

Pregabalin for the Treatment of Fibromyalgia Syndrome

Results of a Randomized, Double-Blind, Placebo-Controlled Trial

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Objective. Fibromyalgia syndrome (FMS) is characterized by widespread musculoskeletal pain and lowered pain threshold. Other prominent symptoms include disordered sleep and fatigue. FMS affects an estimated 2% of the population, predominantly women. This trial was designed to evaluate the efficacy and safety of pregabalin, a novel $\alpha_2\text{-}\delta$ ligand, for treatment of symptoms associated with FMS.

Methods. This multicenter, double-blind, 8-week, randomized clinical trial compared the effects of pla-

cebo with those of 150, 300, and 450 mg/day pregabalin on pain, sleep, fatigue, and health-related quality of life in 529 patients with FMS. The primary outcome variable was the comparison of end point mean pain scores, derived from daily diary ratings of pain intensity, between each of the pregabalin treatment groups and the placebo group.

Results. Pregabalin at 450 mg/day significantly reduced the average severity of pain in the primary analysis compared with placebo (-0.93 on a 0–10 scale) ($P \leq 0.001$), and significantly more patients in this group had $\geq 50\%$ improvement in pain at the end point (29%, versus 13% in the placebo group; $P = 0.003$). Pregabalin at 300 and 450 mg/day was associated with significant improvements in sleep quality, fatigue, and global measures of change. Pregabalin at 450 mg/day improved several domains of health-related quality of life. Dizziness and somnolence were the most frequent adverse events. Rates of discontinuation due to adverse events were similar across all 4 treatment groups.

Conclusion. Pregabalin at 450 mg/day was efficacious for the treatment of FMS, reducing symptoms of pain, disturbed sleep, and fatigue compared with placebo. Pregabalin was well tolerated and improved global measures and health-related quality of life.

Fibromyalgia syndrome (FMS) affects ~3–6 million people in the US, with a prevalence in the general population estimated at 2% and an increased frequency among women (1). A characteristic symptom complex of chronic widespread musculoskeletal pain, disordered sleep, and fatigue associated with a lowered pain threshold is shared among those patients meeting the American College of Rheumatology (ACR) classification criteria for FMS (2). The etiology and pathogenesis of FMS are not well understood, but they are probably

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multifactorial (3). Available evidence points toward dysregulation of neurotransmitter function and central pain sensitization as fundamental mechanisms (4). The symptoms of FMS overlap considerably with those of other chronic illnesses, such as chronic fatigue syndrome, irritable bowel syndrome, temporomandibular disorder, and chronic headache syndromes (5). The lifetime prevalence of anxiety and depression is higher among patients with FMS than it is in the normal population (6). However, the presence of psychiatric comorbidity is neither necessary nor sufficient for the diagnosis of FMS (7).

At present, treatment of FMS is symptom based, aiming to alleviate pain, increase restorative sleep, and improve physical function. Nonpharmacologic therapies include education, psychological or cognitive-based therapies, and exercise-based treatments (8). Pharmacologic treatments include medications that have a neuromodulatory function, such as tricyclic compounds, selective serotonin reuptake inhibitor and serotonin/norepinephrine reuptake inhibitor antidepressants, analgesics, muscle relaxants, and hypnotics (8,9). No single agent has demonstrated consistent efficacy across all symptom domains (9). While some interventions offer benefits for some patients, additional treatment options are needed for patients with FMS in whom currently available treatments are either ineffective or poorly tolerated.

Pregabalin is an $\alpha_2\text{-}\delta$ ligand that has analgesic, anxiolytic-like, and anticonvulsant activity in animal models. Biochemical studies identified $\alpha_2\text{-}\delta$ (type 1) as the primary binding site for both pregabalin and the related compound, gabapentin (10). Alpha₂-delta is an auxiliary protein associated with voltage-gated calcium channels. Although there are 4 subtypes of $\alpha_2\text{-}\delta$ proteins, pregabalin and gabapentin bind with high affinity only to subtypes 1 and 2 (11,12). The experimental coexpression of $\alpha_2\text{-}\delta$ with various types of calcium channel α_1 subunits (the pore-forming protein of calcium channels) causes greater cellular expression of calcium channels and alters the kinetics and voltage dependence of calcium currents (13,14).

