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Gabapentin in the Treatment of Fibromyalgia

A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial

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Objective. **To assess the efficacy and safety of gabapentin in patients with fibromyalgia.**

Methods. **A 12-week, randomized, double-blind study was designed to compare gabapentin (1,200–2,400 mg/day) (n = 75 patients) with placebo (n = 75 patients) for efficacy and safety in treating pain associated with fibromyalgia. The primary outcome measure was the Brief Pain Inventory (BPI) average pain severity score (range 0–10, where 0 = no pain and 10 = pain as bad as you can imagine). Response to treatment was defined as a reduction of ≥30% in this score. The primary analysis of efficacy for continuous variables was a longitudinal analysis of the intent-to-treat sample, with treatment-by-time interaction as the measure of effect.**

Results. **Gabapentin-treated patients displayed a significantly greater improvement in the BPI average pain severity score ($P = 0.015$; estimated difference between groups at week 12 = −0.92 [95% confidence interval −1.75, −0.71]). A significantly greater proportion of gabapentin-treated patients compared with placebo-treated patients achieved response at end point (51% versus 31%; $P = 0.014$). Gabapentin compared with placebo also significantly improved the BPI average pain interference score, the Fibromyalgia Impact Questionnaire total score, the Clinical Global Impression of Severity, the Patient Global Impression of Improvement, the Medical Outcomes Study (MOS) Sleep Problems Index, and the MOS Short Form 36 vitality score, but not the mean tender point pain threshold or the Montgomery Asberg Depression Rating Scale. Gabapentin was generally well tolerated.**

Conclusion. **Gabapentin (1,200–2,400 mg/day) is safe and efficacious for the treatment of pain and other symptoms associated with fibromyalgia.**

Fibromyalgia is a common, chronic musculoskeletal pain disorder that is characterized by widespread pain and tenderness and is frequently accompanied by fatigue, insomnia, depression, and anxiety (1,2). Fibromyalgia occurs in ~2% of the US general population, is more common in women (3.4% of women and 0.5% of men) (3), and is associated with substantial morbidity and disability.

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The pathophysiology of fibromyalgia is unknown, but evidence suggests that fibromyalgia is associated with aberrant central nervous system (CNS) processing of pain (4–7). As frequently observed in patients with neuropathic or inflammatory pain conditions, fibromyalgia patients often develop an increased response to painful stimuli (hyperalgesia) and experience pain from stimuli that are not usually noxious (allodynia) (6), which may reflect enhanced CNS processing of both painful and other stimuli that is characteristic of central sensitization (8). Unlike neuropathic or inflammatory pain disorders, fibromyalgia is not associated with damage to or a lesion of the peripheral nervous system or CNS (9). However, fibromyalgia may share pathogenic mechanisms with neuropathic or inflammatory pain conditions (10,11).

In preclinical pain models, gabapentin, a structural analog of the neurotransmitter γ-aminobutyric acid (GABA), exerted robust analgesic and anti-allodynic effects in syndromes secondary to sensitization of pain responses (12,13), but had minimal effects in models of acute, transient pain (14). Taylor et al (15) suggested that gabapentin did not appear to reduce immediate pain from injury, but appeared to be effective in reducing abnormal hypersensitivity (allodynia and hyperalgesia) induced by inflammatory responses or nerve injury. The antinociceptive effects of gabapentin are hypothesized to be mediated by modulation of calcium channels via $\alpha_2\delta$ binding, modulation of transmission of GABA, and possibly other additional unidentified mechanisms (16).

Gabapentin has been found to have substantial analgesic effects in randomized, controlled clinical trials in diabetic neuropathy (17,18), postherpetic neuralgia (19,20), migraine prophylaxis (21), and other neuropathic pain conditions (22). In addition to its antinociceptive properties, data from placebo-controlled, randomized trials indicate that gabapentin also has an anxiolytic effect and beneficial effects on sleep (17,23–25).

