Gabapentin for the Symptomatic Treatment of Painful Neuropathy in Patients With Diabetes Mellitus

A Randomized Controlled Trial

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Context.—Pain is the most disturbing symptom of diabetic peripheral neuropathy. As many as 45% of patients with diabetes mellitus develop peripheral neuropathies.

Objective.—To evaluate the effect of gabapentin monotherapy on pain associated with diabetic peripheral neuropathy.

Design.—Randomized, double-blind, placebo-controlled, 8-week trial conducted between July 1996 and March 1997.

Setting.—Outpatient clinics at 20 sites.

Patients.—The 165 patients enrolled had a 1- to 5-year history of pain attributed to diabetic neuropathy and a minimum 40-mm pain score on the Short-Form McGill Pain Questionnaire visual analogue scale.

Intervention.—Gabapentin (titrated from 900 to 3600 mg/d or maximum tolerated dosage) or placebo.

Main Outcome Measures.—The primary efficacy measure was daily pain severity as measured on an 11-point Likert scale (0, no pain; 10, worst possible pain). Secondary measures included sleep interference scores, the Short-Form McGill Pain Questionnaire scores, Patient Global Impression of Change and Clinical Global Impression of Change, the Short Form–36 Quality of Life Questionnaire scores, and the Profile of Mood States results.

Results.—Eighty-four patients received gabapentin and 70 (83%) completed the study; 81 received placebo and 65 (80%) completed the study. By intent-to-treat analysis, gabapentin-treated patients' mean daily pain score at the study end point (baseline, 6.4; end point, 3.9; n = 82) was significantly lower ($P<.001$) compared with the placebo-treated patients' end-point score (baseline, 6.5; end point, 5.1; n = 80). All secondary outcome measures of pain were significantly better in the gabapentin group than in the placebo group. Additional statistically significant differences favoring gabapentin treatment were observed in measures of quality of life (Short Form–36 Quality of Life Questionnaire and Profile of Mood States). Adverse events experienced significantly more frequently in the gabapentin group were dizziness (20 [24%] in the gabapentin group vs 4 [4.9%] in the control group; $P<.001$) and somnolence (19 [23%] in the gabapentin group vs 5 [6%] in the control group; $P = .003$). Confusion was also more frequent in the gabapentin group (7 [8%] vs 1 [1.2%]; $P = .06$).

Conclusion.—Gabapentin monotherapy appears to be efficacious for the treatment of pain and sleep interference associated with diabetic peripheral neuropathy and exhibits positive effects on mood and quality of life.

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DIABETES MELLITUS is the most common cause of neuropathy in the Western world.[1] In a cohort of 4400 patients with diabetes studied for 20 to 25 years, 45% developed neuropathy during the course of their disease.[2] Improved methods to determine the incidence, prevalence, and course of diabetic peripheral neuropathy have been precisely described and applied in large longitudinal studies.[3-13] Pain due to diabetic neuropathy affects the feet and ankles most often and, to a lesser extent, lower extremities above the knees and upper extremities.[14] The pain may be severe and often has an unusual "dysesthetic"

See also pp 1837 and 1863.

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Mss Hes and LaMoreaux and Dr Garofalo are employees of Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Co, and own stock and hold options to purchase further stock in the company. Drugs and compensation for study expenses were supplied by Parke-Davis, the study sponsor.

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quality. If inadequately treated, it is frequently associated with mood and sleep disturbances. Attempts to treat diabetic neuropathies can be divided into those directed at modification of the underlying disease process and those directed toward symptom suppression. Improved glycemic control is the mainstay of efforts to modify the incidence and course of the disease, although aldose reductase inhibitors may also play a role.[15-18] There is strong evidence that tricyclic antidepressants (TCAs) effectively reduce pain and weaker evidence that anticonvulsants, antiarrhythmics, and topical agents are useful, although dose-limiting adverse effects may reduce the effectiveness of these agents.[16,17,19-21]

