A Randomized, Double-blind, Placebo-Controlled, Phase III Trial of Pregabalin in the Treatment of Patients with Fibromyalgia

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ABSTRACT. ***Objective.*** To evaluate the efficacy and safety of pregabalin for symptomatic relief of pain associated with fibromyalgia (FM) and for management of FM.

Methods. This multicenter, double-blind, placebo-controlled trial randomly assigned 748 patients with FM to receive placebo or pregabalin 300, 450, or 600 mg/day (dosed twice daily) for 13 weeks. The primary outcome variable for study objective 1, symptomatic relief of pain associated with FM, was comparison of endpoint mean pain scores between each pregabalin group and placebo. The outcome variable for study objective 2, management of FM, included endpoint mean pain scores, Patient Global Impression of Change (PGIC), and Fibromyalgia Impact Questionnaire (FIQ)–Total Score. Secondary outcomes included assessments of sleep, fatigue, and mood disturbance.

Results. Patients in all pregabalin groups showed statistically significant improvement in endpoint mean pain score and in PGIC response compared with placebo. Improvements in FIQ–Total Score for the pregabalin groups were numerically but not significantly greater than those for the placebo group. Compared with placebo, all pregabalin treatment groups showed statistically significant improvement in assessments of sleep and in patients' impressions of their global improvement. Dizziness and somnolence were the most frequently reported adverse events.

Conclusion. Pregabalin at 300, 450, and 600 mg/day was efficacious and safe for treatment of pain associated with FM. Pregabalin monotherapy provides clinically meaningful benefit to patients with FM. (First Release Feb 15 2008; J Rheumatol 2008;35:502–14)

Key Indexing Terms:
FIBROMYALGIA PAIN SLEEP PREGABALIN RHEUMATOLOGY

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Fibromyalgia (FM) is a common, chronic pain disorder characterized by widespread musculoskeletal pain and tenderness and frequently accompanied by a variety of other symptoms, such as fatigue, sleep disturbance, and mood disorders[1-4]. FM affects roughly 2% of the US population[5] and 0.5% to 5% in other countries[6]. Although it can develop in men and children, FM is substantially more common in adult women than in men.

The etiology of FM is unknown, but emerging research suggests alterations in the regulation of neurotransmitters, particularly serotonin, norepinephrine, and substance-P, and abnormality of sensory processing within the central nervous system (CNS) are involved in its pathophysiology[1,3,7-10]. Nonrestorative deep, slow-wave sleep has also been reported as a contributing factor to the chronic pain and fatigue associated with FM[11].

Criteria for classifying FM, differentiating it from other musculoskeletal disorders, were published in 1990 by the American College of Rheumatology (ACR)[4]. The diagnosis is still made clinically, because no laboratory or radiographic abnormalities have achieved diagnostic status. Moreover, symptoms of FM may mimic or overlap disorders such as

myofascial pain syndrome, irritable bowel syndrome, chronic fatigue syndrome, hypothyroidism, and many of the inflammatory rheumatic diseases; thus the diagnosis must be carefully considered[12,13].

The key domain of FM, and the primary focus of therapy, is pain. Other health domains that warrant consideration in treatment strategies include fatigue, sleep disturbance, health-related quality of life, and function[14]. Few current therapies in FM have demonstrated consistent or adequate efficacy in these domains in large controlled clinical trials. Common pharmacologic treatments, varying considerably in their effectiveness, include antidepressants, muscle relaxants, benzodiazepines, nonsteroidal antiinflammatory agents (NSAID), hypnotics, corticosteroids, opiates, and soft tissue injections of topical anesthetics[1,3,15]. Most patients fail to achieve relief from any available monotherapy[15].

Pregabalin is an amino acid structurally related to the neurotransmitter GABA, but it is inactive at GABA receptors[16]. Pregabalin binds to the α_2-δ-1 subunit of voltage-gated calcium channels of presynaptic neurons and modifies channel functional properties[17,18]. Pregabalin modulates hyperexcited neurons via its potent binding at the α_2-δ-1 subunit that is associated with decreased calcium influx at nerve terminals and reduced release of several excitatory neurotransmitters (e.g., glutamate, noradrenaline, serotonin, dopamine, and substance P)[19-25]. Preclinical studies using mice with a mutation leading to the substitution of arginine at position 217 with alanine on the α_2-δ-1 subunit firmly established this subunit as a target for pain control and demonstrated that it is by binding to the α_2-δ-1 subunit that pregabalin achieves its analgesic activity[26]. Additionally, animal models have demonstrated that pregabalin has anticonvulsant[27] and anxiolytic-like[28] activity.

Pregabalin is approved in Canada[29] and the US[30] for management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN). In the US, it is also approved for adjunctive treatment of partial-onset seizures in adults with epilepsy and, most recently, for the treatment of FM. It is also approved in the European Union for the treatment of peripheral and central neuropathic pain in adults, as adjunctive therapy for partial seizures in adults with epilepsy, and for the treatment of generalized anxiety disorder in adults[31].

In a randomized controlled 8-week trial comparing pregabalin 150, 300, and 450 mg/day (dosed 3 times daily) with placebo in 529 patients with FM, pregabalin 450 mg/day significantly improved pain, sleep disturbance, fatigue, global measures, and several domains of health-related quality of life[32]. Pregabalin 300 mg/day also improved sleep and fatigue, as well as global measures, compared with placebo. The present trial was designed to confirm and extend the findings of this previous trial by addressing dual primary objectives, as follows.

Objective 1. to assess the efficacy and safety of 3 dosages of pregabalin (300, 450, and 600 mg/day) administered twice daily compared with placebo for the symptomatic relief of pain associated with FM.

If treatment with pregabalin met Objective 1 by significantly improving pain compared with placebo, then Objective 2 would be assessed.

Objective 2. to evaluate the efficacy of pregabalin for the management of FM by assessing improvement in 2 additional outcomes: the Patient Global Impression of Change (PGIC) and the Fibromyalgia Impact Questionnaire (FIQ)–Total Score.

Secondary objectives included evaluation of the efficacy of pregabalin to improve sleep, fatigue, mood disturbance, and additional measures of pain, health status, and functioning.

MATERIALS AND METHODS

This randomized, double-blind, placebo-controlled trial was conducted at 79 research sites in the US after it was approved by the respective institutional review boards. All patients provided written informed consent before trial procedures were initiated.

Men and women were eligible if they were at least 18 years old, met the ACR classification criteria for FM (i.e., widespread pain present for at least 3 months and pain in at least 11 of 18 specific tender point sites)[4], had an average pain score ≥ 4 on an 11-point numeric rating scale (NRS; 0 = "no pain" to 10 = "worst possible pain") during the baseline assessment, and reported a score ≥ 40 mm on the 100-mm visual analog scale (VAS) of the Short-Form McGill Pain Questionnaire (SF-MPQ)[33] at both screening and randomization visits. Women of childbearing potential were required to use an adequate method of contraception.

