# Efficacy of Gabapentin in Migraine Prophylaxis

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**Objective.—To compare gabapentin with placebo for use as a prophylactic agent in patients with migraine (with or without aura).**

**Study Design and Treatment.—After screening, a 4-week, single-blind, placebo baseline period was followed by a 12-week, double-blind, treatment period. The 12-week treatment period consisted of a 4-week titration phase and an 8-week stable-dosing phase. During the 4-week titration phase, patients were started on one 300-mg capsule of gabapentin or matching placebo. Patients were titrated weekly from 900 mg/day (end of week 1) to 2400 mg/day (end of week 4) and had to be receiving a stable dose of study medication by the end of the titration period. Study medication was to be given on a three-times-a-day dosing regimen.**

**Methods.—The study hypothesis was defined a priori as a lower 4-week migraine rate during the second stabilization period for the gabapentin-treated patients as compared with the placebo-treated patients. The analyses were performed with the 4-week migraine rate at baseline as a covariate and center as a blocking factor.**

**Results.—At seven participating centers, 143 patients with migraine were randomized in a 2:1 ratio and received either gabapentin (n = 98) or matching placebo (n = 45). Thirty-three patients (24.1%) discontinued prematurely from the study, including 24 (24.5%) of 98 gabapentin-treated patients and 9 (20.0%) of 45 placebo-treated patients; the majority of patients discontinued due to adverse events (16 [16.3%] of 98 gabapentin-treated patients; 4 [8.9%] of 45 placebo-treated patients). Patients included in the analysis were evenly balanced for age, sex, race, weight, and height. The majority of these patients were white (80 [92.0%] of 87) and women (72 [82.8%] of 87), with a mean age of approximately 39.4 years and a history of migraine episodes for a mean of about 21 years. At the end of the 12-week treatment phase, the median 4-week migraine rate was 2.7 for the gabapentin-treated patients maintained on a stable dose of 2400 mg/day and 3.5 for the placebo-treated patients ($P = .006$), compared with 4.2 and 4.1, respectively, during the baseline period. Additionally, 26 (46.4%) of 56 patients receiving a stable dose of 2400 mg/day gabapentin and 5 (16.1%) of 31 patients receiving placebo showed at least a 50% reduction in the 4-week migraine rate ($P = .008$). The average number of days per 4 weeks with migraine was also statistically significant and favored gabapentin ($P = .006$) during stabilization period 2. The median change in 4-week headache rate was statistically significant as well ($P = .013$). The most frequently reported adverse events for both treatment groups were asthenia, dizziness, somnolence, and infection. Adverse events determined by the investigator to be associated with study drug resulted in patient withdrawal in 13 (13.3%) of 98 gabapentin-treated patients and 3 (6.7%) of 45 placebo-treated patients. Somnolence and dizziness accounted for many of the premature withdrawals among those taking gabapentin.**

**Conclusion.—Gabapentin is an effective prophylactic agent for patients with migraine. In addition, gabapentin appears generally well tolerated with mild to moderate somnolence and dizziness.**

**Key words: gabapentin, migraine, prophylaxis**

**Abbreviations: SP2 stabilization period 2, MITT modified intent-to-treat**

(*Headache* 2001;41:119-128)

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**Accepted for publication October 2, 2000.**

Goals of prophylactic migraine therapy are to reduce the frequency and severity of migraine attacks, to make acute migraine attacks more responsive to abortive therapy, and to improve the quality of life for patients. Although many classes of drugs are used, prophylactic pharmacotherapy of migraine is less than satisfactory, because of poor efficacy, associated unacceptable side effects, tachyphylaxis, and drug interactions. An extensive meta-analysis of all randomized, double-blind, placebo-controlled trials of prophylactic migraine medications by Ramadan et al[1] concluded that the majority of such trials lacked scientific rigor. This meta-analysis found that none of the drugs had therapeutic gains (defined as percentage of patients responding to active agents minus percentage of patients responding to placebo) of more than 50%. Even given this modest efficacy, preventive treatment of migraine is considered worthwhile, particularly for patients who have frequent and debilitating attacks.

