Efficacy and Safety of Pregabalin in Patients with Fibromyalgia and Comorbid Depression Taking Concurrent Antidepressant Medication: A Randomized, Placebo-controlled Study

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ABSTRACT. *Objective.* To assess pregabalin efficacy and safety in patients with fibromyalgia (FM) with comorbid depression taking concurrent antidepressant medication.

Methods. This randomized, placebo-controlled, double-blind, 2-period, 2-way crossover study was composed of two 6-week treatment periods separated by a 2-week taper/washout phase. Patients with FM (aged ≥ 18 yrs) taking a stable dose of a selective serotonin reuptake inhibitor (SSRI) or a serotonin/norepinephrine reuptake inhibitor (SNRI) for depression were randomized 1:1 to receive pregabalin/placebo or placebo/pregabalin (optimized to 300 or 450 mg/day). Antidepressant medication was continued throughout the study. The primary efficacy outcome was the mean pain score on an 11-point numerical rating scale. Secondary efficacy outcomes included measures of anxiety, depression, patient function, and sleep.

Results. Of 197 patients randomized to treatment, 181 and 177 received ≥ 1 dose of pregabalin and placebo, respectively. At baseline, 52.3% of patients were taking an SSRI and 47.7% an SNRI, and mean pain score was 6.7. Mean pain scores at endpoint were statistically significantly reduced with pregabalin (least squares mean difference from placebo –0.61, 95% CI –0.91 – –0.31, p = 0.0001). Pregabalin significantly improved Hospital Anxiety and Depression Scale-Anxiety (difference –0.95, p < 0.0001) and -Depression (difference –0.88, p = 0.0005) scores, Fibromyalgia Impact Questionnaire total score (difference –6.60, p < 0.0001), and sleep quality (difference 0.57, p < 0.0001), but not EuroQol 5-Dimensions score (difference 0.02, p = 0.3854). Pregabalin safety was consistent with previous studies and current product labeling.

Conclusion. Compared with placebo, pregabalin statistically significantly improved FM pain and other symptoms in patients taking antidepressant medication for comorbid depression. ClinicalTrials.gov identifier: NCT01432236. (J Rheumatol First Release June 1 2015; doi:10.3899/jrheum.141196)

Key Indexing Terms:
DEPRESSION   FIBROMYALGIA   SELECTIVE SEROTONIN REUPTAKE INHIBITOR
SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITOR   PREGABALIN

Fibromyalgia (FM) is a common pain disorder characterized by chronic widespread pain and tenderness, often accompanied by disrupted sleep and fatigue[1,2,3,4]. FM is also associated with mood disorders, most commonly depression[5,6]. About 50% to 70% of patients with FM report a lifetime history of major depression[1,6,7], and 20% to 30%

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of patients with FM have current major depression[1,6,8]. About 25% to 60% of patients with FM take antidepressant medication for their depression[1,8].

Pregabalin is indicated for the treatment of FM in the United States[9], Japan, and other countries. A number of clinical trials have demonstrated the efficacy of pregabalin in improving FM pain[10,11,12,13,14], but required patients to discontinue antidepressant medication prior to enrolling. The safety and efficacy of pregabalin in patients with FM taking concurrent antidepressant medication for comorbid depression have not been examined in a controlled clinical trial.

The primary objective of the present study was to determine the efficacy of pregabalin in patients with FM and comorbid depression concurrently taking a selective serotonin reuptake inhibitor (SSRI) or a serotonin/norepinephrine reuptake inhibitor (SNRI) for the treatment of depression. The secondary objective was to evaluate the safety and tolerability of pregabalin in this patient population.

MATERIALS AND METHODS

Study design. This was a randomized, placebo-controlled, double-blind, 2-period, 2-way crossover study conducted at 38 centers in Spain, Italy, Canada, and the United States between November 2011 and July 2013. A crossover design was used because of reduced variability inherent in the design, with patients serving as their own controls[15]. A previous, placebo-controlled crossover study of pregabalin in patients with FM demonstrated that the design could be applied successfully in this patient population[16]. The study consisted of two 6-week double-blind treatment periods separated by a 2-week taper/washout period (Figure 1). Patients were not aware of the timing of transitions from 1 period of the study to the next, including the taper and washout. The same number of pills (placebo or pregabalin) was taken throughout to protect the blind. The study was conducted in accordance with the Council for International Organizations of Medical Sciences International Ethical Guidelines for Biomedical Research Involving Human Subjects, the International Conference on Harmonisation Good Clinical Practice Guidelines, and the Declaration of Helsinki. Written informed consent was obtained from each patient prior to inclusion. The study protocol and informed consent documents were reviewed and approved by an institutional review board or independent ethics committee at each participating site (ClinicalTrials.gov identifier: NCT01432236).