Because this was a monotherapy trial, patients must have discontinued skeletal muscle relaxants, antidepressants, antiepileptic drugs, corticosteroids, benzodiazepines, opioid narcotics, mexiletine, and anti-Parkinson's disease medications ≥ 7 days before their screening visit; tender point injections and fluoxetine ≥ 30 days before; tramadol, dextromethorphan, and NSAID ≥ 2 days before; and zolpidem and diphenhydramine ≥ 1 day before. Aspirin for cardiac prophylaxis (≤ 325 mg/day) and acetaminophen (≤ 4 g/day) as rescue medication for pain were permitted during the trial. Patients were instructed to maintain their normal daily routine and not to alter exercise regimens, and they were allowed to continue stable (i.e., for ≥ 30 days prior to screening) nonpharmacologic therapy, such as physical therapy, massage, chiropractic care, and psychological therapy, through the course of the trial.

Key exclusion criteria included previous participation in a trial of pregabalin, evidence of inflammatory or rheumatologic disease, other severe pain disorders, clinically significant or unstable medical or psychological conditions, a calculated creatinine clearance ≤ 60 ml/min[34], severe depression, or receiving or applying for disability benefits.

At the end of a 1-week baseline phase, qualified patients were randomized to one of 4 treatment groups: pregabalin 300, 450, or 600 mg/day or placebo. Treatment was administered in 2 divided daily doses. All pregabalin treatment groups began with a dosage of 150 mg/day, and the dosage was escalated to the fixed, randomized dosage within the first week of treatment. Dosage escalation was followed by 12 weeks of treatment at the fixed, randomized dosage. In addition to screening and randomization visits, patients were scheduled for clinic visits at Weeks 1, 2, 5, 9, 13 (termination), and 14 (followup).

Efficacy assessments. Primary efficacy measures. For Objective 1, the single primary endpoint was mean pain score from patients' daily pain

diaries, as measured by the 11-point NRS. Each day on awakening, patients rated their pain during the previous 24 hours. The proportion of responders, defined as patients with a ≥ 30% reduction in mean pain score from baseline to endpoint[35], was determined as a supplemental measure of the primary efficacy measure, as was weekly mean pain score.

If treatment with pregabalin met Objective 1, the PGIC[36] and the FIQ–Total Score[37], administered at termination visit, were used as additional primary endpoints to evaluate the efficacy of pregabalin for meeting Objective 2, the management of FM. The PGIC is a patient-rated instrument that measures change in patients' overall status on a scale ranging from 1 = "very much improved" to 7 = "very much worse." The PGIC score allows the patient to assess their own improvement or worsening on pain and other symptoms, physical or emotional functioning, and side effects, and it can be used to evaluate the clinical significance of the treatment effect[38,39]. The FIQ is a 20-item patient-reported instrument that contains 10 subscales, which are combined to yield a total score. Eleven questions are specifically related to physical functioning; the remaining items assess pain, fatigue, stiffness, tiredness on awakening, difficulty working, days felt good, and symptoms of anxiety and depression.

Secondary efficacy measures. Patients rated their sleep quality on an 11-point NRS (0 = "best possible sleep" to 10 = "worst possible sleep") included in their daily diaries[40-42]. The Medical Outcomes Study (MOS)–Sleep Scale[43] was administered as an additional measure of sleep. Functioning was assessed by the Short-Form 36 (SF-36) Health Survey[44], the Sheehan Disability Scale (SDS)[45,46], and the Fibromyalgia Health Assessment Questionnaire (F-HAQ)[47,48]. The Short-Form McGill Pain Questionnaire (SF-MPQ)[33] served as an additional measure of pain, while the Multidimensional Assessment of Fatigue (MAF)[49] was used to evaluate fatigue and the degree to which it interferes with daily activities. Finally, mood disturbances were evaluated via the Hospital Anxiety and Depression Scale (HADS)[50]. Most of these secondary efficacy measures, with the exception of the daily sleep diary, were performed at baseline, termination, and at 2 additional timepoints during the trial (Weeks 5 and 9).

Statistical analysis. The trial was powered for the expected treatment effect on pain. The proposed sample size of 185 patients per group also provided additional power to support the management (Objective 2) analyses.

The primary and secondary efficacy analyses were performed on the full analysis set. Randomized patients who took at least one dose of study medication, but who had no postbaseline information for any given measure, were to carry forward their baseline scores for that measure. All statistical testing was 2-sided and was performed using SAS® procedures[51]. The method of last observation carried forward was used for all endpoint analyses. For visit-specific analyses, observed cases were used, and patients with missing values at a particular timepoint did not contribute to that specific analysis or timepoint.

The primary analysis for relief of pain associated with FM (Objective 1) compared the endpoint mean pain score between the treatment groups using an analysis of covariance (ANCOVA) with treatment and center in the model and baseline mean pain score as covariate[52]. Hochberg's approach was used to protect the Type I error rate at the 0.05 level[53]. The supplemental responders analysis was accomplished using the Cochran-Mantel-Haenszel procedure[54], adjusting for center. The weekly mean pain scores were analyzed using a repeated measures analysis, including factors for the fixed, categorical effects of treatment, center, week, and treatment by week interaction, and baseline pain as the covariate.

If Objective 1 was positive, the additional endpoints to meet Objective 2 (management of FM) were to be evaluated. The PGIC was analyzed separately for each pregabalin treatment group versus the placebo group using the Cochran-Mantel-Haenszel procedure with modified ridit scores adjusting for center. FIQ–Total Score was analyzed using an ANCOVA with treatment and study centers in the model and the respective baseline score as a covariate. The study was considered positive for Objective 2 if the PGIC and FIQ–Total Score were each significant at the α=0.05 level (in addition to a significant pain finding). Because Objective 2 required all three measures to be significant, the PGIC and FIQ–Total Score were tested at the α = 0.05 level for each dosage, without adjustment for multiple comparisons with placebo. Interpretation focused on those dosages that demonstrated significant efficacy in endpoint mean pain score.

Secondary efficacy measures, except for the MOS–Sleep Scale Optimal Sleep subscale, were analyzed at endpoint using an ANCOVA with treatment and study centers in the model and the respective baseline score as a covariate. Weekly sleep quality score was analyzed using the same repeated measures model as weekly pain score. The MOS–Sleep Scale Optimal Sleep subscale was analyzed using a logistic regression model, with treatment and study center in the model and Optimal Sleep at baseline as the covariate.

Safety assessments. Adverse events (AE), whether volunteered by patients or observed by the clinicians, were recorded at each trial visit. Clinical laboratory evaluations were performed at baseline, Week 5, and termination. A physical examination, an abbreviated neurologic examination, and a 12-lead electrocardiogram were completed at baseline and termination.