Based on these preclinical and clinical findings, we hypothesized that gabapentin would be safe and efficacious in reducing pain severity in patients with fibromyalgia. To test this hypothesis, we conducted a randomized, double-blind, placebo-controlled, parallel-group, flexible-dose study to assess the safety and efficacy of gabapentin (dosage range 1,200–2,400 mg/day, administered in 3 doses) in 150 outpatients who met the American College of Rheumatology (ACR) criteria for fibromyalgia (1). To our knowledge, this is the first randomized, controlled study of gabapentin in the treatment of fibromyalgia.

PATIENTS AND METHODS

Overview. The study was conducted in 3 outpatient research centers in the US. Enrollment began in September 2003, and the study was completed in January 2006. The various Institutional Review Boards approved the protocol, and all patients provided written informed consent after the study was explained and their questions were answered but before study procedures were initiated. Patients were identified by physician referral or response to an advertisement for a fibromyalgia medication trial.

Entry criteria. Female or male patients were eligible for the study if they were ≥18 years of age and met the ACR criteria for fibromyalgia (1). Patients with other rheumatic or medical disorders that contributed to the symptoms of fibromyalgia were excluded. Patients were required to score ≥4 on the average pain severity item of the Brief Pain Inventory (BPI) (26) at screening and randomization. Exclusion criteria consisted of the following: pain from traumatic injury or structural or regional rheumatic disease; rheumatoid arthritis, inflammatory arthritis, or autoimmune disease; unstable medical or psychiatric illness; lifetime history of psychosis, hypomania or mania, epilepsy, or dementia; substance abuse in the last 6 months; serious risk of suicide; pregnancy or breastfeeding; unacceptable contraception in those of childbearing potential; patients who, in the opinion of the investigator, were treatment refractory; prior treatment with gabapentin or pregabalin; and treatment with an investigational drug within 30 days of screening. Concomitant medication exclusions consisted of medications or herbal agents with CNS effects, with the exception of episodic use of sedating antihistamines (antidepressants required a 14-day washout period prior to beginning study medication except for fluoxetine, which required a 30-day washout period); analgesics, with the exception of acetaminophen or over-the-counter nonsteroidal antiinflammatory drugs; and unconventional or alternative therapies.

Study design. Patients who met the entry criteria following the 7–60-day screening phase were randomly assigned to 1 of 2 treatment groups, gabapentin or placebo, in a 1:1 ratio. Treatment was double-blind for 12 weeks. Patients were seen weekly for the first 2 weeks of the 12-week therapy phase; thereafter, study visits were scheduled at 2-week intervals. Patients then entered into a 1-week study-drug tapering phase.

Gabapentin or matching placebo was titrated in the following manner: 300 mg once a day at bedtime for 1 week, 300 mg twice a day for 1 week, 300 mg twice a day and 600 mg once a day at bedtime for 2 weeks, 600 mg 3 times a day for 2 weeks, and 600 mg twice a day and 1,200 mg once a day at bedtime (2,400 mg/day) for the remainder of the study beginning at week 6. If a patient could not tolerate 2,400 mg/day, the dosage was reduced to a minimum of 1,200 mg/day, administered 3 times a day. The study medication dose was stable for at least the last 4 weeks of the therapy phase. During the tapering phase, the dosage was decreased by 300 mg/day until discontinuation. This study used a true intent-to-treat (ITT)

design, whereby patients were assessed regardless of adherence to study medication treatment (27,28).

Outcome measures. The protocol-defined primary outcome measure was pain severity as measured by the self-reported BPI (short form) average pain severity score (26), which assesses average pain severity during the past 24 hours (0–10 scale, where 0 = no pain and 10 = pain as bad as you can imagine). There were several secondary outcome measures. Interference of pain with general activity, mood, walking ability, normal work, relationships with other people, sleep, and enjoyment of life was assessed using the BPI average pain interference score (0–10 scale, where 0 = does not interfere and 10 = completely interferes). Response to treatment was defined as a ≥30% reduction in the BPI average pain severity score.