The pharmacologic actions of pregabalin appear to be restricted to neurons; for example, pregabalin has no effect on blood pressure or heart rate even at high dosages in animal models, unlike the vascular calcium channel blockers. Potent binding of pregabalin at the $\alpha_2\text{-}\delta$ site reduces calcium influx at nerve terminals (15) and, therefore, reduces the release of several neurochemicals, including glutamate, noradrenaline, and substance P (15–18). The reduced neurotransmitter release caused by drug binding at the $\alpha_2\text{-}\delta$ site is presumed to account for the analgesic, anticonvulsant, and anxiolytic-

like actions of pregabalin in animal models. This conclusion is based on results of structure–activity studies of compounds related to pregabalin and on the reduced pharmacologic effects of pregabalin in a mutant mouse strain that has reduced affinity for drug binding to $\alpha_2\text{-}\delta$ type 1 protein (19).

Reduction of neurotransmitter release from neurons in the spinal cord and brain is also proposed as the mechanism of action that may result in clinical benefit for patients with FMS. Pregabalin is inactive at γ -aminobutyric acid (GABA)_A and GABA_B receptors, it is not converted metabolically into GABA_A or a GABA_B antagonist, and it does not block GABA uptake or alter GABA degradation (20). It has no effect on whole-tissue GABA concentrations in the rat brain (21). Pregabalin has a predictable and linear pharmacokinetic profile with ready access to neural tissue, no known drug interactions, and a rapid onset of action (22,23). It has been found to be safe and effective in patients with painful diabetic neuropathy and postherpetic neuralgia (24–26).

The objective of the present 8-week study was to determine whether pregabalin (150, 300, or 450 mg/day) would be efficacious in reducing the severity of pain in patients with FMS. Also to be examined were the effects of this treatment on sleep, on other typical FMS symptoms, and on health-related quality of life.

PATIENTS AND METHODS

Patients. Men or women age ≥ 18 years who met the ACR criteria for the diagnosis of FMS (2) were eligible to enter the study. They were required to have a score of ≥ 40 mm on the 100-mm visual analog scale (VAS) of the Short-Form McGill Pain Questionnaire (SF-MPQ) (27) at screening and randomization. They were also required to have a mean score of ≥ 4 on a 0–10 pain rating scale, based on at least 4 daily pain diary entries, during the week before randomization.

Enrolled patients underwent a physical examination and blood tests at screening. Subjects were excluded if they had evidence of inflammatory rheumatic disease or other severe painful disorders that might confound assessment of FMS pain. Subjects were also excluded if they had clinically significant or unstable medical or psychological conditions that, in the opinion of the investigator, would compromise participation in the study. Subjects with a calculated creatinine clearance rate of ≤ 60 ml/minute (Cockcroft-Gault equation) were specifically excluded. Those who had failed to respond to previous treatment with gabapentin at dosages $\geq 1,200$ mg/day for pain associated with FMS were excluded. Women who were not postmenopausal were tested to confirm that they were not pregnant or breastfeeding during the study, and all women of child-bearing potential were advised to use contraception reliably. Patients who were receiving disability, applying for disability, or engaged in litigation related to FMS were

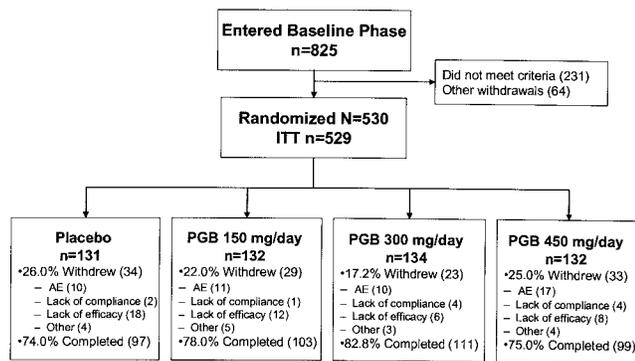


Figure 1. Diagram of patient flow. The diagram represents the outcome of all patients who entered the study. ITT = intent-to-treat; PGB = pregabalin; AE = adverse event.

excluded from the study. All patients gave written, informed consent.

Study design and treatment. This randomized, double-blind, parallel-group study was conducted between September 1999 and April 2000 at 40 study centers in the US. The study was conducted in accordance with the Declaration of Helsinki and received local or central institutional review board approval. The sponsor conducted the study, and clinical laboratory test results were analyzed at the Mayo Medical Laboratory (Rochester, MN).

Patients were randomly assigned to receive either placebo or pregabalin at 150, 300, or 450 mg/day. Study medication was administered 3 times daily in equal doses for 8 weeks. Randomization was by computer-generated code using a block size of 8. Patients randomly assigned to receive 450 mg/day pregabalin received 300 mg/day for the first 3 days and then 450 mg/day thereafter. Patients were required to attend the clinic at screening, randomization (baseline), and weeks 1, 3, 5, and 8 or upon early discontinuation.