RESULTS

Patient disposition. A total of 1328 patients were screened as potential study participants. Of these, 748 were randomized and received study medication. Five hundred fifty-eight patients received pregabalin 300 (n = 185), 450 (n = 183), or 600 (n = 190) mg/day, and 190 patients received placebo. Of the 748 patients who received study medication, 263 (35%) withdrew from the trial during the double-blind treatment phase (Figure 1): 157 (21%) due to an AE, 40 (5%) due to lack of efficacy, and 66 (9%) for other reasons. Of the 40 patients who withdrew due to lack of efficacy, the greatest number of such withdrawals were in the placebo group (22 patients; 12% of the placebo group) followed by the 300 mg/day pregabalin treatment group (9 patients; 5%), 450 mg/day group (6 patients; 3%), and 600 mg/day group (3 patients; 2%). Conversely, of the 157 patients who withdrew due to an AE, the greatest number were in the 600 mg/day treatment group (62 patients; 33%) versus 41 patients (22%) who received 450 mg/day pregabalin, 35 (19%) who received 300 mg/day pregabalin, and 19 (10%) who received placebo.

Baseline characteristics. Demographic and baseline characteristics of the randomized subjects were similar across treatment groups (Table 1). Most patients were Caucasian (90%), female (94%), and between 18 and 64 years of age (94%), with a mean age of 49 years (range 18 to 82). The majority of women were postmenopausal (58%). Most patients in the study had been symptomatic with FM for more than 6 years, with a mean duration of 9.3 years.

Mean baseline values for efficacy measures (Table 2) reflected known characteristics of patients with FM, namely, high levels of baseline pain (mean pain score 7.1), sleep disturbance (MOS–Sleep Disturbance score 67.8), and fatigue (MAF global fatigue index 38.7). The FIQ–Total Score demonstrated a substantial negative influence of FM at baseline (score 64.3). Mean SF-MPQ VAS scores did not change between screening and randomization for the placebo, 300 mg/day, 450 mg/day, and 600 mg/day groups (76.8, 76.6, 75.9, and 75.9, respectively). Finally, baseline mean

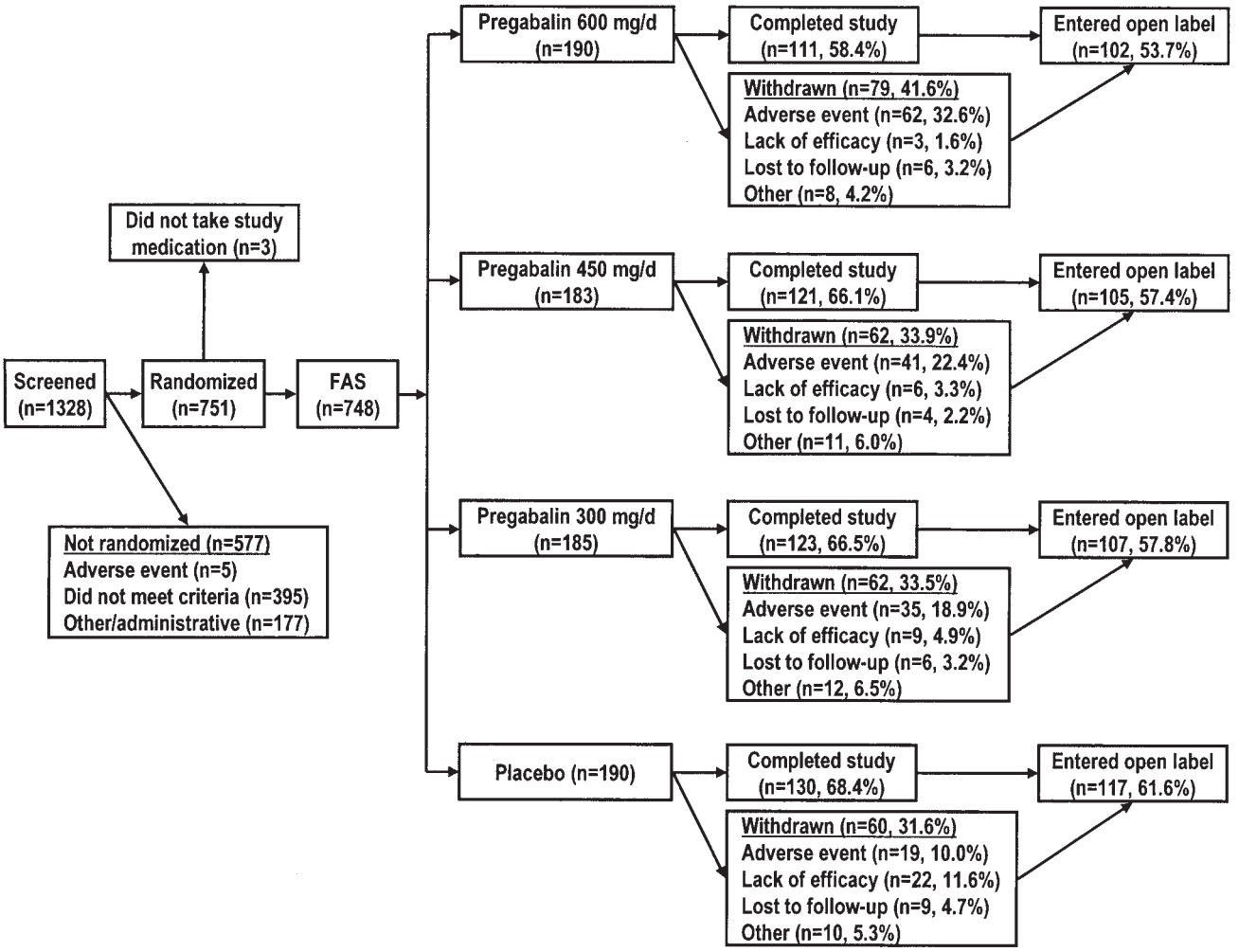

Figure 1. Patient disposition for this study. FAS: full analysis set.

anxiety and depression scores, as assessed by the HADS, were in the mild category, with mean scores of 9.5 for anxiety and 8.3 for depression (both scales range from 0 to 21, and the mild category is 8–10). Numbers of patients in each of the treatment groups at each week are shown in Table 3.

Efficacy

Objective 1. Patients in all 3 pregabalin treatment groups showed statistically significant improvement in endpoint mean pain score compared with patients receiving placebo (Table 4), demonstrating that treatment with pregabalin met trial Objective 1, symptomatic relief of pain. The 600 mg/day pregabalin treatment group showed the greatest improvement compared with placebo: after Hochberg adjustment, treatment differences in change in mean pain score from baseline to endpoint between pregabalin and placebo were –0.43 ($p = 0.0449$) for 300 mg/day, –0.47 ($p = 0.0449$) for 450 mg/day, and –0.66 ($p = 0.0070$) for 600 mg/day.