Gabapentin was introduced as an anticonvulsant in the United States in 1994. Gabapentin has an antinociceptive (analgesic) effect as well as an anticonvulsant effect. In recent years, gabapentin has been used in the treatment of neuropathic pain conditions including diabetic neuropathy, postherpetic neuralgia, and trigeminal neuralgia. Although the mechanism of action of gabapentin is not fully understood, it has been shown to interact with the $\alpha 2\delta$ subunit of $Ca^{2+}$ channels (modulating calcium ion channel current)[2] and to increase the concentration and probably the rate of synthesis of $\gamma$-aminobutyric acid (GABA) in the brain.[3] In addition, the antinociceptive effect of gabapentin may be due to its ability to bind to gabapentin-binding protein, a novel membrane-associated protein in the outer layers of cerebral cortex inhibiting monoamine neurotransmitter release including noradrenaline, dopamine, serotonin, and total cellular calcium content. In addition, gabapentin may be operating at the spinal cord level by altering *N*-methyl-D-aspartate responses.[4]

In 1996, Mathew and Lucker reported results of an open-label study that demonstrated reduced severity and frequency of headaches in patients with migraine (with and without aura) after treatment with gabapentin at 900 to 1800 mg/day.[5] This study provided the basis for further evaluation of gabapentin in migraine prophylaxis. The results of a double-blind, placebo-controlled study are reported here.

## METHODS

This double-blind, randomized, placebo-controlled, multicenter study in patients with migraine (with or without aura) was conducted to determine the efficacy and safety of gabapentin in migraine prophylaxis.

**Study Population.—**Patients were men or nonpregnant, nonlactating women practicing a reliable method of contraception (if sexually active and of childbearing age) between the ages of 16 and 75 years with a history of migraine headaches for at least 6 months, as defined by the International Headache Society.[6] Patients were to have had three to eight migraine headaches episodes per month for each of the 3 months prior to screening, and either had not received past migraine prophylaxis or had failed an adequate trial of no more than two prophylactic antimigraine regimens. Patients who had received prior migraine prophylaxis discontinued treatment for a period of at least five half-lives of the medication before entering the study. All patients who discontinued their prior prophylactic medication did so at least 3 weeks prior to entering the single-blind placebo period.

Patients were excluded from the study if they had migraine aura not associated with headache. Patients were also excluded if they had chronic daily or tension-type headaches occurring more than 10 days per month or if they had cluster headaches. Other exclusion criteria included significant central nervous system (CNS) disease such as CNS neoplasm, CNS infection, demyelinating disease, degenerative neurologic disease, or progressive CNS disease. Also excluded were patients with serious psychological or medical conditions including significant hematologic disease, or severe liver or kidney insufficiency as determined by transaminase enzymes (aspartate aminotransferase or alanine aminotransferase, blood urea nitrogen, or creatinine more than twice the upper limit of normal).

Patients were to be excluded if they required medication that might have confounded study results, including warfarin, $\beta$-adrenergic–blocking agents, monoamine oxidase (MAO) inhibitors, tricyclic antide-

pressants, methysergide, valproate, calcium-channel antagonists, lithium salts, phenobarbital, phenytoin, or carbamazepine. In addition, patients did not use ergotamine preparations for more than 2 days a week, or nonsteroidal anti-inflammatory drugs, analgesics, benzodiazepines, cyproheptadine, baclofen, or selective serotonin receptor inhibitors more than 3 days a week. Patients did not receive experimental drugs in the past 30 days and had not abused illicit drugs or alcohol in the past year. Previous or current treatment with gabapentin or a history of hypersensitivity to gabapentin were also reasons for exclusion.

All patients were capable of compliance, and of understanding and following instructions, completing diaries, and giving informed consent.

**Study Design and Study Drug.—**Written informed consent, which was approved by the Institutional Review Boards of all participating centers, was obtained from all patients enrolled in this study. After screening, there was a 4-week, single-blind, placebo baseline period followed by a 12-week, double-blind, treatment period. The 12-week treatment period consisted of a 4-week titration phase and an 8-week stable-dosing phase (Figure 1).

In evaluating several placebo-controlled studies in migraine prophylaxis, Couch found that, overall, 27.7% of patients receiving placebo experienced at least a 50% decrease in migraine headache index over the study period.[7] He concluded that a 27% to 30% placebo effect should be expected in any drug trial for the treatment of migraine prophylaxis.[7] Because of this high placebo response, a single-blind placebo phase was included in the study in an attempt to diminish the placebo response rate.