Patient population. Inclusion and exclusion criteria were consistent with prior trials of pregabalin in patients with FM[10,12,13,14]. Patients met the 1990 American College of Rheumatology criteria for FM[3], with a pain score of ≥ 4 on an 11-point numerical rating scale (NRS; 0 = no pain, 10 = worst possible pain). Patients had a documented diagnosis of major depressive disorder, dysthymia, or depression not otherwise specified. Patients were taking a single SSRI or SNRI for the treatment of depression for at least 3 months, with no change in medication type, at a stable dose for the 2 months prior to randomization. Patients were excluded if they had pain attributable to other conditions that may confound assessment or self-evaluation of FM pain, severe depression, or were at risk of suicide or self-harm. Medications used for FM or insomnia were prohibited. Acetaminophen up to 3 g/day was permitted as rescue pain medication.

Study medication. Patients were randomized 1:1 to pregabalin followed by placebo (pregabalin/placebo), or placebo followed by pregabalin (placebo/pregabalin; Figure 1). Randomization was by automated telerandomization according to a computer-generated pseudorandom code using the method of random permuted blocks. Pregabalin dose was optimized during the first 3 weeks of each 6-week treatment period. In the first week, patients received the starting dose of 150 mg/day (75 mg twice daily) escalated, based on efficacy and tolerability, at weekly visits to a final dose of 300 mg/day (150 mg twice daily) or 450 mg/day (225 mg twice daily). After the first 6-week treatment period, patients underwent a 2-week taper/washout period to prevent potential carryover effects. Patients were not informed of the timing of the washout period. Doses were administered orally with or without food.

Stable antidepressant medication was continued throughout the study, although adjustments for safety reasons were permissible. Possible antidepressants included the SSRI citalopram, dapoxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and vilazodone, and the SNRI venlafaxine, desvenlafaxine, milnacipran, and duloxetine. Antidepressant medications had to be approved for the treatment of depression in the patient's country.

Efficacy outcomes. The primary efficacy outcome was the endpoint mean pain score (0–10 NRS) based on the mean of the last 7 daily pain scores from daily pain diaries in each treatment period. The use of a daily pain diary and an 11-point NRS to assess pain is validated and accepted in clinical pain studies. Secondary efficacy outcomes were assessed at endpoint. The
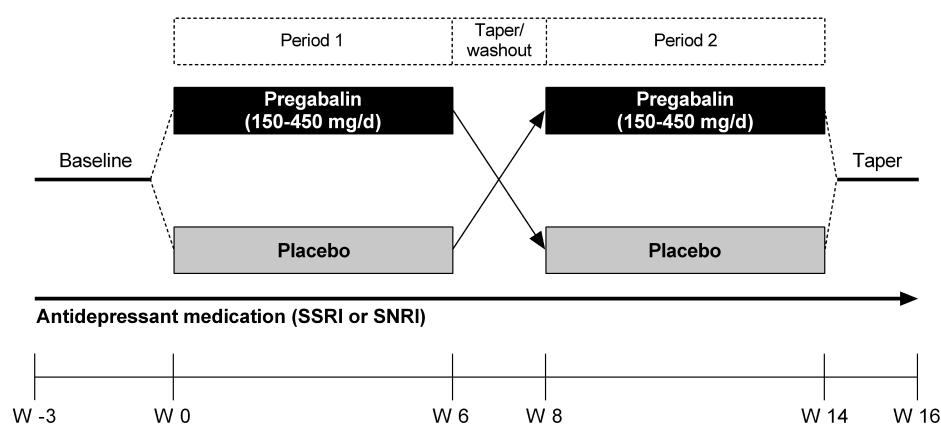
Figure 1. Schematic representation of the study design. Baseline mean pain scores were calculated during the 7 days immediately prior to randomization (Week 0). Period 1 and period 2 were double-blind treatment phases. The initial starting dose of pregabalin was 150 mg/day, optimized to 300 or 450 mg/day during the first 3 weeks of each treatment period. SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin/norepinephrine reuptake inhibitor; W: week.

