviews, this paper aimed to investigate the scope of the condition by analysing the effects of pregabalin on multiple symptoms using outcomes which were deemed clinically significant. Ultimately, the aim was to develop a greater understanding regarding the utility of pregabalin as a standalone treatment for the management of FM in adults.

Objectives
To assess the efficacy and tolerability of pregabalin for the management of FM in adults compared to placebo.

Methods
Criteria for considering studies for this review include:

Types of studies
The studies included in this review were full journal publications of randomised controlled trials (RCTs) which employed a double-blind experimental procedure and lasted for eight weeks or longer. All studies obtained written consent in accordance with the Declaration of Helsinki. Furthermore, trials were required to have at least 20 participants per treatment arm because of the growing evidence of bias in small studies [Dechartres et al, 2013].

Types of participants
Studies included adult participants aged 18 years and above, male or female (neither pregnant nor lactating), with a clinical diagnosis of FM using either the ACR (1990) or (2010) classification criteria [Wolfe et al, 1990] [Wolfe et al, 2010]. Participants were also required to have pain scores of ≥40 mm on the 100-mm visual analogue scale (VAS) following the cessation of any relevant pain or sleep medication(s), as well as a mean pain score of ≥4 (as recorded daily in a pain diary in the week prior to randomisation).

Exclusion criteria included: the evidence of inflammatory or rheumatic diseases other than FM, active infections or malignancies, severe depression, untreated endocrine disorders, concurrent neuropathic disorders; as well as any other condition(s) which may have compromised the reliability of this investigation. Participants who had taken pregabalin in the past and had been non-responsive to treatment were also excluded.

Types of interventions
The studies included in this review investigated the efficacy and tolerability of pregabalin, administered at any dose, by any route, for the management of FM

compared to a placebo. With the exception of aspirin (≤325 mg/day) and paracetamol (≤4 g/day), the use of anti-convulsants (other than pregabalin), antidepressants and other medications for pain and insomnia were prohibited. The use of non-pharmacologic interventions (i.e. physical therapy) was permitted.

Types of outcome measures

The outcome measures for this review related to the efficacy and tolerability of pregabalin for the management of FM. They were derived in part from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) [Dworkin et al, 2008], as well as the Outcomes Measures in Rheumatology (OMERACT) Fibromyalgia Working Group [Mease et al, 2009] and the best practice in the reporting of systematic reviews in chronic pain [Moore et al, 2010b].

„Key symptom domains" defined by FM sufferers and experts [Dworkin et al, 2008; Mease et al, 2009] were used to inform of the most clinically significant outcomes for use in this review. For example, as most patient's view of a successful outcome for chronic pain involved at least a 50% reduction in pain intensity [O'Brien et al, 2010] [Moore et al, 2013], this was deemed clinically significant and included as a primary outcome.

As FM is associated with a multitude of symptoms, the efficacy of pregabalin was also measured by its ability to address a number of other clinically significant outcomes, including improvements to self-reported fatigue, sleep problems, symptoms of anxiety and depression, as well as health-related quality of life.

The safety and tolerability of pregabalin was defined by the incidence of (serious) adverse effects, and participant withdrawal as a consequence. Additionally, the incidence of self-reported dizziness and somnolence were used to support this outcome as they are the two most frequent adverse effects of pregabalin [Toth et al, 2014].

Primary outcomes

1. Reduction in mean pain score
2. Participant-reported pain reduction of 50% or greater
3. PGIC „much or very much improved"
4. Self-reported fatigue (MAF-score)
5. Self-reported sleep problems (MOS-sleep scale)
6. Self-reported quality of life (SF-36)
7. Self-reported anxiety and depression (HADS-score)

Secondary outcomes

1. Participant-reported pain reduction of 30% or greater
2. Participant-withdrawals due to adverse events
3. Participants experiencing any serious adverse event (i.e. any adverse event or effect that, at any dose, results in death, is life-threatening, requires hospitalisation, results in persistent or significant disability/incapacity, is a congenital anomaly or birth defect, is an „important medical event" that may

jeopardise the patient, or may require intervention to circumvent the aforementioned characteristics or consequences).
4. Participants experiencing any specific adverse events, namely dizziness and somnolence

Search methods for identification of studies:

Electronic searches
Electronic searches were performed using the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 1, 2017), MEDLINE accessed through PubMed (1966 to December 2016) and www.clinicaltrials.gov (website of the US National Institute of Health) to December 2016 for unpublished clinical trials.

Searching other resources
Searches were performed on the bibliographies of existing reviews to retrieve relevant articles (i.e. RCTs).

Data collection and analysis

Selection of studies
The titles and abstracts of potential studies were scrutinised to determine their eligibility for inclusion. Those which obviously did not satisfy the basic inclusion criteria (i.e. double-blind, RCT) were excluded outright. Full copies of potential studies were obtained and read in-depth to ascertain their eligibility for inclusion. Included is a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart (figure 1).

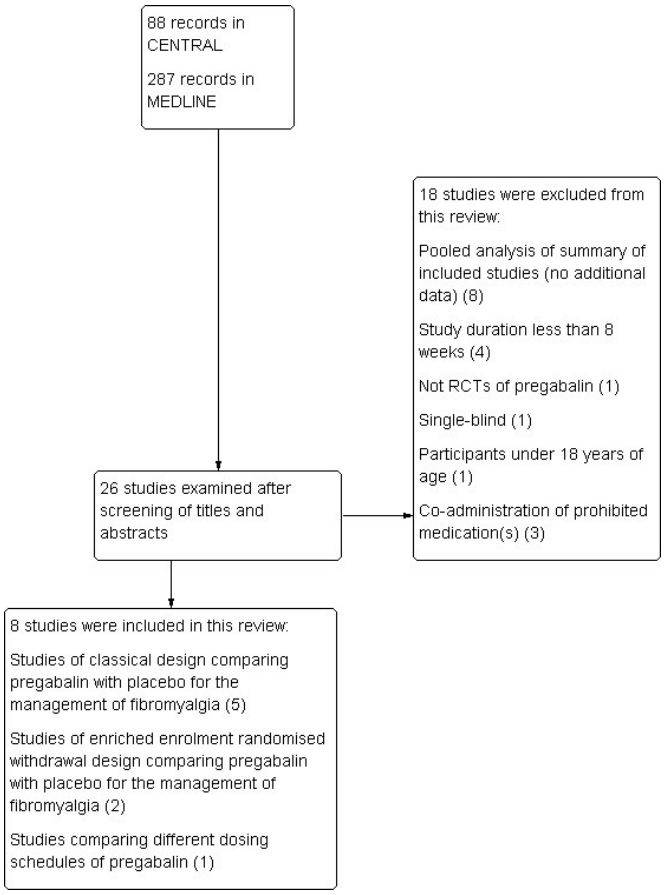

Figure 1: Study flow diagram

Data extraction and management

Data was extracted and double-checked for accuracy prior to entry into Review Manager 5 [RevMan, 2014].

Assessment of risk of bias in included studies

The Oxford Quality Score was employed as the basis for inclusion [Jadad et al, 1996], meaning studies had to be randomised and double-blind as a bare minimum. The risk of bias for each study was determined using the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions.*

1. Random sequence generation (selection bias): Selection bias was deemed as being either a „low‟ or „unclear risk‟ depending on whether or not the methods used to generate random allocation sequences (i.e. computer random number generator) was described. Non-randomised processes were deemed as having a high risk of selection bias and were not included in this review.

2. Allocation concealment (selection bias): Depending on whether the method used to conceal allocation sequences to interventions was described in sufficient detail (i.e. telephone randomisation), studies were deemed as being either „low risk‟ or „unclear risk‟ respectively. Studies which did not conceal

allocation sequences to interventions were deemed as having a high risk of selection bias and were not included in this review.

3. Blinding of participants and personnel (performance bias): Performance bias was deemed as being „low risk‟ if the measures used to blind participants and personnel from knowing which intervention a participant had received was described (i.e. use of identical tablets, matched in appearance and smell). Studies which state to be blinded but did not describe such measures were deemed as having an „unclear risk‟ of performance bias. Studies which were not double-blinded were excluded from this review.

4. Blinding of outcome assessments (detection bias): Studies were deemed as having a low risk of detection bias if the measures used to blind outcome assessors from which intervention a participant received was described. Studies which state to be blinded, but did not describe such measures were deemed as having an „unclear risk‟ of detection bias. Studies which were not double-blinded were excluded from this review.

5. Incomplete outcome data (attrition bias): Studies were deemed as having a low risk of attrition bias if the measures used to deal with incomplete data were described (i.e. baseline-observation carried forward), or less than 10% of participants did not complete the study. Alternatively, studies were labelled as having an „unclear risk‟ of attrition bias if last observation carried forward (LOCF) imputation was used. This is due to the fact that LOCF imputation has the potential to over-estimate or underestimate the magnitude of treatment effect.

6. Selective outcome reporting (reporting bias): Studies were deemed as having a „low risk‟ of reporting bias if all relevant outcomes had been reported. If this was not the case, reporting bias was stated as being „high risk‟.

7. Other sources of bias: Due to the growing evidence of the risk of bias in small studies [Dechartres et al, 2013], those with less than 199 participants, or less than 50 participants per treatment arm were deemed as having either an „unclear risk‟ of bias or „high risk‟ of bias respectively.

Measures of treatment effect

For dichotomous outcomes the measure of treatment effect was determined by the relative risk ratio (RR). Additionally, the numbers needed to treat for an additional beneficial (NNTB) or harmful (NNTH) outcome was calculated for statistically significant results using guidance from [Cook and Sackett, 1995].

For continuous outcomes, the standardised mean difference (SMD) was calculated. This is because different assessment measures were employed between studies (i.e. psychometric scales for depression), and the SMD can standardise the results to a uniform scale. The magnitude of effect size was ascertained using Cohen's categories whereby small effects: SMD =0.2; medium effects: SMD = 0.5; and large effects: SMD = 0.8 [Cohen, 2013]. The expanded descriptors for effect size

described by [Sawilkowsky, 2009] (i.e. SMD = <0.2 = very small) were also employed in this review.

Uncertainty was expressed using 95% confidence intervals (CIs) using a random model.

Unit of analysis issues
When multiple doses of pregabalin were being compared to a single placebo group, the number of participants in the placebo group was split between the different doses of the pregabalin group.

Dealing with missing data
An intention-to-treat (ITT) analysis was performed for participants who did not comply with the treatment protocol. However, this was only possible for participants who had been randomised and taken at least one dose of pregabalin to provide a post-baseline assessment; they were otherwise assigned zero improvement.

Unless otherwise stated, standard deviation (SD) was extracted from existing meta analyses or calculated from t-values, confidence intervals or standard errors.

Assessment of heterogeneity
Statistical heterogeneity was assessed using the I^2 statistic, which describes "the percentage of total variation across studies that is due to heterogeneity rather than chance" [Higgins et al, 2003]. An I^2 value of ≥25% indicates low heterogeneity; 2550% indicates moderate heterogeneity; and ≥50% indicates significant heterogeneity [Higgins et al, 2003].

Assessment of reporting biases
Reporting bias was assessed by inspection, ensuring there were no discrepancies between the results of quantitative analyses and the purported outcomes stated in the methods section.

Data synthesis
Each meta-analysis was performed using a random effects model in RevMan5 [RevMan, 2014].

Subgroup analysis and investigation of heterogeneity
Subgroup comparisons were performed for the different doses (150, 300, 450 and 600 mg daily) of pregabalin to ascertain whether there was a significant difference regarding their efficacy and tolerability.
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Sensitivity analyses
No sensitivity analyses were performed.

Results

Description of studies

This paper includes eight studies which were all full journal publications. They included: Arnold et al, [2008; 2014], Crofford et al, 2005; 2008], Mease et al, [2008], Nasser et al, [2014], Ohta et al, [2012] and Pauer et al, [2011].

Results of the search

A total of 26 studies were examined for possible inclusion in this review, 8 of which were included and 18 were excluded (see figure 1). Additionally, an on-going study was identified on Clinicaltrials.gov (NCT02146430).

Included studies

A total of 8 studies were included in this review, including 5 studies (3812 participants) of „classical" design [Arnold et al, 2008], [Crofford et al, 2005; Mease et al, 2008; Ohta et al, 2012; Pauer et al, 2011] and two studies (687 participants) of an „enriched enrolment randomised withdrawal (EERW) design" [Arnold et al, 2014; Crofford et al, 2008]. There was one study which compared a single nightly dose of pregabalin with twice-daily dosing [Nasser et al, 2014] but was not included in the analysis.

- Classical Design: Participants were randomised to pregabalin or placebo at the start of the trial using fixed-dose titrations.

- EERW Design: Participants underwent fixed-dose titrations to effect/tolerance with pregabalin. Those successfully reaching targets were then randomised a second time to continue receiving pregabalin, or to undergo a phased withdrawal of pregabalin to placebo.

The vast majority of participants in these studies were female (89%-95%) and of Caucasian ethnicity (76%-96%); the mean age of participants was 47 to 50 years.

There was a significant degree of geographical variation with regards to where the studies were performed, including Canada and the US, Australia, Asia and Europe. All participants were diagnosed with FM in accordance with either the ACR (1990) [Wolfe et al, 1990] or ACR (2010) criteria [Wolfe et al, 2010]. Where mentioned, participants reported their symptoms to have lasted for an average of ≈4 years.

Of the studies of classical design, three lasted eight weeks [Arnold et al, 2007; Crofford et al, 2005; Nasser et al, 2014], and the rest lasted for 13-14 weeks [Arnold et al, 2008; Mease et al, 2008; Ohta et al, 2012; Pauer et al, 2011].
Of the EERW studies, Arnold et al, [2014] had a double-blind treatment period of 13 weeks following randomisation, and Crofford et al, [2008] had a double-blind treatment period of 26 weeks following randomisation.

All the included studies investigated the efficacy and tolerability of pregabalin for the treatment of FM. Of the studies of classical design, four tested fixed doses of

pregabalin at 300, 450 and 600mg daily against placebo [Arnold et al, 2008; Mease et al, 2008; Pauer et al 2011]; one included a 150mg daily dose (in addition to 300 and 400 mg daily) [Crofford et al, 2005]; and the study by Ohta et al, [2012] utilised a flexible dose of 300/450mg daily. Of the EERW studies, Arnold et al, [2014] used pregabalin controlled release of doses 330 to 495mg daily, whereas Crofford et al, [2008] used fixed doses of 300, 450 and 600mg daily.