During the single-blind phase, patients received one placebo capsule, taken in the evening for 4 weeks. At the end of this phase, patients who continued to meet inclusion and exclusion criteria were randomized to double-blind study medication. During the 4-week titration phase, patients were started on one 300-mg capsule of gabapentin or matching placebo. Patients were titrated to three capsules per day (end of week 1), five capsules per day (end of week 2), seven capsules per day (end of week 3), and eight capsules per day (end of week 4) in order to achieve the 2400 mg/day dose by the completion of the titration phase. For gabapentin-treated patients, this corresponded to a dose of 900 mg/day at the end of week 1, 1500 mg/day at the end of week 2, 2100 mg/day at the end of week 3, and 2400 mg/day at the end of week 4. If a patient was unable to tolerate the 2400 mg/day dose, the dose was reduced to 1800 mg/day.

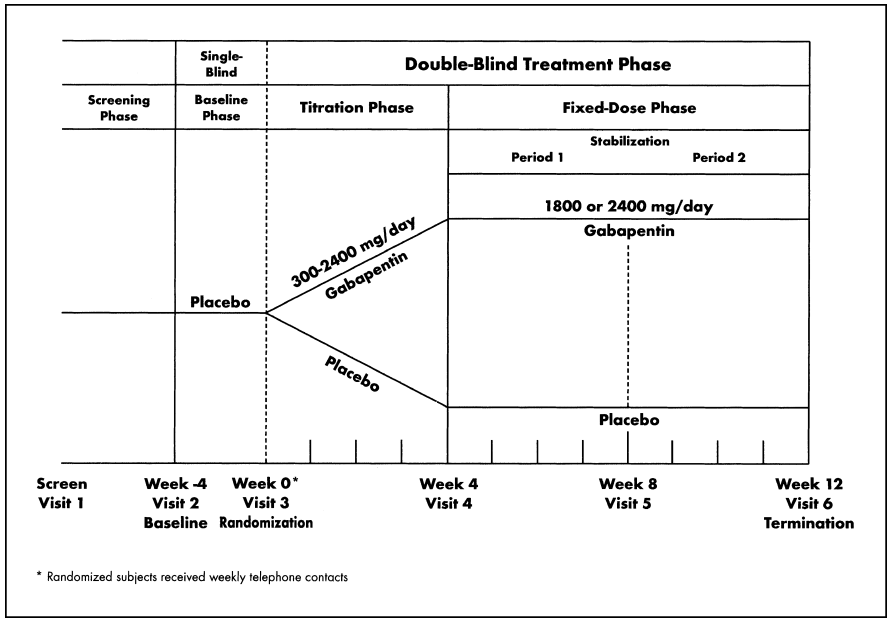


**Fig 1.—Study design.**

However, the patient had to be receiving a stable dose of study medication by the end of the titration period. Study medication was to be given on a three-times-a-day dosing regimen.

Each investigator was provided with "blinded" medication, according to a computer-generated randomization schedule prepared by Parke-Davis before the beginning of the trial. Patients were randomized in a 2:1 ratio using a block size of six stratified by center. During the double-blind phase, investigators, patients, study monitors, and observers were blinded to codes until after the clinical database was locked.

**Efficacy Measurements.—**In diaries, patients recorded time of onset and end of each migraine, aura symptoms, peak intensity of migraine pain, functional ability at peak migraine intensity, medication taken for relief of acute migraine attack, associated headache symptoms, rating of migraine relief, precipitative events, side effects, and study medication received. Patients were instructed to complete their diaries at the same time each day, preferably in the evening.

The primary outcome measure was the 4-week migraine rate during stabilization period 2 ([SP2] the last 4 weeks of the stable-dosing period) for patients who had received a stable dose of 2400 mg/day. This time frame was chosen because, historically, medication given for migraine prophylaxis may require several months of use in order for meaningful efficacy to be demonstrated.[8] The 4-week migraine headache rate was based upon diary information and calculated as:

$$\frac{\text{Migraine Headache Count During SP2}}{\text{No. of SP2 days} - \text{No. of Days in Unreliable Intervals}} \times 28$$

The migraine headache count was based on the requirement that more than 24 hours elapse between the end of the one headache and the beginning of the next. The unreliable intervals were defined as those for which the patient did not return a diary or for which incomplete information was available in the diary to determine if a migraine headache had occurred.

