An evidence-based review of pregabalin for the treatment of fibromyalgia

Lesley Arnold[a], Ernest Choy[b], Daniel J. Clauw[c], Hiroshi Oka[d], Ed Whalen[e], David Semel[e], Lynne Pauer[f] and Lloyd Knapp[e]

[a]University of Cincinnati College of Medicine, 260 Stetson Street, Suite 3200, Cincinnati, OH 45219, USA; telephone: 513 558 4622; email: arnoldlm@ucmail.uc.edu; [b]Institute of Infection and Immunity, Cardiff University School of Medicine, Tenovus Building, Heath Park Campus, Cardiff CF14 4XN, UK; telephone: (44) 2920 687350; email: ChoyEH@cardiff.ac.uk; [c]Department of Anesthesiology, University of Michigan, 1500 E Medical Center Drive, Ann Arbor, MI 48109-5048, USA; telephone: 734 998 6961; email: dclauw@umich.edu; [d]Tokyo Rheumatism Pain Clinic, Echizenya-Bldg 2nd Floor, Kyobashi 1-1-6, Chuo-ku, Tokyo 104-0031, Japan; telephone: +81 3 6202 9080; email: hoka@tokyo-med.ac.jp; [e]Pfizer Inc, 235 East 42nd St, New York, NY 10017, USA; telephone: 212 733 1943; email: david.semel@pfizer.com; [f]Pfizer Inc, 445 Eastern Point Road, Groton, CT 06340, USA; telephone: 734 417 3988; email: lynne.pauer@pfizer.com

Corresponding author: Lynne Pauer, Pfizer Inc, 445 Eastern Point Road, Groton, CT 06340, USA.

Telephone: +1 734 417 3988

Fax: +1 860 686 7883

Email: lynne.pauer@pfizer.com

Number of words: 10773

ABSTRACT (254 words)

Objectives: Pregabalin, an α2-δ agonist, is approved for the treatment of fibromyalgia (FM) in the United States, Japan, and 37 other countries. The purpose of this article was to provide an in-depth, evidence-based summary of pregabalin for FM as demonstrated in randomized, placebo-controlled clinical studies, including open-label extensions, meta-analyses, combination studies, and post-hoc analyses of clinical study data.

Methods: PubMed was searched using the term 'pregabalin AND fibromyalgia' and the Cochrane Library with the term 'pregabalin'. Both searches were conducted on 2 March 2017 with no other date limits set.

Results: Eleven randomized, double-blind, placebo-controlled clinical studies were identified including parallel group, 2-way crossover, and randomized withdrawal designs. One was a neuroimaging study. Five open-label extensions were also identified. Evidence of efficacy was demonstrated across the studies identified with significant and clinically relevant improvements in pain, sleep quality, and patient status. The safety and tolerability profile of pregabalin is consistent across all the studies identified, including in adolescents, with dizziness and somnolence the most common adverse events reported. These efficacy and safety data are supported by meta-analyses (13 studies). Pregabalin in combination with other pharmacotherapies (7 studies) is also efficacious. Post-hoc analyses have demonstrated the onset of pregabalin efficacy as early as 1–2 days after starting treatment, examined the effect of pregabalin on other aspects of sleep beyond quality, and shown it is effective irrespective of the presence of a wide variety of patient demographic and clinical characteristics.

Conclusions: Pregabalin is a treatment option for FM; its clinical utility has been comprehensively demonstrated.

KEYWORDS

Pregabalin; fibromyalgia; pain; sleep

Short title: Pregabalin for fibromyalgia

Introduction

Fibromyalgia (FM) is a chronic pain disorder that affects ~1%–10% of the general adult population [1]. Prevalence rates vary by country, age, gender, education levels, and socioeconomic status, and may further depend on disease awareness, diagnosis rates, methodology, and diagnostic criteria [1-12]. FM can be considered a prototypical centralized pain state resulting in augmented central pain processing [13]. Neuroimaging studies have documented changes to the pain processing systems associated with FM including the brain activation patterns associated with pain augmentation [14,15], alterations to functional connectivity [16-18], and aberrant neurotransmitter systems, including glutamatergic neurotransmission [19-21]. A 'neurophysiological signature' for FM may exist [22]. In addition to chronic widespread pain, FM may also be characterized by multiple symptom domains including sleep disturbance, fatigue, anxiety, depression, and cognitive dysfunction [2,23,24], all of which can negatively impact patients' function and generate a significant clinical burden [25-28].

The clinical heterogeneity of FM has led to the development of multiple therapeutic options, including pharmacological and non-pharmacological treatments [29,30]. Treatments generally ameliorate symptoms rather than eliminating them. Pregabalin is an α2-δ calcium channel subunit ligand [31], but its mechanism of action in FM is not fully elucidated. As noted above, aberrant glutamatergic neurotransmission has been implicated in FM pathophysiology [13], and elevated levels of glutamate have been reported in specific brain regions associated with chronic pain, notably the insula [19]. Pregabalin may target this aberrant glutamatergic neurotransmission. Binding of pregabalin to the α2-δ subunit reduces calcium influx into the pre-synaptic terminal thereby impeding glutamate release [32,33].

Pregabalin is approved for the pharmacological management of FM in the United States (US) [34], Japan, and 37 other countries. Milnacipran and duloxetine are also approved pharmacological treatments of FM in the US [35,36]. National and international FM management guidelines recommend pregabalin for the treatment of FM [37-41]. The approvals of pregabalin and recommendations for FM treatment are based on a clinical trial program that demonstrated its efficacy and safety in multiple randomized, placebo-controlled clinical studies [42-47]. Using the patient data from these clinical studies, post-hoc analyses have been conducted to further explore the effectiveness and safety of pregabalin for FM. Systematic review and meta-analysis techniques have also examined the efficacy and safety of pregabalin, and poly-drug therapy involving pregabalin and other pharmacological treatments has been clinically evaluated. As a result, there is a large body of evidence assessing pregabalin for the treatment of FM. The purpose of this article was to provide an in-depth, evidence-based summary of the clinical studies, including combination studies, meta-analyses, and post-hoc analyses that have evaluated pregabalin for the treatment of FM.

Materials and Methods

PubMed was searched using the search term ‘pregabalin AND fibromyalgia’ on 2 March 2017. A search of the Cochrane Library database using the term ‘pregabalin’ was also conducted on the same date. For both searches, no other date limits were set but identified articles were limited to the English language. We also examined reference lists in identified articles and personal lists of references for additional items, as well as drawing upon personal knowledge of recently completed studies. Articles that assessed pregabalin clinical studies, meta-analyses, combination studies, and post-hoc analyses of pregabalin clinical data were evaluated. Identified studies included both pregabalin immediate release (IR) and controlled release (CR) formulations. Clinical studies were included if they were double-blind, placebo-

or comparator-controlled randomized trials, as they represent the gold standard for reporting clinical data. All identified randomized, controlled studies were included irrespective of the type of primary endpoint or evaluation. Open-label extension studies of randomized, controlled trials were included because these studies provided longer-term safety information for the subject evaluated in the randomized, controlled trials. Combination studies of pregabalin with other treatments were included, whether randomized or not. Other open-label studies, observational studies, and non-blinded studies were excluded. Post-hoc analyses, based on data captured in the randomized, controlled trials, were included if the authors believed they added important information to the clinical profile of pregabalin. Studies that had health economic or outcomes research as primary objectives were not included as part of this review. All the authors agreed upon the inclusion of articles. Data were reviewed to provide an evidence-based, clinical summary of pregabalin efficacy and safety. Different types of studies, eg randomized controlled trials or meta-analyses, were considered separately, and individual studies were summarized separately.

Results

A total of 284 items were captured in PubMed and 28 from the Cochrane Library database. The following sections summarize the clinical profile of pregabalin based on study type.

Randomized, double-blind, placebo-controlled, clinical studies

Eleven clinical studies were identified as randomized, double-blind, placebo-controlled, studies [42-52]. Table 1 shows a summary of the studies (see also Table 1 of the Supplemental Online Material for more details of each study). Studies were conducted globally, including in North and South America, Europe, Asia, and Australia. Six studies were of parallel group design, three were two-way crossover studies, and two were randomized withdrawal studies. Ten studies were in adults and one study was in adolescents.

Nine of the studies examined the efficacy and safety of the pregabalin IR capsule formulation at doses of 75–600 mg/day, and in one study pregabalin was assessed as a CR formulation at doses of 330 and 495 mg/day. One study was a neuroimaging study of pregabalin at a dose of 450 mg/day that examined changes in brain area connectivity and neurochemical alterations in patients with FM following pregabalin treatment. In seven of the studies, the primary efficacy endpoint was the placebo-adjusted change in mean pain score from baseline, based on an 11-point numeric rating scale (NRS), ranging from 0 (no pain) to 10 (worst possible pain). The primary efficacy endpoint in the randomized withdrawal trials was the time to loss of therapeutic response (LTR). One study [48] evaluated pregabalin in adult FM patients with disrupted sleep utilizing polysomnography (PSG) for the primary efficacy endpoint of wake after sleep onset (WASO). Mean pain score and sleep quality score, both reported on an 11-point NRS, were also captured as secondary efficacy endpoints during this study. In the neuroimaging study [49], the primary efficacy evaluation was the voxel-wise blood oxygen level dependent brain activation signal assessed using functional magnetic resonance imaging (fMRI). Of note, some authors are involved in a randomized, placebo-controlled study in a Chinese FM population that has recently completed and results are pending. Importantly, the following sections include findings from positive and negative trials, and report positive and negative efficacy endpoints.