Various outcomes were investigated, including pain, fatigue, self-reported sleep problems, depression, anxiety and health-related quality of life.
It is important to note that the studies of EERW design investigated the primary outcome as the loss of therapeutic response (LTR). As this outcome is fundamentally different to studies of classical design, they are considered separately in this review.

Excluded studies
A total of 18 studies were excluded from this review, including: Arnold et al, [2007; 2012; 2014b; 2014c; 2015; 2016]; Byon et al, [2010]; Emir et al, [2010]; Hauser et al, [2009]; Moore et al, [2007; 2009]; Ohta et al, [2013]; Ramzy et al, [2016]; Roth et al, [2012]; Russel et al, [2009], NCT00760474, NCT01268631 and NCT01904097. The reasons for exclusion are described in the *characteristics of studies* table.

Risk of bias in included studies
Figure 2 shows the overall „Risk of bias" assessment for included studies. „Risk of bias assessments for each criterion is shown in figure 3 and the *characteristics of included studies* table.

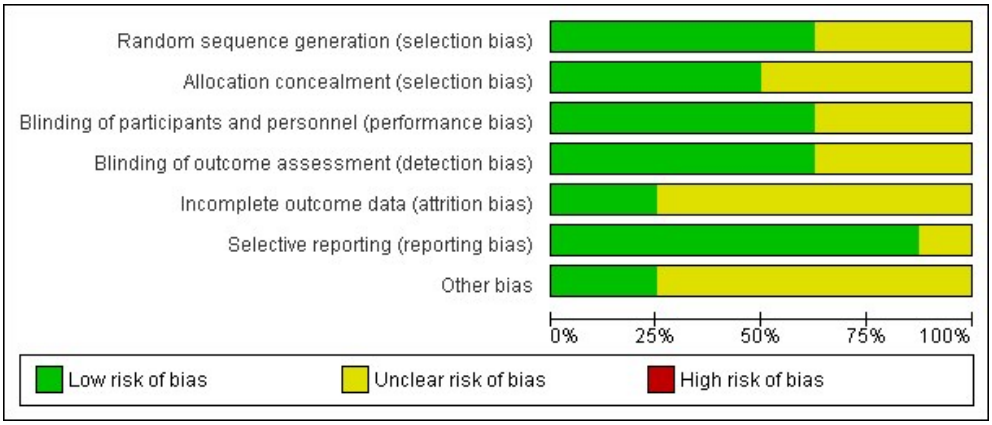

Figure 2: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

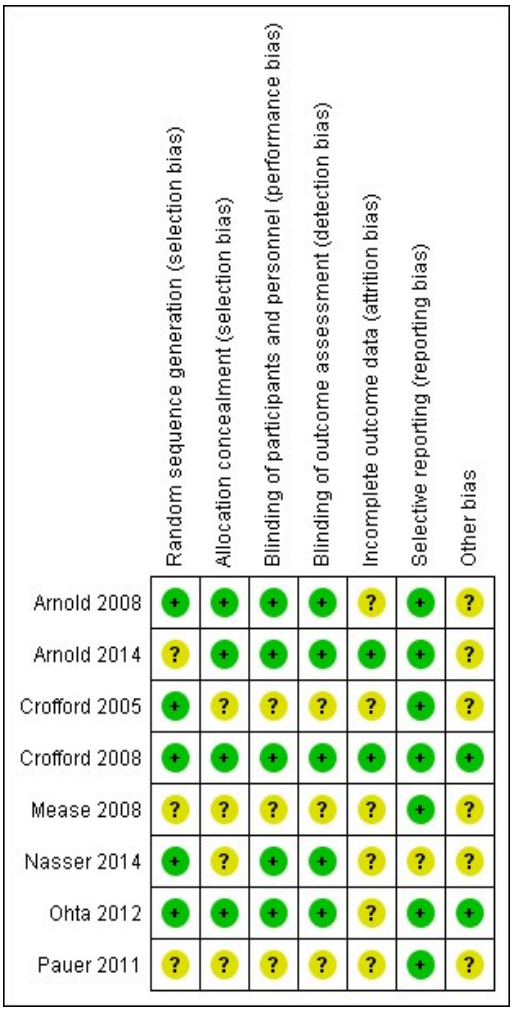

Figure 3: Risk of bias summary: review authors' judgements about each risk of bias item for each included study

Allocation

Of the included studies (all of which were randomised), five provided descriptions for the methods used to generate random sequences. These included: Arnold et al, [2008]; Crofford et al, [2005; 2008], Nasser et al, [2014] and Ohta et al, [2012]. Arnold et al, [2008], Crofford et al, [2008] and Ohta et al, [2012] provided adequate descriptions for the methods used to facilitate allocation concealment, but Crofford et al, [2005], Mease et al, [2008], Nasser et al, [2014] and Pauer et al, [2011] did not.

Blinding

All the included studies were described as double-blind, however, Crofford et al, [2005], Mease et al, [2008] and Pauer et al, [2011] did not provide adequate descriptions for the methods used to ensure that participants and personnel were unable to differentiate between pregabalin and placebo.

Incomplete outcome data

Despite the studies by Arnold et al, [2014] and Crofford et al, [2008] whom had no missing data, the studies of classical design [Arnold et al, 2008; Crofford et al, 2005; Mease et al, 2008; Ohta et al, 2012; Pauer et al, 2011]) used last observation carried

forward (LOCF) imputation for missing data. Nasser et al, [2014] did not provide any information regarding the imputation method for missing data.

Selective reporting
All the relevant outcomes of the included studies were reported.

Other potential sources of bias
No other significant sources of bias were noted.

Effects of interventions

Because the outcomes investigated in studies of classical design and EERW design are fundamentally different, they are considered separately.

1. Studies of classic design
Pregabalin at varying doses (150, 300, 450 and 600mg) was administered in two parts per day and compared with placebo. The study by [Nasser et al, 2014] compared the benefit of nightly dosing versus twice daily dosing but found no benefit. Efficacy outcomes for the included studies are described below.

Primary outcomes

Pregabalin versus placebo: reduction in mean pain score following treatment:

Five studies with a total of 3252 participants were entered into RevMan5 for analysis of the effect of pregabalin on reducing mean pain scores (figure 4). The overall effect of pregabalin on the reduction of mean pain scores was statistically significant (SMD: -0.26; 95% CI; -0.34 to -0.19; P = <0.00001), but based on Cohen's categories the magnitude of effect following treatment was small (SMD <0.5). There were no statistically significant overall differences regarding the efficacy of each dose in reducing mean pain scores following treatment (P = 0.64).

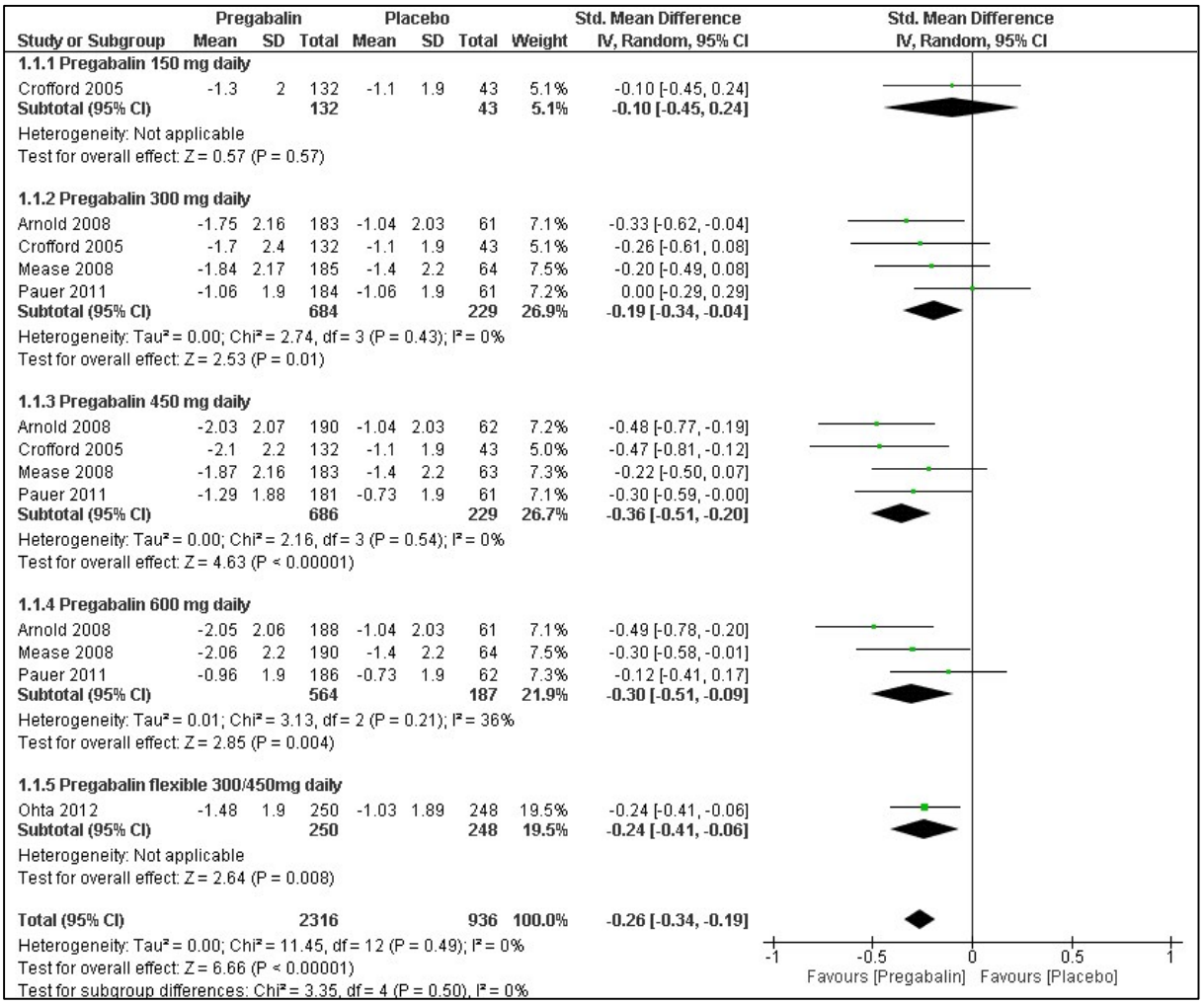

Figure 4: Forest plot of comparison: Pregabalin versus placebo, outcome 1.1: reduction in mean pain scores following treatment.

<u>Pregabalin versus placebo: at least a 50% reduction in pain intensity from baseline following treatment:</u>

Five studies with a total of 3256 participants were entered into RevMan5 for analysis of the ability of pregabalin to reduce pain intensity by ≥50% (figure 5). A total of 514/2319 (22.2%) and 128/937 (13.7%) participants achieved ≥50% pain reduction following treatment with either pregabalin or placebo respectively. The overall effect of pregabalin in reducing pain intensity by ≥50% was statistically significant (RR: 1.61; 95% CI; 1.35 to 1.93; P = 0.00001); the NNTB by pregabalin over placebo was ≈12. There were no statistically significant overall differences regarding the efficacy of each dose in achieving a ≥50% reduction in pain intensity following treatment (P = 0.59).

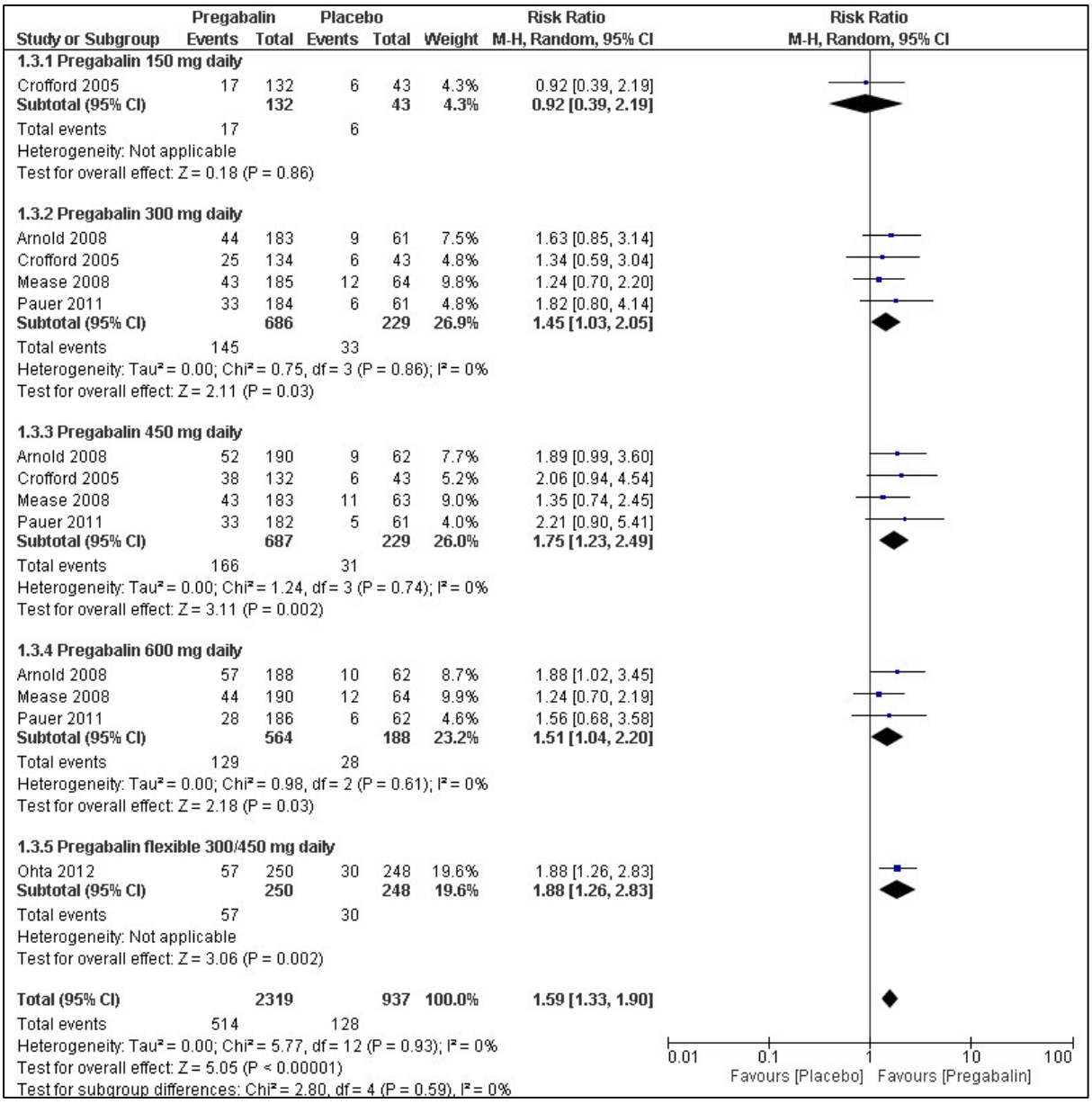

Figure 5: Forest plot of comparison: Pregabalin versus placebo, outcome 1.3: participants achieving at least 50% reduction in pain intensity following treatment.