Gabapentin (1-[aminomethyl]-cyclohexaneacetic acid; Neurontin, Parke-Davis, Division of Warner-Lambert Co, Morris Plains, NJ) is an anticonvulsant approved in the United States in 1994 for use in adult patients with partial epilepsy that has been reported anecdotally and in open-label case series to be effective in the treatment of pain syndromes, including painful diabetic neuropathy.[22,23] Gabapentin is structurally related to γ-aminobutyric acid (GABA), a neurotransmitter that plays a role in pain transmission and modulation. Gabapentin is not metabolically converted to GABA or a GABA antagonist and is not an inhibitor of GABA uptake or degradation.[24] Unlike systemically administered GABA, gabapentin readily crosses the blood-brain barrier.[25,26] Gabapentin is eliminated entirely by renal excretion and its clearance is reduced in patients with renal insufficiency, especially those with a creatinine clearance of less than 60 mL/min.[7] The evidence for each of gabapentin's pharmacological actions, including interaction with the system L-amino acid transporter, alteration of synthesis and release of GABA in the brain, high affinity binding to the α-2-Δ subunit of voltage-activated calcium channels, inhibition of voltage-activated sodium channels, alteration of monoamine neurotransmitter release and blood serotonin levels, and neuroprotection in laboratory models of amyotrophic lateral sclerosis, has been summarized elsewhere in the literature.[27]

Gabapentin has been shown to be effective in various animal models of chronic neuropathic pain. The analgesic effects of gabapentin were seen in the chronic constriction injury model of neuropathic pain in rats.[28] Gabapentin administered intraperitoneally in clinically relevant doses ranging from 10 to 75 mg/kg led to significant dose-related improvement in heat hyperalgesia and mechanoallodynia.[29] Heat hyperalgesia was also significantly reduced following intrathecal gabapentin administration, indicating that the antihyperalgesic properties of gabapentin are at least partially modulated through spinal cord mechanisms.[29] In addition, gabapentin was effective in significantly reducing late-phase tactile allodynia in both the rat formalin[30] and carrageenan footpad tests and hyperalgesia in the rat streptozotocin model (Parke-Davis Pharmaceutical Research, unpublished data, 1997). These findings, coupled with an established favorable safety profile,[24] suggest gabapentin as a promising candidate for use in the treatment of neuropathic pain. The purpose of this study was to evaluate the safety and efficacy of gabapentin monotherapy for the treatment of pain associated with diabetic neuropathy.

METHODS

Study Population

All participating clinical sites received investigational review board approval of the study protocol, and all patients provided written informed consent prior to study participation. At screening, eligible patients had pain attributed to diabetic neuropathy for 1 to 5 years, a diagnosis of diabetes mellitus (type 1 or 2), and a pain rating score of at least 40 mm on the 100-mm visual analog scale (VAS) of the Short-Form McGill Pain Questionnaire (SF-MPQ).[31] Patients with an average pain score of at least 4 on an 11-point Likert scale and at least 4 observations recorded in daily pain diaries over the next week were randomized. Only patients with a hemoglobin A_{1c} level of 0.11 or less (normal range, 0.048-0.067) were randomized. Exclusion criteria included the presence of other severe pain that could confound assessment or self-evaluation of the pain due to diabetic neuropathy, receipt of any investigational drug within 30 days prior to screening, and amputations other than toes. An additional exclusion criterion was a creatinine clearance of less than 60 mL/min to avoid the necessary dosage adjustments (reductions) that would be required for patients with renal impairment.[24] Creatinine clearance was estimated from patients' serum creatinine levels, using the following formulas[32]: adult male C_{cr} = (140 − age) × weight in kilograms/(72 × serum creatinine in milligrams per deciliter); and adult female C_{cr} = [(140 − age) × weight in kilograms/(72 × serum creatinine in milligrams per deciliter)] × 0.85, where C_{cr} indicates creatinine clearance.

Medication dosages for diabetes control were to remain stable during the study. Medications that could affect symptoms of painful diabetic neuropathy were prohibited with the exception of (1) acetaminophen (up to 3 g/d) or aspirin (up to 325 mg/d for prophylaxis for myocardial infarction or transient ischemic attacks) and (2) serotonin reuptake inhibitors (with no dosage change within 30 days prior to the study or during the study). The following medications were prohibited within 30 days prior to randomization and during the study: TCAs, mexiletine hydrochloride, carbamazepine, phenytoin, valproate sodium, dextromethorphan, opioids, capsaicin, nonsteroidal anti-inflammatory drugs, skeletal muscle relaxants, benzodiazepines, other Schedule II medications, and over-the-counter medications with centrally acting properties.