Mean pain scores

A comparison of the placebo-adjusted mean pain scores at the end of treatment for the parallel group and crossover studies is summarized in Table 2 and shown in Figure 1A. For the crossover studies, data from the different treatment periods were analyzed using standard crossover design methods to produce the efficacy endpoint estimate. Pregabalin numerically improved mean pain score relative to placebo in all the treatment arms across all the studies,

and was statistically significant in 11 arms. Placebo-adjusted improvements in mean pain score ranged from –0.33 to –0.98 for doses of 300 and 450 mg/day. The magnitude of the response was comparable in adults and adolescents, although the improvement in mean pain score relative to placebo was not significant in adolescents. With the exception of the adolescent trial, in all the other studies, significant improvement for pregabalin over placebo occurred during the first week of treatment, demonstrating rapid onset of pain reduction. Pregabalin was generally found to maintain significant improvement over placebo at each week through the duration of the study.

Secondary endpoints

The effects of pregabalin versus placebo on commonly assessed secondary evaluations at the end of treatment are summarized in Table 2 and shown in Figure 1B and C (see also Figure 1 of the Supplemental Online Material). Endpoints include sleep quality, Patient Global Impression of Change (PGIC) responder rates, 30% and 50% pain responder rates, Fibromyalgia Impact Questionnaire (FIQ) total score, Multidimensional Assessment of Fatigue (MAF) global index, and Hospital Anxiety and Depression Scale-Anxiety (HADS-A) and -Depression (HADS-D). In general, pregabalin numerically and consistently improved scores for these secondary evaluations relative to placebo, with many, but not all, statistically significant (Table 2). The data for doses of 300 and 450 mg/day are summarized below. Improvements in sleep quality, scored on an 11-point NRS, were consistently significantly better with pregabalin than placebo (Figure 1B). In six studies, sleep quality was scored from 0 = best possible sleep to 10 = worst possible sleep and scores ranged from –0.48 to –1.31 relative to placebo. In two studies, sleep quality scores were reversed (0 = worst possible sleep and 10 = best possible sleep) and pregabalin was also significantly better than placebo in both of them. Note that in Figure 1B, the direction for Roth et al. 2012 and Arnold et al.

2015 is the same as for the other studies to enable consistent interpretation of the data. PGIC scores were also consistently significantly better with pregabalin than placebo (Figure 1C). The proportion of patients who were PGIC responders, i.e., whose symptoms were 'much improved' or 'very much improved', ranged from 31.9% to 51.6%, compared with 23.5%–34.8% with placebo. The proportion of 30% pain responders, i.e., those patients with a ≥30% improvement in mean pain score, ranged from 32.6% to 49.5% compared with 18.5%–34.7% for placebo (Supplemental Online Material Figure 1). The proportion of 50% pain responders ranged from 17.9% to 28.9% for pregabalin compared with 9.2%–20% for placebo (Supplemental Online Material Figure 1). Placebo-adjusted improvements in FIQ total scores (scored from 0 to 100, with higher scores indicating greater impact) ranged from –1.17 to –6.60 (Supplemental Online Material Figure 1). MAF was assessed in four studies and improvements with pregabalin were rarely significantly better than placebo (Supplemental Online Material Figure 1). HADS-A and HADS-D scores with pregabalin were rarely significantly better than placebo (Supplemental Online Material Figure 1). The effect of pregabalin on these secondary endpoints was comparable in adults and adolescents.

Polysomnography study

In the crossover PSG study the primary efficacy endpoint was WASO and secondary efficacy evaluations mostly focused on other PSG measures [48] (see Table 1 of the Supplemental Online Material for more details of the study). Relative to placebo, pregabalin significantly decreased WASO at the end of the study (–19.33 min; $p < 0.001$) (Table 2). Of the other PSG items, compared with placebo, pregabalin also significantly improved the total sleep time (TST), sleep efficiency, the number of awakenings after sleep onset, wake time during sleep, the latency to persistent sleep, and amount of slow wave sleep, but not wake time after sleep. Sleep was also assessed using a patient-reported subjective sleep questionnaire in this study.

Of the subjective items, pregabalin significantly improved WASO, TST, latency to sleep onset, and sleep efficiency compared with placebo at the end of study treatment. Sleep quality was also better with pregabalin than placebo in this study (Figure 1B).

Randomized withdrawal studies

In the two randomized withdrawal studies, the primary efficacy endpoint was the time to LTR (see Table 1 of the Supplemental Online Material for more details of these studies including definitions of LTR for each study). In Crofford et al. 2008 [44], the time to LTR was significantly longer for patients treated with pregabalin than placebo ($p < 0.001$) (Table 2). Median time to LTR was 19 days for placebo but was not reached for pregabalin because half the group had not lost their therapeutic response by the end of the study (26 weeks of double-blind treatment). In addition, individual pregabalin doses of 300, 450, and 600 mg/day were associated with a significantly longer time to LTR compared with placebo-treated patients (all $p < 0.001$). All secondary efficacy evaluations, including PGIC, FIQ total score, Medical Outcomes Study-Sleep Scale (MOS-Sleep Scale), and MAF, showed significantly longer times to LTR for all doses of pregabalin combined than placebo (all $p < 0.001$). In Arnold et al. 2014 [50], the median time to LTR during the double-blind phase was significantly longer for pregabalin than placebo (58 vs. 22 days; $p < 0.05$) (Table 2). Treatment differences for the secondary efficacy evaluations of mean pain score, 30% and 50% pain responder rates, PGIC, FIQ total score, HADS-D, sleep quality, and MOS-Sleep Scale were better for pregabalin compared with placebo, but not significantly.

Neuroimaging study

The randomized, placebo-controlled neuroimaging study [49] used a series of three complementary brain imaging techniques, proton magnetic resonance spectroscopy, fMRI,

and functional connectivity magnetic resonance imaging, to assess the clinical action of pregabalin versus placebo in alleviating FM pain (briefly summarized in Table 1; see Table 1 of the Supplemental Online Material for more details of the study). The study tested the hypothesis that pregabalin was exerting its effect by modulating glutamatergic activity in key brain regions involved in pain processing, such as the insula, and that by doing so it reduced aberrant connectivity between the insula and networks such as the default mode network (DMN) [16,17,19,21]. These *a priori* hypotheses were largely borne out. Pregabalin but not placebo reduced combined glutamate/glutamine levels in the posterior insula. Pregabalin-related pain relief was associated with reduced connectivity between the posterior insula and the DMN, and pregabalin but not placebo reduced the response of the DMN to experimental pain. This study also appeared to identify neuroimaging markers for pregabalin responses. Higher pre-pregabalin glutamate/glutamine levels in the posterior insula and greater resting state connectivity from the insula to the DMN both predicted the subsequent analgesic response to pregabalin, but not placebo.

Safety and tolerability

Table 3 summarizes the safety and tolerability data from the 11 clinical studies described above (see also Supplemental Online Material Figure 2). Data for doses of 300 and 450 mg/day, including flexible 300–450 mg/day dosing, and corresponding placebo treatment arms are included below. The proportion of patients reporting an adverse event (AE) ranged from 77.3% to 91.8%, compared with 59.9%–77.1% for placebo. Serious AEs (SAEs) occurred infrequently with pregabalin (range 0.6%–4.4%), similar to placebo (range 0.4%–2.2%). Discontinuations due to AEs varied considerably for pregabalin (range 6.1%–22.4%) and were more common compared with placebo (range 3.4%–10.9%). The incidences of the most commonly occurring AEs were generally dose dependent, with the exception of

headache which occurred at rates similar to placebo (Supplemental Online Material Figure 2). Dizziness and somnolence were the most commonly reported AEs and were also the most common AEs leading to discontinuation. The safety profile of pregabalin was similar in adolescents and adults, although the incidence of somnolence was lower in adolescents and incidences of nausea and fatigue were higher (data not shown) [52]. AE duration was reported for a limited number of patients in two studies [42,43]. In Crofford et al. 2005 [42], the median duration of dizziness dose-dependently increased from 6 days to 15 days for 300 mg/day and 450 mg/day, respectively. Conversely, the median duration of somnolence dose-dependently decreased from 21 days to 18 days for the same doses. In Mease et al. 2008 [43], the median duration of dizziness dose-dependently increased from 19 days to 28 days for 300 and 450 mg/day, respectively. By comparison, the median duration of somnolence dose-dependently decreased from 88 days to 79.5 days for the same doses. The median durations of weight gain increased from 64 days to 69.5 days for 300 and 450 mg/day, respectively.