All 3 pregabalin treatment groups separated from placebo group results at Week 1, but they did not all remain consistently improved at every week (Figure 2). Mean pain scores in the 300 mg/day pregabalin group were not significantly superior to those in the placebo group at Weeks 4, 8, 9, and 10, and in the 450 mg/day group, they were not significantly superior to placebo at Weeks 8, 9, 10, and 13. However, patients in the 600 mg/day group showed statistically significant improvement versus placebo at every weekly timepoint throughout the trial duration.

The proportions of patients classified as responders (≥ 30% decrease in mean pain score) were 43%, 43%, and 44% among patients receiving 300, 450, and 600 mg/day pregabalin, compared with 35% for placebo. Although all pregabalin responder rates were higher than the placebo response rate, these differences did not reach statistical significance for any pregabalin dosage.

Objective 2. As treatment with pregabalin met Objective 1 of the trial, outcome measures to meet Objective 2, efficacy for the management of FM, were evaluated. Significant differences in the PGIC response favoring pregabalin were

Table 1. Demographic characteristics of randomized patients with primary fibromyalgia.

Characteristics	Placebo	Pregabalin 300 mg/day	Pregabalin 450 mg/day	Pregabalin 600 mg/day	All Pregabalin-treated Patients
N	190	185	183	190	558
Age, mean (SD) yrs	48.6 (11.3)	50.1 (10.4)	47.7 (10.8)	48.7 (11.2)	48.8
18–64, n (%)	177 (93.2)	172 (93.0)	173 (94.5)	180 (94.7)	525 (94.1)
≥ 65, n (%)	13 (6.8)	13 (7.0)	10 (5.5)	10 (5.3)	33 (5.9)
Women, n (%)	183 (96.3)	174 (94.1)	169 (92.3)	180 (94.7)	523 (93.7)
Postmenopausal, n (%)	107 (58.5)	108 (62.1)	89 (52.7)	107 (59.4)	304 (58.1)
Race					
Caucasian, n (%)	167 (87.9)	169 (91.4)	169 (92.3)	170 (89.5)	508 (91.0)
Black, n (%)	10 (5.3)	10 (5.4)	7 (3.8)	8 (4.2)	25 (4.5)
Hispanic, n (%)	12 (6.3)	5 (2.7)	7 (3.8)	9 (4.7)	21 (3.8)
Other	1 (0.5)	1 (0.5)	0 (0)	3 (1.6)	5 (0.9)
Body mass index*	30.0	31.4	30.2	30.5	30.7
Estimated CL_{cr} at BL, mean (SD) ml/min	98.7 (33.8)	101.1 (28.7)	100.2 (28.7)	101.3 (33.9)	100.9 (30.5)
Duration of FM prior to BL, mean (SD) mo	105.7 (82.8)	115.4 (103.5)	114.7 (101.5)	111.0 (91.4)	113.7 (98.7)
No. of painful tender points, mean (SD)	17.0 (1.9)	17.1 (1.6)	17.3 (1.3)	17.0 (1.6)	17.1 (1.5)
BL pain score, mean (SD)	7.2 (1.2)	7.1 (1.4)	7.1 (1.4)	7.0 (1.3)	7.1 (1.4)
Nonpharmacologic T_x, n (%)					
Chiropractic	24 (12.6)	21 (11.4)	25 (13.7)	25 (13.2)	71 (12.7)
Exercise/stretch	87 (45.8)	91 (49.2)	90 (49.2)	95 (50.0)	276 (49.5)
Heat/cold	76 (40.0)	81 (43.8)	84 (45.9)	76 (40.0)	241 (43.2)
Massage	29 (15.3)	21 (11.4)	32 (17.5)	35 (18.4)	88 (15.8)
Physical	11 (5.8)	11 (5.9)	9 (4.9)	10 (5.3)	30 (5.4)
Psychologic	7 (3.7)	5 (2.7)	8 (4.4)	5 (2.6)	18 (3.2)

* (mean weight, kg)/(mean height, cm)$^2 \times 10^4$. BL: baseline.

observed for the 3 treatment groups versus placebo (p = 0.0183, p = 0.0467, and p = 0.0127 for 300, 450, and 600 mg/day; Figure 3). Overall, the percentage of patients reporting at least minimal improvement in PGIC at endpoint was 71% for 300 mg/day, 72% for 450 mg/day, and 69% for 600 mg/day pregabalin, compared with 56% in the placebo group. The percentage of patients reporting at least "much improved" on the PGIC at endpoint was 43% for 300 mg/day, 41% for 450 mg/day, and 46% for 600 mg/day pregabalin, compared with 35% in the placebo group.

The FIQ–Total Score at endpoint was the second outcome used to assess efficacy for Objective 2. Although all patients improved from baseline, with greater improvement seen in the pregabalin groups, no treatment differences achieved statistical significance for this measure.

Secondary efficacy measures. Among the secondary outcome variables, all 3 pregabalin dosages were associated with statistically significant improvement in sleep quality at endpoint (Table 4) and at each week (Figure 4) beginning at Week 1 (all p values < 0.001). Similarly, all 3 pregabalin treatment groups showed significant improvement in the MOS–Sleep Disturbance (all p values < 0.0039) and Sleep Problem Index (all p values < 0.0174) at endpoint (Table 4). Improvement was also observed on the MOS–Sleep Quantity subscale, which for all 3 pregabalin treatment groups was statistically significant versus placebo (all p values < 0.0217). While all groups improved on MOS–Sleep Somnolence at endpoint, placebo had the greatest improvement, resulting in statistically significant differences in favor of placebo versus the 450 and 600 mg/day groups. A summary of the global fatigue index scores (of the MAF) showed no statistically significant differences among any of the pregabalin groups versus placebo. Treatment effects in most of the remaining secondary measures were generally in the direction of greater improvement with pregabalin treatment; however, there were no statistically significant differences at endpoint among any of the pregabalin treatment groups compared with placebo.

Safety. The overall safety profile for pregabalin was similar to that seen previously and currently described in the USPI for diabetic peripheral neuropathy and postherpetic neuralgia[30]. Of the 748 patients who received study medication, 656 (88%) experienced at least 1 AE. The occurrence of AE of any type increased with dosage (76%, 89%, 92%, and 94% in placebo, 300, 450, and 600 mg/day pregabalin). The most frequently reported all-cause AE for patients who received pregabalin were dizziness, somnolence, headache, infection, and weight gain, and most AE were of mild or moderate intensity. Rates of treatment-emergent AE considered by the investigators to be associated with treatment are

Table 2. Baseline values of outcomes measures for randomized patients with primary FM.