Pregabalin versus placebo: PGIC 'much or very much improved' following treatment:

Five studies with a total of 3183 participants were entered into RevMan5 for analysis of the effect of pregabalin on patient global impression of change (PGIC) (figure 6). A total of 892/2265 (39.4%) and 256/918 (27.9) participants reported a „much or very much improved" PGIC following treatment with pregabalin or placebo respectively. The overall effect of pregabalin in producing such improvements to PGIC was statistically significant (RR: 1.40; 95% CI; 1.25 to 1.58; P = 0.00001); the NNTB by pregabalin over placebo was ≈9. There were no statistically significant overall differences regarding the efficacy of each dose in achieving a „much or very much improved" PGIC following treatment (P = 0.84).

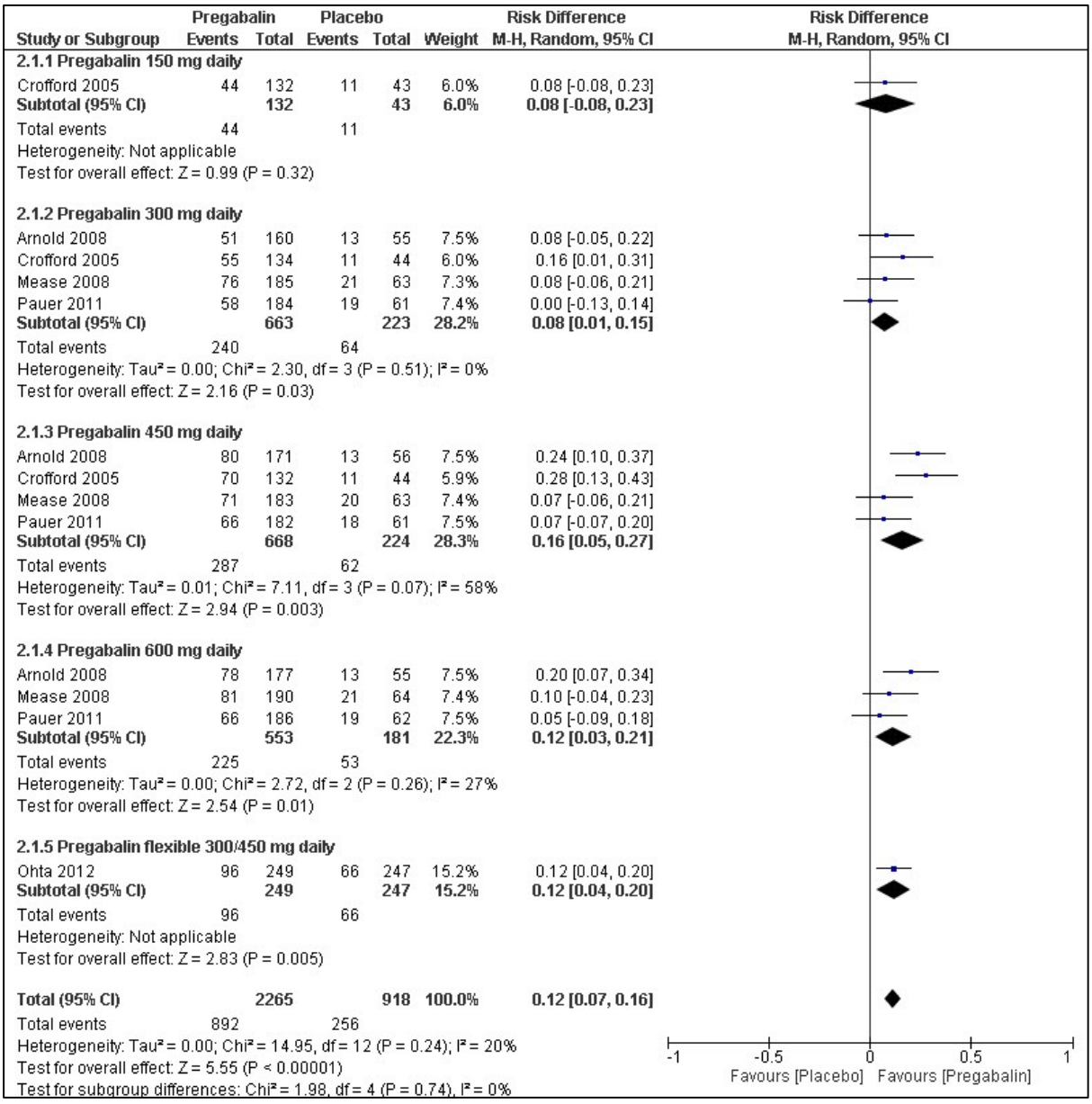

Figure 6: Forest plot of comparison: Pregabalin versus placebo, outcome 2.1: number of participants with PGIC „much or very much improved" following treatment.

<u>Pregabalin versus placebo: improvements to self-reported fatigue following treatment:</u>

Five studies with a total of 3195 participants were entered into RevMan5 for analysis of the effect of pregabalin in reducing self-reported fatigue (figure 7). The overall effect of pregabalin on the reduction of self-reported fatigue was statistically significant (SMD: -0.17; 95% CI; -0.25 to -0.09; P = <0.0001), but based on Sawilkowsky's expanded categories the magnitude of effect following treatment was „very small" (SMD <0.2). There were no statistically significant overall differences regarding the efficacy of each dose in improving self-reported fatigue (P = 0.49).

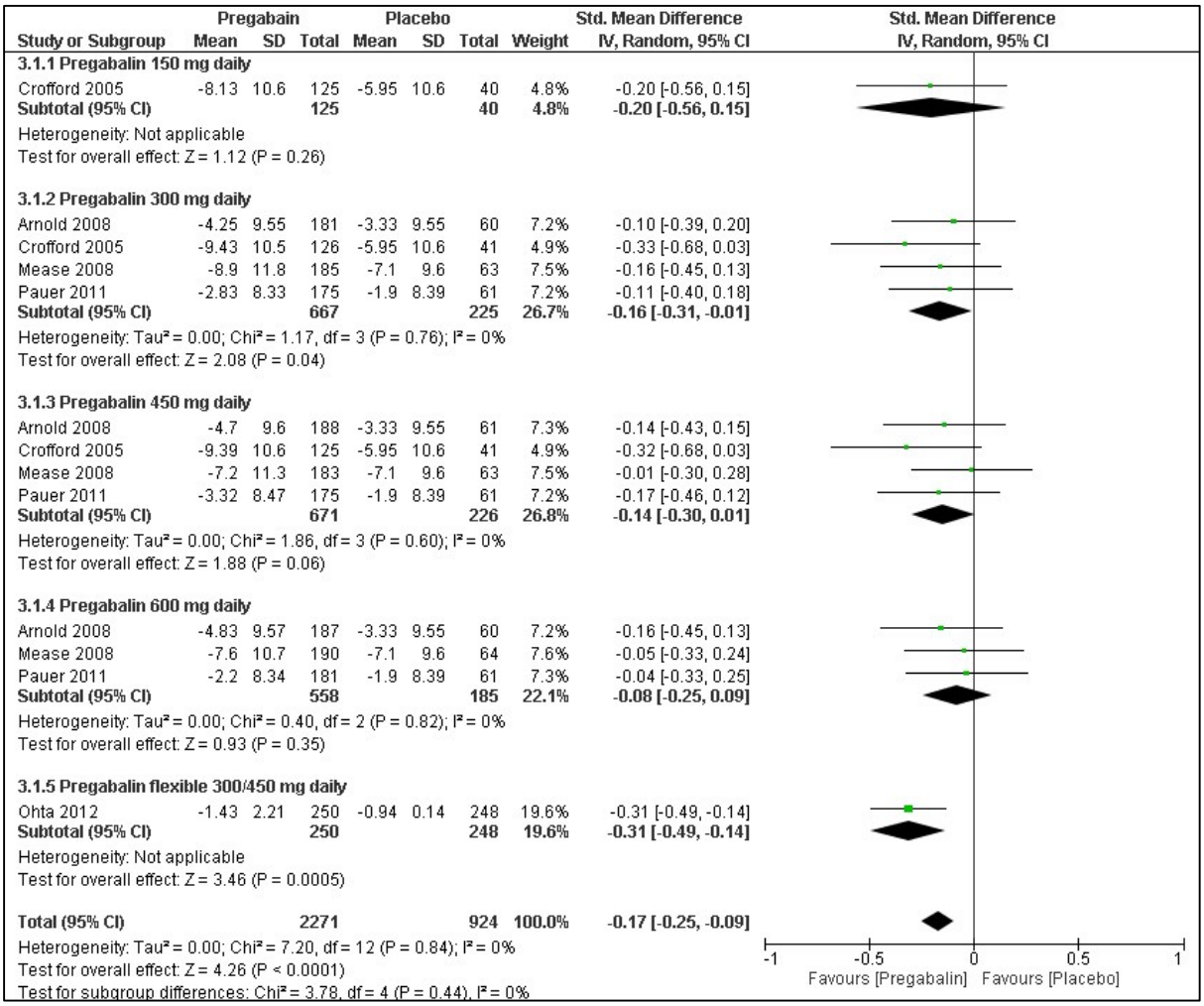

Figure 7: Forest plot of comparison: Pregabalin versus placebo, outcome 3.1: Change in mean multidimensional assessment of fatigue (MAF) score following treatment

<u>Pregabalin versus placebo: improvements to self-reported sleep problems following treatment:</u>

Five studies with a total of 3193 participants were entered into RevMan5 for analysis of the effect of pregabalin in reducing self-reported sleep problems (figure 8). The overall effect of pregabalin on the reduction of self-reported sleep problems was statistically significant (SMD: -0.34; 95% CI; -0.42 to -0.27; P = <0.0001), but based on Cohen's categories the magnitude of effect following treatment was small (SMD <0.5). There were no statistically significant overall differences regarding the efficacy of each dose in improving self-reported sleep problems following treatment (P = 0.29).

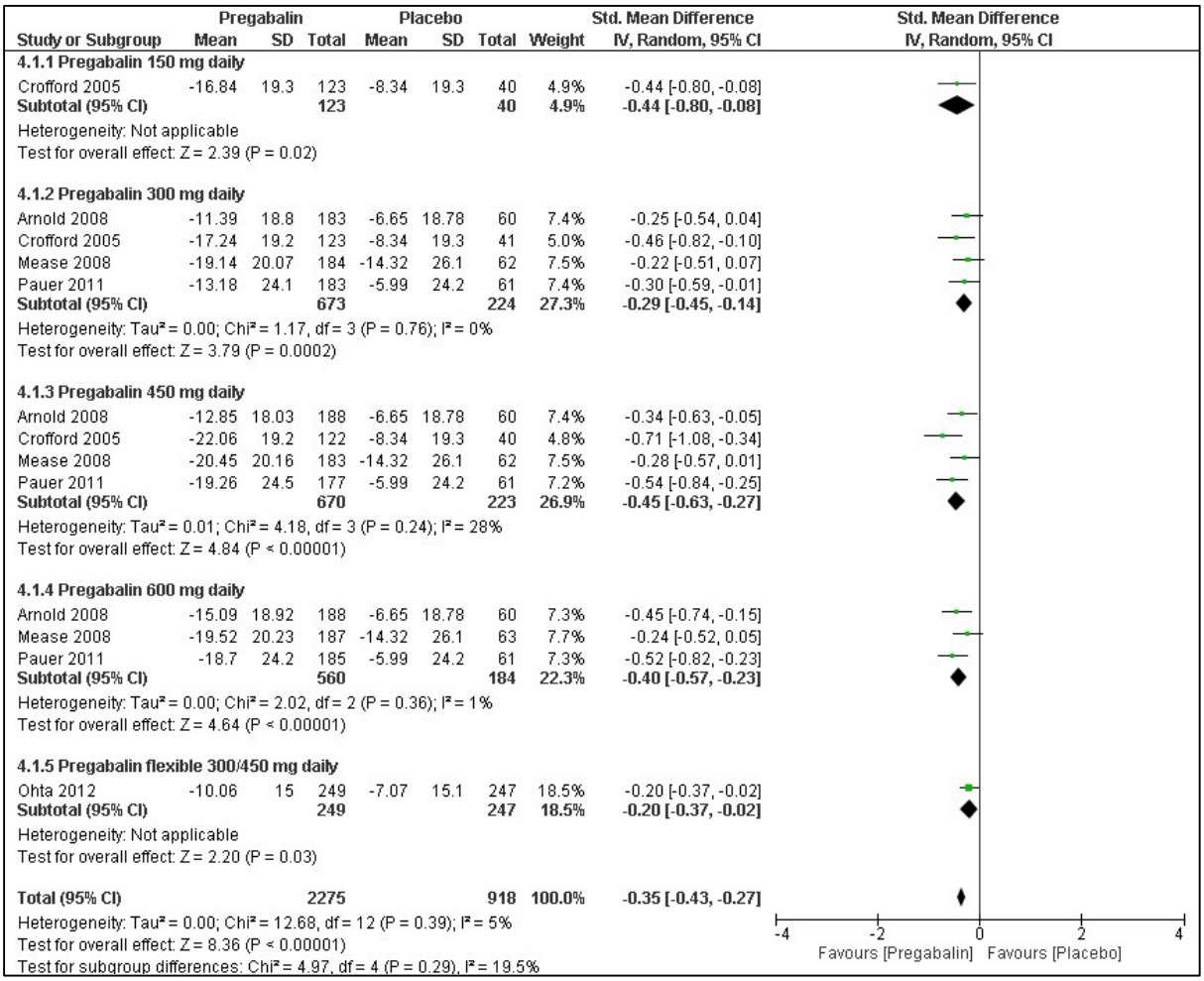

Figure 8: Forest plot of comparison: Pregabalin versus placebo, outcome 4.1: Change in mean medical outcomes study (MOS) sleep index scale score following treatment

<u>Pregabalin versus placebo: improvements to self-reported quality of life following treatment:</u>

Four studies with a total of 2724 participants were entered into RevMan5 for analysis of the effect of pregabalin in improving self-reported quality of life (figure 9). The overall effect of pregabalin on improvements to self-reported quality of life was statistically significant (SMD: -0.17; 95% CI; -0.26 to -0.09; P = <0.0001), but based on Sawilkowsky's expanded categories the magnitude of effect following treatment was very small-small (SMD <0.2). There were no statistically significant overall differences regarding the efficacy of each dose in improving self-reported quality of life (P = 0.75).