Study Design

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study composed of 2 phases, a 7-day screening phase and an 8-week double-blind phase. The 8-week double-blind phase consisted of a 4-week dose titration period followed by a 4-week fixed-dose period.

Screening Phase.—Study eligibility was determined and informed consent obtained at the patients' first visit. At this visit, patients completed the SF-MPQ, had their medical history taken, and had physical and neurological examinations. Blood samples for hemoglobin A_{1c} and serum creatinine (for creatinine clearance estimate) were taken. Patients meeting all criteria were given daily pain and sleep diaries and instructed on how to complete them.

Randomization.—Diaries kept during the screening phase were collected and reviewed. Patients again completed an SF-MPQ at the end of the screening phase. Patients who remained eligible for the study were randomized in a double-blind fashion (in blocks of 4 according to a computer-generated random code) to receive either placebo or gabapentin. They then filled out a Short Form–36 Quality of Life (SF-36 QOL)[33] Questionnaire and Profile of Mood States (POMS),[34] and received their blinded medication and additional diaries.

Double-Blind Treatment Phase Titration Period.—During the first 4 weeks of the study, patients received gradually titrated dosages of gabapentin (week 1, 900 mg/d; week 2, 1800 mg/d; week 3, 2400 mg/d; and week 4, 3600 mg/d) or placebo. Gabapentin (300 mg per capsule) and placebo were supplied to investigational sites in identical gray-gray capsules in blinded fashion. All patients were provided an equal number of capsules and instructed to follow a dosing schedule of 3 times per day. Because this was the first trial to evaluate gabapentin's efficacy in this patient population, all patients' dosages were titrated to tolerability up to 3600 mg/d regard-

less of any efficacy achieved at lower dosages. If intolerable adverse reactions occurred, the dosage was decreased 1 dose step to 900, 1200, 1800, or 2400 mg/d. Patients were reminded by telephone twice weekly to complete their daily diaries and were queried about adverse effects. Patients visited the clinic and completed an SF-MPQ at week 2 and week 4.

Fixed-Dose Period.—During the second 4 weeks of the double-blind treatment phase, patients' treatment remained at their maximum tolerated dosage and daily diaries were continued. At study end (week 8) or early termination, the SF-MPQ, SF-36 QOL Questionnaire, and POMS were completed. Patients turned in the daily pain and sleep interference diaries and completed the Patient Global Impression of Change (PGIC). Investigators independently completed the Clinical Global Impression of Change (CGIC).

Efficacy and Safety Measurements

The primary efficacy parameter was a pain severity rating, recorded by patients in daily diaries using an 11-point Likert scale (0, no pain; 10, worst possible pain). Secondary efficacy parameters were the SF-MPQ scores, the weekly mean sleep interference score from the daily sleep diary, the PGIC, and the CGIC. Patients recorded pain and sleep information in the diaries on awakening for the preceding 24-hour period. The SF-MPQ consisted of 3 sections. In the first section, 15 items that described pain during the past week were rated from 0 (no pain) to 3 (severe pain). The second section was the 100-mm VAS, which rated the patient's pain during the previous week from no pain to worst possible pain. The third section was the Present Pain Intensity (PPI) Scale, which rated pain on a 6-point scale from 0 (no pain) to 5 (excruciating pain). Sleep interference was rated on an 11-point scale that described how pain had interfered with the patient's sleep during the past 24 hours (0, "did not interfere"; 10, "unable to sleep due to pain"). The PGIC was a 7-point scale on which patients rated any change in their overall status that they had experienced since beginning study medication from much improved to much worse. The CGIC was also a 7-point scale on which the clinician rated the change observed in the patient's overall status since the beginning of the study. Quality of life was assessed by the POMS and the SF-36 QOL Questionnaire. The POMS consisted of 65 measures of mood during the previous week, resulting in 6 mood scores: tension/anxiety, depression/dejection, anger/hostility, vigor/activity, fatigue/inertia, confusion/bewilderment, and total mood disturbance. The SF-36 QOL Questionnaire measured each of the following 8 health concepts: physical functioning, role limitations due to physical problems, social functioning, bodily pain, general mental health, role limitations due to emotional problems, vitality, and general health problems.

The safety of gabapentin was assessed using adverse event data (occurrence, intensity, and relationship to study drug) and the results of physical and neurological examinations, including peripheral sensory examinations. All patients randomized to treatment were evaluated for safety.