Five studies [43,45-47,52] had open-label extensions with the main objective of examining long-term safety and tolerability [52-54]. Pooled data from three studies showed that for up to 1 year of treatment at doses up to 600 mg/day, 77.9% of patients reported an AE and 12.4% discontinued treatment owing to an AE [53]. SAEs occurred rarely, with only three patients reporting pregabalin-related SAEs. The most commonly reported AEs were dizziness, somnolence, headache, peripheral edema, and weight gain. In the 1-year open-label extension in Japanese patients, 96.2% of patients reported an AE, 2.8% reported a SAE, and 4.7% discontinued due to AEs [54]. The most common AEs were nasopharyngitis, somnolence, dizziness, constipation, and weight gain. In the 6-month open-label extension in adolescents, 71.4% experienced an AE, 4.8% experienced a SAE, and 3.2% discontinued treatment owing to AEs [52]. The most frequent AEs were weight gain, dizziness, fatigue, and headache.

Other randomized, double-blind, clinical studies

One additional study of pregabalin monotherapy was identified, a double-blind, randomized 8-week trial that compared once-nightly versus twice-daily administration of pregabalin (300 mg/day) in 177 patients not currently taking pregabalin [55]. The within-treatment improvement in mean pain score (11-point NRS) relative to baseline was significant for both once-nightly and twice-daily pregabalin (both $p < 0.001$). No differences were observed between treatment groups. Improvements in secondary efficacy endpoints including 30% and 50% pain responder rates, revised FIQ scores, fatigue scores, sleep disturbance scores, and PGIC were also similar between the two groups. The number of patients who withdrew due to AEs was similar in the two treatment arms, but significantly more patients in the twice-daily group reported AEs compared with the once-nightly group ($p < 0.05$) The incidences of individual AEs were comparable in the two groups. Once-nightly dosing may therefore convey some safety and tolerability advantages over twice-daily dosing, with no adverse impact on efficacy.

Meta-analyses

Thirteen meta-analyses that assessed pregabalin for FM were identified [56-68]. One meta-analysis [56] was excluded because it showed data from the individual treatment arms of individual clinical studies and therefore provided no additional information to that presented above. We also excluded a second meta-analysis [68] because it was an indirect comparison of pregabalin efficacy and tolerability with that of duloxetine and milnacipran, and did not present data on pregabalin alone. Eleven meta-analyses that evaluated the efficacy and tolerability of pregabalin versus placebo were examined further (summarized in Table 1; see Table 2 of the Supplemental Online Material for more details of each meta-analysis) [57-67].

Ten studies analyzed pain responses, typically 30% and 50% pain responder rates, and eight studies analyzed other efficacy endpoints, most commonly PGIC. Seven studies analyzed tolerability, specifically withdrawals due to AEs. One study assessed tolerability alone with no efficacy analysis. Most studies analyzed individual doses of pregabalin. Data on pregabalin at the dose of 150 mg/day is not reported here since that was used in only one treatment arm of one study [42]. However, some studies combined all pregabalin doses for analysis, including 150 mg/day. Not all analyses reported statistical significance.

In summary, the findings of the meta-analyses support the findings of the individual clinical studies (see Table 2 of the Supplemental Online Material for more details). All individual doses of pregabalin (300, 450, and 600 mg/day, as well as flexible 300–450 mg/day dosing) showed a benefit in improving pain versus placebo. Pregabalin also improved PGIC scores and sleep disruption compared with placebo irrespective of dose, also in agreement with the individual clinical studies. The meta-analyses also revealed that fatigue, depression, anxiety, and FIQ total scores were improved with pregabalin versus placebo, generally significantly [58,61,65]. This is in contrast to the majority of the individual clinical studies, and presumably occurs because of the increased power to detect a difference between pregabalin and placebo. The meta-analyses also demonstrated a greater risk for withdrawals due to AEs for pregabalin compared with placebo, similar to the individual clinical studies.

Combination studies

A total of seven combination studies involving pregabalin were identified (summarized in Table 1; see also Table 3 of the Supplemental Online Material for more details of each individual study) [69-75]. The placebo-controlled clinical study in which pregabalin was added on top of an antidepressant [51] because has been discussed in detail above as the

antidepressant was being administered for the treatment of depression alone and not FM. The types of studies varied considerably from a randomized, double-blind, placebo-controlled trial to open-label, uncontrolled studies. However, because combination studies involving pregabalin treatment are uncommon, and poly-drug therapy is a promising area of research, we included all the studies for discussion.

Invariably, pregabalin in combination with another FM treatment improved treatment outcomes, whether related to pain or other symptom domains, compared with placebo or either treatment when administered alone (Supplemental Online Material Table 3). Based on withdrawals due to AEs, the tolerability of pregabalin in combination with another treatment was no worse when compared with placebo or either treatment when administered alone. It is worth noting that the majority of studies discussed here were conducted in relatively small patient populations, with some exceptions [71,73]. Nonetheless, these studies provide a platform for future large-scale, randomized, placebo- or comparator-controlled, double-blind trials of pregabalin in combination with other treatments.

Post-hoc analyses of clinical studies

Clinical aspects of the effectiveness and safety of a drug may only become apparent outside the confines of a single study, or when studies are pooled to create larger patient databases. We therefore examined post-hoc analyses of the randomized, double-blind, placebo-controlled, clinical studies to assess further the clinical effectiveness and safety profile of pregabalin.

Clinically relevant improvement in symptoms

Pooled patient data from four clinical studies were used to assess the proportion of patients who achieved any improvement (≥0%), minimal improvement (≥15%), moderate improvement (≥30%), substantial improvement (≥50%), or extensive improvement (≥70%) in pain response and sleep quality with doses of 300, 450, and 600 mg/day pregabalin versus placebo [76]. For each dose of pregabalin, the proportion of patients reporting substantial or extensive improvement in pain increased every week from baseline until approximately week 6, and then reached a steady state that was maintained until the end of the analysis at 12 weeks. At 6 weeks, the proportions of patients with different levels of improvement for a dose of 300 mg/day were: any, 65%; minimal, 52%; moderate, 36%; substantial, 21%; and extensive, 7.7%. For a dose of 450 mg/day, the proportions were: any, 68%; minimal, 56%; moderate, 39%; substantial, 23%; and extensive, 9.0%. All levels of improvement were greater with pregabalin, irrespective of dose, compared with placebo. Analysis of sleep quality scores reported similar findings. In a pooled analysis of five clinical studies, the change in pain severity from baseline to endpoint was compared for pregabalin versus placebo [77]. Pain severity was based on the 11-point NRS mean pain score, with categories of severe (≥7 to ≤10); moderate (≥4 to <7); and mild (0 to <4). Patients with FM administered fixed doses of 300 or 450 mg/day pregabalin were significantly ($p < 0.05$) more likely to improve pain severity category, i.e., shift from severe to moderate/mild pain, or from moderate to mild pain, compared with placebo. The proportion of patients who shifted pain severity category was also numerically greater in patients who received a flexible dose of 300–450 mg/day pregabalin compared with placebo.

Sleep

As described above, pregabalin significantly improved sleep quality versus placebo across studies for almost all doses of pregabalin, except 150 mg/day. A PSG study also detailed the

effects of pregabalin on sleep architecture [48]. Several post-hoc analyses have further examined other clinical effects of pregabalin on sleep. In patients with either moderate or severe pain at baseline, pregabalin (300–450 mg/day) statistically significantly improved sleep quality compared with placebo [78]. A post-hoc analysis of the PSG study showed that pregabalin at doses of 150–450 mg/day increased the duration of sleep bouts and decreased the duration of wake bouts to improve FM-related sleep disturbance [79]. Analysis of a subset of patients enrolled in the PSG study aimed to demonstrate that the effects of pregabalin observed in the laboratory were detectable at home, as measured using actigraphy [80]. Pregabalin significantly increased sleep efficiency and decreased sleep activity compared with placebo at home. A separate post-hoc analysis that pooled data from two clinical studies showed that pregabalin (300–600 mg/day) improved sleep dysfunction versus placebo primarily through a direct effect on patients' insomnia [81].

Time course of effects

A post-hoc analysis of four clinical studies comprising 12 pregabalin treatment arms (doses of 150–600 mg/day) and four placebo arms determined the time to immediate and sustained clinical improvements in pain and sleep quality [82]. The time to immediate clinical improvement in pain (the first of ≥2 consecutive days for which the mean score for pain or sleep was statistically significantly lower for pregabalin versus placebo) was 1–2 days for the eight treatment arms where pregabalin was better than placebo at endpoint. For the 11 treatment arms where sleep quality was significantly better than placebo at endpoint, the time to immediate clinical improvement was 1 day in all 11 treatment arms. The time to sustained clinical improvement in pain (≥1-point reduction in the pain or sleep score from each individual patient's baseline score) was 3–6 days in the first quartile of pain responders (ie the first 25% of patients to respond), depending on dose, compared with 15 days for placebo.