All medications for pain and sleep disorders were prohibited during the study, except for acetaminophen (≤ 4 gm/day), aspirin (≤ 325 mg/day), and symptomatic migraine treatment. Patients were required to discontinue skeletal muscle relaxants, antidepressants, antiepileptic agents, corticosteroids, benzodiazepines, opioid analgesics, tramadol, mexiletine, and anti-Parkinson's disease medications 7 days before the

study and tender point site injections and fluoxetine 30 days before the study. Patients were instructed to maintain their normal daily routines and not to alter their exercise regimens.

Efficacy assessments. Each morning, patients rated the intensity of their FMS pain during the prior 24 hours in a daily paper diary, using an 11-point numerical rating scale where 0 = no pain and 10 = worst possible pain. They also rated sleep quality during the prior 24 hours in a daily diary as 0 = best possible sleep and 10 = worst possible sleep. To more fully describe core symptoms associated with FMS, a number of secondary measures were used. Patients completed the SF-MPQ at screening, randomization, and weeks 1, 3, 5, and 8. The Medical Outcomes Study (MOS)–Sleep measure (28), the Multidimensional Assessment of Fatigue (MAF) (29), the Hospital Anxiety and Depression Scale (HADS) (30), and the Short Form 36 Health Survey (SF-36) (31) were completed at baseline and end point. The Patient Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC) were rated at end point on a scale from very much improved to very much worse. The Manual Tender Point Survey (MTPS) (32) was administered by a clinician at randomization and end point.

Tolerability and safety assessments. All spontaneously reported or observed treatment-emergent adverse events were recorded at each clinic visit, along with the dates on which they began and ended. The sponsor classified adverse events using *Coding Symbols for a Thesaurus of Adverse Reaction Terms, 4th Edition (COSTART IV)* (33). A 12-lead electrocardiogram was recorded at screening and end point, and clinical laboratory tests (hematology, urinalysis, and chemistry) were performed at screening, week 3, and end point.

Statistical analysis. The primary efficacy variable was the mean pain score at end point (derived from daily pain diaries), defined as the mean of the last 7 diary entries while the patient was receiving study medication. All other efficacy variables were secondary. All patients who received at least 1 dose of study medication were included in the intent-to-treat analysis. End point analyses were based on the last observation carried forward. Data were not imputed for patients with no postbaseline data for a given variable; rather, such patients were treated as missing in the analysis. The mean pain score and mean sleep quality score from the daily diaries, as well as SF-MPQ, FMS intensity from the MTPS, MAF, MOS–Sleep measure, HADS, and SF-36 scores in each of the pregabalin groups were compared with those in the placebo group using

Table 1. Baseline characteristics of the patients*

	Placebo (n = 131)	Pregabalin 150 mg/day (n = 132)	Pregabalin 300 mg/day (n = 134)	Pregabalin 450 mg/day (n = 132)
Age, years	49.7 \pm 10.7	48.0 \pm 10.4	47.7 \pm 10.1	48.9 \pm 11.3
Women, no. (%)	119 (90.8)	126 (95.5)	120 (89.6)	119 (90.2)
White, no. (%)	125 (95.4)	123 (93.2)	123 (91.8)	122 (92.4)
Weight, kg	77.32 \pm 18.07	76.71 \pm 18.04	83.62 \pm 20.99	80.49 \pm 19.46
Fibromyalgia duration, months	103.7 \pm 89.4	102.3 \pm 101.1	109.8 \pm 97.4	114.8 \pm 113.3
Pain score [†]	6.9 \pm 1.2	6.9 \pm 1.5	7.3 \pm 1.2	7.0 \pm 1.3

* Except where indicated otherwise, values are the mean \pm SD.

[†] Based on daily diary entries recording pain on an 11-point scale ranging from 0 (no pain) to 10 (worst pain).