Efficacy Measure (scoring range) n = 748 unless noted	Mean Baseline Score (SD)
Mean pain score (0–10)	7.1 (1.3)
Mean sleep quality score (0–10)	6.7 (1.7)
Hospital Anxiety and Depression Scale	
Anxiety score (0–21)	9.5 (4.6)
Depression score (0–21)	8.3 (4.2)
Fibromyalgia Impact Questionnaire (total, 0–100; items 0–10)	
Total	64.3 (13.6)
Physical function	4.4 (2.3)
Feel good	8.1 (2.1)
Work missed, n = 747	3.6 (3.3)
Do job, n = 742	6.9 (1.9)
FIQ pain, n = 742	7.5 (1.3)
Fatigue, n = 742	8.3 (1.5)
Rested, n = 740	8.3 (1.6)
Stiffness, n = 742	8.0 (1.6)
Anxiety, n = 742	4.8 (3.0)
Depression, n = 742	4.6 (3.0)
SF-36 (each domain, 0–100)	
General health perception, n = 747	45.8 (22.1)
Physical functioning	43.7 (22.9)
Physical role limitations	35.2 (22.7)
Emotional role limitations	60.7 (30.5)
Social functioning	47.1 (26.6)
Mental health	57.9 (21.6)
Bodily pain	26.1 (13.6)
Vitality	23.0 (17.3)
Physical component score, n = 747	31.5 (8.0)
Mental component score, n = 747	39.6 (13.0)
Sheehan Disability Scale (total, 0–30; items, 0–10)	
Work, n = 650	5.9 (2.6)
Social life, n = 744	5.9 (2.5)
Family/home, n = 743	6.2 (2.4)
Total score, n = 649	17.9 (6.9)
Medical Outcomes Study Sleep Scale (items, 0–100, unless noted otherwise)	
Sleep disturbance, n = 744	67.8 (23.4)
Snoring, n = 726	40.6 (35.9)
Awaken short of breath or with headache, n = 744	37.6 (31.1)
Quantity of sleep, n = 747 (no. of hours per night)	5.4 (1.6)
Optimal sleep, n = 747 (% of patients with optimal sleep)	15.1%
Sleep adequacy, n = 745	20.6 (22.0)
Somnolence, n = 743	50.3 (24.1)
Sleep problem index, n = 741	65.0 (16.3)
Fibromyalgia Health Assessment Questionnaire (all items 0–3)	
Dressing, n = 743	0.63 (0.65)
Stand up from chair, n = 741	1.06 (0.70)
Washing, n = 746	0.45 (0.57)
Reach overhead, n = 745	1.00 (0.81)
Bending, n = 743	0.97 (0.68)
Run errands, n = 744	0.89 (0.69)
Get in and out of car, n = 745	0.79 (0.64)
Do chores, n = 744	1.45 (0.80)
F-HAQ total score, n = 747	0.92 (0.51)
Short-Form McGill Pain Questionnaire	
Sensory (0–33)	19.1 (6.4)
Affective, n = 746 (0–12)	5.4 (2.9)
Total (0–45)	24.5 (8.6)
Visual analog scale (0–100)	76.3 (13.7)
Present pain intensity, n = 746 (0–5)	3.0 (0.9)
Multidimensional Assessment of Fatigue (index, 1–50)	
Global fatigue index (n = 741)	38.7 (7.2)

displayed in Table 5. Serious AE occurred in < 2% of all pregabalin-treated patients and in 2.1% of those who received placebo. A dosage-related increase in patients who withdrew due to any AE was observed (11%, 19%, 22%, and 33%, respectively, for placebo, 300, 450, and 600 mg/day pregabalin). Dizziness (9%) and somnolence (6%) were the AE that most frequently led to withdrawal among pregabalin-treated patients. Median times to onset of dizziness and somnolence were similar across the pregabalin treatment groups (approximately 2 days for both events). The median duration of the most common AE (among trial completers) was typically longer in the pregabalin treatment groups than in the placebo group. For the 3 most common AE, median durations were pregabalin 300 mg/day — dizziness, 19 days, somnolence, 88 days, weight gain, 64 days; pregabalin 450 mg/day — dizziness, 28 days, somnolence, 79.5 days, weight gain, 69.5 days; pregabalin 600 mg/day — dizziness, 43.5 days, somnolence, 25 days, weight gain, 77 days; placebo — dizziness, 14 days, somnolence, 69.5 days, weight gain, 88 days.

Overall, 27 patients (14.2%) treated with 600 mg/day, 18 (9.8%) with 450 mg/day, and 17 (9.2%) with 300 mg/day reported weight gain as an AE, and 6 of these discontinued the trial because of weight gain as an AE (3 from 600 mg/day, 1 from 450 mg/day, and 2 from 300 mg/day). All reported AE of weight gain were mild to moderate. Sixty-six pregabalin-treated patients (11.8%) experienced a clinically significant increase in body weight of 7% or more from baseline to end of treatment: 26 (15%) who received 600 mg/day; 22 (13%) who received 450 mg/day; and 18 (11%) who received 300 mg/day. Among patients with observed weight gain of ≥ 7%, none discontinued treatment prematurely. There were no clinically relevant differences in clinical laboratory evaluations, vital signs, physical examination findings, or ECG findings.

DISCUSSION

In this randomized, double-blind, 13-week trial, treatment with pregabalin met trial Objective 1: pregabalin monotherapy, in twice daily dosages of 300, 450, and 600 mg/day, resulted in statistically significant improvement in pain compared with placebo at endpoint. This treatment effect had a rapid onset, as all dosage groups separated from placebo at Week 1, the first timepoint measured. Additionally, pregabalin 600 mg/day demonstrated durability of effect by being statistically significantly superior to placebo at every weekly timepoint throughout the trial's 13 weeks. These results are consistent with the previous 8-week trial of pregabalin in the treatment of FM, in which 450 mg/day (administered in 3 divided doses) significantly improved endpoint mean pain score versus placebo[32].

Objective 2 of the trial was to assess efficacy of pregabalin for the overall management of FM as measured by 3 criteria: symptomatic relief of pain (i.e., Objective 1),

Table 3. Patient exposure to study medication by week.