proportion of 30% or 50% pain responders (≥ 30% or ≥ 50% reduction in mean pain score from baseline) was based on the daily pain diary. The number needed to treat (NNT) for the 30% pain response was calculated posthoc using the difference in proportion from the logistic regression model. The Hospital Anxiety and Depression Scale (HADS) is a validated 14-item questionnaire with 2 measures: anxiety (HADS-A) and depression (HADS-D). Each subscale consists of 7 items scored on a 4-point scale. Scores for each measure range from 0–21, with higher scores indicating greater severity[17]. The Fibromyalgia Impact Questionnaire (FIQ) is a validated measure that consists of 10 subscales that measure functioning, pain, fatigue, difficulty working, and symptoms of anxiety or depression. Each subscale is scored from 0–10. Subscales are summed to generate a total score ranging from 0–100, with higher scores indicating greater impairment[18,19]. The Subjective Sleep Questionnaire (SSQ), based on a daily sleep diary, is a self-reported questionnaire designed to identify subjective behavior in patients with disrupted sleep. The SSQ measures sleep quality, assessed on an 11-point NRS, with higher scores indicating better sleep quality: subjective wake after sleep onset (sWASO), the total amount of time in minutes the patient was awake after initial sleep onset; latency to sleep onset (LSO), the amount of time in minutes taken to fall asleep; the subjective total sleep time (sTST), the amount of time in minutes the patient was asleep; and the subjective number of awakenings after sleep onset (sNAASO). The SSQ is not a validated measure. The Patient Global Impression of Change (PGIC) is a validated and accepted single-item self-rated measure of overall status on a scale ranging from 1 (very much improved) to 7 (very much worse)[20]. PGIC was assessed at the end of treatment period 1. Because of the crossover design of the study and because the recall period for PGIC was from the start of the study medication, PGIC data from period 1 were considered to provide the most representative comparison. A posthoc comparison of data from both treatment periods at study endpoint was also performed. The EuroQol 5-Dimensions (EQ-5D) is a validated, standardized, 5-item questionnaire designed to assess health status. The 5 dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are each scored on a 3-point scale [3-level (3L) version]. Scores are combined to form a single index value from 0–1, with higher scores indicating better health status[21]. The Patient Static Global Assessment (PSGA) is a newly developed single-item self-rated instrument that measures the overall status of the patient during the past week on an 11-point NRS, with higher scores indicating better status (0 = very poor, 10 = very good). PSGA is not a validated measure.

Safety evaluations. Treatment-emergent adverse events (TEAE) were reported throughout the duration of the study and included abnormal laboratory test findings (hematology, blood chemistry, and urinalysis), changes in neurological or physical examination findings, changes in vital signs and electrocardiogram, and progression or worsening of underlying disease. Suicidal ideation and suicidal behaviors were assessed using the Columbia-Suicide Severity Rating Scale[22], a semistructured interview that was conducted by a qualified rater at each visit, including telephone visits. Patients considered at risk of suicide or self-harm, as defined by scores on the suicidality assessments or in the judgment of the investigator, were assessed by a qualified mental health practitioner.

Statistical analyses. For the primary efficacy outcome, a sample size of 140 patients completing the study was estimated to provide 90% power to detect a treatment difference of 0.7 between pregabalin and placebo, with a within-subject SD of 1.8, with enrollment of up to 300 patients in case of higher than anticipated dropout rate. The study was powered to only detect between-group rather than within-subject or within-group differences. An unblinded interim analysis of the primary efficacy outcome for re-estimation of sample size was conducted when 105 patients had completed or discontinued the study. The study team was advised to continue the study without any sample size adjustment. No efficacy claim was made, requiring no adjustment of the nominal p value for the final analysis.

The primary analysis set was the intent-to-treat (ITT) population, defined as those patients who were randomized, received ≥ 1 dose of study medication, and had ≥ 1 postrandomization efficacy evaluation. The primary efficacy outcome was analyzed using a linear mixed-effects model, including sequence, period, and treatment as fixed factors, and subject-within sequence and within-subject error as random factors. The model incorporated only the baseline at randomization and did not consider the start of period 2 to be a new baseline. Imputation of missing data was by last observation carried forward (LOCF). The primary outcome was verified by sensitivity analyses using baseline observation carried forward (BOCF) and mixed-model repeated measures (MMRM) for the imputation of missing data. Sensitivity analysis was conducted for the primary outcome (by LOCF) using the per protocol (PP) analysis set, i.e., all randomized subjects who received study medication and completed the study without a major protocol violation. Prespecified weekly analyses of mean pain scores were conducted as part of the MMRM analysis. Primary analyses were 2-sided and with significance set at α = 0.05. Analyses of the secondary outcomes were conducted on the ITT population only. All secondary analyses were conducted using a 2-sided test with significance set at α = 0.05. No corrections to α were made to control for potential type I errors resulting from multiple comparisons. Separate analyses regarding potential carryover effects were not performed. The safety analysis set consisted of all randomized patients who received ≥ 1 dose of the study medication.