The overall impact of fibromyalgia was measured using the Fibromyalgia Impact Questionnaire (FIQ) (29), a self-administered questionnaire that is used to measure components of health status that are affected by fibromyalgia over the previous week. The total score ranges from 0 to 80; a higher score indicates a more negative impact. For the tender point assessment, the Fischer dolorimeter with a 1-cm^2 rubber disk (30) was applied to the 18 tender point sites defined by the ACR (1), and the pressure was increased at a rate of 1 kg/cm^2/second until the patient indicated verbally that he/she first felt discomfort or pain. The mean tender point pain threshold was calculated from the 18 points and recorded in kg/cm^2.

Other measures included the Clinical Global Impression of Severity scale (1–7 scale, where 1 = normal, not at all ill, and 7 = among the most extremely ill patients) (31), the Patient Global Impression of Improvement scale (1–7 scale, where 1 = very much better and 7 = very much worse), the Medical Outcomes Study (MOS) sleep measure (32), which consists of 12 items that assess key constructs of sleep and generates a Sleep Problems Index that measures sleep adequacy and disturbance, and the Montgomery Asberg Depression Rating Scale (33), a clinician-rated scale with 10 items that measure apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Additional patient-reported health outcomes were measured using the MOS Short Form 36 (SF-36) health survey (34), which consists of 36 items in 8 health domains (subscales): bodily pain, general health, mental health, physical functioning, role–physical, role–emotional, social function, and vitality.

Schedule of assessments. The screening protocol included the medical history and the Mini-International Neuropsychiatric Interview (35), and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, to identify axis I psychiatric disorders (36). Patients also underwent a physical examination, electrocardiography (EKG), and laboratory tests (hematologic studies, chemistry panel, urinalysis, serum pregnancy test, urine drug screening, thyroid-stimulating hormone, antinuclear antibody level, erythrocyte sedimentation rate, and rheumatoid factor), and completed the BPI. At the randomization visit, and at each subsequent visit until the end of the therapy phase, the BPI, FIQ, and Clinical Global Impression of Severity scale were completed, vital signs were checked, and adverse events and concomitant medication were reviewed.

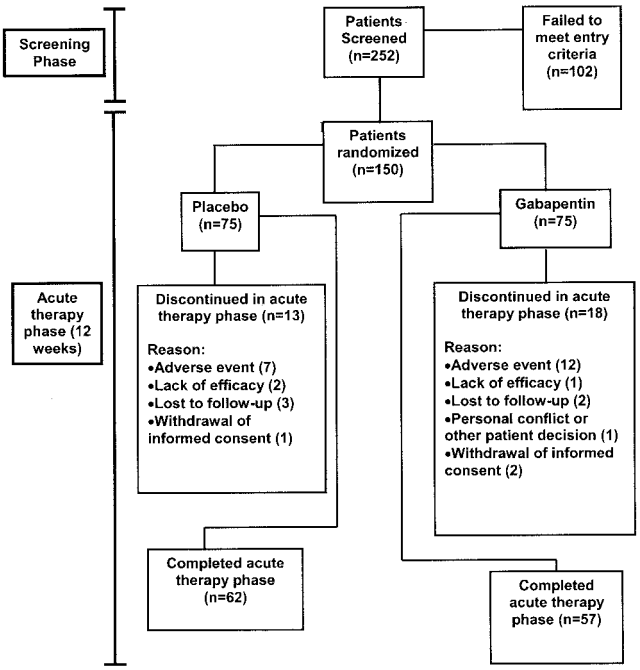

Figure 1. Disposition of study patients from screening to completion of the trial.

Weight and height were measured at randomization, and weight was measured again at the end of the therapy phase. The mean tender point pain threshold, the Montgomery Asberg Depression Rating Scale, and the MOS sleep measure were conducted at randomization and at weeks 4, 8, and at the end of the therapy phase or week 12. The Patient Global Impression of Improvement scale was completed at week 1 and at all subsequent visits. The SF-36 was performed at randomization and at the end of the therapy phase. Laboratory tests (hematologic and chemistry studies) and the EKG were repeated at week 8 (urine pregnancy test conducted at weeks 4 and 8), and a physical examination, EKG, and a urine pregnancy test were conducted at the end of the therapy phase.