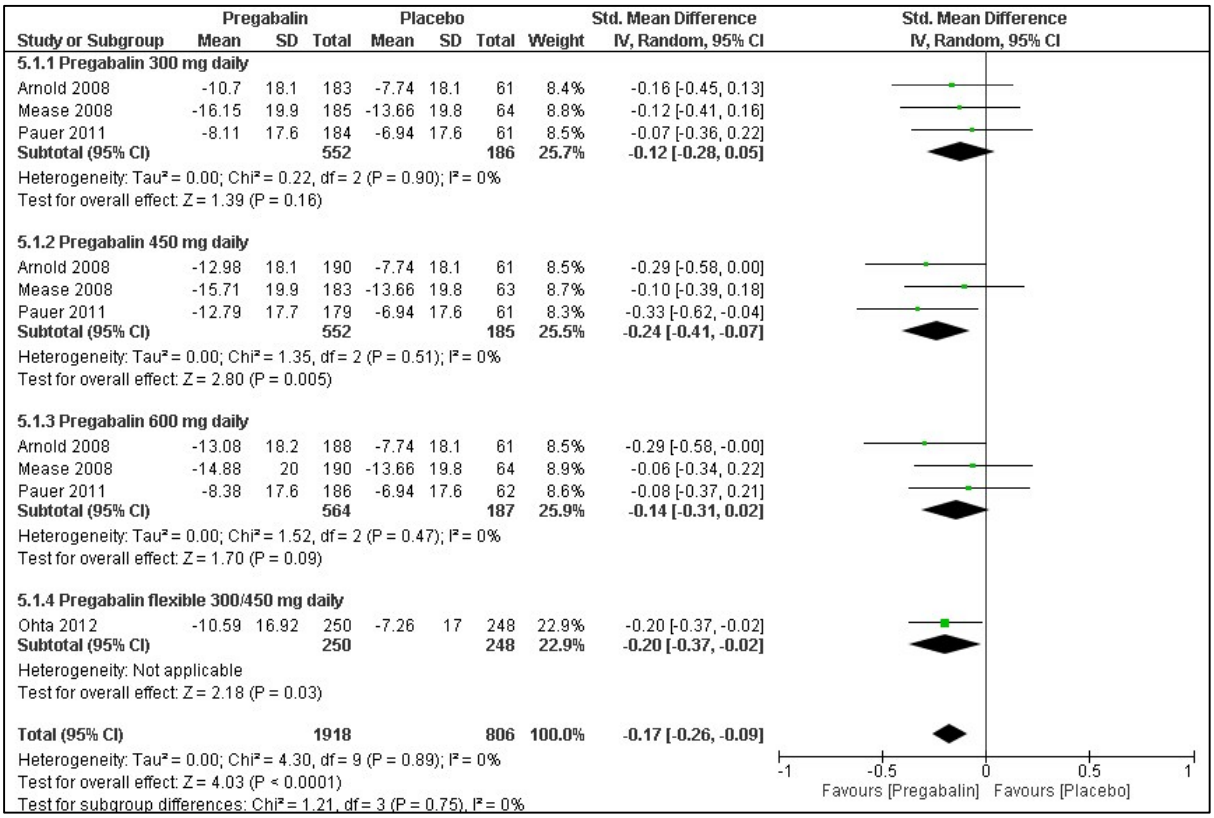

Figure 9: Forest plot of comparison: Pregabalin versus placebo, outcome 5.1: Change in mean short form 36 (SF-36) score (health related quality of life) following treatment.

Pregabalin versus placebo: improvements to self-reported anxiety following treatment:

Five studies with a total of 3215 participants were entered into RevMan5 for analysis of the effect of pregabalin on improvements to self-reported anxiety (figure 10). The overall effect of pregabalin on improvements to self-reported anxiety was statistically significant (SMD: -0.13; 95% CI; -0.21 to -0.06; P = <0.0007), but based on Sawilkowsky's expanded categories the magnitude of effect following treatment was very small (SMD: <0.2). There were no statistically significant overall differences regarding the efficacy of each dose in reducing self-reported anxiety (P = 0.65).

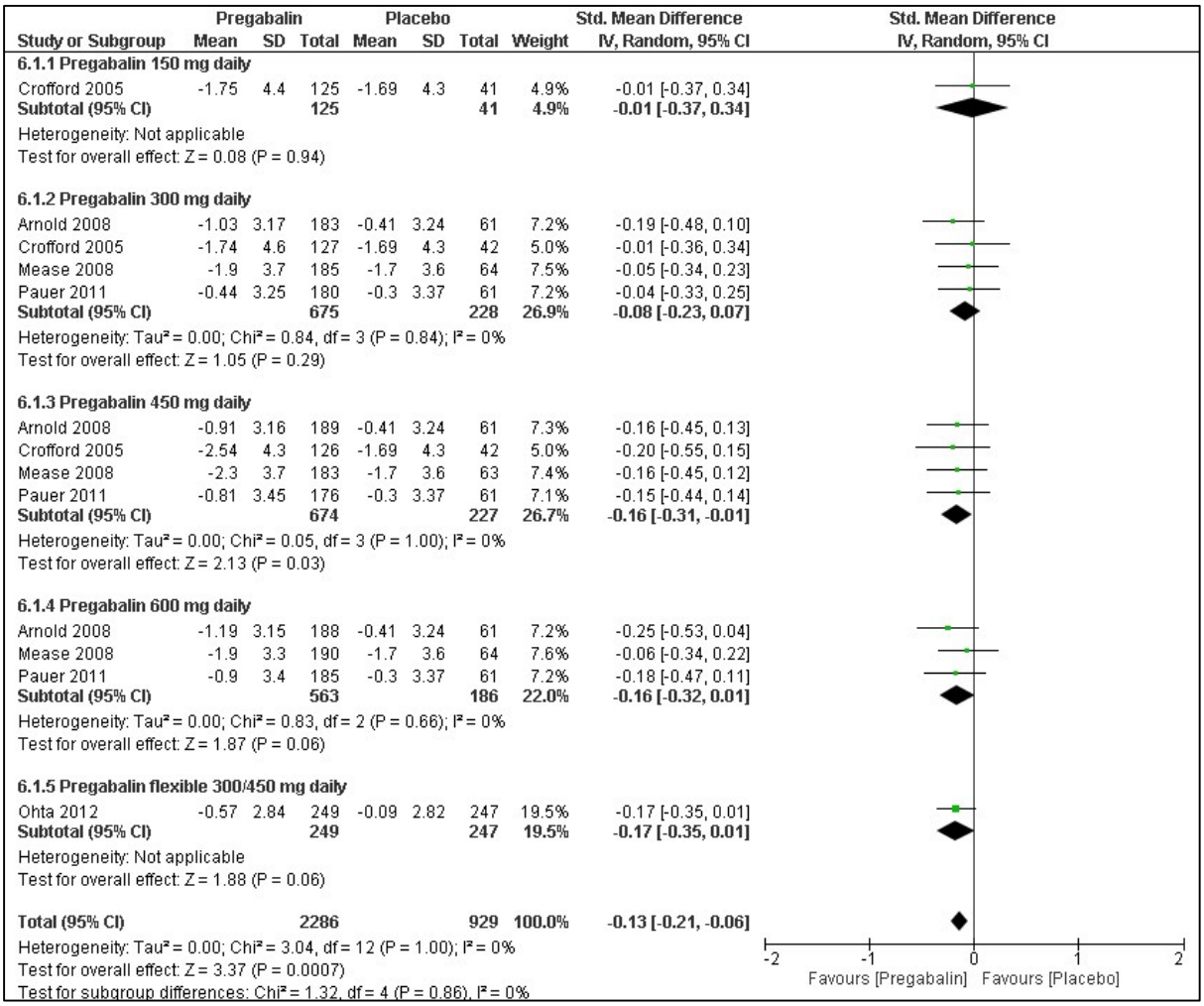

Figure 10: Forest plot of comparison: Pregabalin versus placebo, outcome 6.1: Change in HADS anxiety score following treatment.

Pregabalin versus placebo: improvements to self-reported depression following treatment:

Five studies with a total of 3209 participants were entered into RevMan5 for analysis of the effect of pregabalin on improvements to self-reported depression (figure 11). The overall effect of pregabalin on improvements to depression was statistically significant (SMD: -0.10; 95% CI; -0.18 to -0.02; P=0.01), but based Sawilkowsky's expanded categories the magnitude of effect following treatment was very small (SMD: <0.2). There were no statistically significant overall differences regarding the efficacy of each dose in reducing self-reported depression (P = 0.96) following treatment.

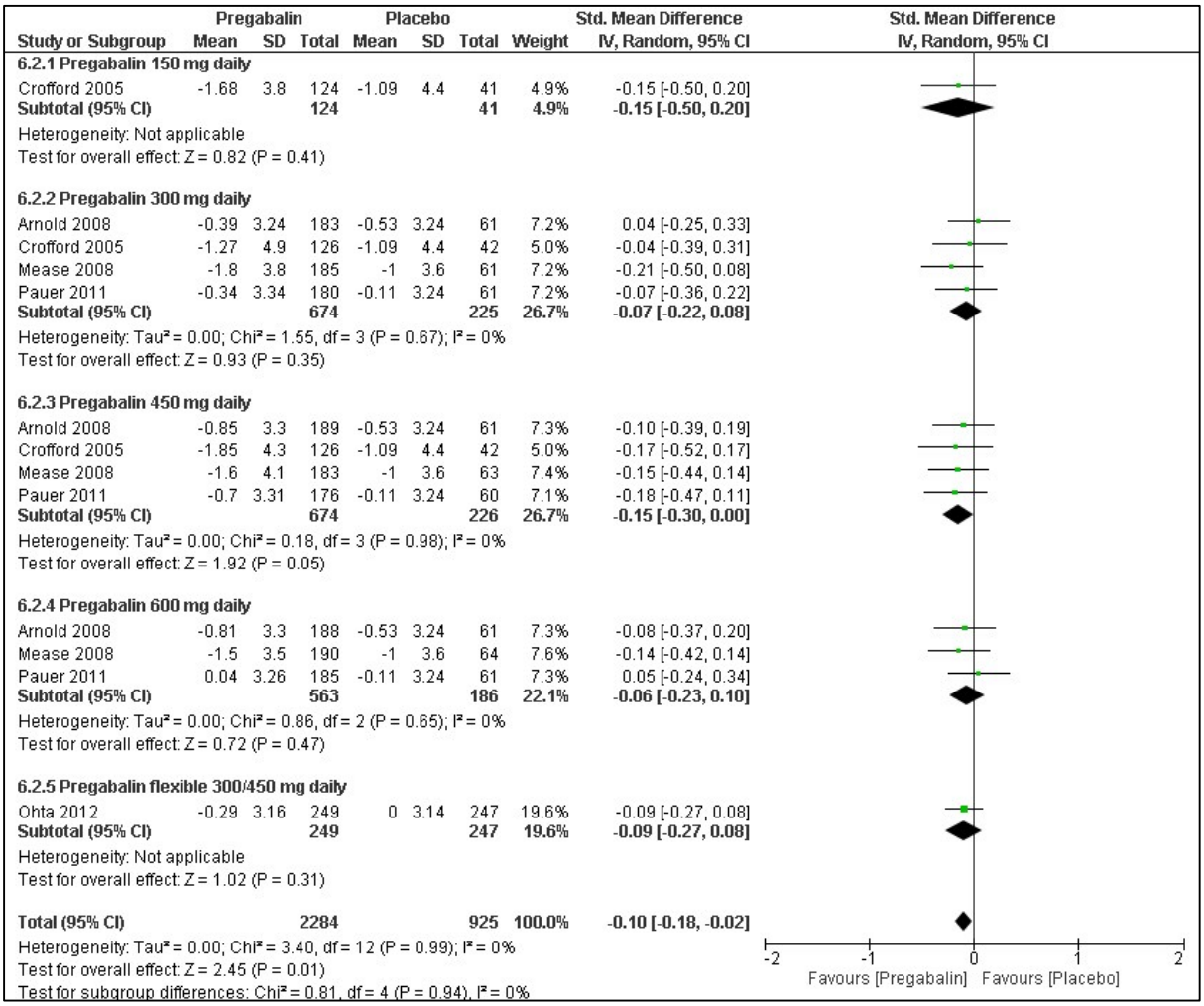

Figure 11: Forest plot of comparison: Pregabalin versus placebo, outcome 6.2: Change in HADS depression score following treatment.

Secondary outcomes:

Pregabalin versus placebo: at least a 30% reduction in pain intensity from baseline following treatment:

Five studies with a total of 3259 participants were entered into RevMan5 for analysis of the ability of pregabalin to reduce pain intensity by ≥30% (figure 12). A total of 928/2319 (40.0%) and 274/940 (29.1%) participants achieved ≥30% pain reductions following treatment either pregabalin or placebo respectively. The overall effect of pregabalin in reducing pain intensity by ≥30% was statistically significant (RR: 1.38; 95% CI; 1.23 to 1.55; P = 0.00001); the NNTB by pregabalin over placebo was ≈9. There were no statistically significant overall differences regarding the efficacy of each dose in in achieving a ≥30% reduction in pain intensity following treatment (P = 0.79).