RESULTS

Patients. A total of 318 patients were screened and 197 randomized to treatment; 193 (98.0%) received ≥ 1 dose of study medication (181 pregabalin and 177 placebo; Figure 2). A total of 22 patients (12.2%) discontinued pregabalin treatment and 22 (12.4%) discontinued placebo; 149 patients completed the study. Patient baseline characteristics for the ITT population are shown in Table 1. At baseline, patients across the ITT population were severely affected by their FM and had mild depression, based on the FIQ total score[23] and HADS-D score[17], respectively (Table 1). The antidepressant medications used for the treatment of depression were the SSRI citalopram (16.6% of patients, mean dose from screening to end of study 29.0 mg), escitalopram (10.4%, 19.8 mg), fluoxetine (9.8%, 35.3 mg), sertraline (9.8%, 96.1 mg), and paroxetine (5.7%, 29.1 mg). The SNRI used were duloxetine (31.6%, 60.5 mg), venlafaxine (13.5%, 119.8 mg), and desvenlafaxine (2.6%, 80.0 mg). No patients took milnacipran because at the time of the study it was not approved for the treatment of depression in any of the participating countries. Weekly descriptive analysis of the number of patients taking each antidepressant and the antidepressant dose demonstrated minimal variability. The mean (range) duration of antidepressant use prior to the start of the study was 4.2 years (0.2–35.1) for SSRI and 2.6 years (0.3–18.2) for SNRI. During fixed-dose treatment, 75.7% of patients received 450 mg/day of pregabalin, and 21.5% received 300 mg/day. The mean (range) dose of pregabalin during fixed-dose treatment was 376.6 mg/day (150.1–466.1) for period 1 and 382.1 mg/day (183.3–450.0) for period 2.

Primary efficacy outcome. At endpoint, the mean [standard error (SE)] pain score (LOCF) was statistically significantly lower for pregabalin than for placebo [4.84 (0.15) vs 5.45 (0.16); Figure 3A], a least squares (LS) mean difference of –0.61 (95% CI –0.91 – –0.31, p = 0.0001). Compared with placebo, pregabalin significantly improved mean pain score
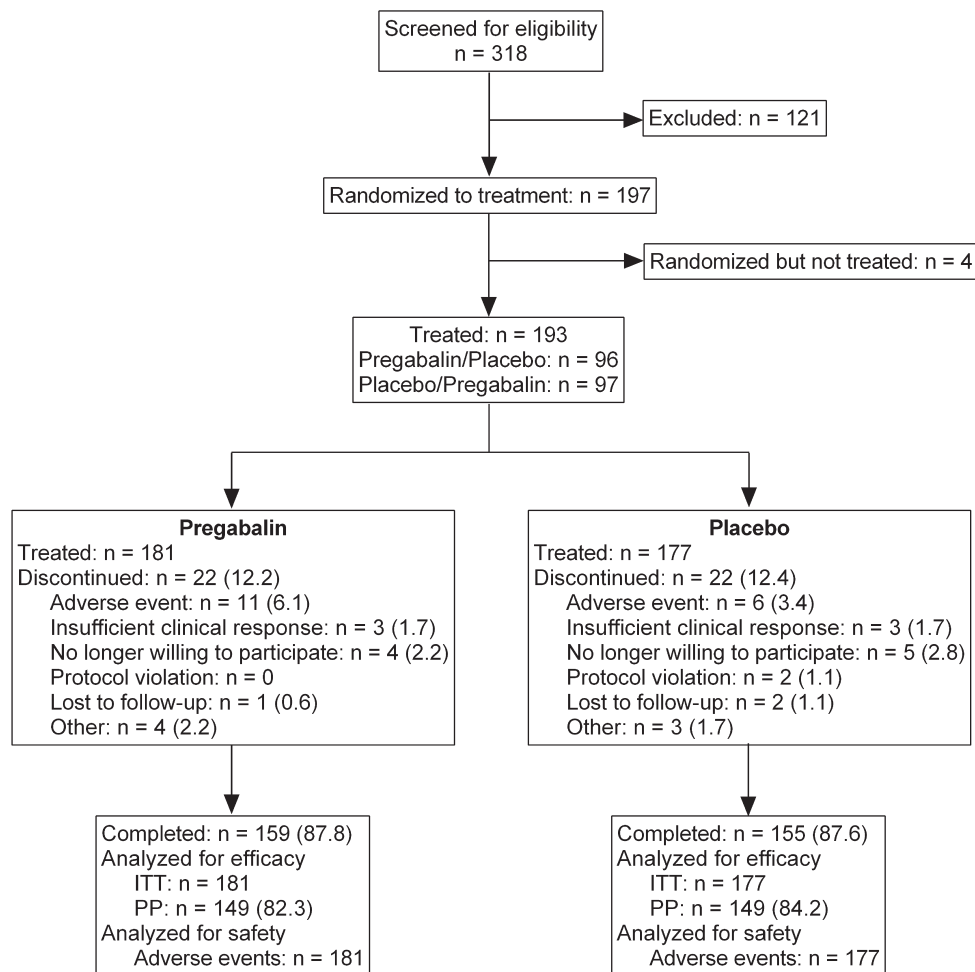
Figure 2. Patient disposition. Four patients were randomized in error, but were not treated. Data are presented as n (%) of patients; percentages are based on the number of patients treated. ITT: intent-to-treat; PP: per protocol.