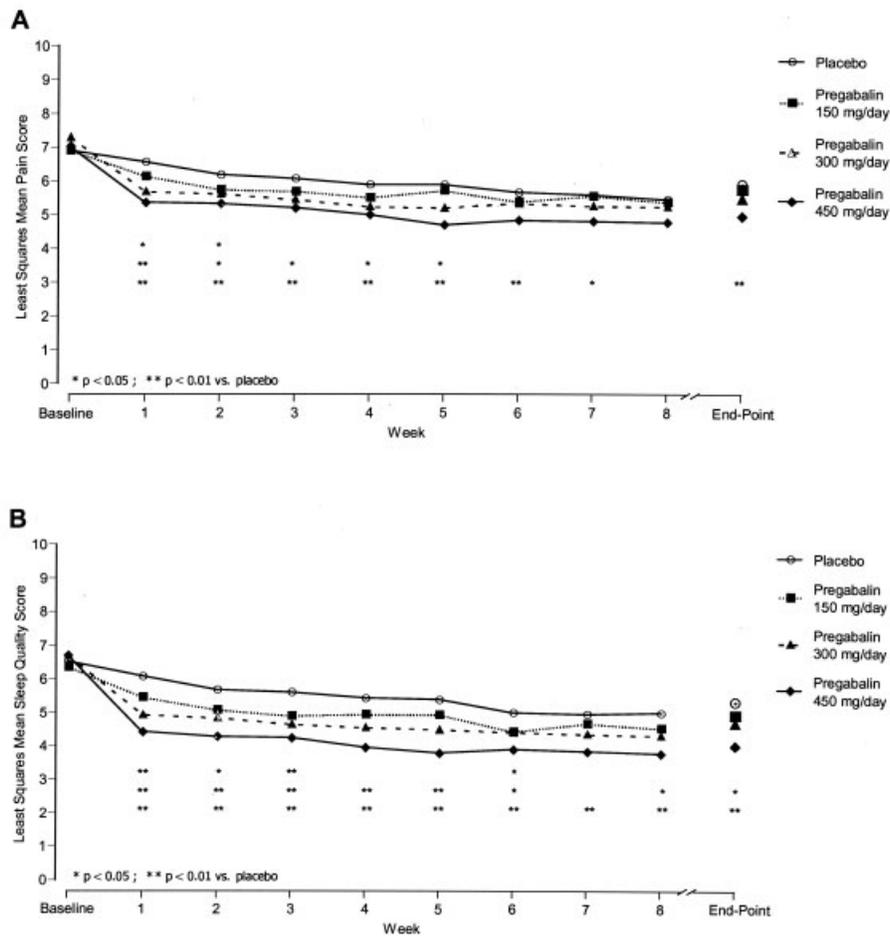


Figure 2. Weekly and end point scores for pain (A) and sleep (B). The data for the mean weekly values obtained from the numerical rating scales recorded daily represent an observed-case analysis, not including values from patients who discontinued. *P* values were derived by analysis of covariance (ANCOVA), with adjustment based on Hochberg’s procedures. End point values are based on an intent-to-treat, last observation carried forward analysis. *P* values for the end point values were derived by ANCOVA, with adjustment based on Hochberg’s procedures. Lower values represent an improvement in pain or sleep quality. Numbers of patients in each of the treatment groups at each week are shown in Table 2.

analysis of covariance, with treatment and center as the main effects and the baseline value as the covariate. In each analysis, adjusted (least squares) means were obtained from the model, and 95% confidence intervals on the difference in least squares means between each dosage of pregabalin and placebo were constructed.

The proportion of responders, defined as patients with $\geq 50\%$ reduction in mean pain score from baseline to end point, was analyzed using the Cochran-Mantel-Haenszel test (34) to test for an association between treatment and response after adjusting for center. The PGIC and CGIC were analyzed using the Cochran-Mantel-Haenszel test with modified ridit scores, which do not assume equal spacing between PGIC or CGIC response categories, adjusting for center (34). All statistical testing was 2-sided and was performed using SAS procedures (35). Because there were 3 principal comparisons (150, 300, and 450 mg/day pregabalin versus placebo), the

Hochberg procedure (36), a modification of the Bonferroni correction for multiple comparisons, was used to confine the Type I error rate to 5%.

Table 2. Numbers of patients in each of the treatment groups at each week

	Week								
	0	1	2	3	4	5	6	7	8
Placebo	131	129	128	122	108	102	98	97	93
Pregabalin, mg/day									
150	132	132	127	124	118	116	109	106	98
300	134	132	125	122	116	114	113	111	107
450	132	128	121	120	110	106	101	98	95

RESULTS

Characteristics of patients who continued and those who withdrew from treatment. Of the 825 patients who were screened, 530 were randomized and 529 took at least 1 dose of study medication (Figure 1). The majority of screening failures were due to the inability of subjects to meet inclusion and exclusion criteria, particularly the inability to discontinue concurrent medications. Baseline characteristics were similar across treatment groups (Table 1). Most patients were women, of whom 59% were postmenopausal, and most were white. The mean duration of FMS was ~9 years, with 61% of patients having been diagnosed at least 5 years earlier. The prevalence of irritable bowel syndrome was 30%. More than half of the patients had normal or mild categories of depressive and anxiety symptoms on the HADS. Patients were categorized as having moderate (28%) or severe (17%) anxiety more frequently than moderate (22%) or severe (9%) depression.

A total of 410 patients (77.5%) completed the 8-week study (Figure 1). Fewer patients in the 450 mg/day (6%) and 300 mg/day (4%) pregabalin groups withdrew due to lack of efficacy, compared with the 150 mg/day pregabalin (9%) and placebo (14%) groups. Adverse events prompted withdrawal of 17 patients (13%), 10 patients (7%), and 11 patients (8%) from the 450, 300, and 150 mg/day pregabalin groups, respectively, and of 10 patients (8%) from the placebo group.