Total Exposure Time	Placebo, n = 190	Pregabalin 300 mg/day n = 185	Pregabalin 450 mg/day n = 183	Pregabalin 600 mg/day n = 190	All Pregabalin, n = 558
≥ 1 day	190	185	183	190	558
≥ 1 week	185	172	170	171	513
≥ 2 weeks	168	157	156	155	468
≥ 3 weeks	159	153	148	144	445
≥ 4 weeks	154	147	146	140	433
≥ 5 weeks	150	145	142	137	424
≥ 6 weeks	145	135	134	130	399
≥ 7 weeks	138	134	131	128	393
≥ 8 weeks	136	131	130	123	384
≥ 9 weeks	134	130	128	118	376
≥ 10 weeks	133	122	124	116	362
≥ 11 weeks	133	122	122	112	356
≥ 12 weeks	128	122	121	107	350
≥ 13 weeks	98	92	95	79	266
≥ 14 weeks	9	7	7	8	22
≥ 15 weeks	1	1	0	2	3

improvement in the PGIC, and improvement in the FIQ–Total Score. The PGIC affords patients the opportunity to assess their own global improvement (or worsening), taking into consideration not only their pain but also their other symptoms, their physical and emotional functioning, and the effects of their AE. All 3 pregabalin dosages were associated with statistically significant improvement in patients' PGIC ratings relative to placebo. The third outcome on which pregabalin must have been associated with statistically significant improvement to meet Objective 2, the FIQ–Total Score, was not statistically improved for any treatment group. Only trends toward significant improvement in the FIQ total score and other functional measures were found in the pregabalin groups compared with placebo. In general, functioning measures in FM trials have been shown to be less sensitive to change than pain assessments. Further, unlike other pain diseases, such as osteoarthritis, in which physical functioning limitations predominate, the influence of FM appears to encompass a myriad of functional limitations beyond merely physical functioning. There is no consensus on how to best assess these limitations or to measure the effects of treatment on function in FM[14].

In addition to significant reduction in pain, patients taking all dosages of pregabalin experienced significant improvements in sleep. Such improvements were demonstrated by the use of 2 different instruments: sleep quality as assessed by the daily sleep diary and the MOS–Sleep scale. Bennett, *et al* recently reported results from an Internet survey completed by more than 2500 persons with FM[55]. The survey found that poor sleep is a key symptom of FM: respondents rated the severity of nonrestorative sleep as greater than pain, anxiety, or depression among their symptoms, while sleeping problems were cited as an FM-aggravating factor by 79% of patients (behind only emotional distress and weather changes). The significant improvements seen on 2 sleep instruments in our study combined with results from the previous trial of pregabalin in FM, in which sleep was also significantly improved with dosages of 300 and 450 mg/day[32], suggest that pregabalin may be beneficial for those FM patients affected by pain and associated sleep disturbance.

On the MOS-Sleep Somnolence Subscale, all treatment groups improved from baseline to endpoint; however, patients receiving placebo had scores that were statistically significantly superior to those of patients treated with pregabalin. Somnolence is an AE commonly associated with pregabalin as treatment of chronic pain syndromes[32,56-63], and in the current trial, somnolence was reported as an AE by 21% to 28% of patients in pregabalin treatment groups. As such, although patients experienced improvements in other items of the MOS-Sleep Scale over placebo, including the Overall Sleep Problem Index, this was not the case for the Somnolence Subscale.

Pregabalin was generally well tolerated. The rate of discontinuation due to AE was dosage-related. Dizziness and somnolence were the most common AE among pregabalin-treated patients, consistent with previously reported pregabalin pain trials. While the incidence of dizziness (42%) and somnolence (26%) in pregabalin-treated patients was higher in this FM patient population than previously reported for pregabalin studies in patient populations with neuropathic pain[56-63], the incidence of withdrawal due to these 2 AE was relatively low (9% and 6%, respectively). These AE tended

Table 4. Endpoint values for outcome measures, full analysis set.

Measure									
Mean Pain Score	n	Mean	Change	T_x Difference†					p
PBO	190	5.70	–1.40						
Pregabalin 300 mg/day	185	5.26	–1.84	–0.43					0.0449§
Pregabalin 450 mg/day	183	5.23	–1.87	–0.47					0.0449§
Pregabalin 600 mg/day	190	5.04	–2.06	–0.66					0.0070§
PGIC, n (%)	n	Very Much Worse	Much Worse	Minimally Worse	No Change	Minimally Improved	Much Improved	Very Much Improved	
PBO	178	6 (3.4)	19 (10.7)	16 (9.0)	37 (20.8)	38 (21.3)	41 (23.0)	21 (11.8)	
Pregabalin 300 mg/day	175	4 (2.3)	11 (6.3)	15 (8.6)	21 (12.0)	48 (27.4)	48 (27.4)	28 (16.0)	0.0183
Pregabalin 450 mg/day	173	7 (4.0)	12 (6.9)	12 (6.9)	17 (9.8)	54 (31.2)	45 (26.0)	26 (15.0)	0.0467
Pregabalin 600 mg/day	175	1 (0.6)	8 (4.6)	11 (6.3)	35 (20.0)	39 (22.3)	54 (30.9)	27 (15.4)	0.0127
FIQ Total Score	n	Mean	Change	T_x Difference†					
PBO	190	50.66	–13.66						
Pregabalin 300 mg/day	185	48.18	–16.15	–2.48					0.2113
Pregabalin 450 mg/day	183	48.62	–15.71	–2.05					0.3040
Pregabalin 600 mg/day	190	49.45	–14.88	–1.21					0.5390
Mean Sleep Quality Score	n	Mean	Change	T_x Difference†					
PBO	190	5.41	–1.32						
Pregabalin 300 mg/day	185	4.54	–2.19	–0.86					0.0001
Pregabalin 450 mg/day	183	4.44	–2.29	–0.97					< 0.0001
Pregabalin 600 mg/day	190	4.20	–2.53	–1.21					< 0.0001
MOS-Sleep Scale	n††	Sleep Disturbance	Snoring	Awaken Short of Breath or with Headache	Quantity of Sleep	Sleep Adequacy	Somnolence	Overall Sleep Problem Index	
PBO	183–190	49.26	37.21	25.91–	5.83	29.97	40.23	50.71	
Pregabalin 300 mg/day	180–185	41.65 (p = 0.0039)	40.83 (p = 0.1547)	24.89 (p = 0.6806)	6.21 (p = 0.0044)	38.03 (p = 0.0051)	40.76 (p = 0.8131)	45.90 (p = 0.0174)	
Pregabalin 450 mg/day	178–183	38.99 (p = 0.0001)	39.02 (p = 0.4756)	20.36 (p = 0.0257)	6.27 (p = 0.0011)	39.97 (p = 0.0005)	44.85 (p = 0.0375)	44.59 (p = 0.0026)	
Pregabalin 600 mg/day	185–189	39.41 (p = 0.0002)	37.47 (p = 0.9183)	19.50 (p = 0.0097)	6.14 (p = 0.0217)	35.24 (p = 0.0653)	44.94 (p = 0.0328)	45.51 (p = 0.0101)	

* Mean change from baseline. † Treatment difference from PBO. †† Ranges indicate that different numbers of patients were available for assessment for individual items of multiitem measures. § Hochberg's approach was used to protect the type I error rate at the 0.05 level. PBO: placebo; PGIC: Patient Global Impression of Change; FIQ: Fibromyalgia Impact Questionnaire; MOS: Medical Outcomes Study.

to diminish with time. The sleep benefits associated with pregabalin did not abrogate the AE of daytime somnolence initially experienced by some patients. The high incidence of dizziness and somnolence could indicate that patients with FM may be more sensitive to CNS-related AE. This trial showed that pregabalin is associated with a benefit:risk ratio that is favorable overall. The availability of multiple effective dosages may maximize benefit and reduce the risk of AE.