Statistical analysis. This study required the enrollment of 150 patients to have at least 90% power to detect a moderately large effect size (0.60) for gabapentin using point and variance estimates based on the results of the Arnold et al study comparing fluoxetine with placebo (37). The BPI average pain severity score was chosen a priori as the primary outcome measure to test the efficacy of gabapentin in the treatment of pain associated with fibromyalgia. Type I error was controlled at a significance level of 0.05 for the analysis of this primary variable. Several secondary efficacy measures were included to confirm the findings of the primary measure. A multiplicity adjustment was not performed for the secondary measures because it was not the intent of the study to assess the secondary measures at the same experimental significance level as was established for the primary outcome variable.

For the primary analysis of continuous variables collected at more than 2 time points, we used a longitudinal analysis that compared the rate of change of the outcome

Table 1. Patient characteristics and scores on efficacy measures at baseline*

	Treatment group	
	Gabapentin (n = 75)	Placebo (n = 75)
Age, years	49.2 ± 10.6	47.3 ± 11.8
Women, no. (%)	70 (93.3)	65 (86.7)
Race, no. (%)		
White	73 (97.3)	73 (97.3)
African American	1 (1.3)	1 (1.3)
Asian	1 (1.3)	0
Other	0	1 (1.3)
Patients with current major depressive disorder, no. (%)	14 (18.7)	15 (20.0)
Patients with current anxiety disorder, no. (%)†	8 (10.7)	6 (8.0)
Brief Pain Inventory average pain severity score, range 0–10	5.7 ± 1.4	6.0 ± 1.5
Brief Pain Inventory average pain interference score, range 0–10	4.7 ± 2.0‡	5.3 ± 1.9
FIQ total score, range 0–80	46.3 ± 11.5	47.7 ± 10.3
CGI Severity scale score, range 1–7	4.4 ± 0.6	4.5 ± 0.6
Mean tender point pain threshold, kg/cm^2	1.8 ± 0.7	1.7 ± 0.7
Medical Outcomes Study Sleep Problems Index score, range 0–100	56.0 ± 16.3	55.8 ± 18.5
Montgomery Asberg Depression Rating Scale score, range 0–60	15.9 ± 7.2	17.1 ± 7.6
SF-36 score, range 0–100		
Physical functioning	47.6 ± 22.6	46.1 ± 21.2
Role–physical	19.0 ± 28.4	11.3 ± 20.3
Social functioning	61.7 ± 25.7	57.8 ± 23.1
Bodily pain	37.0 ± 13.1‡	32.3 ± 14.2
Mental health	67.6 ± 17.1	64.3 ± 20.5
Role–emotional	60.9 ± 42.2	54.2 ± 42.7
Vitality	21.7 ± 15.1	20.1 ± 16.7
General health	52.6 ± 22.3	51.3 ± 24.7

* Except where indicated otherwise, values are the mean ± SD. FIQ = Fibromyalgia Impact Questionnaire; CGI Severity = Clinical Global Impression of Severity; SF-36 = Medical Outcomes Study Short Form 36.
† Generalized anxiety disorder, panic disorder, agoraphobia, posttraumatic stress disorder, or obsessive-compulsive disorder.
‡ $P < 0.05$ versus placebo.

during the treatment period between groups. The difference in rate of change was estimated by random regression methods, as described elsewhere (38,39). We used a model for the mean of the outcome variable that included terms for treatment, time, treatment-by-time interaction, and center. Time was modeled as a continuous variable. To account for the correlation of observations among participants, we used the SAS procedure MIXED (SAS Institute, Cary, NC) with the best fitting of the following covariance structures: unstructured, first-order heterogeneous autoregressive, and first-order autoregressive. The longitudinal analyses used all available observations from all time points from all patients who completed a baseline evaluation. As a secondary analysis, changes from baseline to end point (the last observation carried forward [LOCF] method) were analyzed using an analysis of variance model, with a term for center. We also used this analysis as the primary analysis for the SF-36, which was obtained only at baseline and end point.