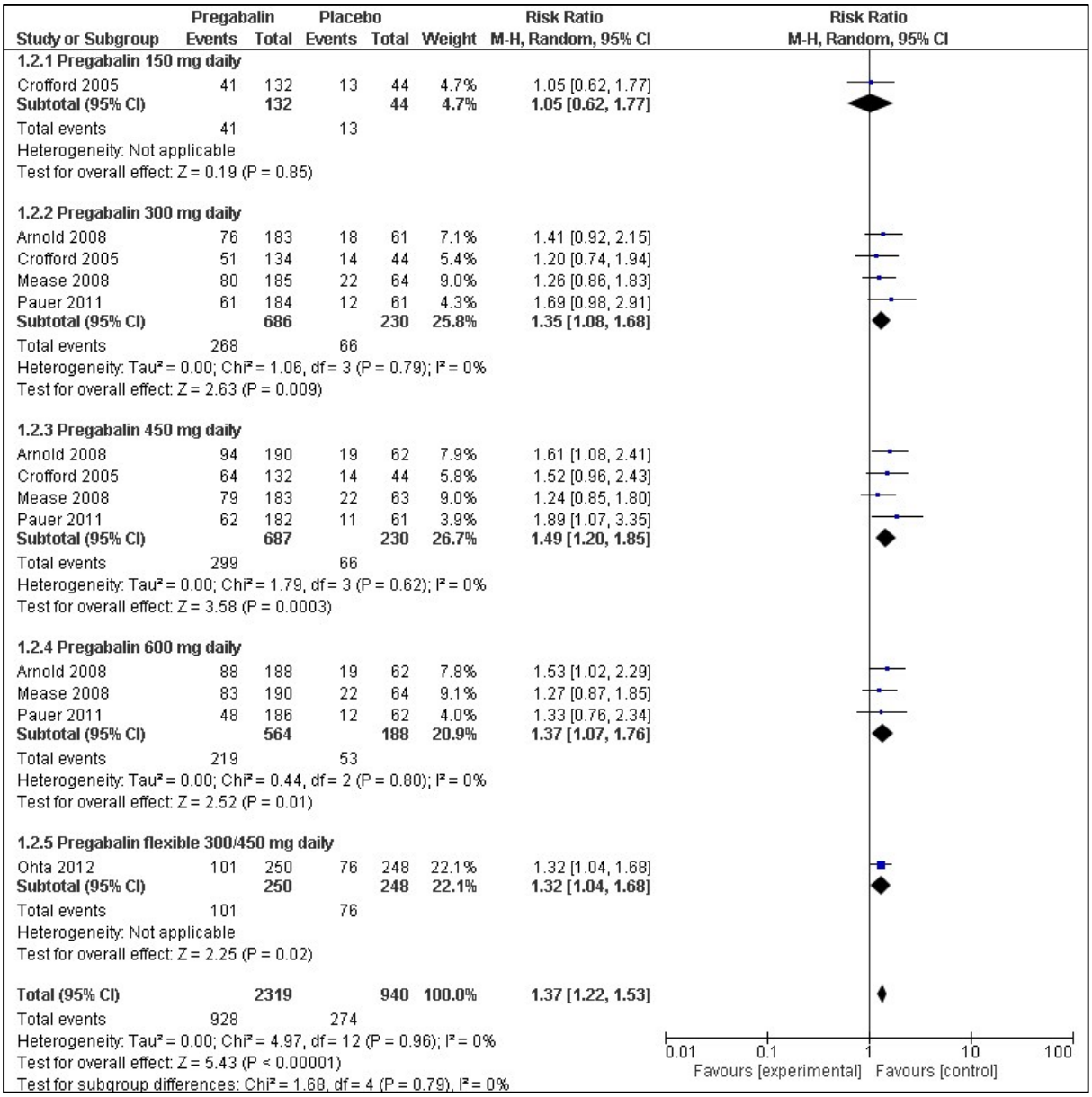

Figure 12: Forest plot of comparison: Pregabalin versus placebo, outcome 1.3: participants achieving at least 30% reduction in pain intensity following treatment.

Pregabalin versus placebo: incidence of participant withdrawal due to adverse effects following treatment:

Five studies with a total of 3259 participants were entered into RevMan5 for analysis of the safety and tolerability of pregabalin, as judged by the number of participant withdrawals following treatment (figure 13). A total of 449/2317 (19.4%) and 104/942 (11.0%) participants withdrew from trials following treatment with pregabalin or placebo respectively. The overall effect of pregabalin in causing participant withdrawal due to adverse effects was statistically significant (RR: 1.75; 95% CI; 1.42 to 2.15; P = 0.00001); the NNTH by pregabalin over placebo was ≈12. There was a statistically significant overall difference regarding the propensity of each dose

to result in participant withdrawal due to adverse effects following treatment (P = 0.04), and this was most evident in the 600mg daily treatment arm.

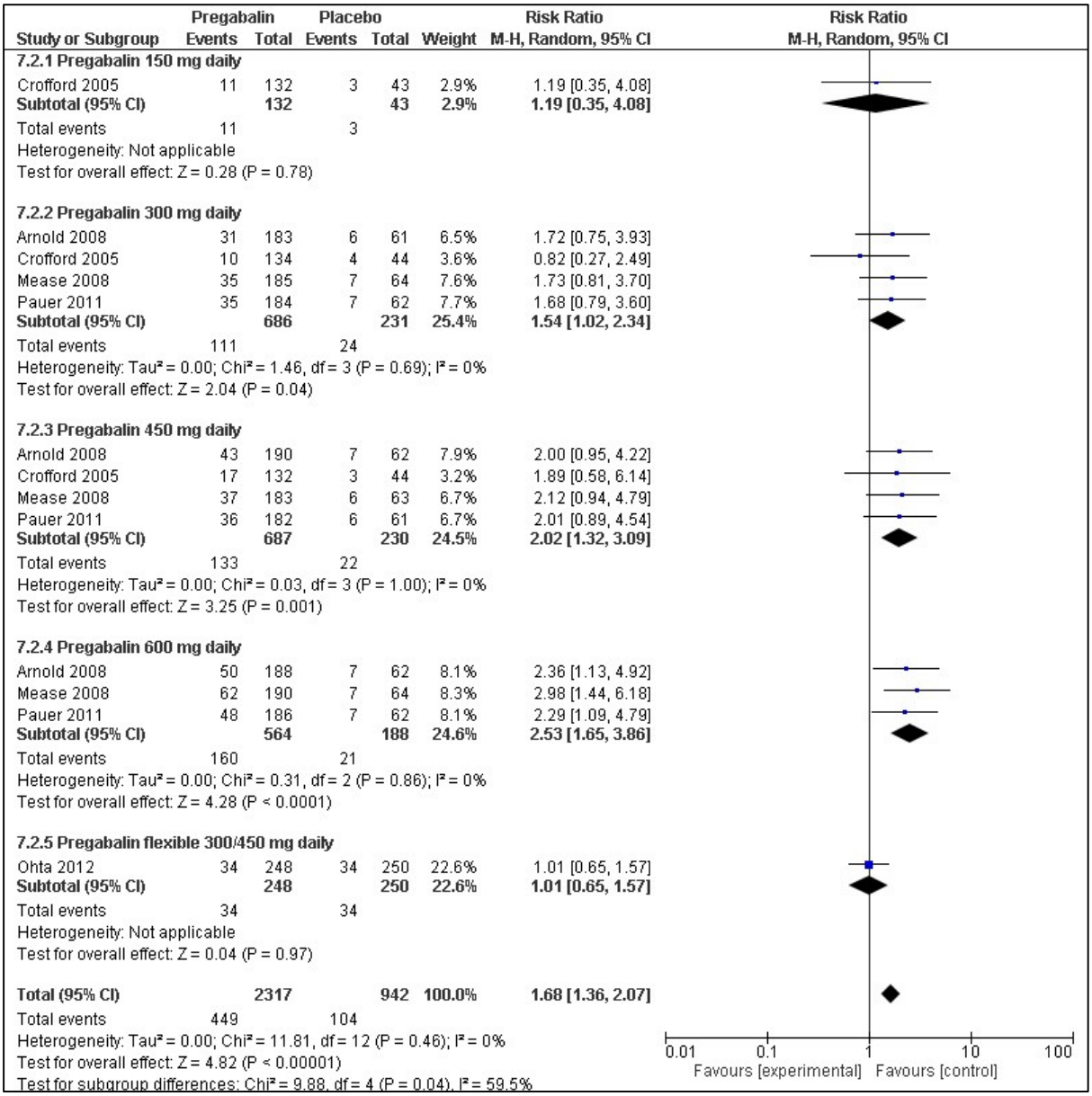

Figure 13: Forest plot of comparison: Pregabalin versus placebo, outcome 7.2: incidence of participant withdrawal due to adverse effects.

<u>Pregabalin versus placebo: incidence of 'serious adverse effects' following treatment:</u>

Four studies with a total of 2729 participants were entered into RevMan5 for analysis of the safety and tolerability of pregabalin, as judged by the incidence of „serious adverse effects" following treatment (figure 14). A total of 100/1921 (5.2%) and 33/808 (4.1%) participants experienced „serious adverse effects" following treatment with pregabalin or placebo respectively. The overall effect of pregabalin in causing „serious adverse effects" was not statistically significant (RR: 1.06; 95% CI; 0.73 to

1.53; P = 0.31), and there were no statistically significant overall differences regarding the propensity of each dose to cause „serious adverse effects" following treatment (P = 0.82).

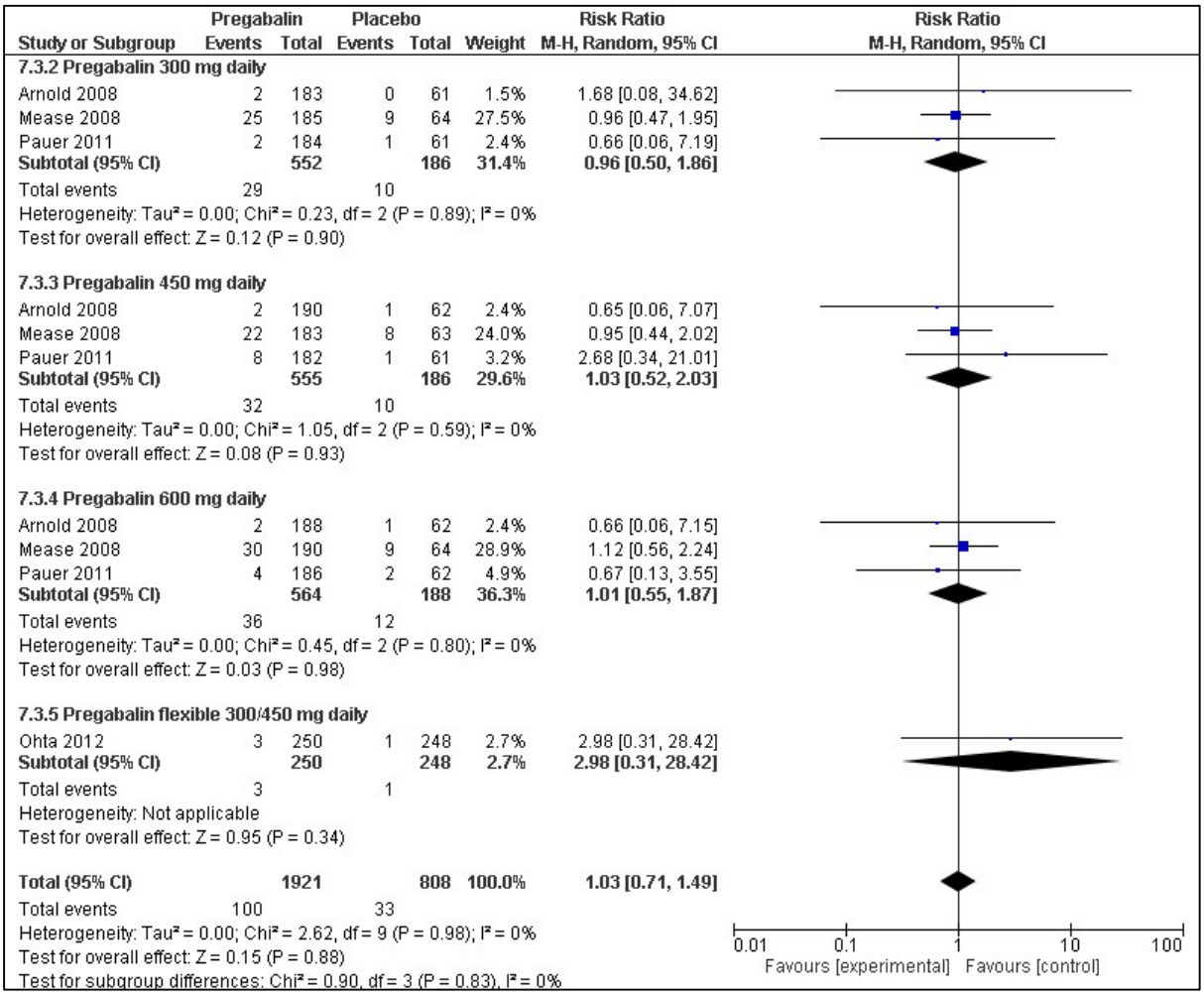

Figure 14: Forest plot of comparison: Pregabalin versus placebo, outcome 7.3: incidence of serious adverse effects following treatment.

<u>Pregabalin versus placebo: incidence of specific adverse effects (dizziness) following treatment:</u>

Five studies with a total of 3257 participants were entered into RevMan5 for analysis of the incidence of dizziness following treatment with pregabalin (figure 15). A total of 883/2319 (38%) and 87/938 (9.28%) participants experienced dizziness following treatment with pregabalin or placebo respectively. The overall effect of pregabalin in causing dizziness was statistically significant: (RR: 3.89; 95% CI; 3.16 to 4.78; P = 0.00001); the NNTH by pregabalin over placebo was ≈3. There were no statistically significant overall differences regarding the propensity of each dose to cause dizziness (P = 0.62) following treatment.