Secondary outcome measures assessed for SP2 included a responder analysis, defined as the proportion of patients receiving a stable dose of 2400 mg/day gabapentin with at least a 50% reduction in the 4-week migraine headache rate from baseline to SP2. This responder rate was calculated using the following formula:

$$\frac{\text{Migraine Headache Rate for SP2} - \text{Migraine Rate for Baseline}}{\text{Migraine Rate for Baseline}} \times 100,$$

where baseline refers to the 4-week, single-blind, placebo baseline period. Other secondary outcome measures were: average severity at peak intensity, average functional ability at the time of peak intensity, average duration of migraine headache, average number of days per 4 weeks with migraine headache, and aura severity.

A sample of 75 gabapentin-treated patients and 37 placebo-treated patients was estimated to be adequate to detect a difference of 2.0 in 28-day headache rate between treatment groups with a standard deviation of 3.5. This assumed a type I error level of 5% and a power of 80%. Because it was also assumed that 80% of patients would be evaluable, 140 patients were to be randomized to achieve the desired goal.

**Safety Measurements.—**Medical histories, including migraine headache histories, were obtained at screening, and physical and neurologic examinations were performed at screening and the final visit (week 12). At screening and at the end of the study, hematology and chemistry evaluations were done. In addition, a serum pregnancy test was performed at screening, and a urine pregnancy test was done at the time of randomization, if applicable. Adverse events were recorded throughout the study.

**Statistical Analysis.—**Analyses of demographic, baseline patient characteristics, and efficacy data were performed for a modified intent-to-treat (MITT) population. This population included any patient who was randomized, took at least one dose of study medication during SP2, maintained a stable dose of 2400 mg/day during SP2, had baseline migraine headache data, and at least 1 day of migraine headache evaluations during SP2.

Demographic and baseline patient characteristics were compared between the two treatments using two-sample $t$ tests for the continuous data and $\chi^2$ tests for categorical data. Ranked transformations were applied to the migraine headache rate data, as these data were not normally distributed. For this reason,

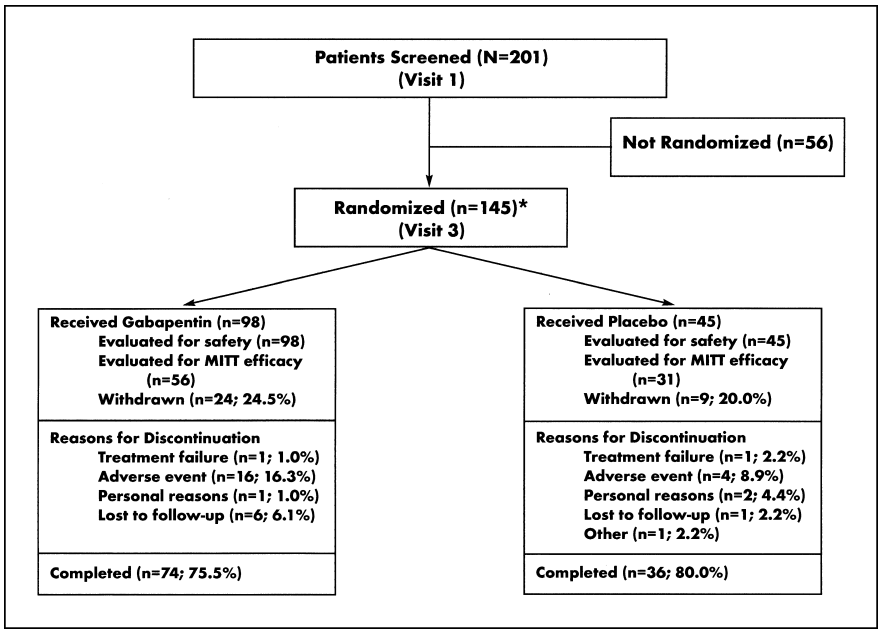


**Fig 2.—Disposition of patients. *Two patients, one from each treatment group, were randomized but did not receive study drug. The percentages included in this figure are based on those who received study drug. MITT indicates modified intent-to-treat.**

median scores are presented. Baseline treatment comparisons were made using a two-way (treatment, center) analysis of variance. A two-way analysis of covariance with baseline data as the covariate was applied to the SP2 data. Results from the full model for tests for treatment-by-center and treatment-by-baseline interaction terms were examined (and not statistically significant) prior to applying the reduced model that did not include the interaction terms.

Responder rates were compared between treatments using Cochran-Mantel-Haenszel test with center as a blocking factor. Inferential analysis for the other secondary parameters was conducted in a manner similar to that used for the primary analysis.