from as early as Week 1, which was maintained for the duration of the study (Figure 3A). A descriptive summary of the change in mean pain score by week is shown in Figure 3B. Improvements were observed for pregabalin versus placebo at each week of the study, with pain scores returning to a common level following washout, regardless of treatment type during period 1 (Figure 3B).

Pregabalin significantly improved mean pain score at endpoint versus placebo when different methods for the imputation of missing values were used for the ITT population (BOCF: LS mean difference –0.59, 95% CI –0.86 – –0.31, p < 0.0001. MMRM: LS mean difference –0.52, 95% CI –0.62 – –0.41, p < 0.0001), and when the PP population was assessed (LS mean difference –0.57, 95% CI –0.89 – –0.25, p = 0.0005).

At baseline, the mean (SD) pain score of patients taking an SSRI [n = 101, 6.67 (1.12)] was similar to those taking an SNRI [n = 92, 6.81 (1.32)]. Mean (SE) pain scores at endpoint were significantly lower with pregabalin treatment versus placebo in patients taking an SSRI [4.63 (0.21) vs 5.12

(0.21), LS mean difference –0.48, 95% CI –0.89 – –0.07, p = 0.0211], and in those taking an SNRI [5.08 (0.22) vs 5.84 (0.22), LS mean difference –0.76, 95% CI –1.21 – –0.31, p = 0.0012).

Secondary efficacy outcomes. Significantly more patients were 30% and 50% pain responders with pregabalin compared with placebo, 45.3% versus 27.7% (p = 0.0007) and 26.0% versus 15.8% (p = 0.0205), respectively (corresponding to an NNT of 5.34 for 30% responders, with 95% CI of 11.91 and 3.44). Scores for HADS-A and HADS-D were significantly improved with pregabalin versus placebo (Table 2). Compared with placebo, pregabalin significantly improved FIQ total score and all subscale scores. Sleep quality, sWASO, and LSO were significantly improved with pregabalin versus placebo, but improvements in sTST and sNAASO were not significantly different. The proportion of PGIC responders (very much or much improved) at the end of period 1 was higher for pregabalin (46.2%, n = 93) versus placebo (30.1%, n = 93), but not significantly (p = 0.0637). Posthoc analysis of data from both treatment periods at

Table 1. Patient characteristics at baseline. Values are mean (SD) unless otherwise specified.

Characteristics	ITT Population, n = 193
Sex, n (%)	
Male	13 (6.7)
Female	180 (93.3)
Age, yrs	50.1 (10.0)
Race, n (%)	
White	181 (93.8)
Black	9 (4.7)
Other	3 (1.6)
Weight, kg	83.2 (21.2)
Height, cm	163.8 (7.4)
Time since FM diagnosis, yrs, mean (range)	6.1 (0.0–32.7)
No. tender points	15.4 (2.2)
Time since depression diagnosis, yrs, mean (range)	12.3 (0.3–45.8)
Depression diagnosis, n (%)	
MDD	84 (43.5)
Dysthymia	8 (4.2)
Depression NOS	101 (52.3)
Antidepressant medication, n (%)	
SSRI	101 (52.3)
SNRI	92 (47.7)
Mean pain score	6.7 (1.2)
FIQ total score	63.3 (12.0)
HADS-A score	8.3 (3.9)
HADS-D score	8.0 (3.6)

ITT: intent-to-treat; FM: fibromyalgia; MDD: major depressive disorder; NOS: not otherwise specified; SSRI: selective serotonin reuptake inhibitor; SNRI: serotonin/norepinephrine reuptake inhibitor; FIQ: Fibromyalgia Impact Questionnaire; HADS-A: Hospital Anxiety and Depression Scale-Anxiety; HADS-D: Hospital Anxiety and Depression Scale-Depression.

endpoint showed a significantly higher proportion of PGIC responders for pregabalin versus placebo (49.1% vs 32.2%, p = 0.0013). At endpoint, PSGA score was significantly higher with pregabalin versus placebo, with higher scores indicating better status. EQ-5D scores at endpoint were not significantly different between pregabalin and placebo.