Sustained clinical improvement in sleep quality occurred in 2–4 days in the first quartile of sleep responders, depending on dose, compared with 9 days for placebo. A second analysis of two clinical studies examined the time to transient and stable improvements in pain in patients stratified by FM severity at baseline, based on FIQ total score [83]. The median time to transient improvement (≥27.9% improvement in mean pain score, considered a clinically meaningful improvement in pain [84]) was 5–7 days for pregabalin, depending on dose, compared with 11–12 days with placebo. The median time to stable improvement (the mean of the daily improvements ≥27.9% relative to baseline over the subsequent duration of the study starting on the day of the transient improvement) was 13–29 days for pregabalin, depending on dose, compared with ≥86 days for placebo. The median time to both transient and stable pain improvement was correlated with baseline FM severity, with longer times to improvement associated with worse FM. The time course of the 30% and 50% pain response has been assessed in a post-hoc analysis of one study [85]. The proportion of patients achieving a 30% pain response with pregabalin peaked in weeks 2 and 3 after the start of treatment, and the proportion of patients who achieved a 50% pain response with pregabalin peaked by week 3 of treatment. This analysis also examined the time to appearance of some of the most commonly reported AEs (somnolence, dizziness, weight gain, and constipation). For each AE, the majority of incidences occurred within 4 weeks of starting treatment. Finally, a post-hoc analysis of one study examined the duration of responses across multiple FM symptom domains [86]. Analysis of FIQ total score, MOS-Sleep Scale, and the 36-item Short-Form Health Survey showed a significantly longer time to LTR for each measure for pregabalin versus placebo.

Effect of patient characteristics at baseline on efficacy

A variety of post-hoc studies that pooled patient data from two or more clinical studies have demonstrated that the efficacy of pregabalin at a dose of 300–450 mg/day is largely unaffected by patient demographic and clinical characteristics at baseline. Patients had significantly better pain relief with pregabalin over placebo irrespective of whether they had moderate or severe pain at baseline [78]. Pregabalin was also significantly better than placebo in patients with a range of comorbid conditions at baseline including osteoarthritis (450 mg/day only) [87], headache [88], immune problems or allergies [88], gastroesophageal reflux disease [88], insomnia [88], depression [88], irritable bowel syndrome (450 mg/day only) [88], neurological conditions [88], asthma [88], and symptoms of anxiety or depression [89]. Prior opioid use is not a barrier to significant pain relief with pregabalin [90], and nor is tender point severity [91]. The magnitude of the pain response may depend on age, pain severity, and sleep score at baseline, with greater improvements in those with more severe baseline pain and sleep, and older patients [92]. A post-hoc analysis of patients with FM taking an selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinepherine reuptake inhibitor (SNRI) for comorbid depression [93] demonstrated that pregabalin was significantly better than placebo irrespective of age, body mass index, FM duration since diagnosis, short-term depression (<10 years), FM as the first diagnosis, number of previous FM medications, depression diagnosis, use of a low dose of antidepressant, presence of headache or osteoarthritis, prior opioid use, baseline pain severity, presence of moderately severe FM, anxiety severity, and sleep disruption severity.

Safety

A small number of post-hoc analyses focused on safety data. In a pooled analysis of three studies, the efficacy of pregabalin was assessed in those patients who reported somnolence as an AE [94]. The effect of pregabalin on pain relief, patient function, and sleep disturbance

was comparable between those patients with and without somnolence. An analysis of patients who reported weight gain as an AE indicated that patients with FM had a mean weight gain of 2.0 kg (median 1.7 kg), or a mean percent weight gain from baseline of 2.7% (median 2.5%) [95].

Discussion

This evidence-based summary evaluated the efficacy and safety of pregabalin for FM as demonstrated in double-blind, randomized, controlled clinical studies, open-label extensions of these clinical studies, meta-analyses, combination studies, and post-hoc analyses. In placebo-controlled clinical studies, pregabalin consistently demonstrates significant improvements versus placebo in pain, sleep, and patient function at doses of 300–600 mg/day. These findings are supported by multiple sets of meta-analyses. Combination studies show that pregabalin is efficacious when used with other pharmacotherapies. Post-hoc analyses have shown that the improvements in FM symptoms occur as early as 1–2 days of starting treatment, that pregabalin also improves other aspects of sleep beyond quality, and that the analgesic effects of pregabalin occur irrespective of a wide variety of patient demographic and clinical characteristics at baseline. These studies also show that pregabalin has a well-established safety and tolerability profile, with rates of discontinuations due to AEs and incidences of AEs increasing dose-dependently. The safety and tolerability data from the individual studies are again supported by meta-analyses. Dizziness and somnolence are the most common AEs reported irrespective of pregabalin dose, and withdrawals due to AEs are more frequent for pregabalin over placebo.

The majority of clinical studies were in adults, but one was in adolescents up to 17 years of age [52]. In comparison with the adult studies, pregabalin did not significantly improve pain

scores at endpoint compared with placebo in adolescents, although the magnitude of response was numerically similar to adults. Some secondary endpoints were significantly better with pregabalin versus placebo, including the proportion of PGIC responders, and most endpoints were numerically better than placebo. The safety profile was consistent with that seen in adults. The discrepancies between adults and adolescents may have occurred because the adolescent study struggled to recruit subjects, and only 107 patients were eventually included. Pregabalin may have more closely replicated efficacy outcomes in adults in a larger sample population.

The magnitude of the placebo-adjusted pain response on the 11-point NRS ranged from –0.33 to –0.98 for doses of 300 or 450 mg/day. The clinical relevance of this effect has been questioned [63], but individual patient responses should also be considered [96], as recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) [97]. As revealed by the 30% and 50% pain responder analyses, pregabalin produces clinically relevant improvements in pain [84] in up to half of patients. Moreover, up to half of patients were PGIC responders, i.e., they reported their symptoms as being very much or much improved by pregabalin. As well as being efficacy endpoints in the randomized, placebo-controlled studies, pain responder rates were also the main efficacy endpoint of interest for most of the meta-analyses. The findings from the meta-analyses confirmed the findings from the randomized, placebo-controlled studies, showing that pain responder rates were higher for pregabalin over placebo irrespective of dose. PGIC responder rates were also assessed in some of the meta-analyses. Again, the data from the meta-analyses support the randomized, placebo-controlled studies, showing that PGIC responder rates are higher for pregabalin over placebo irrespective of dose. As well as statistically and clinically significant improvements in pain, the positive effects of pregabalin on other FM symptoms,

notably disrupted sleep, should also be taken into account [96]. Improvements in pain and sleep can appear as early as 1–2 days after starting treatment [82]. The efficacy of pregabalin demonstrated in the clinical studies is supported by multiple meta-analyses of different efficacy endpoints. The consistency in findings across the meta-analyses reflects the fact that a core number of pregabalin studies were included in each meta-analysis. Nonetheless, it is encouraging that different sets of authors all reached the same conclusions.

Data from the randomized, placebo-controlled studies and the open-label extension studies show that pregabalin has a consistent safety profile across those studies. Although open-label studies are not as rigorous as randomized, controlled studies, in this instance the data from the open-label studies provide additional valuable information on the longer-term safety profile of pregabalin. Dizziness and somnolence were the most commonly reported AEs [42,43,45-48,51]. Some of the commonest AEs (dizziness, somnolence, weight gain, and constipation) may appear within 4 weeks of starting treatment [85], and may last for weeks or longer [42,43]. As a result, discontinuations due to AEs occur in up to a quarter of adult patients receiving doses of 300 or 450 mg/day pregabalin [42,43,45-48,51]. Although safety data were not statistically compared in the randomized, placebo-controlled clinical studies, withdrawal rates due to AEs were statistically compared in some of the meta-analyses. These data show that withdrawals due to AEs occurs significantly more often for pregabalin over placebo, irrespective of dose. In general, the incidences of AEs and discontinuations due to AEs are dose dependent, which highlights the potential importance of titrating patients to the maximally tolerated therapeutic dose. The parallel group or crossover clinical studies of pregabalin included a titration period of 1–3 weeks [42,43,45-48,51,52], but we can hypothesize that a longer titration period may improve tolerability early in treatment. Although there are no practical data to support this, in clinical practice titration is typically

slower than that seen in clinical trials. The goal should be to reach therapeutic doses based on the evidence presented here.

Current product labeling recommends pregabalin dosing twice daily, with the dose equally divided [34]. Studies examining different dosing schedules are rare, but in the single randomized controlled trial that examined this subject [55], once-nightly dosing appeared to confer some safety and tolerability advantages over twice-daily dosing, with no effect on efficacy. Future studies that identify new and appropriate dosing regimens are an important area of research.