Efficacy. In the primary efficacy analysis, the end point mean pain score was statistically significantly lower in the 450 mg/day pregabalin group than in the placebo group (-0.93 ; $P = 0.0009$) (Figure 2A). The end point scores in the 150 and 300 mg/day pregabalin groups were not significantly different from those in the placebo group. In the analysis of weekly mean pain scores, a statistically significant improvement in the 450 mg/day pregabalin group was apparent at week 1 and was maintained through week 7 relative to the placebo group ($-1.2, -0.9, -0.9, -0.9, -1.2, -0.8, \text{ and } -0.8$; $P < 0.05$) (Figure 2A). However, there was no statistically significant difference from placebo at week 8. A statistically significant improvement was observed in the 150 mg/day pregabalin group at weeks 1 and 2 relative to the placebo group (-0.4 at each time point; $P < 0.05$) and in the 300 mg/day pregabalin group from week 1 through week 5 relative to the placebo group ($-0.9, -0.6, -0.6, -0.6, \text{ and } -0.7$; $P < 0.05$). The numbers of patients in each of the treatment groups at each week are shown in Table 2.

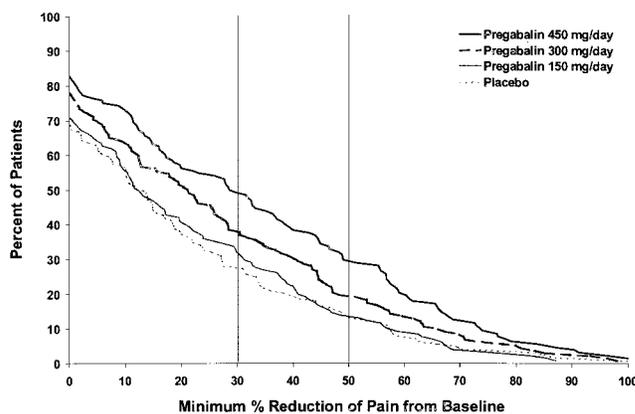


Figure 3. Results of continuous responder analysis. For various degrees of improvement in pain from baseline to study end point, the fraction of patients achieving that degree of improvement is shown. The data in the figure are cumulative, so that patients whose change from baseline is, for example, 50%, are also included at every level of improvement below 50%. The prespecified response rate of 50% reduction in mean pain scores from baseline and the clinically meaningful 30% reduction in mean pain scores from baseline are shown by the vertical lines.

The proportion of patients classified as responders (prespecified as having $\geq 50\%$ improvement from baseline) at end point was significantly greater in the 450 mg/day pregabalin group (28.9%) ($P = 0.003$), but not in the 300 (18.9%) or 150 (13.0%) mg/day pregabalin groups, compared with the placebo group (13.2%) (Figure 3). Using a less stringent difference of 30% improvement from baseline, previously shown to be a clinically meaningful improvement using the numerical rating scale across a range of pain conditions (37), the proportion of patients who would be classified as responders was significantly greater in the 450 mg/day pregabalin group (48.4%) ($P = 0.003$), but not in the 300 (37.9%) or 150 (31.3%) mg/day pregabalin groups, compared with the placebo group (27.1%) (Figure 3).

The mean SF-MPQ VAS, total, sensory, and affective scores in the 450 mg/day pregabalin group were statistically significantly improved at end point compared with those in the placebo group ($-11.1, -4.0, -3.2, \text{ and } -0.8$, respectively; all $P < 0.05$), but the SF-MPQ present pain intensity score was not. The mean FMS intensity scores from the MTPS in the pregabalin groups were not significantly improved compared with that in the placebo group, although the difference approached significance in the 300 and 450 mg/day pregabalin groups (-0.5 at both dosages; $P = 0.052$) (Table 3).