All hypothesis tests were two-tailed with an alpha of 0.05 for the treatment group comparisons and an alpha of 0.10 for interaction terms. SAS version 6.11 (SAS Institute Inc., Cary, NC) was used for all

**Table 1.—Demographic Characteristics for Modified Intent-to-Treat Patients**

| Characteristic | Gabapentin (n = 56) | Placebo (n = 31) | *P* | Overall (N = 87) |
|---|---|---|---|---|
| Sex, No. (%) | | | | |
| Men | 10 (17.9) | 5 (16.1) | .838 | 15 (17.2) |
| Women | 46 (82.1) | 26 (83.9) | | 72 (82.8) |
| Age, mean (SD), y | 39.6 (10.9) | 39.7 (11.8) | .961 | 39.6 (11.2) |
| Race, No. (%) | | | | |
| White, non-Hispanic | 52 (92.9) | 28 (90.3) | .677* | 80 (92.0) |
| Black, non-Hispanic | 1 (1.8) | 0 (0.0) | | 1 (1.1) |
| Hispanic (white or black) | 2 (3.6) | 3 (9.7) | | 5 (5.7) |
| Other | 1 (1.8) | 0 (0.0) | | 1 (1.1) |
| Weight, mean (SD), lb | 158.0 (41.9) | 156.8 (31.8) | .895 | 157.6 (38.4) |
| Height, mean (SD), in | 65.8 (3.7) | 65.8 (2.7) | .982 | 65.8 (3.4) |

**P* value is based on comparison of whites versus nonwhites.

**Table 2.—Baseline Disease Characteristics for the Modified Intent-to-Treat Population With Migraine**

| Characteristic | Gabapentin (n = 56) | Placebo (n = 31) | *P* | Overall (N = 87) |
|---|---|---|---|---|
| Age at onset of headache, mean (SD), y | 19.1 (10.0) | 18.1 (9.6) | .653 | 18.8 (9.8) |
| History of migraine, mean (SD), y | 20.4 | 21.5 | .705 | 20.8 |
| Family history of migraine headache, No. (%) | | | | |
| No | 12 (21.4) | 10 (32.3) | | 22 (25.3) |
| Yes | 40 (71.4) | 20 (64.5) | .450 | 60 (69.0) |
| Uncertain | 4 (7.1) | 1 (3.2) | | 5 (5.7) |
| Migraine headache frequency during last 6 months, mean (SD), per mo | 5.2 (1.6) | 4.4 (1.6) | .045 | 4.9 (1.7) |
| Migraine headache frequency during last 3 months, mean (SD), per mo | 5.3 (1.7) | 4.6 (1.7) | .086 | 5.1 (1.7) |
| Change in migraine headache frequency over last 6 months, No. (%) | | | | |
| Increasing | 10 (17.9) | 7 (22.6) | .512 | 17 (19.5) |
| Decreasing | 2 (3.6) | 0 (0.0) | | 2 (2.3) |
| Unchanged | 44 (78.6) | 24 (77.4) | | 68 (78.2) |
| Average duration of treated migraine headache when severe, h | | | | |
| No. | 53 | 30 | | 83 |
| Mean (SD) | 26.0 (24.8) | 28.6 (25.6) | .657 | 26.9 (25.0) |
| Aura associated, No. (%) | | | | |
| No | 32 (57.1) | 17 (54.8) | .836 | 49 (56.3) |
| Yes | 24 (42.9) | 14 (45.2) | | 38 (43.7) |
| Average peak severity of migraine headaches over last 6 months, No. (%) | | | | |
| Mild | 0 (0.0) | 0 (0.0) | .530 | 0 (0.0) |
| Moderate | 20 (35.7) | 8 (25.8) | | 28 (32.2) |
| Severe | 29 (51.8) | 17 (54.8) | | 46 (52.9) |
| Disabling | 7 (12.5) | 6 (19.4) | | 13 (14.9) |
| Average duration of untreated migraine headache, h | | | | |
| No. | 52 | 30 | | 82 |
| Mean (SD) | 41.3 (22.3) | 49.9 (25.8) | .113 | 44.4 (23.9) |
| Average duration of treated migraine headache when treatment is immediate, h | | | | |
| No. | 54 | 31 | | 85 |
| Mean (SD) | 13.4 (17.8) | 17.0 (22.5) | .423 | 14.7 (19.6) |
| Migraine headache-triggering factors* | | | | |
| Alcohol | 30 (53.6) | 14 (45.2) | NA | 44 (50.6) |
| Certain foods | 28 (50.0) | 5 (61.1) | NA | 33 (37.9) |
| Certain drugs | 3 (5.4) | 2 (6.5) | NA | 5 (5.7) |
| Fatigue | 22 (39.3) | 7 (22.6) | NA | 29 (33.3) |
| Stress | 43 (76.8) | 15 (48.4) | NA | 58 (66.7) |
| Loss of sleep | 24 (42.9) | 8 (25.8) | NA | 32 (36.8) |
| Menses | 26 (46.4) | 13 (41.9) | NA | 39 (44.8) |
| Noise | 9 (16.1) | 3 (9.7) | NA | 12 (13.8) |
| Other | 41 (73.2) | 21 (67.7) | NA | 62 (71.3) |