Studies examining the clinical effects of pregabalin in combination with other pharmacotherapies has not received much attention. Indeed, our searches identified only 7 combination studies, of which only 2 were randomized, controlled studies. We therefore also assessed data from other studies, including open-label and retrospective studies. Our findings show that pregabalin demonstrates efficacy in combination with other pharmacotherapies, and indicates it might be useful as part of a polypharmacy regimen. Many patients may benefit from multi-drug treatment, but the data are limited. Pregabalin may also be beneficial as part of a multimodal therapeutic approach, i.e., pharmacological and non-pharmacological treatments, but again this has not been adequately studied. Patients with FM have multiple symptoms and functional impairment, so clinicians need to be realistic about how useful single pharmacotherapies can be. Combination pharmacotherapy and multimodal treatment of FM is an area ripe for future study.

A review [1] of worldwide FM epidemiology described different prevalence rates across different countries, highlighting that FM is a global problem that has taken many years to

recognize. To date, pregabalin is approved for the treatment of FM in the US [34], Japan, and 37 other countries, underscoring the need for viable treatment options that can help to address the needs of patients worldwide. Most of the pregabalin clinical studies discussed here were based in the US, although several international studies have been conducted [46,48,50-52], and a study specifically in Japanese patients was performed [47]. A study in Chinese patients has recently completed although data are pending. As shown in this review, the safety and tolerability profile of pregabalin was similar among US, international, and Japanese patients, highlighting its utility in different geographic populations.

This review is an evidence-based clinical summary of pregabalin efficacy and safety, and as such is associated with some limitations. Not all the data summarized were from randomized, controlled trials or systematic reviews and meta-analyses. Publication bias was not assessed despite all the randomized, placebo-controlled studies being industry sponsored. Nevertheless, we have included findings from both positive and negative studies, and reported data on both positive and negative efficacy endpoints. Limitations associated with the individual clinical studies may also be important and should be considered. Most of the studies lasted for several weeks, but FM is a long-lasting, chronic condition [24]. Safety data were not statistically compared. Pregabalin was assessed as monotherapy only, but polypharmacy is more likely in the real world. As noted above, titration periods lasted from 1 to 3 weeks, whereas titration may be slower in practice. Each study also had specific patient inclusion and exclusion criteria. Post-hoc analyses were limited to the patients that participated in the clinical trials identified, and the data that were captured as part of those trials.

Conclusions

The purpose of this evidence-based review was to summarize the clinical data supporting the use of pregabalin for the treatment of FM. Data from randomized, placebo-controlled studies have demonstrated its efficacy and safety for the treatment of FM pain as well as multiple other symptoms, including sleep disruption, patient status, and to a lesser extent patient function, fatigue, anxiety, and depression. Some patients have clinically meaningful responses, for instance improvements in 30% and 50% pain responder rates. The clinical study data are supported by multiple meta-analyses. Combining pregabalin with other pharmacotherapies may be beneficial. Post-hoc analyses have further examined the clinical utility of pregabalin for FM. The safety profile of pregabalin is well established and consistent across clinical studies for all populations analyzed, including adolescents. The most common AEs are dizziness and somnolence. Pregabalin continues to be a viable treatment option for FM-related pain and other FM symptoms. The information provided here may help physicians and other healthcare professionals make an informed decision when considering pregabalin for their patients with FM.

Transparency section

Declaration of funding

Authors received no funding in the preparation of this article.

Declaration of financial/other relationships

Dr Lesley Arnold has performed consulting services for Pfizer Inc, Daiichi Sankyo, Innovative Med Concepts, Zynerba Pharmaceuticals Inc, Eli Lilly & Company, CinRx and Astellas, participated on speaker bureau for Pfizer Inc, and received research support from Eli Lilly & Company, Cefaly, Daiichi Sankyo, Allergan, Tonix, and Pfizer Inc. Dr Ernest Choy has served as a member of advisory boards and on speaker bureau for Pfizer. Dr Daniel

Clauw has performed consulting services for Pfizer Inc, Eli Lilly & Company, Pierre Fabre Laboratories, Aptinyx Inc, Cerephex Corporation, IMC Pharma, Zynerba Pharmaceuticals Inc, and Samumed LLC, and received research support from Pfizer Inc, Forest Laboratories, and Cerephex Corporation. Ed Whalen, David Semel, Lynne Pauer, and Lloyd Knapp are employees of Pfizer, and have stocks or stock options in Pfizer. Dr Hiroshi Oka has no conflicts of interest to declare.

Author contributions

All authors were involved in the conception of this article; in the drafting of the article and for critically revising it for intellectual content; approved the final version to be published; and agree to be accountable for all aspects of the work.

Acknowledgments

We thank Andrew Clair of Pfizer for initial discussions on potential topics for review. Medical writing support was provided by David Cope, PhD, of Engage Scientific Solutions, and funded by Pfizer.

References

1. Queiroz LP. Worldwide epidemiology of fibromyalgia. Curr Pain Headache Rep. 2013;17;(8):356.

2. Wolfe F, Ross K, Anderson J, et al. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum. 1995;38;(1):19-28.

3. Wolfe F, Brähler E, Hinz A, et al. Fibromyalgia prevalence, somatic symptom reporting, and the dimensionality of polysymptomatic distress: results from a survey of the general population. Arthritis Care Res (Hoboken). 2013;65;(5):777-785.

4. Vincent A, Lahr BD, Wolfe F, et al. Prevalence of fibromyalgia: a population-based study in Olmsted County, Minnesota, utilizing the Rochester Epidemiology Project. Arthritis Care Res (Hoboken). 2013;65;(5):786-792.

5. Branco JC, Bannwarth B, Failde I, et al. Prevalence of fibromyalgia: a survey in five European countries. Semin Arthritis Rheum. 2010;39;(6):448-453.

6. Haq SA, Darmawan J, Islam MN, et al. Prevalence of rheumatic diseases and associated outcomes in rural and urban communities in Bangladesh: a COPCORD study. J Rheumatol. 2005;32;(2):348-353.

7. Guermazi M, Ghroubi S, Sellami M, et al. [Fibromyalgia prevalence in Tunisia]. Tunis Med. 2008;86;(9):806-811.

8. Senna ER, De Barros AL, Silva EO, et al. Prevalence of rheumatic diseases in Brazil: a study using the COPCORD approach. J Rheumatol. 2004;31;(3):594-597.

9. White KP, Speechley M, Harth M, et al. The London Fibromyalgia Epidemiology Study: the prevalence of fibromyalgia syndrome in London, Ontario. J Rheumatol. 1999;26;(7):1570-1576.

10. McNally JD, Matheson DA, Bakowsky VS. The epidemiology of self-reported fibromyalgia in Canada. Chronic Dis Can. 2006;27;(1):9-16.

11. Mas AJ, Carmona L, Valverde M, et al. Prevalence and impact of fibromyalgia on function and quality of life in individuals from the general population: results from a nationwide study in Spain. Clin Exp Rheumatol. 2008;26;(4):519-526.

12. Topbas M, Cakirbay H, Gulec H, et al. The prevalence of fibromyalgia in women aged 20-64 in Turkey. Scand J Rheumatol. 2005;34;(2):140-144.

13. Clauw DJ. Fibromyalgia and related conditions. Mayo Clin Proc. 2015;90;(5):680-692.

14. Gracely RH, Petzke F, Wolf JM, et al. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum. 2002;46;(5):1333-1343.

15. Cook DB, Lange G, Ciccone DS, et al. Functional imaging of pain in patients with primary fibromyalgia. J Rheumatol. 2004;31;(2):364-378.

16. Napadow V, LaCount L, Park K, et al. Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. Arthritis Rheum. 2010;62;(8):2545-2555.

17. Napadow V, Kim J, Clauw DJ, et al. Decreased intrinsic brain connectivity is associated with reduced clinical pain in fibromyalgia. Arthritis Rheum. 2012;64;(7):2398-2403.

18. Jensen KB, Loitoile R, Kosek E, et al. Patients with fibromyalgia display less functional connectivity in the brain's pain inhibitory network. Mol Pain. 2012;8:32.

19. Harris RE, Sundgren PC, Craig AD, et al. Elevated insular glutamate in fibromyalgia is associated with experimental pain. Arthritis Rheum. 2009;60;(10):3146-3152.

20. Foerster BR, Petrou M, Edden RA, et al. Reduced insular gamma-aminobutyric acid in fibromyalgia. Arthritis Rheum. 2012;64;(2):579-583.

21. Harris RE, Sundgren PC, Pang Y, et al. Dynamic levels of glutamate within the insula are associated with improvements in multiple pain domains in fibromyalgia. Arthritis Rheum. 2008;58;(3):903-907.

22. Lopez-Sola M, Woo CW, Pujol J, et al. Towards a neurophysiological signature for fibromyalgia. Pain. 2017;158;(1):34-47.