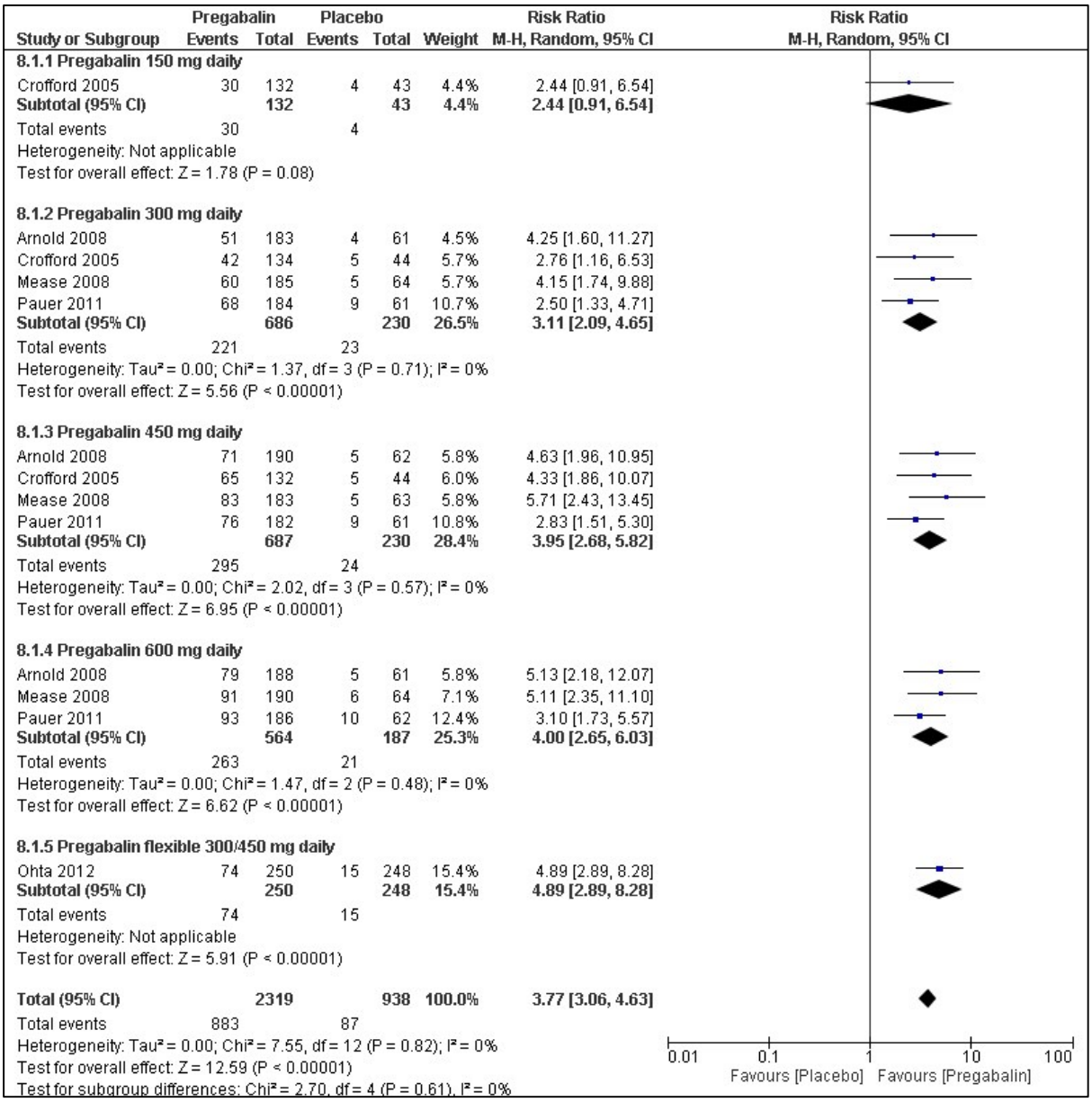

Figure 15: Forest plot of comparison: Pregabalin versus placebo, outcome 8.1: incidence of dizziness following treatment.

<u>Pregabalin versus placebo: incidence of specific adverse effects (somnolence) following treatment:</u>

Five studies with a total of 3257 participants were entered into RevMan5 for analysis of the incidence of somnolence following treatment with pregabalin (figure 16). A total of 543/2319 (23.4%) and 79/938 (8.4%) participants experienced somnolence following treatment with pregabalin or placebo respectively. The overall effect of pregabalin in causing somnolence was statistically significant (RR: 3.42; 95% CI; 2.71 to 4.32; P = 0.00001); the NNTH by pregabalin over placebo was ≈7. There were no statistically significant overall differences regarding the propensity of each dose to cause somnolence (P = 0.31) following treatment.

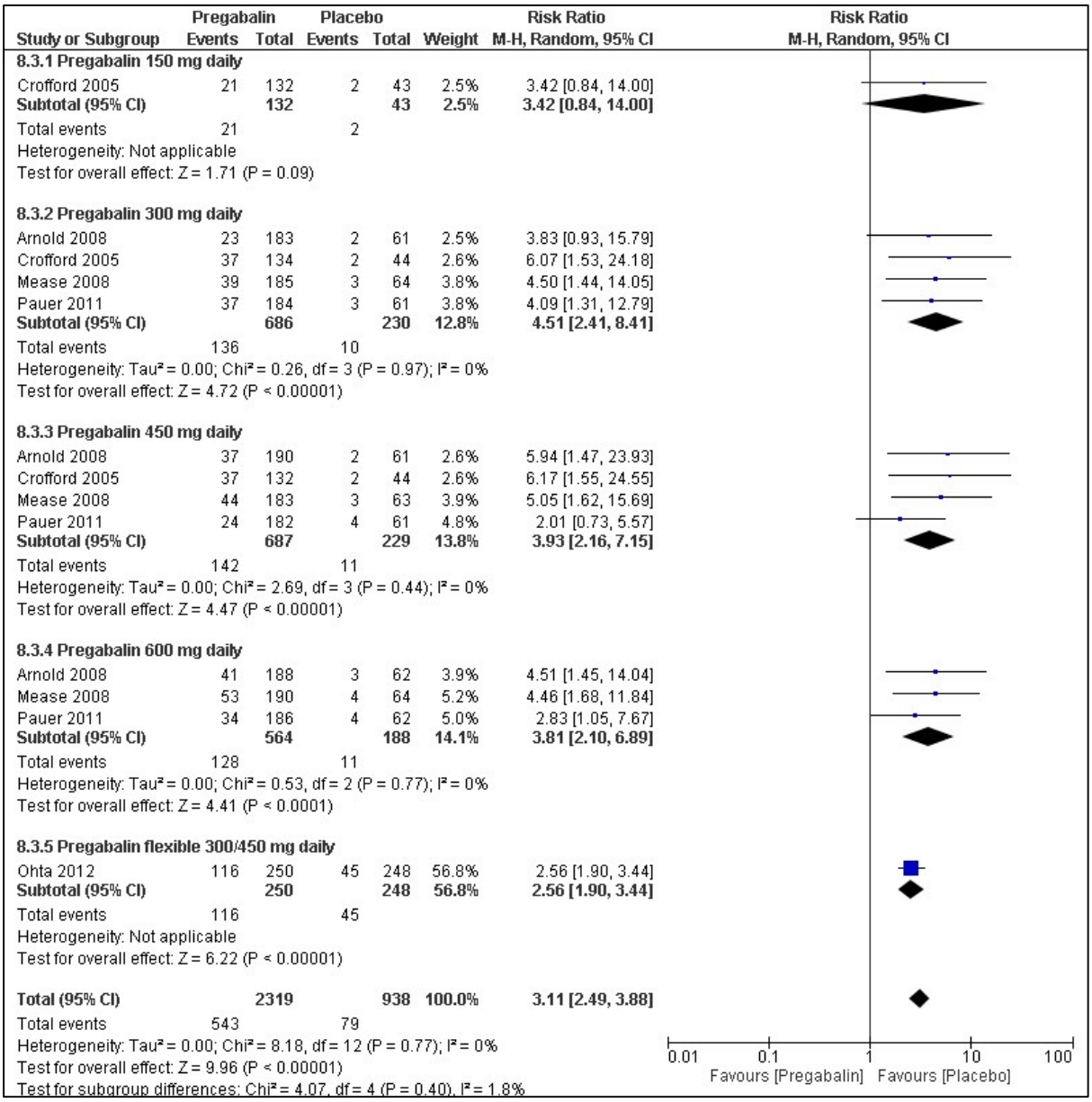

Figure 16: Forest plot of comparison: Pregabalin versus placebo, outcome 8.2: incidence of somnolence following treatment.

2. Studies of EERW design

Two studies of enriched enrolment randomised withdrawal (EERW) design were included in this review [Arnold et al, 2014; Crofford et al, 2008]. Although both studies screened participants for eligibility using the same inclusion criteria as the studies of classic design, they used a fundamentally different experimental design. Unlike the studies of classical design, eligible participants were first administered single-blind pregabalin at increasing dosage over three weeks to ascertain the maximum tolerated dose (MTD). In this regard, both studies required at least a 50% reduction in pain intensity from baseline within the next 3 weeks; the study by Crofford et al, [2008] also required significant improvements to the patient global impression of change (PGIC). Participants achieving these outcomes (responders)

were then eligible for entry into the double-blind treatment phase which involved randomisation to either a double-blind treatment with maintenance dose pregabalin, or a phased-dose reduction to placebo over the following week. Treatment with either intervention was then continued for 13 weeks [Arnold et al, 2014] or 26 weeks [Crofford et al, 2008] respectively.

It is important to note that different doses of pregabalin were employed between the two studies. Arnold et al, [2014] used pregabalin controlled release (CR) of doses 330 to 495mg daily, whereas Crofford et al, [2008] used fixed doses of 300, 450 and 600mg daily.

In both studies, the primary outcome was the loss of therapeutic response (LTR). Arnold et al, [2014] defined the LTR as <30% pain reduction relative to the baseline value recorded following single-blind treatment; or the incidence of patient withdrawal due to lack of efficacy or adverse-effects experienced during the double-blind treatment phase. Conversely, Crofford et al, [2008] described LTR as <30% reduction in visual pain analogue scale (VAS) score from the baseline value for two consecutive recordings during the double-blind phase; or following the observation that the symptoms of FM worsened with treatment, ultimately requiring the use of alternative medication.

Using guidance from Derry et al, [2016], the primary outcome for these studies was defined in this review by the maintenance of therapeutic response (MTR). MTR is a positive value which is essentially the opposite of LTR; it encompasses both a ≥30% reduction in pain intensity and requires the continuation of treatment (all-cause withdrawal being considered a treatment failure) with any adverse effects being tolerable [Derry et al, 2016]. Using this definition, the results of both studies can be compared with each other, and to outcomes described in the studies of classical design (i.e. at least 30% reduction in pain intensity following treatment).

EERW outcomes

Pregabalin versus placebo: maintenance of therapeutic effect (MTR):

Two studies with a total of 687 participants were entered into RevMan5 for analysis of the maintenance of therapeutic effect (MTR) following treatment with pregabalin (figure 17). A total of 136/342 (39.8%) and 72/345 (20.9%) participants achieved MTR following treatment either pregabalin or placebo respectively. The overall effect of pregabalin in achieving MTR was statistically significant (RR: 1.9; 95% CI; 1.5 to 2.4; P = 0.00001). The NNTB by pregabalin over placebo was ≈5.

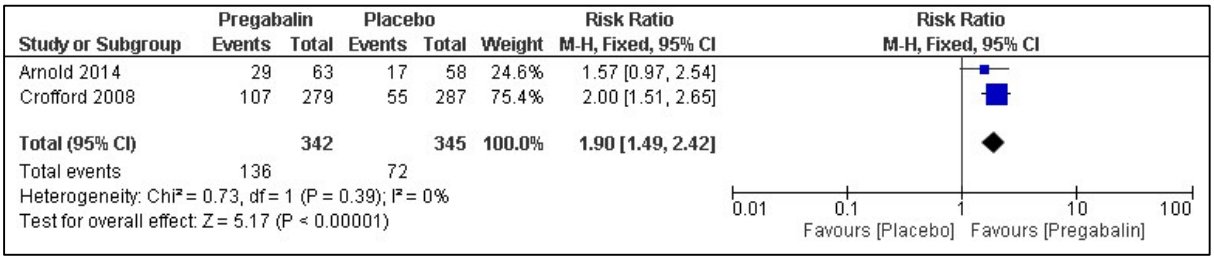

Figure 17: Forest plot of comparison: Pregabalin versus placebo, outcome 9.1: participants achieving a maintained therapeutic response following treatment.

Pregabalin versus placebo: incidence of participant withdrawal for any reason:

Two studies with a total of 687 participants were entered into RevMan5 for analysis of the incidence of all-cause withdrawal following treatment with pregabalin (figure 18). A total of 189/342 (55.3%) and 243/345 (70.4%) participants withdrew from study following treatment either pregabalin or placebo respectively. The overall effect of pregabalin in causing all-cause withdrawal was not statistically significant (RR: 0.79; 95% CI; 0.71 to 0.89; P = 0.0001). The NNTH by pregabalin over placebo was ≈7.

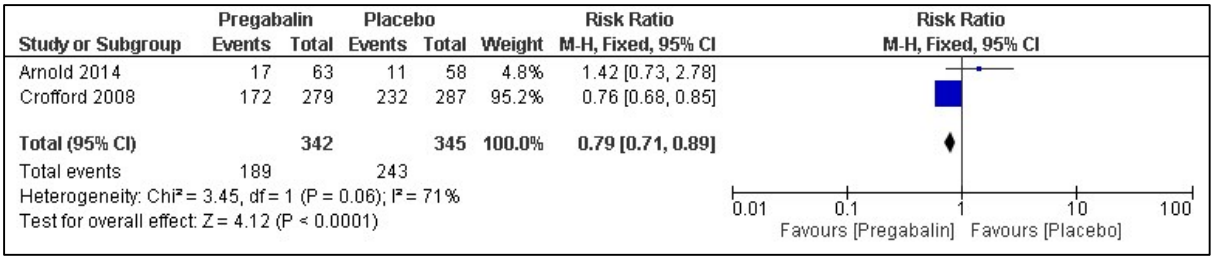

Figure 18: Forest plot of comparison: Pregabalin versus placebo, outcome 9.2: incidence of all-cause withdrawal following treatment.

Pregabalin versus placebo: incidence of adverse effects following treatment:

Two studies with a total of 687 participants were entered into RevMan5 for analysis of the safety and tolerability of pregabalin, as judged by the incidence of adverse effects following treatment (figure 19). A total of 222/342 (64.9%) and 168/345 (48.7%) participants experienced at least one adverse effect following treatment with pregabalin or placebo respectively. The overall effect of pregabalin in causing adverse effects was statistically significant (RR: 1.3; 95% CI; 1.2 to 1.5; P = 0.000028). The NNTH by pregabalin over placebo was ≈6.