Statistical Analysis

Power Calculation.—Published results of clinical trials in painful diabetic neuropathy indicate wide variation in placebo response, ranging from approximately 10% to 40%.[19,35-38] Response in these trials was based on measures such as "global pain relief of moderate or better" and "at least moderate improvement"; the trial with the longest duration of placebo administration (6 weeks) had the smallest placebo response (10%). Therefore, in this trial of 8 weeks' duration, we considered 30% a conservative estimate of placebo response, that is, at least moderate improvement on the CGIC. A gabapentin response of 55% to 60% on the same scale would be considered a clinically important finding. A sample size of 75 patients per group would provide more than 90% power to detect a difference of 30% and more than 80% power to detect a difference of 25% between placebo and gabapentin, given the assumptions stated herein.

Analyses.—All testing was 2-sided at the .05 α level and was done using SAS statistical software (SAS Institute Inc, Cary, NC) procedures. All analyses were conducted using the intent-to-treat population, defined as all randomized patients who received at least 1 dose of study medication. Patients with no data recorded for a particular parameter were automatically excluded from the analyses of that parameter. For each analysis of covariance (ANCOVA), adjusted (least squares) means were obtained from the model and 95% confidence intervals for the difference between placebo and gabapentin were constructed.

The end-point mean pain score and sleep interference score were calculated as the mean score for the last 7 diary entries while the patient was taking the study drug. The end-point mean pain score was analyzed for the intent-to-treat population (except for patients with no pain diary data during either screening or treatment) using ANCOVA. The model included main effects for treatment and center, using the screening mean pain score as the covariate. Consistency across sites was assessed by a second ANCOVA model that included a treatment-by-center interaction term. The end-point mean sleep interference score was analyzed for the intent-to-treat population (except for patients with no sleep diary data during either screening or treatment), using the screening mean sleep score as the covariate. The last observations for total pain score, VAS, and PPI of the SF-MPQ were analyzed, using ANCOVA with the respective scores at randomization as the covariates. The CGIC and PGIC were analyzed using a modified ridit transformation with the Cochran-Mantel-Haenszel procedure, adjusting for center. Each domain of the SF-36 QOL Questionnaire was analyzed separately using ANCOVA, with the response at randomization used as covariate. Supplemental analyses were performed at each week; the Hochberg procedure[39] was used to adjust for multiple measurements over time of the mean pain, mean sleep interference, and SF-MPQ scores. Each item of the POMS and the overall score of mood disturbance was analyzed separately using ANCOVA, with scores at randomization as the covariate.

Table 1.—Patient Demographics and Baseline Characteristics

Characteristics	Treatment: Gabapentin (n = 84)	Treatment: Placebo (n = 81)
Sex, No. (%)		
Male	49 (58.3)	50 (61.7)
Female	35 (41.7)	31 (38.3)
Race/ethnicity, No. (%)		
White	67 (79.8)	67 (82.7)
Black	5 (6.0)	6 (7.4)
Other	12 (14.3)	8 (9.9)
Age, mean (SD), y	53.0 (10.5)	53.0 (10.2)
Height, mean (SD), cm	173 (13.2)	174 (10.2)
Weight, mean (SD), kg	95.1 (22.6)	94.5 (19.2)
Duration of diabetes, mean (SD), y	12.0 (9.6)	11.2 (8.7)
Distribution of neuropathic pain, No. (%)		
Foot/toe	81 (96.4)	78 (96.3)
Calf	51 (60.7)	43 (53.1)
Finger/hand	32 (38.1)	36 (44.4)
Thigh	20 (23.8)	12 (14.8)
Forearm	7 (8.3)	6 (7.4)

RESULTS

Of the 165 patients randomized, 84 were randomized to gabapentin and 81 to placebo. Patient demographics and baseline characteristics were similar between groups (Table 1). Approximately 75% of patients in each group had type 2 diabetes. The majority of patients had neuropathic pain involving the foot/toe and calf, and the mean pain score at baseline was similar between treatment groups. The pain descriptors of the SF-MPQ were similar between the placebo and gabapentin groups and between pa-