23. Mease PJ, Arnold LM, Crofford LJ, et al. Identifying the clinical domains of fibromyalgia: contributions from clinician and patient Delphi exercises. Arthritis Rheum. 2008;59;(7):952-960.

24. Clauw DJ. Fibromyalgia: a clinical review. JAMA. 2014;311;(15):1547-1555.

25. Schaefer C, Chandran A, Hufstader M, et al. The comparative burden of mild, moderate and severe fibromyalgia: results from a cross-sectional survey in the United States. Health Qual Life Outcomes. 2011;9:71.

26. Perrot S, Schaefer C, Knight T, et al. Societal and individual burden of illness among fibromyalgia patients in France: association between disease severity and OMERACT core domains. BMC Musculoskelet Disord. 2012;13:22.

27. Schaefer C, Mann R, Masters ET, et al. The Comparative Burden of Chronic Widespread Pain and Fibromyalgia in the United States. Pain Pract. 2016;16;(5):565-579.

28. Robinson RL, Kroenke K, Mease P, et al. Burden of illness and treatment patterns for patients with fibromyalgia. Pain Med. 2012;13;(10):1366-1376.

29. Hauser W, Walitt B, Fitzcharles MA, et al. Review of pharmacological therapies in fibromyalgia syndrome. Arthritis Res Ther. 2014;16;(1):201.

30. Lauche R, Cramer H, Häuser W, et al. A Systematic Overview of Reviews for Complementary and Alternative Therapies in the Treatment of the Fibromyalgia Syndrome. Evid Based Complement Alternat Med. 2015;2015:610615.

31. Taylor CP, Angelotti T, Fauman E. Pharmacology and mechanism of action of pregabalin: the calcium channel alpha2-delta (alpha2-delta) subunit as a target for antiepileptic drug discovery. Epilepsy Res. 2007;73;(2):137-150.

32. Fink K, Dooley DJ, Meder WP, et al. Inhibition of neuronal Ca(2+) influx by gabapentin and pregabalin in the human neocortex. Neuropharmacology. 2002;42;(2):229-236.

33. Cunningham MO, Woodhall GL, Thompson SE, et al. Dual effects of gabapentin and pregabalin on glutamate release at rat entorhinal synapses in vitro. Eur J Neurosci. 2004;20;(6):1566-1576.

34. Lyrica® Prescribing Information. [Internet]. New York, NY: Pfizer Inc; 2016. Available from: http://labeling.pfizer.com/ShowLabeling.aspx?id=561 [Last accessed June 8, 2016].

35. Cymbalta® Prescribing Information. [Internet]. Indianapolis, IN: Lilly USA, LLC; 2016. Available from: http://pi.lilly.com/us/cymbalta-pi.pdf [Last accessed September 21, 2016].

36. Savella® Prescribing Information. [Internet]. Irvine, CA: Allergan USA, Inc; 2016. Available from: http://www.allergan.com/assets/pdf/savella_pi [Last accessed September 21, 2016].

37. Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis. 2017;76;(2):318-328.

38. Fitzcharles MA, Ste-Marie PA, Goldenberg DL, et al. 2012 Canadian Guidelines for the diagnosis and management of fibromyalgia syndrome: executive summary. Pain Res Manag. 2013;18;(3):119-126.

39. Sommer C, Häuser W, Alten R, et al. [Drug therapy of fibromyalgia syndrome. Systematic review, meta-analysis and guideline]. Schmerz. 2012;26;(3):297-310.

40. Ablin JN, Amital H, Ehrenfeld M, et al. [Guidelines for the diagnosis and treatment of the fibromyalgia syndrome]. Harefuah. 2013;152;(12):742-747, 751, 750.

41. Ablin J, Fitzcharles MA, Buskila D, et al. Treatment of fibromyalgia syndrome: recommendations of recent evidence-based interdisciplinary guidelines with special emphasis on complementary and alternative therapies. Evid Based Complement Alternat Med. 2013;2013:485272.

42. Crofford LJ, Rowbotham MC, Mease PJ, et al. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2005;52;(4):1264-1273.

43. Mease PJ, Russell IJ, Arnold LM, et al. A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. J Rheumatol. 2008;35;(3):502-514.

44. Crofford LJ, Mease PJ, Simpson SL, et al. Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6-month, double-blind, placebo-controlled trial with pregabalin. Pain. 2008;136;(3):419-431.

45. Arnold LM, Russell IJ, Diri EW, et al. A 14-week, randomized, double-blinded, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia. J Pain. 2008;9;(9):792-805.

46. Pauer L, Winkelmann A, Arsenault P, et al. An international, randomized, double-blind, placebo-controlled, phase III trial of pregabalin monotherapy in treatment of patients with fibromyalgia. J Rheumatol. 2011;38;(12):2643-2652.

47. Ohta H, Oka H, Usui C, et al. A randomized, double-blind, multicenter, placebo-controlled phase III trial to evaluate the efficacy and safety of pregabalin in Japanese patients with fibromyalgia. Arthritis Res Ther. 2012;14;(5):R217.

48. Roth T, Lankford DA, Bhadra P, et al. Effect of pregabalin on sleep in patients with fibromyalgia and sleep maintenance disturbance: a randomized, placebo-controlled, 2-way crossover polysomnography study. Arthritis Care Res (Hoboken). 2012;64;(4):597-606.

49. Harris RE, Napadow V, Huggins JP, et al. Pregabalin rectifies aberrant brain chemistry, connectivity, and functional response in chronic pain patients. Anesthesiology. 2013;119;(6):1453-1464.

50. Arnold LM, Arsenault P, Huffman C, et al. Once daily controlled-release pregabalin in the treatment of patients with fibromyalgia: a phase III, double-blind, randomized withdrawal, placebo-controlled study. Curr Med Res Opin. 2014;30;(10):2069-2083.

51. Arnold LM, Sarzi-Puttini P, Arsenault P, et al. Efficacy and Safety of Pregabalin in Patients with Fibromyalgia and Comorbid Depression Taking Concurrent Antidepressant Medication: A Randomized, Placebo-controlled Study. J Rheumatol. 2015;42;(7):1237-1244.

52. Arnold LM, Schikler KN, Bateman L, et al. Safety and efficacy of pregabalin in adolescents with fibromyalgia: a randomized, double-blind, placebo-controlled trial and a 6-month open-label extension study. Pediatr Rheumatol Online J. 2016;14;(1):46.

53. Arnold LM, Emir B, Murphy TK, et al. Safety profile and tolerability of up to 1 year of pregabalin treatment in 3 open-label extension studies in patients with fibromyalgia. Clin Ther. 2012;34;(5):1092-1102.

54. Ohta H, Oka H, Usui C, et al. An open-label long-term phase III extension trial to evaluate the safety and efficacy of pregabalin in Japanese patients with fibromyalgia. Mod Rheumatol. 2013;23;(6):1108-1115.

55. Nasser K, Kivitz AJ, Maricic MJ, et al. Twice daily versus once nightly dosing of pregabalin for fibromyalgia: a double-blind randomized clinical trial of efficacy and safety. Arthritis Care Res (Hoboken). 2014;66;(2):293-300.

56. Hauser W, Bernardy K, Uçeyler N, et al. Treatment of fibromyalgia syndrome with gabapentin and pregabalin--a meta-analysis of randomized controlled trials. Pain. 2009;145;(1-2):69-81.

57. Moore RA, Straube S, Wiffen PJ, et al. Pregabalin for acute and chronic pain in adults. Cochrane Database Syst Rev. 2009;(3):CD007076.

58. Hauser W, Petzke F, Sommer C. Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome. J Pain. 2010;11;(6):505-521.

59. Straube S, Derry S, Moore RA, et al. Pregabalin in fibromyalgia: meta-analysis of efficacy and safety from company clinical trial reports. Rheumatology (Oxford). 2010;49;(4):706-715.

60. Tzellos TG, Toulis KA, Goulis DG, et al. Gabapentin and pregabalin in the treatment of fibromyalgia: a systematic review and a meta-analysis. J Clin Pharm Ther. 2010;35;(6):639-656.

61. Choy E, Marshall D, Gabriel ZL, et al. A systematic review and mixed treatment comparison of the efficacy of pharmacological treatments for fibromyalgia. Semin Arthritis Rheum. 2011;41;(3):335-345 e336.

62. Roskell NS, Beard SM, Zhao Y, et al. A meta-analysis of pain response in the treatment of fibromyalgia. Pain Pract. 2011;11;(6):516-527.

63. Nuesch E, Häuser W, Bernardy K, et al. Comparative efficacy of pharmacological and non-pharmacological interventions in fibromyalgia syndrome: network meta-analysis. Ann Rheum Dis. 2013;72;(6):955-962.

64. Zaccara G, Perucca P, Gangemi PF. The adverse event profile of pregabalin across different disorders: a meta-analysis. Eur J Clin Pharmacol. 2012;68;(6):903-912.

65. Üçeyler N, Sommer C, Walitt B, et al. Anticonvulsants for fibromyalgia. Cochrane Database Syst Rev. 2013;(10):CD010782.