The primary analysis for response to treatment and for participant ratings of global improvement was the Cochran-Mantel-Haenszel test for end point values, using LOCF. All analyses employing LOCF used all available observations of subjects who had at least one postbaseline assessment.

The primary analysis for all variables was based on the ITT sample, which included observations of participants regardless of whether they were adherent to study medication treatment. We also performed a secondary analysis using only observations from visits while patients were adherent to study medication treatment.

We evaluated the differences between groups in the incidence of treatment-emergent adverse events using Fisher's exact test. We compared the baseline characteristics of each group using Fisher's exact test for categorical variables, and the 2-sample *t*-test for continuous variables. Treatment effects were tested at a 2-sided significance level of 0.05.

RESULTS

Patient disposition. A total of 252 patients were screened to identify 150 who met the entry criteria. They were randomly assigned to either the gabapentin (n = 75) or the placebo (n = 75) group. Thirty-one patients (21%) withdrew during the 12-week therapy phase, 18 (24%) from the gabapentin group and 13 (17%) from the placebo group ($P = 0.42$ by Fisher's exact test) (Figure 1). Of 1,200 possible study visits, the number of

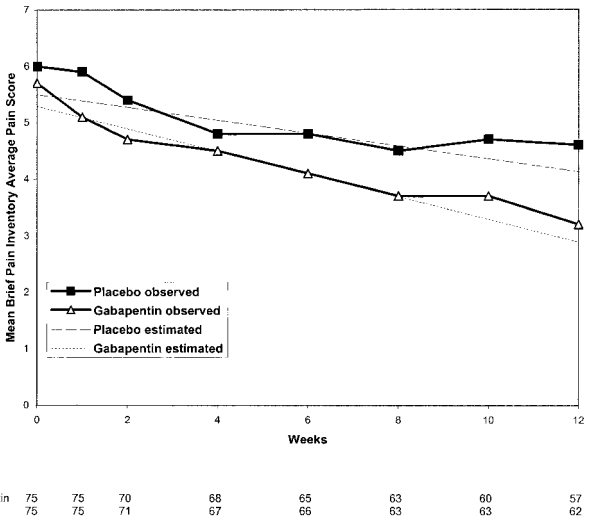

Figure 2. Mean observed and estimated Brief Pain Inventory average pain severity scores in the gabapentin and placebo groups during the 12 weeks of treatment. Estimates were obtained by longitudinal analysis.

observed visits was 1,077 (90.0%), of which 989 (82.4% of total possible) were obtained while participants were adherent to study medication treatment.

Baseline clinical and demographic characteristics. The majority of the patients were women (90%) and white (97%). There were no significant differences between the treatment groups in demographic or clinical variables (Table 1). For most outcome variables, there were no significant differences between the groups at baseline. However, the groups had significantly different ratings in the BPI average pain interference score and the bodily pain domain of the SF-36 (Table 1).

Efficacy. The median dosage at the end point for patients treated with gabapentin was 1,800 mg/day (interquartile range 1,200–2,400 mg/day). The mean BPI average pain severity scores decreased over time in both treatment groups, but more so in the gabapentin group (Figure 2). In the primary longitudinal analysis, compared with the placebo group, the gabapentin group had a significantly greater improvement in the BPI average pain severity score (Table 2). Gabapentin was also significantly superior to placebo in all secondary efficacy measures except for the mean tender point pain threshold and the Montgomery Asberg Depression Rating Scale (Table 2). Analysis of the BPI average pain severity score response rates (defined as ≥30% reduction from baseline to end point) revealed a significant difference between patients treated with gabapentin (38 of 75 [51%]) compared with patients treated with placebo (23 of 75 [31%]) ($P = 0.014$). Compared with placebo, gabapentin was associated with a significantly higher level of global improvement in patient ratings at the end point ($P < 0.001$) (Figure 3). The vitality domain of the SF-36 was the only domain that improved significantly more in the gabapentin group compared with the placebo group ($P = 0.032$) (data not shown).