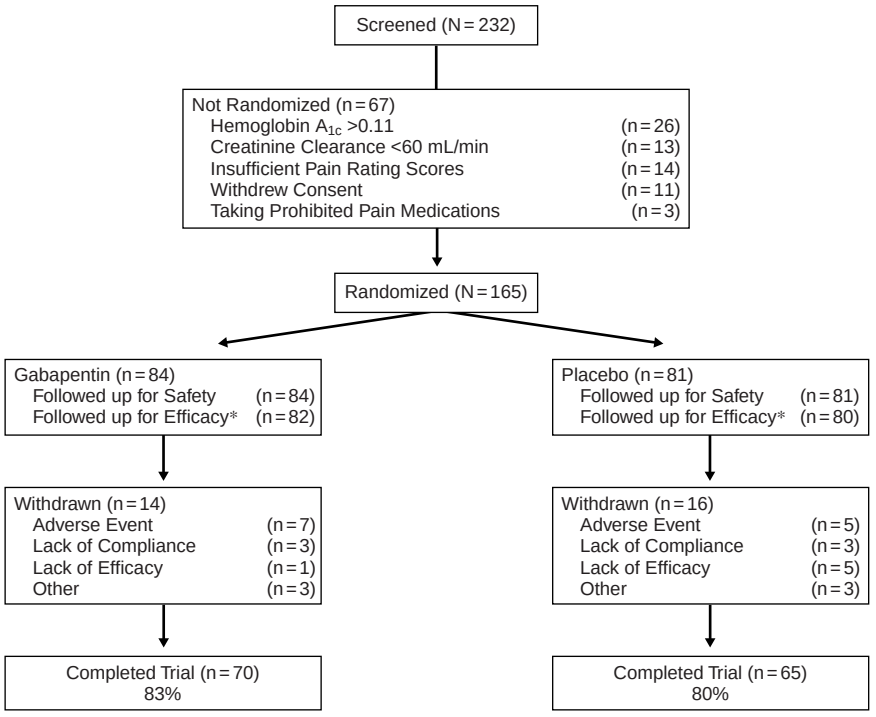

Figure 1.—Profile of the randomized controlled trial. Asterisks indicate provided at least 1 efficacy assessment.

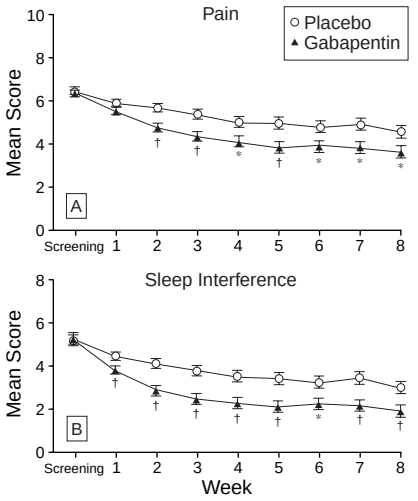

Figure 2.—A, Weekly mean pain score as measured on an 11-point Likert scale from 0 (no pain) to 10 (worst possible pain). B, Weekly mean sleep interference scores as rated on an 11-point Likert scale that described how pain had interfered with the patient's sleep during the past 24 hours, from 0 (did not interfere) to 10 (unable to sleep due to pain). Asterisks indicate $P<.05$; daggers, $P<.01$.

Table 2.—Summary of Analysis of Baseline and Last Observation or End Point for Efficacy Variables*

	Gabapentin			Placebo			Gabapentin vs Placebo		
Parameters	No.	Baseline Mean	End Point Mean	No.	Baseline Mean	End Point Mean	Difference at End Point	*P* Value	95% CI
Mean pain score	82	6.4	3.9	80	6.5	5.1	−1.2	<.001	−1.9 to −0.6
Mean sleep interference score	82	5.2	2.3	80	5.1	3.8	−1.47	<.001	−2.2 to −0.8
Total SF-MPQ	82	20.5	10.9	79	21.0	16.8	−5.9	<.001	−8.8 to −3.1
SF-MPQ VAS	82	67.7	36.9	79	71.2	53.8	−16.9	<.001	−25.3 to −8.4
SF-MPQ PPI	81	2.4	1.2	79	2.4	1.8	−0.6	<.001	−0.9 to −0.3
Short Form–36 QOL Questionnaire†									
Bodily pain	77	40.6	55.2	76	37.5	47.4	7.8	.01	1.8 to 13.8
Mental health	78	72.0	75.7	76	66.5	70.4	5.4	.03	0.5 to 10.3
Vitality	78	41.5	53.5	76	40.8	43.7	9.7	.001	3.9 to 15.5
POMS									
Anger/hostility	76	7.6	5.5	73	10.1	7.7	−2.2	.02	−4.1 to −0.3
Vigor/activity†	77	15.8	16.5	73	14.6	14.6	1.96	.01	0.5 to 3.5
Fatigue/inertia	77	12.8	9.3	73	12.4	11.3	−1.96	.01	−3.4 to −0.5
Total mood	76	33.0	22.8	73	40.0	31.9	−9.14	.03	−17.3 to −1.0