*Migraine headache triggering factors were not mutually exclusive. Patients could have more than one triggering factor. NA indicates not applicable.

analyses. Centers contributing less than two patients to each treatment group were pooled for analysis, provided that the size of the combined group was not greater than the median size of the remaining centers.

## RESULTS

**Patient Disposition.—**One hundred forty-five patients with migraine (with or without aura) were randomized in a 2:1 ratio to receive gabapentin (n = 99)

**Table 3.—Modified Intent-to-Treat Analysis: 4-Week Migraine Headache Rate for Stabilization Period 2**

| Time Point | Gabapentin (n = 56) | Placebo (n = 31) | *P* |
|---|---|---|---|
| Baseline median (min, max) | 4.2 (1.9, 10.0) | 4.1 (2.2, 11.0) | NS |
| SP2 median (min, max) | 2.7 (0.0, 12.0) | 3.5 (1.0, 11.0) | .006 |
| Median change (min, max) from baseline to SP2* | −2.0 (−7.9, 3.0) | −0.8 (−4.0, 2.6) | .013 |

*Median change from baseline would not be equal to median stabilization period 2 (SP2) minus median baseline. NS indicates not significant.

or matching placebo (n = 46) at the seven participating centers. One hundred forty-three patients actually received study drug (gabapentin, n = 98 patients; placebo, n = 45). The disposition of these patients is presented in Figure 2. Thirty-three patients (24.1%) discontinued prematurely from the study, including 24 (24.5%) of 98 gabapentin-treated patients and 9 (20.0%) of 45 placebo-treated patients; the majority of patients discontinued for adverse events (16 [16.3%] of 98 gabapentin-treated patients; 4 [8.9%] of 45 placebo-treated patients). Two patients terminated for treatment failure, and 11 patients terminated for administrative or personal reasons.

**Patient Characteristics.—**The demographic characteristics for the MITT population (Table 1) were evenly balanced for age, sex, race, weight, and height. The majority of patients were white (80 [92.0%] of 87) and women (72 [82.8%] of 87), with a mean age of approximately 39.4 years. Baseline disease characteristics for the MITT population were also evenly balanced between treatment groups (Table 2), except for migraine headache frequency during the 6 months prior to study enrollment (5.2 per month for gabapentin-treated patients and 4.4 per month for placebo-treated patients, $P = .045$). However, there was no indication that the gabapentin-treated group was improving before the baseline placebo-controlled period. Patients had a history of migraine for a mean of approximately 21 years prior to entry into the study.

Because an MITT analysis was performed, protocol deviators (those who failed to meet the minimum or maximum baseline 4-week migraine headache rate, those with poor study drug compliance, and those with unacceptable concomitant medication) were still evaluated and were included in the statistical analyses.

**Study Drug Administration.—**The majority of patients who reached stable dosing were prescribed the recommended dose of 2400 mg/day or its equivalent number of placebo capsules (56 [67%] of 84 gabapentin-treated patients; 33 [84.6%] of 39 placebo-treated patients). Most of the remaining patients were prescribed 1800 mg/day or its equivalent number of placebo capsules (15 [17.9%] of 84 gabapentin-treated patients; 5 [12.8%] of 39 placebo-treated patients). Of the patients who received study medication during SP2, 56 (72.7%) of 77 gabapentin-treated patients and 31 (86.1%) of 36 placebo-treated patients were maintained at a stable dose of 2400 mg/day or the equivalent number of placebo capsules.