The mean sleep quality scores improved signifi-

Table 3. Baseline and end point ANCOVA values for outcome measures*

Parameter, scale	Overall mean at baseline†	End point							
		Placebo		Pregabalin 150 mg/day		Pregabalin 300 mg/day		Pregabalin 450 mg/day	
		n	LSM	n	LSM	n	LSM	n	LSM
Pain diary, 0–10	7.0	129	5.88	131	5.74	132	5.47	128	4.94‡
SF-MPQ									
VAS, 0–100 mm	74.8	131	60.63	132	58.83	131	55.05	130	49.49§
PPI, 0–5	2.8	131	2.15	132	2.16	131	1.94	130	1.88
Sensory, 0–33	17.9	131	14.77	132	13.88	131	13.71	130	11.60§
Affective, 0–12	5.2	131	3.71	132	3.49	131	3.28	130	2.89¶
Total, 0–45	23.1	131	18.50	132	17.38	131	16.98	130	14.50§
FMS intensity score, 0–10	6.1	123	5.17	123	5.05	127	4.65	126	4.65
Sleep quality diary, 0–10	6.6	129	5.30	131	4.91	132	4.68¶	128	3.99‡
MOS–Sleep problems index, 0–100	62.5	121	54.16	123	45.66‡	123	45.26‡	122	40.44‡
MAF global fatigue index, 1–50	38.8	122	32.85	125	30.67	126	29.37¶	125	29.41¶
HADS, 0–21									
Anxiety	10.1	125	8.41	124	8.35	127	8.36	126	7.56
Depression	8.5	125	7.41	124	6.82	126	7.23	126	6.65
SF-36, 0–100									
Physical functioning	40.8	125	46.14	124	48.21	126	48.66	127	51.22
Role-physical	15.4	125	23.08	124	28.22	127	31.07	127	32.89
Social functioning	49.2	125	56.73	124	62.30	127	61.20	127	64.31¶
Bodily pain	27.8	125	35.32	124	38.41	126	40.19	127	42.96§
Mental health	58.9	125	64.46	124	66.29	127	63.80	127	67.58
Role-emotional	46.4	125	58.90	124	64.28	127	52.21	127	65.53
Vitality	20.5	125	26.90	124	31.94	127	32.14	127	33.56¶
General health	47.7	124	49.34	123	53.89¶	127	55.28§	127	54.38¶

* Lower numbers suggest improvement for all parameters except the Short Form 36 Health Survey (SF-36), for which higher numbers suggest improvement. ANCOVA = analysis of covariance; LSM = least squares mean; SF-MPQ = Short-Form McGill Pain Questionnaire; VAS = visual analog scale; PPI = present pain intensity; FMS intensity score = fibromyalgia syndrome intensity score from the Manual Tender Point Survey; MOS = Medical Outcomes Study; MAF = Multidimensional Assessment of Fatigue; HADS = Hospital Anxiety and Depression Scale.

† Baseline values are based on all patients included in each analysis.

‡ $P \leq 0.001$ versus placebo (Hochberg-adjusted for 3-dose comparisons).

§ $P \leq 0.01$ versus placebo (Hochberg-adjusted for 3-dose comparisons).

¶ $P \leq 0.05$ versus placebo (Hochberg-adjusted for 3-dose comparisons).

cantly in the 300 and 450 mg/day pregabalin groups at end point relative to that in the placebo group (−0.6 [$P = 0.0348$] and −1.3 [$P = 0.0003$], respectively). All 3 pregabalin dosages were associated with statistically significant improvements at various time points during the study (Figure 2B). Several of the scales of the MOS–Sleep measure showed statistically significant improvements, including the sleep problems index for all 3 pregabalin groups (150, 300, and 450 mg/day) at end point compared with placebo (−8.5, −8.9, and −13.7, respectively; all $P < 0.001$). Significant improvements in the MAF global fatigue index scores were observed in the 300 and 450 mg/day pregabalin groups relative to that in the placebo group (−3.5 and −3.4, respectively; both $P = 0.019$). The HADS anxiety and depression scores were not significantly improved with pregabalin at any dosage (Table 3).

Pregabalin at 450 mg/day improved health-related quality of life, and end point scores were statis-

tically significantly superior to those in the placebo group in the social functioning, bodily pain, vitality, and general health perception domains of the SF-36 (differences of 7.6, 7.6, 6.7, and 5.0, respectively; all $P < 0.05$) (Table 3). Pregabalin at 150 and 300 mg/day was also associated with significantly improved end point scores in general health perception compared with placebo (differences of 4.6 and 5.9, respectively; both $P < 0.05$). The proportion of patients who were much or very much improved on the PGIC compared with baseline was 52% for those taking 450 mg/day pregabalin, 45% for those taking 300 mg/day pregabalin, and 32% for those taking 150 mg/day pregabalin, compared with 26% for those taking placebo. The proportion of patients who were much or very much improved on the CGIC compared with baseline was 52% for those taking 450 mg/day pregabalin, 41% for those taking 300 mg/day pregabalin, and 33% for those taking 150 mg/day pregabalin, compared with 25% for those taking placebo.