*End point measures apply to patients' mean pain and mean sleep interference scores and were derived from patients' last 7 days of diary entries while taking study drug. CI indicates confidence interval; SF-MPQ, Short-Form McGill Pain Questionnaire; VAS, visual analog scale; PPI, Present Pain Intensity Scale; QOL, Quality of Life; and POMS, Profile of Mood States.
†Increase in score denotes improvement.

tients with type 1 and type 2 diabetes at baseline. Fifty-six gabapentin-treated patients (67%) achieved the 3600 mg/d dosage. Of the 84 patients randomized to gabapentin, 70 (83%) completed the study, 7 (8%) withdrew because of adverse events, 1 (1%) withdrew because of lack of efficacy, and 6 (7%) withdrew for other reasons. Of the 81 patients randomized to placebo, 65 (80%) completed the study, 5 (6%) withdrew because of adverse events, 5 (6%) withdrew because of lack of efficacy, and 6 (7%) withdrew for other reasons. A summary profile of the trial is presented in Figure 1.

Efficacy

Differences between gabapentin and placebo were significant at end point for the mean pain score, mean sleep interference score, and total pain, VAS, and PPI scores of the SF-MPQ (Table 2). When each week's results were analyzed separately, there was a significant difference ($P<.05$) between the gabapentin and placebo groups in mean pain scores from week 2 through week 8. Significant differences ($P<.05$) between patients randomized to the 2 groups were also observed in mean sleep interference scores at week 1 through week 8 (Figure 2). On the SF-MPQ, patients taking gabapentin had significantly lower mean total pain ($P<.01$), mean VAS ($P<.01$), and mean PPI ($P<.05$) scores at weeks 2, 4, and 8 when compared with patients taking placebo (Figure 3). Of the patients who assessed PPI at the termination visit, 12 (15%) of 80 patients taking placebo and 21 (26%) of 82 patients taking gabapentin gave a rating of no pain. As measured by both PGIC and CGIC scales, patients treated with gabapentin had significantly ($P = .001$) greater improvement in pain than patients randomized to placebo (Figure 4). Approximately 60% of patients receiving gabapentin had at least a moderate improvement on the PGIC scale, whereas only 33% of patients receiving placebo had that degree of improvement. Additionally, 2 gabapentin-treated patients reported a score of worse on the PGIC scale, whereas 13 patients receiving placebo reported this score. Three gabapentin-treated patients scored worse on the CGIC scale compared with 10 patients receiving placebo. Gabapentin had a significant effect on 4 items of the POMS (anger/hostility, $P = .02$; vigor/activity, $P = .01$;