66. Wiffen PJ, Derry S, Moore RA, et al. Antiepileptic drugs for neuropathic pain and fibromyalgia - an overview of Cochrane reviews. Cochrane Database Syst Rev. 2013;(11):CD010567.

67. Derry S, Cording M, Wiffen PJ, et al. Pregabalin for pain in fibromyalgia in adults. Cochrane Database Syst Rev. 2016;9:CD011790.

68. Lee YH, Song GG. Comparative efficacy and tolerability of duloxetine, pregabalin, and milnacipran for the treatment of fibromyalgia: a Bayesian network meta-analysis of randomized controlled trials. Rheumatol Int. 2016;36;(5):663-672.

69. Calandre EP, Morillas-Arques P, Rodriguez-Lopez CM, et al. Pregabalin augmentation of quetiapine therapy in the treatment of fibromyalgia: an open-label, prospective trial. Pharmacopsychiatry. 2007;40;(2):68-71.

70. Calandre EP, Morillas-Arques P, Molina-Barea R, et al. Trazodone plus pregabalin combination in the treatment of fibromyalgia: a two-phase, 24-week, open-label uncontrolled study. BMC Musculoskelet Disord. 2011;12:95.

71. Metyas S, Ibrahim M, Ortiz EC, et al. Monotherapy versus combination therapy in the treatment of fibromyalgia. Ann Rheum Dis. 2013;71;(Suppl 3):276.

72. Gilron I, Chaparro LE, Tu D, et al. Combination of pregabalin with duloxetine for fibromyalgia: a randomized controlled trial. Pain. 2016;157;(7):1532-1540.

73. Mease PJ, Farmer MV, Palmer RH, et al. Milnacipran combined with pregabalin in fibromyalgia: a randomized, open-label study evaluating the safety and efficacy of adding milnacipran in patients with incomplete response to pregabalin. Ther Adv Musculoskelet Dis. 2013;5;(3):113-126.

74. Del Giorno R, Skaper S, Paladini A, et al. Palmitoylethanolamide in Fibromyalgia: Results from Prospective and Retrospective Observational Studies. Pain Ther. 2015;4;(2):169-178.

75. Ramzy EA. Comparative Efficacy of Newer Antidepressants in Combination with Pregabalin for Fibromyalgia Syndrome: A Controlled, Randomized Study. Pain Pract. 2017;17;(1):32-40.

76. Straube S, Derry S, Moore RA, et al. Pregabalin in fibromyalgia--responder analysis from individual patient data. BMC Musculoskelet Disord. 2010;11:150.

77. Parsons B, Argoff CE, Clair A, et al. Improvement in pain severity category in clinical trials of pregabalin. J Pain Res. 2016;9:779-785.

78. Clair A, Emir B. The safety and efficacy of pregabalin for treating subjects with fibromyalgia and moderate or severe baseline widespread pain. Curr Med Res Opin. 2016;32;(3):601-609.

79. Roth T, Bhadra-Brown P, Pitman VW, et al. Pregabalin Improves Fibromyalgia-related Sleep Disturbance. Clin J Pain. 2016;32;(4):308-312.

80. Peterson BT, Resnick M, Brosnan M, et al. Effect of pregabalin on home sleep and daytime activity patterns in patients with fibromyalgia and sleep maintenance difficulties. Sleep. 2011;34:A232.

81. Russell IJ, Crofford LJ, Leon T, et al. The effects of pregabalin on sleep disturbance symptoms among individuals with fibromyalgia syndrome. Sleep Med. 2009;10;(6):604-610.

82. Arnold LM, Emir B, Pauer L, et al. Time to improvement of pain and sleep quality in clinical trials of pregabalin for the treatment of fibromyalgia. Pain Med. 2015;16;(1):176-185.

83. Bushmakin AG, Cappelleri JC, Chandran AB, et al. Evaluation of the fibromyalgia impact questionnaire at baseline as a predictor for time to pain improvement in two clinical trials of pregabalin. Int J Clin Pract. 2013;67;(1):52-59.

84. Farrar JT, Young JP, Jr., LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001;94;(2):149-158.

85. Parsons B, Emir B, Clair A. Temporal analysis of pain responders and common adverse events: when do these first appear following treatment with pregabalin. J Pain Res. 2015;8:303-309.

86. Pauer L, Atkinson G, Murphy TK, et al. Long-term maintenance of response across multiple fibromyalgia symptom domains in a randomized withdrawal study of pregabalin. Clin J Pain. 2012;28;(7):609-614.

87. Argoff CE, Emir B, Whalen E, et al. Pregabalin Improves Pain Scores in Patients with Fibromyalgia Irrespective of Comorbid Osteoarthritis. Pain Med. 2016;17;(11):2100-2108.

88. Bhadra P, Petersel D. Medical conditions in fibromyalgia patients and their relationship to pregabalin efficacy: pooled analysis of Phase III clinical trials. Expert Opin Pharmacother. 2010;11;(17):2805-2812.

89. Arnold LM, Leon T, Whalen E, et al. Relationships among pain and depressive and anxiety symptoms in clinical trials of pregabalin in fibromyalgia. Psychosomatics. 2010;51;(6):489-497.

90. Argoff CE, Clair A, Emir B, et al. Prior Opioid Use Does Not Impact the Response to Pregabalin in Patients With Fibromyalgia. Clin J Pain. 2016;32;(7):555-561.

91. Starz T, Wilson H, Robinson J, et al. The effect of baseline tender point severity on treatment outcome in pregabalin clinical trials. J Pain. 2010;11:S37.

92. Emir B, Murphy TK, Petersel DL, et al. Treatment response to pregabalin in fibromyalgia pain: effect of patient baseline characteristics. Expert Opin Pharmacother. 2010;11;(14):2275-2280.

93. Silverman SL, Backonja M, Pauer L, et al. Effect of Baseline Characteristics on the Pain Response to Pregabalin in Fibromyalgia Patients with Comorbid Depression. Pain Med. 2017 [Epub ahead of print].

94. Pauer L, Gary A, Petersel DL, et al. The effect of somnolence on pain, function, and sleep responses to pregabalin in patients with fibromyalgia. Arthritis Rheum. 2009;60;(Suppl 10):93.

95. Cabrera J, Emir B, Dills D, et al. Characterizing and understanding body weight patterns in patients treated with pregabalin. Curr Med Res Opin. 2012;28;(6):1027-1037.

96. Arnold LM, Cappelleri JC, Clair A, et al. Interpreting effect sizes and clinical relevance of pharmacological interventions for fibromyalgia. Pain Ther. 2013;2;(1):65-71.

97. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. 2008;9;(2):105-121.

98. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum. 1990;33;(2):160-172.

99. Yunus MB, Masi AT. Juvenile primary fibromyalgia syndrome. A clinical study of thirty-three patients and matched normal controls. Arthritis Rheum. 1985;28;(2):138-145.

100. Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken). 2010;62;(5):600-610.

Table 1. Summary of placebo-controlled clinical studies, meta-analyses, and combination studies of pregabalin for fibromyalgia

Study type	Objective	Entry criteria	References
Placebo-controlled clinical studies			
Parallel group	Efficacy and safety	Pregabalin-naïve adults with FM[a] without painful disorders that may confound assessment of FM pain and not taking prohibited pain or sleep medications, except acetaminophen	[42,43,45-47]
		Adolescents (12–17 years old) with FM[b] without painful disorders that may confound assessment of FM pain and not taking certain prohibited pain or sleep medications, except acetaminophen, NSAIDs, coxibs, zolpidem, or eszopiclone	[52]
Randomized withdrawal	Efficacy and safety	Adults with FM[a] without painful disorders that may confound assessment of FM pain	[44,50]
Crossover	Efficacy and safety	Adults with FM[a] taking an SSRI or SNRI for comorbid depression	[51]
PSG	Effects on PSG measures of sleep	Adults with FM[a] and disturbed sleep despite normal sleep-wake schedule with no active sleep disorder, except insomnia disorder, and no history of any	[48]

		sleep or circadian rhythm sleep disorder in the past 5 years	
Neuroimaging	Identify clinical action of pregabalin	Right-handed adults with FM[a] without painful disorders that may confound assessment of FM pain, and able to complete the neuroimaging procedures	[49]
Meta-analyses	Efficacy	Randomized, placebo-controlled studies	[58,61,63,65,66]
	Tolerability		[64]
	Efficacy and tolerability		[57,59,60,62,67]
Combination therapy	Efficacy and safety together with duloxetine or milnacipran	i. Patients with FM ii. Adults with FM[a] and without a distinct condition of similar or greater pain severity than FM iii. Adults with FM[a] with incomplete response to pregabalin	[71-73]
	Efficacy and safety together with other medications	i. Adult female patients with FM taking quetiapine for ≥6 months ii. Patients with FM[a] taking trazadone for ≥12 weeks iii. Patients with FM taking duloxetine plus pregabalin for 6 months and administered PEA	[69,70,74,75]

		iv. Female adults with FM[c] taking pregabalin and randomized to an antidepressant	

FM = fibromyalgia; NSAID = non-steroidal anti-inflammatory drug; PEA = palmitoylethanolamide; PSG = polysomnography; SNRI = serotonin/norepinephrine reuptake inhibitor; SSRI = serotonin-selective reuptake inhibitor.