In the secondary end point analysis of the primary outcome measure, the gabapentin group had significantly greater improvement in the BPI average pain severity score (mean ± SD score at week 12 using LOCF 3.8 ± 2.2 for the gabapentin group versus 5.0 ± 2.6 for the placebo group). The estimated mean difference in scores from baseline to week 12 was −0.95 (95% confidence interval [95% CI] −1.68, −0.23) ($P = 0.010$). The results of the end point analysis for the secondary outcome measures were consistent with the findings

Table 2. Observed values and model-based estimates of differences in outcome measures between groups after 12 weeks of treatment with gabapentin or placebo*

	Gabapentin (n = 57)	Placebo (n = 62)	Difference between groups	
			Estimate (95% CI)†	*P*
Brief Pain Inventory average pain severity score, range 0–10	3.2 ± 2.0	4.6 ± 2.6	−0.92 (−1.75, −0.71)	0.015
Brief Pain Inventory average pain interference score, range 0–10	2.2 ± 2.2	3.6 ± 2.8	−0.81 (−1.56, −0.07)	0.032
FIQ total score, range 0–80	26.2 ± 15.1	37.3 ± 18.1	−8.4 (−13.0, −3.3)	0.001
CGI Severity scale score, range 1–7	3.1 ± 1.0	3.8 ± 1.3	−0.66 (−1.08, −0.24)	0.002
Mean tender point pain threshold, kg/cm^2	2.0 ± 0.9	1.8 ± 1.0	0.17 (−0.04, 0.39)	0.11
Medical Outcomes Study Sleep Problems Index score, range 0–100	33.4 ± 19.5	47.8 ± 20.9	−11.5 (−18.6, −4.4)	0.001
Montgomery Asberg Depression Rating Scale score, range 0–60	9.1 ± 9.4	13.9 ± 8.9	−2.79 (−6.13, 0.56)	0.067

* Values are the mean ± SD. FIQ = Fibromyalgia Impact Questionnaire; CGI Severity = Clinical Global Impression of Severity.
† Estimate is the mean (week 12 minus baseline) for gabapentin minus the mean (week 12 minus baseline) for placebo. The test statistic is the treatment-by-time interaction term, which represents the mean difference in rate of change between the gabapentin and placebo groups, with time modeled as weeks since baseline. The estimate and 95% confidence interval (95% CI) were obtained by multiplying the treatment-by-time interaction and 95% CI by 12.

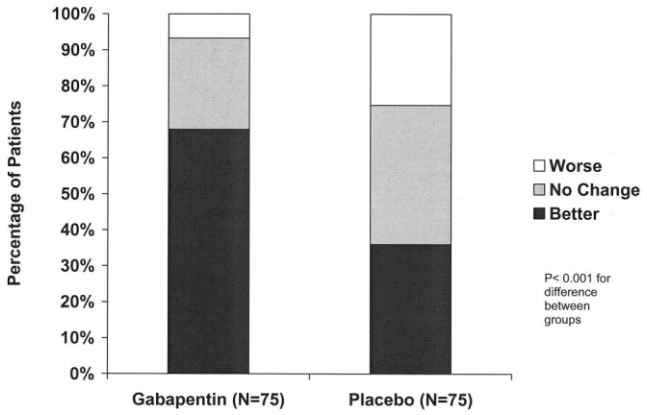

Figure 3. Participant ratings of global improvement at week 12 (last observation carried forward) in the gabapentin and placebo groups.

obtained in the primary longitudinal analysis. The analyses using only observations from visits at which participants remained adherent to study medication treatment also showed significant improvement in the BPI average pain severity score (at week 12, estimated mean difference between groups −0.86 [95% CI −1.69, −0.04], $P = 0.039$, for the longitudinal analysis; −0.87 [95% CI −1.63, −0.11], $P = 0.025$, for the end point analysis). The results of the secondary outcomes in both the longitudinal and end point analyses were consistent with the findings obtained in the ITT analysis.