Safety. TEAE were reported in 77.3% and 59.9% of patients receiving pregabalin and placebo, respectively (Table 3). The majority of TEAE were of mild or moderate severity. One death of unknown cause occurred prior to randomization. Four patients had adverse events (AE) that were considered serious: 3 (1.7%) with pregabalin (pain in extremity, detoxification, and anxiety) and 1 (0.6%) with placebo (malignant brain neoplasm); none were considered treatment-related by the investigator. The patient who experienced detoxification with pregabalin entered the study with drug/alcohol abuse (a protocol violation unknown to the investigator at randomization), and was removed from the study and excluded from the PP analysis. The most frequently reported TEAE with pregabalin were dizziness, somnolence, and constipation (Table 3). Depression was reported as an AE in 5 patients (2.8%) receiving pregabalin and in 4 (2.3%) receiving placebo. One patient (0.6%) receiving placebo discontinued

treatment because of heightened depression. Suicidal ideation was reported as an AE in 2 patients (1.1%) receiving pregabalin. Suicidal ideation resolved during the treatment and neither patient discontinued treatment. There were no clinically relevant changes in vital signs, echocardiogram, or clinical laboratory assessments.

Suicidal ideation was reported in 3 patients (1.7%) receiving pregabalin, 4 patients (2.3%) receiving placebo, and 2 patients receiving both treatments, primarily in the least severe "wish to die" category[22]. Three patients had reported prior suicidal ideation at screening [2 (1.1%) pregabalin and 1 (0.6%) placebo]. One patient (0.6%) receiving placebo reported a suicidal behavior consisting of a preparatory act (Internet search); this patient did not report further suicidal behaviors after initiating pregabalin treatment.

DISCUSSION

Depression is a frequent comorbidity with FM[5,6], and many patients with FM take antidepressant medication to treat depression[1]. How to manage FM pain in patients with comorbid depression who are taking antidepressant medication is an important clinical question. To our knowledge, this is the first study to examine the efficacy and safety of pregabalin in this patient population.

In our study, the treatment difference was similar to that seen in 5 pivotal studies in patients with FM not receiving concurrent antidepressant medication[10,12,13,14,24]. In those studies, the difference in mean pain score between pregabalin (300 or 450 mg/day) and placebo ranged from –0.33 to –0.98, compared with –0.61 in this study. Sensitivity analyses using different methods for the imputation of missing values (BOCF, MMRM) confirmed the robustness of this result. Patient demographics and baseline clinical characteristics were similar across these studies; however, it should be noted that only the current study used a crossover design and included patients taking antidepressant medication. Significantly more patients were 30% and 50% pain responders with pregabalin treatment than placebo. A 30% improvement in pain severity may be clinically meaningful[25,26], suggesting that 45.3% of patients had a clinically meaningful improvement in pain with pregabalin treatment, versus 27.7% of placebo-treated patients.

Pregabalin improved diverse FM clinical domains, including severity of anxiety and depression, patient function and global status, and sleep behaviors, consistent with previous studies that used doses of 300 or 450 mg/day[10,12,13,14,16,24,27]. HADS-A and HADS-D scores significantly improved with pregabalin treatment versus placebo. Although patients had mild depressive symptoms at baseline, depression was reported as an AE in few patients. This suggests that pregabalin treatment did not interfere with the ongoing treatment of depression in these patients, and that there was no worsening of depression.