The baseline data collected in this study, using the 1990 ACR classification criteria for primary FM, were consistent with previous epidemiologic and clinical studies[5]. Patients in this trial were primarily women with a long history of FM symptoms who suffered from substantial pain, sleep disturbance, and fatigue. Pain scores at screening were similar to those at randomization. Concerns about the effects of disease activity–related entry and exclusion criteria on the generalizability of results from randomized controlled trials (RCT) to clinical practice were recently examined by Wolfe and Michaud in the setting of rheumatoid arthritis[64]. The authors found that in order to satisfy entry criteria, study patients generally have greater baseline disease activity than is commonly found in clinical practice; however, this does not necessarily jeopardize the validity of RCT results, since disease severity would be well matched among treatment arms. Wolfe and Michaud also noted that improvement in an RCT is a combination of treatment effect, measurement error, regression to the mean, and participation effect. They

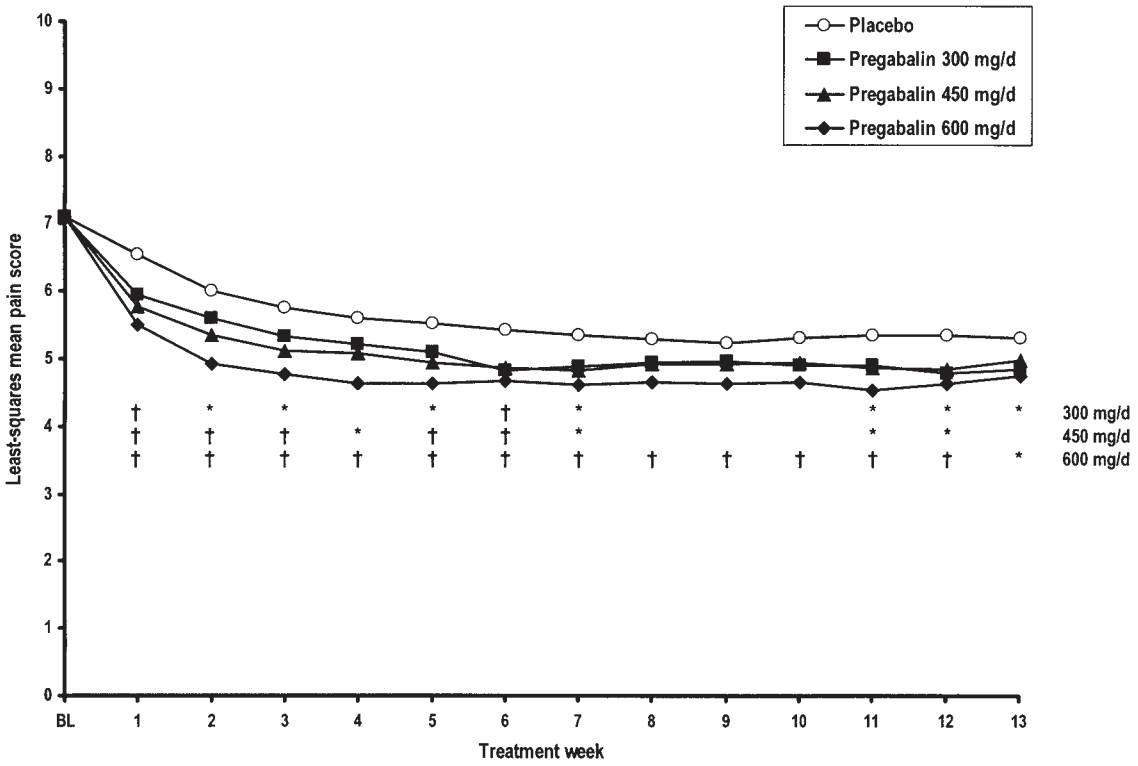

Figure 2. Weekly least-squares mean pain scores. *p ≤ 0.05 vs placebo; †p ≤ 0.01 vs placebo.

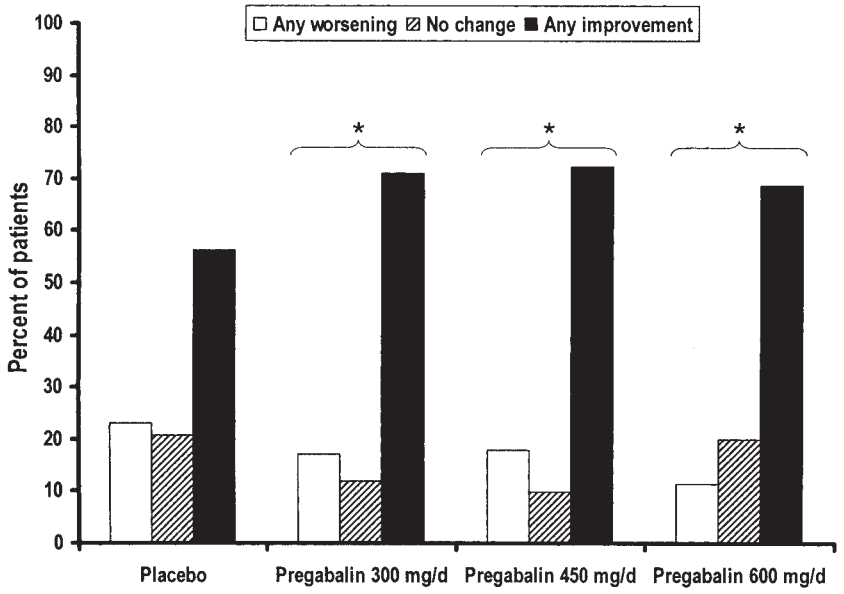

Figure 3. Change in Patient Global Impression of Change scores. *p ≤ 0.05 vs placebo.

suggest that RCT are biased in favor of increased response and contend that the ideal method to evaluate drugs in the community is to continuously evaluate patients who do and do not receive study drug years before and after treatment begins.