Table 4. Summary of most frequently reported treatment-emergent adverse events*

	Placebo (n = 131)	Pregabalin 150 mg/day (n = 132)	Pregabalin 300 mg/day (n = 134)	Pregabalin 450 mg/day (n = 132)
Dizziness	14 (10.7)	30 (22.7)	42 (31.3)	65 (49.2)
Somnolence	6 (4.6)	21 (15.9)	37 (27.6)	37 (28.0)
Headache	25 (19.1)	16 (12.1)	20 (14.9)	17 (12.9)
Dry mouth	2 (1.5)	9 (6.8)	8 (6.0)	17 (12.9)
Peripheral edema	1 (0.8)	7 (5.3)	9 (6.7)	14 (10.6)
Infection	22 (16.8)	11 (8.3)	13 (9.7)	13 (9.8)
Asthenia	8 (6.1)	7 (5.3)	12 (9.0)	11 (8.3)
Euphoria	1 (0.8)	2 (1.5)	11 (8.2)	10 (7.6)
Thinking abnormal	4 (3.1)	7 (5.3)	5 (3.7)	10 (7.6)
Weight gain	2 (1.5)	10 (7.6)	13 (9.7)	9 (6.8)
Sinusitis	3 (2.3)	6 (4.5)	5 (3.7)	9 (6.8)
Pharyngitis	3 (2.3)	3 (2.3)	2 (1.5)	8 (6.1)
Accidental injury	4 (3.1)	3 (2.3)	7 (5.2)	7 (5.3)
Confusion	0 (0.0)	1 (0.8)	5 (3.7)	7 (5.3)
Diarrhea	8 (6.1)	2 (1.5)	6 (4.5)	7 (5.3)
Flu syndrome	8 (6.1)	8 (6.1)	8 (6.0)	7 (5.3)
Incoordination	2 (1.5)	1 (0.8)	7 (5.2)	7 (5.3)

* Values are the number (%) of affected patients. Included are adverse events reported by at least 5% of patients in the 450 mg/day pregabalin group. Events are shown in decreasing order of frequency in the 450 mg/day pregabalin group.

Tolerability and safety. Treatment-emergent adverse events were reported by most patients in each group (78%, 88%, and 92% of patients in the 150, 300, and 450 mg/day pregabalin groups, respectively, and 77% of patients in the placebo group). Most adverse events were mild or moderate. Dizziness and somnolence were the two most frequently reported adverse events and tended to be dose related across pregabalin groups (Table 4). The median time to onset for dizziness and somnolence was ≤ 1 day in all 4 groups. The median duration of dizziness in patients who did not withdraw from the study was 4 days in those taking 150 mg/day pregabalin, 6 days in those taking 300 mg/day pregabalin, and 15 days in those taking 450 mg/day pregabalin. The median duration of somnolence in patients who did not withdraw from the study was 31 days in those taking 150 mg/day pregabalin, 21 days in those taking 300 mg/day pregabalin, and 18 days in those taking 450 mg/day pregabalin. Dizziness led to the withdrawal of 1 patient in the placebo group and of 2, 4, and 5 patients in the 150, 300, and 450 mg/day pregabalin groups, respectively. Somnolence led to the withdrawal of 2, 3, and 5 patients in the 150, 300, and 450 mg/day pregabalin groups, respectively.

Non-central nervous system (CNS) events that were more frequent in the pregabalin groups included weight gain and peripheral edema. No patient withdrew due to weight gain, and peripheral edema led to the withdrawal of 1 patient from the 450 mg/day pregabalin

group. While the mechanism of pregabalin-induced peripheral edema is unclear, no changes in cardiovascular or renal function were seen in patients who developed peripheral edema. There were no clinically important findings in the analyses of hematology, blood chemistry, or urine. Similarly, there were no clinically significant findings in the visual function, physical, or neurologic examinations or on the electrocardiograms.

DISCUSSION

This study demonstrated that 450 mg/day pregabalin as monotherapy is efficacious in relieving pain in patients with FMS. In addition, pregabalin is associated with decreased fatigue and with improved sleep and health-related quality of life. Patients enrolled in this study were primarily women with a long history of FMS who had substantial symptomatic complaints and diminished health-related quality of life. The baseline assessments demonstrated that this patient population was similar to those in other studies of patients with FMS (32,38,39).

Pregabalin at 450 mg/day was statistically significantly more efficacious than placebo in the primary and secondary analyses of pain. Similar results were obtained when the data were analyzed for the female subjects only. The efficacy of 450 mg/day pregabalin was apparent as early as the first week of treatment and persisted through week 7. The loss of a statistically

significant reduction of pain at week 8 could potentially have resulted from many different factors, including reduced statistical power at later time points, comparison with a group likely to comprise many placebo responders, a lack of durability of analgesic effect, or symptom fluctuation. However, since the study ended at week 8, it is not possible to distinguish between these possibilities. Clearly, longer studies are required.