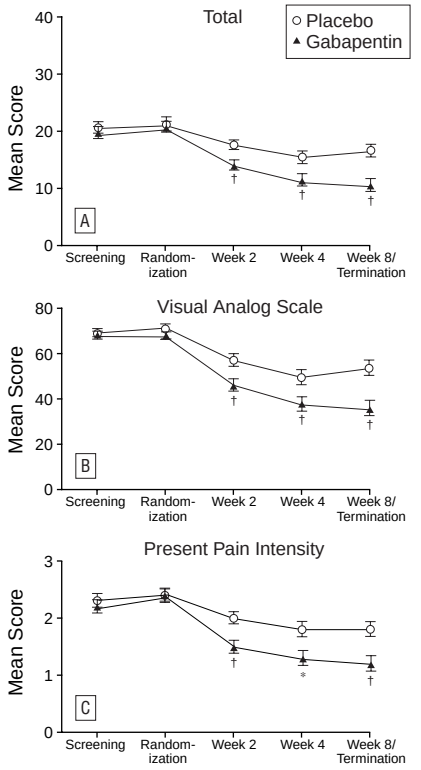

Figure 3.—A, Total score from the Short-Form McGill Pain Questionnaire. Patients assessed pain based on 15 sensory and affective descriptors on a scale of 0 (none) to 3 (severe). Total pain score was the sum of intensity ratings for all 15 descriptors. B, Visual analog scale score from the Short-Form McGill Pain Questionnaire. Patients placed a slash on a 100-mm line from 0 (no pain) to 100 (worst possible pain). C, Present Pain Intensity of the Short-Form McGill Pain Questionnaire. Present pain intensity was indicated using a scale of 0 (no pain), 1 (mild pain), 2 (discomfort), 3 (distressing), 4 (horrible), and 5 (excruciating). Asterisks indicate $P<.05$; daggers, $P<.01$.

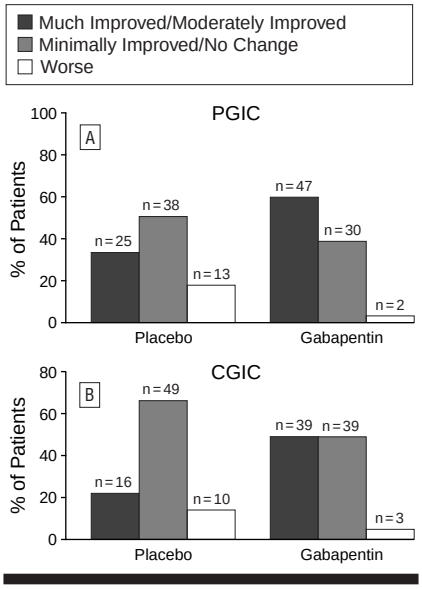

Figure 4.—A, The Patient Global Impression of Change (PGIC) was a 7-point scale on which patients rated any change in their overall status that they had experienced since beginning study medication. B, The Clinical Global Impression of Change (CGIC) was a 7-point scale on which the clinician rated the change observed in the patient's overall status since the beginning of the study. $P = .001$ using the Cochran-Mantel-Haenszel test.

fatigue/inertia, $P = .01$; and total mood disturbance, $P = .03$) compared with placebo. Gabapentin also had a positive effect on quality of life, as seen by significant differences from placebo on the bodily pain ($P = .01$), mental health ($P = .03$), and vitality ($P = .001$) scores of the SF-36 QOL Questionnaire. All other items of the QOL Questionnaire trended in the direction of a positive effect of gabapentin; however, none were significantly different than placebo.

Safety

A total of 7 gabapentin-treated patients (8%) withdrew from the study because of a total of 13 adverse events: dizziness and somnolence (2 patients each), abdominal pain, asthenia, body odor, headache, diarrhea, abnormal thinking, nausea, confusion, and hypesthesia (1 patient each). A total of 5 patients (6%) who received placebo withdrew because of a total of 8 adverse events: dyspepsia, constipation, flatulence (2 patients each), infection, and somnolence (1 patient each). The most frequently reported adverse events are shown in Table 3. Most adverse events in patients treated with gabapentin were of mild or moderate intensity. There were no significant changes in hemoglobin A_{1c} levels from baseline to the end of treatment in either group, indicating that glycemic control was maintained during the study. Neurological examination data revealed no group differences in the rate of disease progression. Specifically, the proportion of patients with a change from normal or decreased at baseline to absent at study termination was similar between groups (<14% in each case) for the 3 sensory modalities tested (temperature, light touch, and pin prick). Additionally, evaluation of reflex changes and changes in gait showed no difference between groups.

Table 3.—Most Frequently Reported Adverse Events*

Preferred Terms	Gabapentin (n = 84)	Placebo (n = 81)	*P* Value†
Dizziness	20 (23.8)	4 (4.9)	<.001
Somnolence	19 (22.6)	5 (6.2)	.004
Headache	9 (10.7)	3 (3.7)	.13
Diarrhea	9 (10.7)	7 (8.6)	.79
Confusion	7 (8.3)	1 (1.2)	.06
Nausea	7 (8.3)	4 (4.9)	.54

*Data are number (percentage).
†Data were calculated using the Fisher exact test.