There are several limitations to these trial results. First, the requirement to discontinue all medications used to treat FM prior to enrollment may have excluded the most severely affected patients and those with substantial psychiatric comorbidity. Second, the results may not generalize to

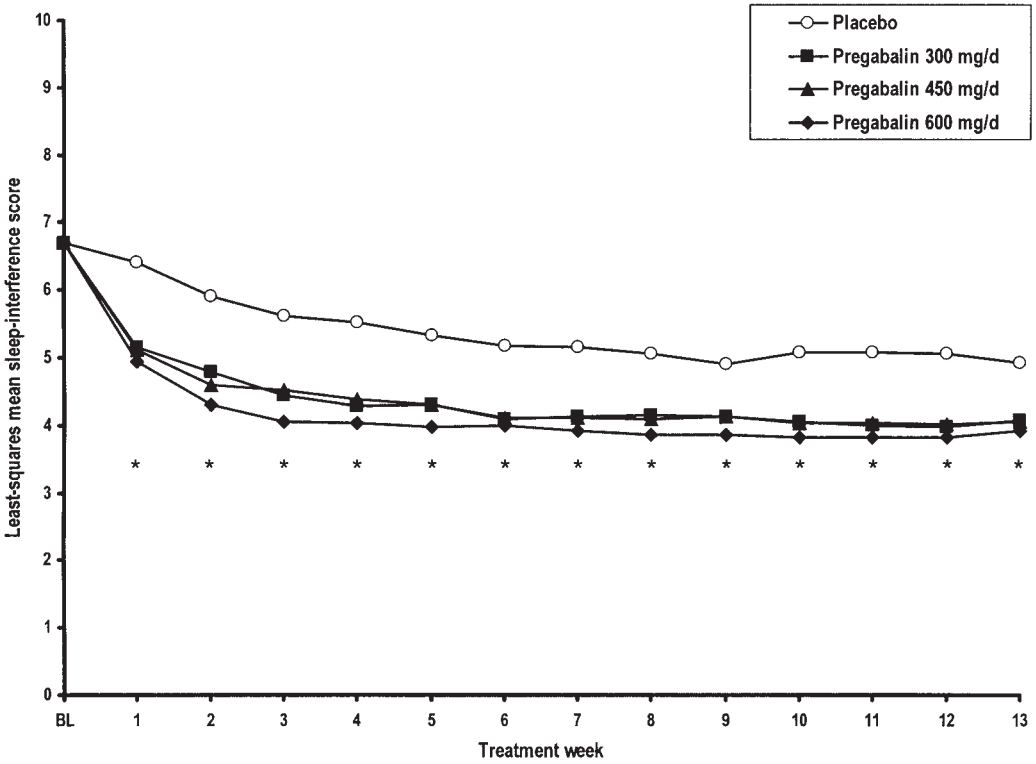

Figure 4. Weekly least-squares mean sleep quality scores. *p ≤ 0.001 for all treatment groups vs placebo.

Table 5. Treatment-emergent associated adverse events, i.e., reported by at least 5% of patients in any treatment group. Ordered by decreasing frequency in the 600 mg/day treatment group.

Adverse Event/ Preferred Term	Placebo, n = 190 (%)	Pregabalin 300 mg/day n = 185 (%)	Pregabalin 450 mg/day, n = 183 (%)	Pregabalin 600 mg/day, n = 190 (%)
Dizziness	16 (8.4)	60 (32.4)	80 (43.7)	88 (46.3)
Somnolence	10 (5.3)	39 (21.1)	44 (24.0)	53 (27.9)
Weight gain	5 (2.6)	15 (8.1)	16 (8.7)	26 (13.7)
Dry mouth	4 (2.1)	14 (7.6)	19 (10.4)	20 (10.5)
Nausea	11 (5.8)	9 (4.9)	8 (4.4)	20 (10.5)
Amblyopia (blurred vision)	3 (1.6)	12 (6.5)	12 (6.6)	17 (8.9)
Thinking abnormal	2 (1.1)	15 (8.1)	12 (6.6)	17 (8.9)
Constipation	1 (0.5)	9 (4.9)	12 (6.6)	16 (8.4)
Headache	12 (6.3)	15 (8.1)	17 (9.3)	15 (7.9)
Increased appetite	3 (1.6)	4 (2.2)	15 (8.2)	15 (7.9)
Amnesia	4 (2.1)	5 (2.7)	7 (3.8)	14 (7.4)
Euphoria	5 (2.6)	6 (3.2)	11 (6.0)	14 (7.4)
Ataxia	1 (0.5)	3 (1.6)	8 (4.4)	13 (6.8)
Asthenia	5 (2.6)	13 (7.0)	10 (5.5)	11 (5.8)
Incoordination	0 (0.0)	5 (2.7)	7 (3.8)	10 (5.3)
Nervousness	2 (1.1)	2 (1.1)	0 (0.0)	10 (5.3)
Peripheral edema	2 (1.1)	5 (2.7)	4 (2.2)	10 (5.3)

patients with secondary FM, because those with other painful or inflammatory rheumatologic disorders were excluded. Third, the results are based on an acute trial of 13 weeks, and they may not generalize to a longer duration of treatment. Studies of the longterm efficacy of FM treatments are needed, because FM is a chronic condition that will likely require treatment for longer than 13 weeks. In a trial of amitriptyline and cyclobenzaprine that was extended to 26 weeks, neither drug exerted significantly greater efficacy than placebo in reducing FM pain[65]. Recognizing the impor-

tance of studying the effect of pregabalin for a longer period of time, a 6-month study in FM was recently completed that demonstrated durable effects on several domains of FM including pain, patient global assessment of change, function, and sleep[66]. Finally, our study did not include an active medication comparator, because the study was designed to confirm and extend the previous findings of the efficacy of pregabalin compared with placebo in FM[32]. Future trials should compare pregabalin with other medications in the treatment of FM, including gabapentin, another α_2-δ-1 ligand that has been shown to be efficacious in reducing pain associated with FM[67]. Although pregabalin and gabapentin share a similar mechanism of action, they are different molecules with differences apparent in pharmacokinetics and pharmacodynamics[68] that may influence efficacy and tolerability measures. Further, FM will likely respond best to a multidisciplinary approach and a combination of pharmacologic and nonpharmacologic treatments[69]. A study evaluating the combination of pregabalin with nonpharmacologic treatments such as cognitive behavioral therapy, which may improve patients' active coping skills[70], is needed.

The results of this randomized, placebo-controlled trial demonstrated that treatment with pregabalin was associated with symptomatic relief of pain in patients with FM, improvement in patients' assessments of their global health status, and improvements in multiple measures of sleep. Improvements in pain and sleep with pregabalin were of rapid onset, being evident at Week 1, the first timepoint measured, and pain relief was maintained at every weekly timepoint over 13 weeks with 600 mg/day pregabalin, while improvements in sleep were significant at every weekly timepoint for all 3 dosages. The incidence of dizziness and somnolence in this study suggests that FM patients may be more sensitive to CNS-related AE than patients with other pain disorders, although withdrawal rates for these 2 AE were low. Slower escalation to effective dosages may decrease the incidence of AE and will be explored in future trials. Combined with data reported among FM patients[26], our trial supports a role for use of pregabalin in treatment of pain and sleep disturbance in patients with FM.

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