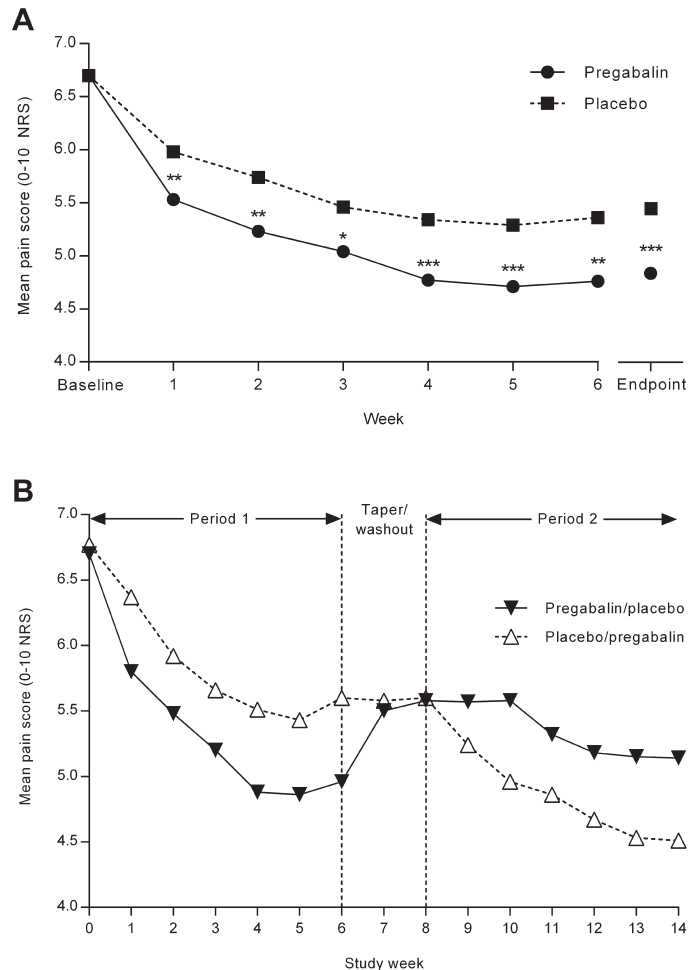The number of PGIC responders at the end of period 1

Figure 3. Weekly mean pain scores during treatment, at endpoint, and across treatment periods. A. Weekly least squares mean pain scores on an 11-point NRS (0 = no pain, 10 = worst possible pain) were calculated as the mean of the last 7 days and were derived from daily pain diaries. Imputation of missing data at endpoint was based on LOCF. B. Weekly least squares mean pain scores on an 11-point NRS (0 = no pain, 10 = worst possible pain) were calculated as the mean of the last 7 days and were derived from daily pain diaries. Data are descriptive only. * $p < 0.01$. ** $p < 0.001$. *** $p = 0.0001$. NRS: numerical rating scale; LOCF: last observation carried forward.

was not significantly different from placebo, although there was a trend toward improvement with pregabalin. A posthoc analysis at endpoint showed a significantly higher proportion of PGIC responders with pregabalin versus placebo, probably because all patients who received each treatment were represented at this timepoint. PSGA is a static assessment that is not affected by the crossover study design, and may be a useful tool in future crossover studies, although this measure would need to be assessed further before widespread implementation. Pregabalin did not significantly improve EQ-5D scores versus placebo. In this trial, the EQ-5D version with 3 levels of problems (3L) was used, which has a restricted ability to discriminate small to moderate differences in health status[28].

Pregabalin was generally well tolerated. The discontinu-ation rate owing to AE was similar to that seen in previous studies and the safety profile of pregabalin was consistent with previous studies in patients not taking concurrent anti-depressant medication[10,12,13,14,24]. There appeared to be no unexpected safety concerns in the current study. The combi-nation of pregabalin and an SSRI or SNRI does not appear to have a negative effect on pregabalin safety or tolerability.

Because patients with severe depression or unstable condi-tions were excluded and the concurrent use of only 2 classes of antidepressant was permitted to limit potential variability, these findings may not generalize to all patients with FM who have comorbid depression and are taking antidepressant medication. It is possible that the concomitant use of anti-depressants affected efficacy results. Trials with a crossover design have inherent benefits and limitations. Carryover

Table 2. Endpoint values for secondary outcome measures. Sleep quality is based on an 11-point numerical rating scale, with higher scores indicating better sleep quality. Values are least squares mean (standard error) unless otherwise specified.