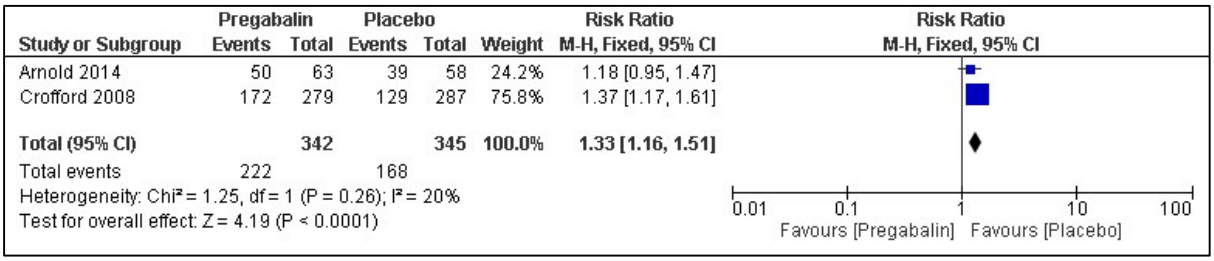

Figure 19: Forest plot of comparison: Pregabalin versus placebo, outcome 9.3: incidence of serious adverse effects following treatment.

Discussion

Summary of main results

This review aimed to investigate the efficacy and tolerability of pregabalin for the management of FM. The results of this review were derived from 8 studies of both classical and enriched enrolment with randomised withdrawal (EERW) design; all of which employed the same inclusion criteria and investigated similar outcome measures.

Although typically characterised by chronic diffuse pain, FM is associated with a constellation of symptoms. Subsequently, this review attempted to collate data for multiple outcomes for different symptoms to best reflect the condition as a whole. This means that although pain scores were included as primary outcomes, sleep disturbances, fatigue, anxiety, depression, health-related quality of life and patient impression of change were also investigated. Additionally, the safety and tolerability of pregabalin was determined by the incidence of adverse-effects (including somnolence and dizziness) following treatment, as well as the incidence of participant withdrawal as a result.

1. Studies of classical design:

Five studies (3283 participants) of classical design were included in this review.

Of the studies of classical design, Arnold et al, [2008], Crofford et al [2005], Mease et al, [2008], Ohta et al, [2012] and Pauer et al, [2011] investigated the efficacy and tolerability of pregabalin for the management of FM syndrome and were included for quantitative analysis. Several doses of pregabalin were compared with a placebo for the outcomes described, including fixed doses of 150, 300, 450 and 600mg daily. Only one study [Crofford et al, 2005] investigated the efficacy and tolerability of 150mg pregabalin daily, and the study by Ohta et al, [2012] was slightly different in the fact it used a „flexible dose" of either 300 or 450mg daily. For this reason, it was considered a discrete dose in this review.

Overall, the use of pregabalin for FM produced a small overall benefit to pain and sleep problems; however, its effect on fatigue, anxiety, depression and health-related quality of life was less profound. For the dichotomous outcomes, the numbers needed to treat for an additional beneficial outcome (NNTB) were ≈12 for a 50% reduction in pain intensity, and ≈9 for a 30% reduction in pain intensity. Furthermore,

the NNTB for a „much or very much improved patient global impression of change (PGIC) was ≈9. Of the meta-analyses for efficacy, all of the results were statistically significant. Generally speaking there was no dose-response relationship for efficacy outcomes, although 450mg daily tended to yield the best results.

With regards to the safety and tolerability of pregabalin, the incidence of participant withdrawal is significantly higher with pregabalin than placebo. The numbers needed to treat for an additional harmful outcome (NNTH) by pregabalin over placebo for participant withdrawal due to adverse effects was ≈12. Moreover, there was a statistically significant difference between the incidence of specific adverse effects, namely somnolence and dizziness between pregabalin and placebo. The NNTH by pregabalin over placebo for the incidence of somnolence and dizziness was ≈7 and ≈3 respectively. Of the meta-analyses for safety and tolerability, all of the results were statistically significant except for the incidence of „serious adverse effects". Generally speaking there was no dose-response relationship for safety and tolerability, although adverse effects tended to occur most frequently in the 600mg daily treatment arm.

2. Studies of enriched enrolment with randomised withdrawal (EERW) design:

Two studies (1492 participants) of enriched enrolment with randomised withdrawal (EERW) design were included in this review. However, due to the fact participants were first required to undergo a single-blind titration period, only 687 of these participants were deemed eligible for entry into the double-blind treatment phase. Both trials investigated the efficacy and tolerability of pregabalin for the management of FM syndrome and were included for quantitative analysis.

As with the studies of classical design, several doses of pregabalin were compared with a placebo for the outcomes described. However, different dosing regimens were employed between the two studies. Arnold et al, [2014] used pregabalin controlled release (CR) of doses 330 to 495mg daily, whereas Crofford et al, [2008] used fixed doses of 300, 450 and 600mg daily.

The primary efficacy outcome for these studies was the maintenance of therapeutic response (MTR), defined by the number of participants achieving at least a 30% reduction in pain intensity without withdrawal for the duration of the trial(s). The benefit of pregabalin in this regard was statistically significant, with ≈20% more individuals achieving MTR with pregabalin than placebo. Furthermore, the numbers needed to treat for an additional beneficial outcome (NNTB) by pregabalin over placebo was ≈5. Considering that only half (687/1492) of participants entered the double-blind trial, assuming all participants were eligible the NNTB would have been ≈10 – and this is comparable to the results of studies classical design where the NNTB by pregabalin over placebo was ≈9 for 30% pain reduction.

With regards to the safety and tolerability of pregabalin, the incidence of adverse effects following treatment was significantly higher with pregabalin than placebo. Approximately 15% more participants in the pregabalin group experienced adverse effects compared to the placebo group; the NNTH by pregabalin over placebo was ≈6.

Overall completeness and applicability of the evidence
The studies included in this review provide a current and accurate representation of the efficacy and tolerability of pregabalin for the treatment of FM. However, there are certain limitations regarding its external validity.

Firstly, although the participants of included studies were typically representative of FM sufferers in general (i.e. primarily middle-aged women of Caucasian ethnicity), the lack of variation amongst them means it is not necessarily possible to extrapolate these results to the general population. For example, male participants were not excluded from this review; however, they were not well represented by the studies included. A possible reason for this may reside in how the condition is diagnosed, as following the introduction of the 2010 diagnostic criteria [Wolfe et al, 2010] the proportion of female: male sufferers was estimated to have changed from ≈30:1 (as with the 1990 ACR classification) to ≈2:1. [Derry et al, 2016] The included studies did not employ stringent guidelines regarding how FM was diagnosed, simply stating that participants were diagnosed using either the 1990 or 2010 diagnostic criteria. Subsequently, it is advised that future studies investigating FM should attempt to be more inclusive to male participants, and restrict eligible participants to those diagnosed with 2010 diagnostic criteria, as opposed to the 1990 diagnostic criteria. Furthermore, these results cannot be applied to children or adolescents as they were excluded from this review. The reason for this was due to the fact juvenile-onset fibromyalgia (JFM) is a relatively rare phenomenon which is difficult to diagnose [Kashikar-Zuck et al, 2014] and was only investigated by a limited number of studies which were generally <8 weeks in duration.

Secondly, due to the fact that stringent inclusion criteria were employed by this study, there is possibility that the results of this review cannot necessarily be applied to the wider population of FM sufferers. For example, as FM is often a comorbid condition (i.e. with chronic depression), and this review did not permit the use of concurrent medication (besides paracetamol and aspirin), otherwise eligible participants were not included in studies if they were unwilling or unable to stop taking their medication. As described by Üçeyler et al, [2013], this may have biased participant selection towards individuals who could manage their symptoms well. Additionally, due to the fact that participants with concurrent neuropathic or rheumatic diseases (i.e. rheumatoid arthritis) were excluded from this review, patients who may have developed FM as a consequence of another condition (secondary fibromyalgia) were also excluded from this review.

Furthermore, although a range of doses have been investigated for the outcomes described, generally speaking there was no significant difference between them with regards to efficacy and tolerability. This may be due to the fact that the majority of the included studies were of insufficient duration to ascertain the effects of their long-term use. However, the study by Crofford et al, [2008] had a duration of 6 months and did not report any significantly different results to the studies of shorter duration, indicating that pregabalin is in fact effective for long term use. This observation is

supported by the findings of extension studies which demonstrated the efficacy and tolerability of pregabalin for up to one year [Arnold et al, 2012; Ohta et al, 2013].

Quality of the evidence

The included studies were all described as being randomised and double-blind. Studies had a minimum duration of 8 weeks, and included samples of adequate size to minimise the risk of random chance errors or small study biases [Dechartres et al, 2013]. However, the studies of classical design employed a „last observation carried forward‟ (LOCF) imputation for missing data (i.e. in the instance of participant withdrawal, pain scores at the time of withdrawal were recorded as if they had been scored at the end of the trial). Unfortunately, LOCF imputation has the potential to over-estimate and/or underestimate the magnitude of treatment effect, and subsequently the results of these studies were considered second-tier evidence. Conversely, the studies of EERW design did not require imputation, and were therefore considered first-tier evidence. However, due to the fact that access to the results of these studies was only possible via the review by Derry et al, [2016], it is possible that negative study results may not have been published, or the data may have been manipulated in some way.

Potential biases in the review process

All relevant outcomes have been reported where possible. Despite the results EERW studies which were obtained through the results section of a review by Derry et al, [2016], the data was obtained from the original papers and not altered in any way. No other considerable sources of bias in the review process are known.

Agreements and disagreements with other studies or reviews

The results of this review are in significant agreement with past reviews which investigated similar outcomes. For example, the systematic review by Straube et al, [2010] used 4/6 of the studies of classical design ([Arnold et al, 2008; Crofford et al, 2005; Mease et al, 2008; Pauer et al, 2011]) and reported that pregabalin had a significant benefit over placebo for both the dichotomous and continuous efficacy outcomes reported in this review. Additionally, the use of Cohen's categories (as well as Sawilkowsky's expanded categories) to define the magnitude of effect for continuous outcomes produced results that were in considerable agreement with that of Moore et al, [2009], who also observed that most participants experienced only a „small‟ benefit for the outcomes described.

For the studies of EERW design ([Arnold et al, 2014; Crofford et al, 2008]) which investigated the maintenance of therapeutic response (MTR) as the primary outcome, the numbers needed to treat (NNT) obtained for efficacy outcomes were in considerable agreement with a previous review by Derry et al, [2016], suggesting that this review had sound statistical methodology.

Despite the fact 450mg daily seemed to be the most efficacious dose (possibly due to the number of participants), there was generally no significant difference regarding

the efficacy of pregabalin for the outcome described, and this is consistent with the findings of Tzellos et al, [2010] and Uceyler et al, [2013].

With regards to the safety and tolerability of pregabalin, and with the exception of serious adverse effects (for which there was no significant difference), there was a statistically significant increase in the incidence of adverse events and participant withdrawal following treatment with pregabalin. The incidence of named adverse effects (somnolence and dizziness) also correlated with this trend. Although there was generally no dose-response relationship, they tended to occur most frequently in the 600mg daily treatment arm. These findings were also consistent with the results of past reviews [Derry et al, 2016; Straube et al, 2010; Tzellos et al, 2010; Uceyler et al, 2013].

Authors conclusions

1. Implications for practice

FM is a condition characterised primarily by chronic pain, but also by symptoms including: sleep problems, fatigue, disability, anxiety and depression. Although pregabalin has the potential to significantly improve such symptoms, generally speaking changes were not substantial and observed in a minority of participants. Furthermore, the use of pregabalin is associated with a number of side effects (i.e. somnolence and dizziness), albeit fairly mild, which occur more frequently at higher doses. Although 450 mg daily may achieve an equitable balance between efficacy and tolerability, the possible benefits and harms of pregabalin should be discussed between the patient and doctor prior to prescription. Treatment regimens should be considered on the basis of individual circumstance and closely monitored thereafter to ensure the safety of the patient [Gahr et al, 2013].

2. Implications for research

Recommendations for future research on the efficacy and tolerability of pregabalin for the management of FM include:

- Comparison with an active comparator (i.e. other anti-convulsants): This is recommended as it is more significant to clinical practice (i.e. where multiple treatment options are possible).

- Inclusion of co-morbid patients: This is recommended as it is more significant to clinical practice and better representative of the general population.

- Gradual dosing regimen: Clinical trials employ rapid dose increments, and this is not necessarily representative of clinical practice where dosing is more gradual.

- Variation in dosing regimen: Although the study by [Nasser et al, 2014] found no benefit between nightly dosing versus twice daily dosing

pregabalin, it had a relatively small number of participants (177) and did find a decrease in the incidence of adverse-effects in the nightly-dosing treatment arm. As there is little research into this area, it should be investigated further to substantiate or dispute such findings, as variation to dosing regimen may be appropriate in some cases (i.e. for comorbid patients who take multiple mediations).

- Post-hoc baseline observation carried forward (BOCF) imputation: BOCF imputation uses the final response from the patient, regardless of the reason for patient drop-out or the scores at the time of withdrawal for missing endpoint data. This is considered more conservative than LOCF imputation as it is less likely to overestimate the magnitude of treatment effect. It should therefore be considered for post-hoc analyses to strengthen the significance of findings and any conclusions made.