[a]FM diagnostic criteria detailed in reference [98].

[b]FM diagnostic criteria detailed in reference [99].

[c]FM diagnostic criteria detailed in reference [100].

Table 2. Summary of efficacy results from the randomized, double-blind, placebo-controlled clinical studies

Study	Dose (mg/kg)	Domain										
		Pain				Sleep		Status	Function		Mood	
		Mean Score	LTR	30% Responders	50% Responders	Quality	WASO	PGIC Responders	FIQ	Fatigue	Anxiety	Depression
Adults												
Crofford et al. 2005 [42]	150											
	300					✓		✓		✓		
	450	✓			✓	✓		✓		✓		
Mease et al. 2008 [43]	300	✓				✓		✓				
	450	✓				✓		✓				
	600	✓				✓		✓				
Crofford et al. 2008 [44]	All		✓									
Arnold et al.	300	✓		✓	✓	✓		✓				

Table 3. Summary of safety and tolerability results from the randomized, double-blind, placebo-controlled clinical studies

Study	Pregabalin dose (mg/day)	All-causality treatment-emergent AEs, %		
		Patients with AEs	Patients with SAEs	Discontinuations due to AEs
Crofford et al. 2005 [42]	Placebo	77.1	0.8	7.6
	150	78.0	0	8.3
	300	88.1	2.2	7.5
	450	91.7	0.8	12.9
Mease et al. 2008 [43]	Placebo	76.3	2.1	10.5
	300	89.2	3.2	18.9
	450	91.8	1.1	22.4
	600	93.7	1.1	32.6
Crofford et al. 2008 [44]	All doses[a]	82.1	0.8	18.6
Arnold et al. 2008 [45]	Placebo	71.7	1.1	10.9
	300	80.9	1.1	16.4
	450	88.4	1.1	21.6
	600	88.3	1.1	26.1
Pauer et al. 2011 [46]	Placebo	73.4	2.2	10.9
	300	84.8	1.1	19.0
	450	90.1	4.4	19.8
	600	91.9	2.2	25.8
Ohta et al.	Placebo	70.6	0.4	3.6

2012 [47]	All doses[b]	90.0	1.2	9.6
Roth et al. 2012 [48]	Placebo	29.7	0	0.9
	All doses[c]	65.2	0	1.8
Arnold et al. 2014 [50]	All doses[a]	80.0	1.1	12.2
Arnold et al. 2015 [51]	Placebo	59.9	0.6	3.4
	All doses[b]	77.3	1.7	6.1
Arnold et al. 2016 [52]	Placebo	64.2	0	7.5
	All doses[d]	70.4	1.9	7.4

AEs = adverse events; SAEs = serious adverse events.

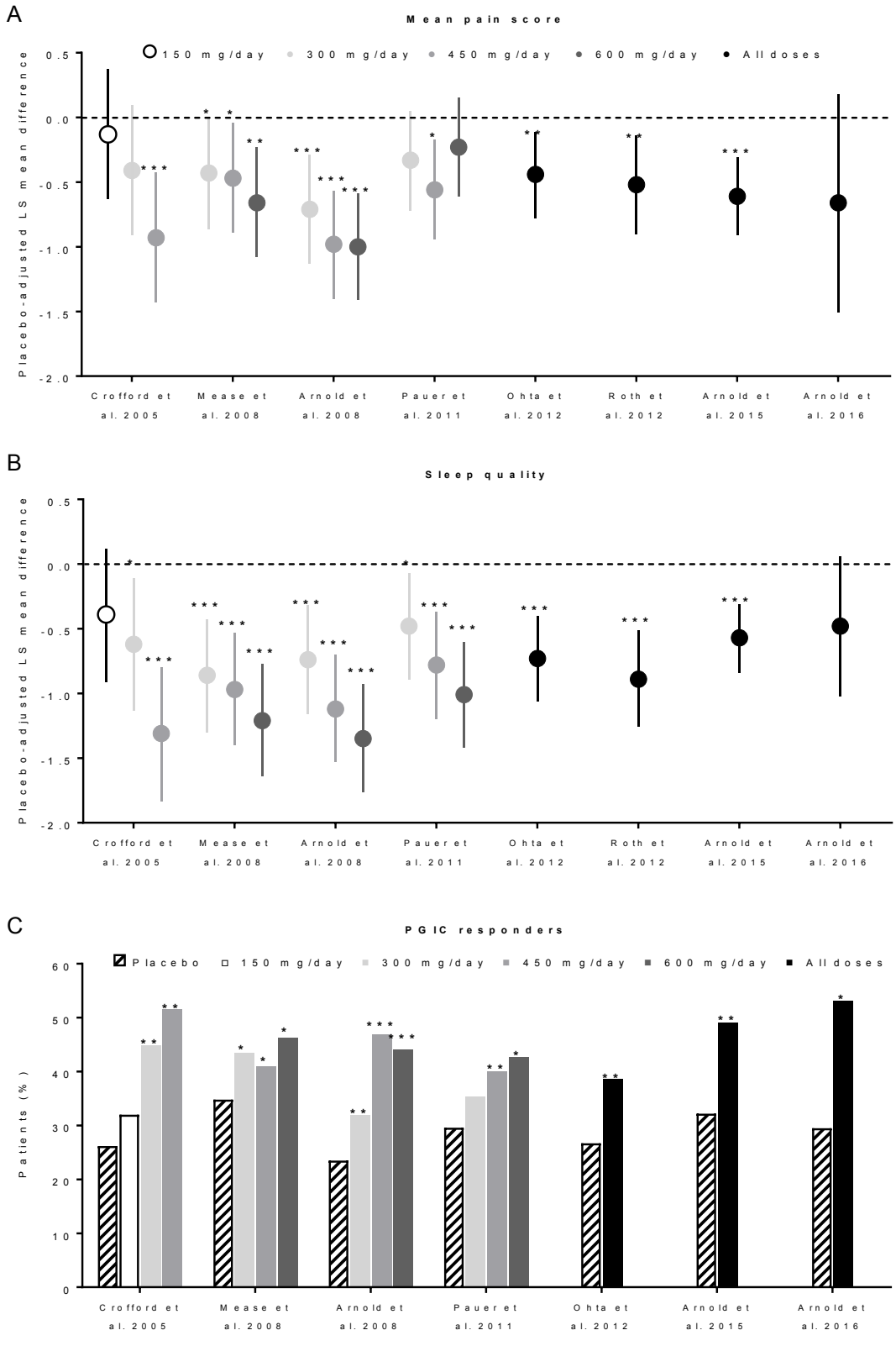
[a]Determined during the single-blind treatment phase only.

[b]Pregabalin data are for doses of 300 and 450 mg/day combined.

[c]Pregabalin data are for doses of 150, 300, and 450 mg/day combined.

[d]Pregabalin data are for doses of 75, 150, 300, and 450 mg/day combined.

Figure 1. Placebo-adjusted mean pain scores, sleep quality scores, and proportion of PGIC responders at the end of treatment in the parallel group and crossover studies by study and by pregabalin dose



(A,B) Error bars are the 95% confidence intervals. Dotted line indicates no change versus placebo. Key in (A) also applies to (B). Sleep quality was scored on an 11-point NRS in all studies. For Crofford et al. 2005, Mease et al. 2008, Arnold et al. 2008, Pauer et al. 2011, Ohta et al. 2012, and Arnold et al. 2016, scores ranged from 0 = best possible sleep to 10 = worst possible sleep. For Roth et al. 2012 and Arnold et al. 2015, scores ranged from 0 = worst possible sleep to 10 = best possible sleep. For the purpose of consistent interpretation of the data, Roth et al. 2012 and Arnold et al. 2015 have been reversed so that the directionality is the same as for the other studies. PGIC responders were defined as those patients whose FM symptoms were 'much improved' or 'very much improved' at the end of treatment. Data in Ohta et al. 2012 and Arnold et al. 2015 are for doses of 300 and 450 mg/day combined. Data in Roth et al. 2012 are for doses of 150, 300, and 450 mg/day combined. Mean pain scores and sleep quality scores at study endpoint were not evaluated for this study; data are for week 4 of active treatment. Data in Arnold et al. 2016 are for doses of 75, 150, 300, and 450 mg/day combined. Note that Roth et al. 2012, Harris et al. 2013, and Arnold et al. 2015 are 2-way crossover studies. Data from the 2 treatment periods in these studies were combined to produce a single data point. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ versus placebo.

LS = least squares; NRS = numeric rating scale; PGIC = Patient Global Impression of Change.