Table 3. Most frequently reported treatment-emergent adverse events*

	Gabapentin (n = 75)	Placebo (n = 75)
Headache	20 (26.7)	16 (21.3)
Dizziness	19 (25.3)†	7 (9.3)
Sedation	18 (24.0)‡	3 (4.0)
Nausea	16 (21.3)	16 (21.3)
Somnolence	14 (18.7)	6 (8.0)
Edema	12 (16.0)	6 (8.0)
Lightheadedness	11 (14.7)§	1 (1.3)
Insomnia	9 (12.0)	6 (8.0)
Diarrhea	8 (10.7)	5 (6.7)
Pharyngitis	7 (9.3)	11 (14.7)
Asthenia	6 (8.0)	5 (6.7)
Depression	6 (8.0)	3 (4.0)
Flatulence	6 (8.0)	4 (5.3)
Nervousness	6 (8.0)	1 (1.3)
Weight gain	6 (8.0)†	0
Amblyopia	5 (6.7)	1 (1.3)
Anxiety	5 (6.7)	2 (2.7)
Cold virus	5 (6.7)	11 (14.7)
Dry mouth	5 (6.7)	3 (4.0)

* Values are the number (%) of affected patients. Adverse events shown are those reported by at least 5% of the patients in the gabapentin group.
† $P < 0.05$ versus placebo.
‡ $P < 0.001$ versus placebo.
§ $P < 0.01$ versus placebo.

Safety. Of the 150 randomized patients, a total of 19 patients discontinued the study during the therapy phase due to adverse events, with no significant differences between treatment groups (12 in the gabapentin group [16%] and 7 in the placebo group [9%]; $P = 0.34$, by Fisher's exact test) (Figure 1). Gabapentin-treated patients reported dizziness, sedation, lightheadedness, and weight gain significantly more frequently than did placebo-treated patients (Table 3). Notably, there were no significant differences in weight change between gabapentin- and placebo-treated patients from baseline to end point, as measured in the clinic (mean ± SD change 1.7 ± 6.2 kg increase in the gabapentin group versus 1.1 ± 5.8 kg increase in the placebo group) ($P = 0.56$). Most treatment-emergent adverse events were mild to moderate in severity, and there were no significant group differences in the percentage of serious treatment-emergent adverse events. There were no clinically important findings in the laboratory results, physical examinations, or EKGs.

DISCUSSION

In this 12-week, randomized, double-blind, flexible-dose trial, gabapentin (1,200–2,400 mg/day), compared with placebo, significantly reduced pain associated with fibromyalgia, as measured by the BPI average pain severity score, which was the primary efficacy measure. In addition, patients taking gabapentin compared with those taking placebo experienced a significant reduction in their total level of pain interference on the BPI. A significantly greater proportion of gabapentin-treated patients compared with placebo-treated patients achieved response at end point, defined as ≥30% reduction in the BPI average pain severity score from baseline to end point, which is considered to be a clinically meaningful change in pain intensity (40).

Although fibromyalgia is defined by the ACR criteria as a chronic, widespread condition that is associated with pain at ≥11 of 18 specific tender point sites on the body (1), 75–80% of patients with fibromyalgia also experience fatigue and sleep disturbance (1). In the analysis of secondary outcomes, gabapentin, compared with placebo, significantly improved sleep on the MOS Sleep Problems Index and the vitality domain of the SF-36. Thus, treatment with gabapentin may result in broad relief of important symptom domains associated with fibromyalgia. Indeed, both clinicians and patients rated significantly greater global improvement with

gabapentin compared with placebo, and gabapentin-treated patients reported significant reduction in the total impact of fibromyalgia.