Characteristics of studies

Characteristics of included studies (ordered by study ID)

1. Arnold 2008

Methods	14-week randomised, placebo-controlled, double-blind, parallel-group trial.
Participants	Fibromyalgia according to ACR classification and pain of at least 40/100 mm and pain score ≥ 4 on the 11-point numerical rating scale in the week before randomisation N = 750 (745 analysed) Mean age 50 years, 95% female, 91% white Baseline mean pain score: 6.7/10
Interventions	1-week single-blinded placebo run-in phase, 2-week double-blinded dose escalation phase, 12week fixed dose Pregabalin 300 mg daily, n = 183 Pregabalin 450 mg daily, n = 190 Pregabalin 600 mg daily, n = 188 Placebo daily, n = 184
Outcomes	Pain: Daily diary mean pain (NRS 0-10); 30%/50% reductions in pain intensity Fatigue: MAF (NRS 1-50) Sleep: MOS Sleep Problems Index (NRS 0-100) Depression: HADS (NRS 0-21) Anxiety: HADS (NRS 0-21) Health Related Quality of Life: SF-36 (NRS 50-0) Patient-perceived improvement: PGIC (1-7) AEs: Observed or spontaneously reported AEs; laboratory results, physical examinations, ECG
Notes	Pfizer sponsored. LOCF used to account for missing data and participant withdrawals

Risk of bias table

Bias	Authors Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random assignment to treatment regimens used a 1:1:1:1 ratio according to a computer-generated pseudorandom code using the method of random permuted blocks (i.e., block size of 4)"

Allocation concealment (selection bias)	Low risk	"Random assignment was managed by a telerandomisation system"
Blinding of participants and personnel (performance bias	Low risk	"To maintain the blinding, all doses of pregabalin and placebo were packaged using identical encapsulation. At each visit, all patients received 1 bottle of capsules that were identical in appearance and taste from which they took 1 capsule twice a day"
Blinding of outcome assessment (detection bias)	Low risk	"To maintain the blinding, all doses of pregabalin and placebo were packaged using identical encapsulation. At each visit, all patients received 1 bottle of capsules that were identical in appearance and taste from which they took 1 capsule twice a day"
Incomplete outcome data (attrition bias)	Unclear risk	LOCF Imputation.
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	Unclear risk	Size - 50 to 199 participants were selected per treatment arm

2. Arnold 2014

Methods	A 13-week multicentre, controlled-release, double-blind, placebo-controlled, EERW trial
Participants	Fibromyalgia according to ACR classification and a pain score ≥ 4 on the 11-point numerical rating scale prior to randomisation N = 441 entered dose-titration phase, 121 randomised to double-blind phase Mean age 50 years, 91% female, 90% white Baseline mean pain score: 6.8/10
Interventions	4 Phases: (1) Baseline [1 week], (2) single-blind (participants blinded) treatment [6 weeks], (3) double-blind treatment [13 weeks] and (4) a double-blind taper period [1 week] Pregabalin controlled release 330 to 495 mg daily, N=63 Placebo, N=58
Outcomes	Pain intensity on an 11-point numerical rating scale using daily pain diary Adverse effects Withdrawals
Notes	Pfizer sponsored

Risk of bias table

Bias	Authors Judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised ("randomly assigned") however the method of sequence generation is not described
Allocation concealment (selection bias)	Low risk	"telephone using the interactive voice recognition system (IVRS)"
Blinding of participants and personnel (performance bias	Low risk	Stated to be double-blind; used a matching placebo or optimal open-label dosage of pregabalin
Blinding of outcome assessment (detection bias)	Low risk	Stated to be double-blind; used a matching placebo or optimal open-label dosage of pregabalin
Incomplete outcome data (attrition bias)	Low risk	All participants were included in analysis

Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	Unclear risk	Size - 50 to 199 participants were selected per treatment arm

3. Crofford 2005

Methods	8-week multicentre, randomised, double-blind, placebo-controlled, parallel-group trial
Participants	Fibromyalgia according to ACR classification. Pain of at least 40/100 mm and pain diary score ≥ 4 on 11-point numerical rating scale in week before randomisation N = 529 Mean age 49 years, 92% female, 93% white Baseline mean pain score: 7/10
Interventions	8-week fixed dose (except for pregabalin 450 mg/day who received 300 mg/day for the first 3 days, and then 450 mg/day) Pregabalin 150 mg daily, n = 132 Pregabalin 300 mg daily, n = 134 Pregabalin 450 mg daily, n = 132 Placebo daily, n = 131
Outcomes	Pain: SF-MPQ (VAS 0-100) Fatigue: MAF (NRS 1-50) Sleep: MOS Sleep Problems Index (NRS 0-100) Depression: HADS (NRS 0-21) Anxiety: HADS (NRS 0-21) Health Related Quality of Life: Not assessed Patient-perceived improvement: PGIC (1-7) AEs: Observed or spontaneously reported AEs; laboratory results, physical examinations, ECG
Notes	Pfizer sponsored. LOCF used to account for missing data and participant's withdrawals.

Risk of bias table

Bias	Authors Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was by computer-generated code using a block size of 8"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias	Unclear risk	Double-Blind - no further details of methods used.
Blinding of outcome assessment (detection bias)	Unclear risk	Double-Blind - no further details of methods used.
Incomplete outcome data (attrition bias)	Unclear risk	LOCF Imputation.
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported
Other bias	Unclear risk	Size - 50 to 199 participants were selected per treatment arm

4. Crofford 2008

Methods	26-week randomised, double-blind, placebo-controlled, parallel-group, EERW trial. Participants initially screened for response (≥ 50% decrease in pain and PGIC of much or very much improved). Responders to initial titration selected for randomisation to placebo or continued use of maximum tolerated dose (MTD).
Participants	Fibromyalgia according to ACR classification and pain of at least 40/100 mm in week before randomisation, with 6 months of follow-up N = 1051 entered open-label phase (6 weeks); 566 randomised to double-blind phase (26 weeks) Mean age 49 years, 93.5% female, 90% white Baseline mean pain score: 78/100
Interventions	Pregabalin titrated to a maximum of 600 mg daily, n = 279 (300 mg = 63; 450 mg = 73; 600 mg = 143) Placebo daily, n = 287
Outcomes	Loss of therapeutic response (worsening of pain or other symptoms, pain reduction less than 30% of baseline on several occasions, withdrawal) measured in days Adverse events Withdrawals
Notes	Pfizer sponsored

Risk of bias table

Bias	Authors Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A tele-randomisation system randomised responders to either matching placebo or optimal open label dosage of pregabalin (1:1)"
Allocation concealment (selection bias)	Low risk	A tele-randomisation system was used.
Blinding of participants and personnel (performance bias	Low risk	"matching placebo or optimal open-label dosage of pregabalin"
Blinding of outcome assessment (detection bias)	Low risk	"matching placebo or optimal open-label dosage of pregabalin"
Incomplete outcome data (attrition bias)	Low risk	All participants were included in analysis.
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	Low risk	No other sources of significant bias were observed

5. Mease 2008

Methods	12-week multicentre, randomised, double-blind, placebo-controlled, parallel-group trial.
Participants	Fibromyalgia according to ACR classification and pain of at least 40/100 mm in week before randomisation N = 748 Mean age 49 years, 94% female, 90% white Baseline mean pain score: 7.1/10
Interventions	1-week dose escalation (all participants started at 150 mg), 12 weeks with fixed dose Pregabalin 300 mg daily, n = 185 Pregabalin 450 mg daily, n = 183 Pregabalin 600 mg daily, n = 190 Placebo daily, n = 190
Outcomes	Pain: Daily diary mean pain (NRS 0-10); 30%/50% reductions in pain intensity Fatigue: MAF (NRS 1-50) Sleep: MOS Sleep Problems Index (NRS 0-100) Depression: HADS (NRS 0-21) Anxiety: HADS (NRS 0-21) Health Related Quality of Life: SF-36 (NRS 50-0) Patient-perceived improvement: PGIC (1-7) AEs: Observed or spontaneously reported AEs; laboratory results, physical examinations, ECG
Notes	Pfizer sponsored. LOCF used to account for missing data and participant withdrawals.

Risk of bias table

Bias	Authors Judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised however the method of sequence generation is not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias	Unclear risk	Double-Blind - no further details of methods used.
Blinding of outcome assessment (detection bias)	Unclear risk	Double-Blind - no further details of methods used.
Incomplete outcome data (attrition bias)	Unclear risk	LOCF imputation.
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	Unclear risk	Size - 50 to 199 participants were selected per treatment arm

6. Nasser 2014

Methods	8-week multicentre, randomised, double-blind comparison of 2 dosing schedules (nightly versus twice daily.

Participants	Females with fibromyalgia according to ACR classification and pain diary score ≥ 4 on 11-point numerical rating scale N = 177 Mean age 50 years, 96% white Baseline mean pain score: 7.1/10
Interventions	300 mg dose taken once nightly (placebo in the morning) or as a divided dose, twice daily Once nightly (week 1: 75 mg; week 2: 150 mg; week 3: 225 mg; weeks 4 to 8: 300 mg; week 9: taper dose, n = 89) Twice daily (week 1: 75 mg x 2; week 2 to 8: 150 mg x 2; week 9: taper dose, n = 88)
Outcomes	Pain: Daily diary mean pain (NRS 0-10) Fatigue: VAS (0-100 mm) Sleep: VAS sleep disturbance (0-100 mm) Patient-perceived improvement: PGIC (1-7) AEs: Observed or spontaneously reported AEs; laboratory results, physical examinations, ECG
Notes	Pfizer sponsored.

Risk of bias table

Bias	Authors Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomised using a random number generator to assign patients to either group"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias	Low risk	Double blind; placebo replaced morning dose for nightly dosing
Blinding of outcome assessment (detection bias)	Low risk	Double blind; placebo replaced morning dose for nightly dosing
Incomplete outcome data (attrition bias)	Unclear risk	LOCF imputation.
Selective reporting (reporting bias)	Unclear risk	All relevant outcomes were reported.
Other bias	Unclear risk	Size - 50 to 199 participants were selected per treatment arm

7. Ohta 2012

Methods	A 12-week multicentre, randomised, double-blind, placebo-controlled trial
Participants	Japanese participants with fibromyalgia according to ACR classification. Pain of ≥ 40/100 mm and pain diary score ≥ 4 on 11-point numerical rating scale before randomisation N = 498 Mean age 48 years, 89% female Baseline mean pain score: 6.5/10
Interventions	4 phases: 1-week single-blind run-in period, 3-week dose escalation, 12-week fixed dose at 300 or 450 mg, 1-week taper phase Pregabalin all doses, n = 250 Placebo, n = 248

Outcomes	Pain: Daily diary mean pain (NRS 0-10); 30%/50% reductions in pain intensity Fatigue: FIQ Fatigue single scale (VAS 0-10) Sleep: MOS Sleep Problems Index (NRS 0-100) Depression: HADS (NRS 0-21) Anxiety: HADS (NRS 0-21) Health Related Quality of Life: SF-36 (NRS 50-0) Patient-perceived improvement: PGIC (1-7) AEs: Observed or spontaneously reported AEs; laboratory results, physical examinations, ECG
Notes	Pfizer sponsored.

Risk of bias table

Bias	Authors Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation control system (IMPALA), which provided subject randomisation numbers"
Allocation concealment (selection bias)	Unclear risk	"Randomisation control system (IMPALA), which provided subject randomisation numbers"
Blinding of participants and personnel (performance bias	Low risk	"Pregabalin and placebo capsules were prescribed by the investigator using blinded drug numbers issued by IMPALA" "Identical placebo"
Blinding of outcome assessment (detection bias)	Low risk	"Pregabalin and placebo capsules were prescribed by the investigator using blinded drug numbers issued by IMPALA" "Identical placebo"
Incomplete outcome data (attrition bias)	Unclear risk	LOCF imputation.
Selective reporting (reporting bias)	Unclear risk	All relevant outcomes were reported.
Other bias	Unclear risk	N/A

8. Pauer 2011

Methods	14-week multicentre, randomised, double-blind, placebo-controlled trial
Participants	Fibromyalgia according to ACR classification. Pain ≥ 40/100 mm and pain diary score ≥ 4 on 11-point numerical rating scale in week before randomisation N = 747 Mean age 49 years, 91% female, 76% white Baseline mean pain score: 6.7/10
Interventions	1-week placebo run-in phase, 2-week randomised dose escalation phase, 12-week fixed-dose phase Placebo, n = 184 Pregabalin 300 mg, n = 184 Pregabalin 450 mg, n = 182 Pregabalin 600 mg, n = 186
Outcomes	Pain: Daily diary mean pain (NRS 0-10); 30%/50% reductions in pain intensity Fatigue: MAF (NRS 1-50) Sleep: MOS Sleep Problems Index (NRS 0-100) Depression: HADS (NRS 0-21) Anxiety: HADS (NRS 0-21) Health Related Quality of Life: SF-36 (NRS 50-0) Patient-perceived improvement: PGIC (1-7) AEs: Observed or spontaneously reported AEs; laboratory results, physical examinations, ECG

Notes	Pfizer sponsored. LOCF used to account for missing data and participant withdrawal.

Risk of bias table

Bias	Authors Judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated to be randomised however the method of sequence generation is not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias	Unclear risk	Double-Blind - no further details of methods used
Blinding of outcome assessment (detection bias)	Unclear risk	Double-Blind - no further details of methods used
Incomplete outcome data (attrition bias)	Unclear risk	LOCF imputation.
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported.
Other bias	Unclear risk	Size - 50 to 199 participants were selected per treatment arm (182 to 186)

Characteristics of excluded studies

Arnold 2007

Reason for exclusion	Pooled analysis using results from a previous study by [Crofford et al, 2005]

Arnold 2012

Reason for exclusion	Pooled analysis of three open-label extension studies

Arnold 2014b

Reason for exclusion	Participants selected were already receiving anti-depressant medication

Arnold 2014c

Reason for exclusion	Participants selected were already receiving anti-depressant medication

Arnold 2015

Reason for exclusion	Duration of the study was less than 8 weeks.

Arnold 2016

Reason for exclusion	Participants selected were under the age of 18 years.

Byon 2010

Reason for exclusion	Summary report of 4 randomised controlled trials

Emir 2010

Reason for exclusion	Summary report of 4 randomised controlled trials

Häuser 2009

Reason for exclusion	Summary report of 5 randomised controlled trials

Moore 2007

Reason for exclusion	Summary report of 5 randomised controlled trials

NCT00760474 2012

Reason for exclusion	Duration of the study was less than 8 weeks.

NCT01268631 2010

Reason for exclusion	Cross-over study (2x2 weeks)

NCT01904097 2013

Reason for exclusion	Not double-blind

Ohta 2013

Reason for exclusion	Non-randomised; open-label extension trial

Ramzy 2016

Reason for exclusion	Participants were co-administered anti-depressant medication

Roth 2012

Reason for exclusion	Duration of the study was less than 8 weeks

Russel 2009

Reason for exclusion	Summary report of 2 randomised controlled trials

Characteristics of ongoing studies

NCT02146430

Study name	A randomized, double-blind, placebo- and active-controlled study of DS-5565 for treatment of pain associated with fibromyalgia
Methods	13-week randomised, parallel, double-blind, placebo- and active controlled study
Participants	≈1294 Participants Clinical diagnosis using the American College of Rheumatology (ACR) classification criteria; pain intensity ≥ 40/100 Men and women over 18 years
Interventions	DS-5565 (mirogabalin) 15 mg tablet, once daily DS-5565 (mirogabalin) 15 mg tablet, twice daily Pregabalin 150 mg capsule, twice daily Placebo tablet matching DS-5565 tablet Placebo capsule matching pregabalin capsule Participants take half daily dose in first week
Outcomes	≥ 30% and ≥ 50% responders at 13 weeks PGIC Fibromyalgia symptoms Adverse events Withdrawals
Starting date	May 2014
Contact information	Daiichi Sankyo Inc, Domenico Merante, MD
Notes	Estimated completion date: March 2017

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