**Treatment Efficacy.—***Primary Efficacy Variable.*—The migraine headache rate during the second 4 weeks of the SP2 for patients maintaining a stable dose of 2400 mg/day gabapentin is presented in Table 3 for the placebo- and gabapentin-treatment groups. There was a statistically significant difference ($P = .006$) between treatment groups at the end of the SP2 for the primary efficacy parameter.

*Secondary Efficacy Variables.*—Twenty-six (46.4%) of 56 patients receiving a stable dose of 2400 mg/day gabapentin had at least a 50% reduction in the 4-week migraine headache rate, whereas only 5 (16.1%) of 31 patients receiving placebo had this degree of improvement ($P = .008$) (Figure 3).

Results for the average number of days per 4 weeks with migraine headache were statistically significant and favored gabapentin ($P = .006$) during the SP2 (gabapentin, 3.4 days; placebo, 5.0 days). Other secondary outcome measures related to migraine headaches included average severity at peak intensity, average functional ability at time of peak intensity, average duration of migraine headache, and aura

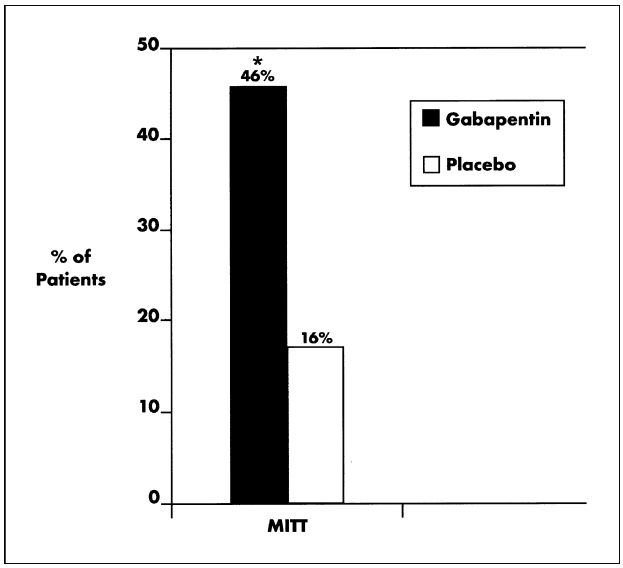


**Fig 3.—Percentage of patients achieving at least a 50% reduction in 4-week migraine headache rate. *$P<.01$. MITT indicates modified intent-to-treat.**

severity. No statistically significant differences between treatment groups were detected at baseline or at the end of the SP2 for any of these parameters.

*Safety Analysis.*—Adverse events regardless of causality were reported by 81 (82.7%) of 98 patients receiving gabapentin and 35 (77.8%) of 45 patients receiving placebo. The majority of these events were mild to moderate in severity for both treatment groups. Adverse events occurring in more than 10% of the gabapentin-treated patients are presented in Table 4.

The most frequently reported events for both treatment groups regardless of study drug relationship were dizziness, somnolence, asthenia, and infection. Asthenia and, to a greater degree, infection occurred at a higher incidence among placebo-treated patients, while dizziness and somnolence were noted more often among gabapentin-treated patients. It is noteworthy that weight gain, an undesirable effect for many young women, was not commonly reported (3 of 98 [3.1%] gabapentin-treated patients; 1 of 45 [2.2%] placebo-treated patients). Moreover, hair loss and menstrual irregularities were not reported by any patient.

Adverse events designated as probably, possibly, or definitely related to study drug were reported by 66 of 98 (67.3%) patients receiving gabapentin and 22 of 45 (48.9%) patients receiving placebo. Somnolence, dizziness, and asthenia also were the most frequently reported events (Table 5). Findings of somnolence, dizziness, and asthenia in gabapentin-treated patients are consistent with the known side effect profile of the drug, and may have resulted from the rapid dose escalation employed in this study.

Adverse events considered to be associated with drug treatment resulted in patient withdrawal in 13 of 98 (13.3%) gabapentin-treated patients and 3 of 45 (6.7%) placebo-treated patients. Among gabapentin-treated patients, asthenia, dizziness, and somnolence were the only adverse events that resulted in study withdrawal in more than one patient.