Other secondary outcomes, including depressive symptoms and tender point pressure pain thresholds, did not significantly improve in patients taking gabapentin compared with those taking placebo. The mean Montgomery Asberg Depressive Rating Scale scores at baseline were mild, which may have limited the possibility for significant change in depressive symptoms, although the gabapentin-treated patients showed numerically superior improvement in depressive symptoms compared with patients taking placebo. Tender points have been unresponsive in some previous clinical trials of fibromyalgia (41), suggesting that they may be less responsive to treatment than other symptoms of fibromyalgia (42) or that gabapentin may not affect the underlying mechanism that causes tender points.

The results of the present study are consistent with the pregabalin trial of fibromyalgia (43) in which pain, but not tender points, significantly improved in patients taking 450 mg/day pregabalin compared with placebo. In addition, pregabalin was associated with significant improvement in other important symptom domains, including sleep and fatigue, and other measures of health status. Pregabalin, like gabapentin, is thought to exert its antinociceptive effects primarily by modulation of calcium channels via $\alpha_2\delta$ binding, which reduces the release of several neurotransmitters involved in pain processing, such as glutamate, noradrenaline, and substance P (43). The results of the pregabalin and gabapentin trials provide substantial evidence that $\alpha_2\delta$ ligands have the potential to benefit patients with fibromyalgia.

Gabapentin was generally well tolerated. Significantly more gabapentin-treated patients than placebo-treated patients reported dizziness, sedation, lightheadedness, and weight gain, although upon clinical measurement, there were no significant differences in weight gain between patient groups. Most gabapentin-treated patients who reported weight gain also reported edema, which may explain some of the patients' perception of weight gain. There were no significant differences between treatment groups in the number of patients who discontinued participation in the study due to treatment-emergent adverse events. The safety findings are generally consistent with the findings in studies of gabapentin in patients with other pain disorders (22).

This clinical trial was designed to allow for a true ITT analysis. Thus, patient outcomes were collected at all patient visits, regardless of the patient's adherence to study medication. The advantage of this design is that it preserves the validity of comparisons between treatment groups established by randomization (27,28). However, there continues to be debate about the advantages and disadvantages of this design compared with one in which data are included only from time points at which participants remain adherent to assigned treatment (27). Therefore, we included secondary analyses that used a modified ITT design in which only outcomes from the visits during which participants remained adherent to medication treatment were included in the analyses. Importantly, the results of these secondary analyses were consistent with the primary analysis.

Several limitations of this study should be considered. First, because the trial was 12 weeks in duration, the results may not generalize to longer treatment periods, and the long-term efficacy of gabapentin should be explored in future clinical trials. Second, the treatment groups were relatively small, and the study may have lacked the power to detect potentially relevant differences between groups, particularly on tender points. Third, the trial used a flexible-dose design, which limited our ability to establish a single effective dose of gabapentin, although the median dose of gabapentin used in the present study is within the range recommended for the treatment of other chronic pain disorders (22). Finally, the results of the trial may not generalize to patients with some comorbid psychiatric disorders, such as bipolar disorder or psychosis, patients with comorbid rheumatologic or other painful musculoskeletal disorders, or those with unstable psychiatric or medical disorders because patients with these conditions were excluded from the trial.

In summary, this is the first randomized, placebo-controlled study to evaluate gabapentin in the treatment of fibromyalgia. The results demonstrated that gabapentin, taken for up to 12 weeks, is effective and safe in the treatment of pain and other symptoms associated with fibromyalgia.

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AUTHOR CONTRIBUTIONS

Dr. Arnold had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Arnold, Goldenberg, Sandhu, Keck, Hess, Hudson.
Acquisition of data. Arnold, Goldenberg, Sharon Stanford, Lalonde, Sandhu, Hess, Hudson.
Analysis and interpretation of data. Arnold, Lalonde, Keck, Welge, Kevin Stanford, Hess, Hudson.
Manuscript preparation. Arnold, Goldenberg, Sandhu, Keck, Hess, Hudson.
Statistical analysis. Welge, Bishop, Kevin Stanford, Hudson.
Database design. Bishop.

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