Clinical significance of the treatment effect can be assessed using responder analysis and PGIC. Significantly more patients in the 450 mg/day pregabalin group (29%) had a $\geq 50\%$ decrease in pain ratings between baseline and end point than did patients in the placebo group (13%). It has been demonstrated that a 30% reduction in pain intensity represents a clinically meaningful change using the daily numerical rating scale for pain intensity as employed in this and other pain studies (37), and 48% of patients in the 450 mg/day pregabalin group achieved this level of reduction in pain intensity. Pregabalin at 150 and 300 mg/day was not statistically significantly more efficacious than placebo in the primary analysis of pain, but statistically significant improvement was observed at some time points during the study in both groups. The global change assessments by patients and clinicians indicated significantly greater improvement in patients taking 300 and 450 mg/day pregabalin than in those taking placebo. The MTPS did not demonstrate statistically significant changes, although there was a trend toward increased pressure pain tolerance in the 300 and 450 mg/day pregabalin groups.

While pain has been the primary construct that defines FMS, studies have shown that the majority of patients (75–80%) also experience sleep disturbance and fatigue (40,41). Pregabalin at both 300 and 450 mg/day was associated with statistically significant improvements in these symptoms, which indicates that pregabalin may offer benefits in the treatment of FMS that extend beyond the pain relief observed at the highest dosage. The 450 mg/day pregabalin dosage resulted in improvement in the general health perception, bodily pain, social functioning, and vitality domains of the SF-36, suggesting that the improvements in pain, sleep, and fatigue translate into an improvement in health status. Since the SF-36 addresses various aspects of function (e.g., physical/social-emotional and mental/anxiety/depression), we chose to use this outcome measure to assess function. However, neither anchor- nor distribution-based cutoffs have been developed for the SF-36 scales for patients with FMS or with chronic pain more generally, that would allow us to evaluate the

clinical significance of the statistically significant changes in the SF-36 domains.

The study subjects were asked to discontinue all medications used to treat FMS prior to enrollment in the study. This requirement could potentially exclude the most severely affected patients and those with clinically meaningful psychiatric comorbidity. Patients taking medications such as opioids and benzodiazepines, which are problematic to discontinue and tend to be used only in the most symptomatic patients, could have been disproportionately excluded. One of the exclusion criteria was failure to respond to previous gabapentin treatment for pain associated with FMS. It could be argued that this methodology increased the likelihood of finding a beneficial effect of pregabalin. Prior beneficial response to gabapentin was not systematically recorded, so it is not possible to determine whether these patients were more likely to respond to treatment with pregabalin.

The efficacy of pregabalin for treating symptoms of generalized anxiety disorder has been demonstrated in several clinical trials (42,43). As such, it is possible that improvements in pain scores reported by patients could be a by-product of a positive anxiolytic effect. However, in the present trial, there were no significant changes in HADS anxiety scores at end point from those at baseline. This suggests that patient-reported changes in pain scores are not a product of improvements in symptoms of anxiety; rather, improvements in pain scores are independent of anxiety symptom status.

Since patients were required to discontinue antidepressants, the study population could represent a group of FMS patients with less severe mood disturbance. The rates of depressive symptoms in the final study population defined by the baseline HADS depression score (9% with severe depression, 22% with moderate depression) were consistent with those previously reported in patients with FMS (39). Nevertheless, mean baseline HADS scores were mild, thus limiting the scope for significant improvement.

Pregabalin was generally well tolerated. The rate of discontinuation due to adverse events was low in the pregabalin and placebo groups. The most frequently reported adverse events were CNS-related dizziness and somnolence, which tended to occur within a day or two of initiation of pregabalin treatment. Few patients withdrew due to these symptoms, and 78.4% of patients from all treatment groups (76% of the placebo group, 78% of the 150 mg/day pregabalin group, 84% of the 300 mg/day pregabalin group, and 76% of the 450 mg/day pregabalin group) entered the open-label extension, suggesting that patients tolerate these adverse events even though they

are common. Patients taking pregabalin also experienced a higher incidence of peripheral edema than those taking placebo, although the mechanism of pregabalin-induced peripheral edema is unclear.

In summary, this study is the first prospective, randomized trial to evaluate pregabalin in the treatment of FMS. The results demonstrated that this agent reduces the pain and other core symptoms of the syndrome, including fatigue and sleep disturbance, over an 8-week period. Furthermore, pregabalin monotherapy was effective in improving health-related quality of life for patients with longstanding FMS. The data presented in this report suggest that pregabalin provides clinically significant benefits in patients with FMS, and these data support further study of this agent for treatment of patients with this prevalent and often disabling syndrome.

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