One patient had a serious adverse reaction during the double-blind period of the study. This event occurred in a 42-year-old white man who had been randomized to receive gabapentin. The patient had been receiving study drug for approximately 8 weeks when symptoms of dizziness, lightheadedness, unsteady gait, headache, tongue swelling, dysphasia, and a sharp pain to the right side of the neck developed. The patient

**Table 4.—Incidence of Overall Adverse Events Occurring in More Than 10% of Gabapentin-Treated Patients***

| Adverse Event | Gabapentin (n = 98) | Placebo (n = 45) | *P* |
|---|---|---|---|
| Dizziness | 25 (25.5) | 5 (11.1) | .075 |
| Somnolence | 24 (24.5) | 5 (11.1) | .075 |
| Asthenia | 22 (22.4) | 12 (26.7) | .673 |
| Infection | 11 (11.2) | 11 (24.4) | .049 |

*Values are number (percentage).

**Table 5.—Incidence of Associated Adverse Events Occurring in More Than 10% of Gabapentin-Treated Patients***

| Adverse Event | Gabapentin (n = 98) | Placebo (n = 45) | *P* |
|---|---|---|---|
| Somnolence | 24 (24.5) | 4 (8.9) | .040 |
| Dizziness | 22 (22.4) | 5 (11.1) | .166 |
| Asthenia | 19 (19.4) | 9 (20.0) | 1.000 |

*Values are number (percentage).

was hospitalized but discharged the following day. It was considered unlikely that the event was related to study drug; symptoms continued to abate despite reinstitution of study drug.

## COMMENTS

This controlled clinical trial demonstrated that gabapentin was effective as a prophylactic agent in reducing the frequency of headaches in patients with migraine. For the MITT population, the median 4-week migraine rate was significantly lower for those treated with a stable dose of 2400 mg/day of gabapentin compared with those treated with placebo. Moreover, the responder rate was significantly higher in the 2400 mg/day gabapentin group than in the placebo group (26 [46.4%] of 56 gabapentin-treated patients; 5 [16.1%] of 31 placebo-treated patients). The study drug was well tolerated with only minor adverse effects reported—primarily somnolence and dizziness. Eight (8.2%) of 98 patients prematurely withdrew from the study due to somnolence and dizziness in the gabapentin-treated group, whereas only 1 of 45 patients (2.2%) withdrew prematurely for somnolence in the placebo-treated group. All patients who withdrew were women.

The mechanism of action of gabapentin and its relationship to the pathophysiology of migraine remains uncertain. Although the initial event in migraine headache is not clear, prominent neurologic symptoms localizable to the cerebral cortex can be demonstrated. The slowly spreading nature of the clinical symptoms and transient reduction in blood flow observed during the migraine aura have been linked to an evolving cortical neuronal hypofunction often referred to as the "spreading depression of Leão."[9] During this process, there are marked ionic changes and a loss of membrane resistance. There is evidence that the latter is due to excitatory neurotransmitters such as glutamate.[10] Release of glutamate may be essential in the propagation of spreading cortical depression. Neuroexcitatory plasma amino acids, in particular glutamate and aspartate, have been found to be significantly higher in patients with migraine compared with normal controls and patients with tension headaches.[11]

The effect of gabapentin to increase GABA concentrations in the brain may provide a possible explanation for its mechanism of action in migraine prophylaxis. Increases in GABA may suppress the abnormal cortical activities that underlie migraine aura and reduce central neuronal hyperexcitability. In addition, the membrane-stabilizing effects of gabapentin at voltage-sensitive $Ca^{2+}$ channels may work to modulate intracellular $Ca^{2+}$ influx, thereby stabilizing the neuronal activity.

In this double-blind, randomized, placebo-controlled study, gabapentin-treated patients exhibited a significant improvement in the 4-week migraine headache rate while experiencing few side effects. Moreover, relatively few patients discontinued prematurely from the study due to associated adverse events (13 [13.3%] of 98 gabapentin-treated patients; 3 [6.7%] of 45 placebo-treated patients).

Projected estimates indicate that there are 18 million women and 5.6 million men suffering from severe migraine, with 3.4 million women and 1.1 million men experiencing one or more attacks per month.[12] From such estimates, it can be inferred that the public health toll and societal costs of this disease are significant. Therefore, prophylactic treatment in the appropriate setting is needed. However, the potential for toxicity is also an important factor in selecting a suitable therapy for migraine prophylaxis. Many of the drugs used for migraine prophylaxis are associated with significant adverse side effects. Given the efficacy of gabapentin in migraine prophylaxis and its good tolerability profile, it should be considered an important addition in the management of patients who are candidates for migraine prophylaxis.

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