Variables	Pregabalin, n = 181	Placebo, n = 177	Difference	95% CI	p
HADS scores					
HADS-A	6.01 (0.28)	6.96 (0.28)	–0.95	–1.40 – –0.50	< 0.0001
HADS-D	6.17 (0.31)	7.05 (0.31)	–0.88	–1.37 – –0.39	0.0005
FIQ scores					
Total	43.78 (1.42)	50.38 (1.43)	–6.60	–9.33 – –3.87	< 0.0001
Subscales					
Physical impairment	3.35 (0.17)	3.77 (0.17)	–0.42	–0.74 – –0.11	0.0078
Feel good	4.69 (0.23)	5.53 (0.23)	–0.85	–1.36 – –0.33	0.0014
Work missed	2.02 (0.21)	2.62 (0.21)	–0.59	–1.01 – –0.18	0.0050
Do work	4.56 (0.20)	5.31 (0.20)	–0.75	–1.14 – –0.36	0.0002
Pain	4.91 (0.17)	5.54 (0.17)	–0.64	–1.00 – –0.28	0.0006
Fatigue	6.32 (0.19)	6.76 (0.19)	–0.44	–0.85 – –0.04	0.0315
Rested	5.64 (0.19)	6.41 (0.19)	–0.76	–1.17 – –0.35	0.0003
Stiffness	5.24 (0.19)	5.95 (0.19)	–0.71	–1.11 – –0.31	0.0007
Anxiety	3.80 (0.20)	4.35 (0.21)	–0.55	–0.93 – –0.17	0.0048
Depression	3.20 (0.20)	4.13 (0.20)	–0.92	–1.32 – –0.53	< 0.0001
SSQ scores					
Sleep quality	6.15 (0.14)	5.57 (0.14)	0.57	0.31–0.84	< 0.0001
sWASO	33.38 (2.73)	41.18 (2.76)	–7.81	–12.66 – –2.96	0.0018
LSO	33.54 (2.68)	39.33 (2.71)	–5.80	–10.29 – –1.31	0.0117
sTST	422.98 (5.42)	414.63 (5.48)	8.35	–0.04–16.74	0.0511
sNAASO	0.48 (0.07)	0.61 (0.07)	–0.13	–0.29–0.03	0.1139
PSGA score	5.83 (0.17)	5.27 (0.17)	0.55	0.14–0.97	0.0085
EQ-5D score	0.58 (0.02)	0.56 (0.02)	0.02	–0.02–0.06	0.3854

HADS: Hospital Anxiety and Depression Scale; HADS-A: HADS-Anxiety; HADS-D: HADS-Depression; FIQ: Fibromyalgia Impact Questionnaire; SSQ: subjective sleep questionnaire; sWASO: subjective wake after sleep onset; LSO: latency to sleep onset; sTST: subjective total sleep time; sNAASO: subjective number of awakenings after sleep onset; PSGA: Patient Static Global Assessment.

Table 3. TEAE by treatment group (all causalities). Values are n (%) unless otherwise specified.

Variables	Pregabalin, n = 181	Placebo, n = 177
Total no. TEAE	468	245
Patients with TEAE	140 (77.3)	106 (59.9)
Patients with SAE	3 (1.7)	1 (0.6)
Discontinuation because of TEAE	11 (6.1)	6 (3.4)
TEAE in ≥ 5% of patients		
Dizziness	51 (28.2)	12 (6.8)
Somnolence	36 (19.9)	8 (4.5)
Constipation	19 (10.5)	4 (2.3)
Nausea	17 (9.4)	12 (6.8)
Diarrhea	16 (8.8)	7 (4.0)
Weight increased	16 (8.8)	3 (1.7)
Headache	14 (7.7)	17 (9.6)
Insomnia	13 (7.2)	1 (0.6)
Dry mouth	12 (6.6)	1 (0.6)
Fatigue	12 (6.6)	8 (4.5)
Nasopharyngitis	5 (2.8)	10 (5.6)

TEAE: treatment-emergent adverse event; SAE: serious adverse event.

effects of study drugs from 1 treatment period to the next have been reported, including in the treatment of chronic pain[29,30]. There is the risk of unblinding when patients switch treatments, although patients in the current study were blinded to the transitions between study periods. However, unlike a parallel-group study, all patients knew they would be receiving both active treatment and placebo, which may help to reduce placebo responses[31,32]. In addition, sample size was reduced because individual patients served as their own controls, and between-subject variability of symptoms was eliminated[15,29].

In patients with FM taking an SSRI or SNRI for comorbid depression, pregabalin significantly reduced pain severity versus placebo as early as the first week of treatment and for the duration of the study. Significant pain improvements with pregabalin versus placebo were seen irrespective of the class of antidepressant medication taken. Based on 30% and 50% pain responder analysis, more patients had a clinically meaningful improvement in pain with pregabalin than placebo. No worsening of depressive symptoms was observed in this depressed patient population. Statistically significant improvements in secondary efficacy outcomes including patient function, sleep quality, and anxiety were observed with pregabalin relative to placebo. Safety and tolerability were consistent with previous studies and current product labeling. These findings suggest that pregabalin may be an appropriate treatment option for patients with FM taking antidepressant medication for comorbid depression.

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