COMMENT

We have determined the efficacy and safety of gabapentin in reducing pain attributed to peripheral neuropathy in a population of patients with diabetes mellitus by conducting a large, double-blind, placebo-controlled, randomized, parallel-group trial. Gabapentin monotherapy proved effective in decreasing pain associated with diabetic peripheral neuropathy. Several aspects of the study design and conduct are important to consider in interpreting the results. We chose to perform a large, simple clinical trial in which patient diagnosis was made clinically and was not dependent on electrophysiological data. This type of trial is appropriate, especially when the treatment is designed to affect symptoms rather than alter the disease process. The Michigan Neuropathy Screening Instrument, a questionnaire and clinical screening examination, predicted the result of electrophysiological tests in 28 of 29 patients with diabetes,[40] demonstrating that a history and physical examination alone are adequate for the diagnosis of neuropathy in this population. A similar strategy was used in 2 large clinical trials of mexiletine for the symptomatic relief of diabetic peripheral neuropathy.[41,42]

Because the study end point of pain was subjective, we explored the possibility that the occurrence of adverse events resulted in unblinding of the study, biasing the result of our efficacy analysis (Table 2). Dizziness and somnolence, the 2 most frequent adverse events, were also those with the largest difference in incidence between the gabapentin and placebo groups. To assess the effect that patients with these events had on the primary efficacy variable we excluded their data and reanalyzed the efficacy data. After excluding data from patients who reported dizziness, the mean pain score between groups differed by –1.19 ($P = .002$), favoring the gabapentin group (gabapentin [n = 62] mean, 4.02; placebo [n = 75] mean, 5.21). After excluding data from patients who reported somnolence, the mean pain score between groups differed by –0.81 ($P = .03$), also favoring the gabapentin group (gabapentin [n = 63] mean, 4.19; placebo [n = 75] mean, 5.21). Thus, inclusion of patients who experienced these central nervous system adverse effects in the original analysis did not account for the overall efficacy seen in the trial.

Recent systematic reviews discuss treatment regimens that intended to modify the incidence of neuropathy in a cohort of patients with diabetes, alter the course of an established neuropathy, or reduce symptoms alone.[15-18] These reviews support the effectiveness of long-term glycemic control in a reduction of the incidence of neuropathy in patients with diabetes, the potential use of aldose

reductase inhibitors to slow the progression of neuropathy, and the effectiveness of TCAs to reduce pain. A systematic review of the results of controlled clinical trials for the reduction of pain in peripheral neuropathy due to any cause revealed "clear evidence" for the effectiveness of TCAs; "consistent support" for intravenous and topical lidocaine, carbamazepine, and topical aspirin; and "contradictory" trial data for the effectiveness of mexiletine, phenytoin, topical capsaicin, oral nonsteroidal anti-inflammatory medications, and opiates. Intravenous morphine was considered "probably effective." Codeine, propranolol, lorazepam, and phentolamine were considered "ineffective."[20]

The magnitude of effect on pain observed with gabapentin treatment is similar to that reported in trials of TCAs,[37] and the onset of action is more rapid. By the first week (900 mg/d), an improvement was observed in the mean sleep interference scores (Figure 2) and by the second week (1800 mg/d), improvements were seen for all pain rating scales (Figure 2 and Figure 3). Gabapentin's positive effect on quality of life measures (Table 2) suggests that this effect is clinically significant.

Dose-limiting adverse effects remain a problem for patients with neuropathic pain. The effectiveness of TCA therapy is often limited by intolerable adverse effects (sedation, urinary retention, orthostatic hypotension, cardiac arrhythmias) or a delayed onset of action.[21]

In this study, gabapentin appeared to be well tolerated, with 56 (67%) of the 84 patients achieving the forced maximum dosage of 3600 mg/d. The frequency of dizziness and somnolence may be attributed in part to the high dosage chosen for study. Since efficacy was achieved before completion of the titration phase of the study (Figure 2 and Figure 3), dose titration while observing the therapeutic response might reduce the incidence of dizziness and somnolence we observed.

Gabapentin monotherapy produced rapid onset of clinically meaningful pain relief with relatively minor and potentially avoidable adverse effects in this trial. Gabapentin is a promising new agent for use in patients with neuropathic pain when therapeutic options are limited and offers advantages over currently available treatments as a first-line agent.

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