Topiramate 100 mg/day in migraine prevention: a pooled analysis of double-blind randomised controlled trials

G. BUSSONE,1 H.-C. DIENER,2 J. PFEIL,3 S. SCHWALEN4
Neurological Institute "C.Besta", Milan, Italy,1 Department of Neurology, University of Essen, Essen, Germany,2 Estimate Medical Statistics BV, Doesburg, The Netherlands,3 Department of Medical Affairs, Janssen-Cilag EMEA, Beerse, Belgium4

SUMMARY
Topiramate has been shown to be effective as a preventive treatment for migraine in three large placebo-controlled, dose-ranging trials. Because the protocols were similar in design using the same primary and secondary endpoints, data from these studies were pooled to evaluate the consistency of efficacy, efficacy by gender and tolerability of topiramate 100 mg/day \((n = 386)\) versus placebo \((n = 372)\). Topiramate was superior to placebo as measured by the reduction in mean monthly migraine frequency, monthly migraine days and monthly migraine duration. The responder rates, defined as at least 50% reduction for the respective parameters, were significantly in favour of topiramate \((p < 0.001)\), for example 46.3% of patients on topiramate achieved at least 50% reduction in monthly migraine period frequency compared with 22.8% on placebo \((p < 0.001)\). Use of medication to treat the acute migraine attack was significantly reduced by topiramate compared with placebo \((p < 0.001)\). The therapeutic effect was consistent throughout the different studies and independent of gender. The most common adverse effect was paraesthesia, mostly of mild-to-moderate severity. The findings confirm that, at a dose of 100 mg/day, topiramate is an effective and well-tolerated drug for migraine prevention.

Keywords: Migraine; prevention; prophylaxis; placebo-controlled trial; topiramate; pooled analysis

INTRODUCTION
Migraine is one of the most common neurological disorders, affecting about 6–8% of men, 8–12% of women and 4% of children (1). Migraine attacks significantly affect professional life and social function (2). Patients most appropriate for migraine prevention treatment are those with frequent attacks, severe migraine attacks, abortive treatment failure, contraindications to acute treatment, overuse of acute medication possibly resulting in medication-overuse headache (3,4) or focal neurological symptoms during the migraine attacks (5).

The most widely used preventive migraine treatments are \(\beta\)-blockers, calcium channel blockers, neuromodulators or antiepileptic drugs, tricyclic antidepressants and the serotonin-antagonist pizotifen. Most of these drugs are usually effective in less than half of patients and have limitations due to their tolerability profile (6,7,8). Moreover, many studies of these drugs were limited to small numbers of patients treated for periods no longer than 3 months. The choice of drug is based on efficacy, adverse events and coexistent or co-morbid conditions.

Topiramate has been studied in three large trials for prevention of migraine, recently reviewed and published (8,9,10,11). Topiramate is a neuromodulatory compound that has a unique pharmacological profile, which includes effects on excitatory neurotransmitter receptors and voltage-gated ion channels, actions considered relevant to migraine treatment (8).

The objective of this pooled analysis was to evaluate the efficacy, consistency of effect and tolerability after pooling data sets obtained with 100 mg topiramate in three pivotal trials in migraine prevention, comparing topiramate with placebo. This 100-mg dose is the target dose in the prescribing information for topiramate for preventive treatment of migraine. In clinical trials, lower doses were less effective. Higher doses did not offer better efficacy and resulted in a less favourable tolerability profile. The three individual studies analysed the 50% response rate for the primary efficacy parameter (reduction in mean monthly migraine periods) and included few men. This pooled analysis provides greater precision with respect to the 75 and 100% response rates, as well as the response by gender. This pooled analysis also assessed the responder rates of the secondary efficacy parameters to confirm consistency of the findings.
METHODS

Pooled studies

In the topiramate development programme for migraine, three randomised, double-blind, placebo-controlled, parallel-group, multicenter trials evaluated topiramate as prophylactic treatment in adults with migraine with or without aura [MIGR-001 (9), MIGR-002 (10) and MIGR-003 (11)]. All three trials included a parallel-controlled dose-ranging design with topiramate dosages of 50, 100 and 200 mg/day in two studies (MIGR-001 and MIGR-002) and 100 and 200 mg/day in a third study, which also included a propranolol 160 mg/day active control arm (MIGR-003). The trials followed a classical design in which eligible subjects were assigned to one of four treatment groups in equal ratios. The trials were conducted according to Good Clinical Practice and in line with the Declaration of Helsinki (protocol approval by ethics committee, intensive monitoring and signed informed consent from the patient). In this analysis, all data sets of patients from the three studies, who were randomised to topiramate 100 mg \((n = 391)\) or placebo \((n = 383)\), were pooled for analysis.

Patient Characteristics

To be eligible to enter double-blind treatment, patients had to be 12–65 years of age and to have an established history of migraine with or without aura, as assessed using International Headache Society (IHS) criteria, (12) for at least 6 (MIGR-001 and MIGR-002) or 12 months (MIGR-003) prior to screening. During the prospective baseline period, patients were required to have between 3 and 12 migraines (see analysis for definition of migraine frequency) but no more than 15 headache days (migraine or non-migraine) per month (28 days). A headache day was defined as a calendar day during which the subject experienced headache pain for at least 30 min. Women were required to be postmenopausal, surgically incapable of bearing children or practising adequate methods of birth control.

Exclusion criteria included headaches other than migraine, episodic tension headaches, prior treatment failure with more than two adequate courses of migraine preventive medications, onset of migraine after age 50 years and overuse of analgesics or acute migraine treatments (such as use of more than 8 days/month of ergotamines or triptans, or more than 6 treatments/month with potent opioids). Patients were also excluded if they required continued use of any of the following medications potentially interfering with study outcome, such as β-blockers, tricyclic antidepressants, anticonvulsants, calcium channel blockers, 5-HT2 antagonists (such as pizotifen), monoamine oxidase inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs) on a daily basis, magnesium supplements at high doses (e.g. 600 mg/day), riboflavin at high doses (e.g. 100 mg/day), corticosteroids, local anaesthetics, botulinum toxin or herbal preparations such as feverfew or St. John’s wort. Nonpharmacological prophylactic approaches could be continued throughout the study, provided they were started at least 1 month before enrolment. Other reasons for exclusion included a history of nephrolithiasis, previous treatment with topiramate for more than 2 weeks and participation in a topiramate or other experimental study within 30 days of screening. In MIGR-003, patients with a history of asthma, bradycardia, uncontrolled diabetes or any other limitation to the use of β-blockers were excluded.

Study Design

In each study, eligible subjects entered a washout period of up to 14 days, during which any migraine preventive medications were tapered. This period was followed by a prospective baseline phase of 28 days, during which patients recorded their headaches and medications and were permitted to take rescue medication to treat acute migraine attacks or headaches as needed. Those meeting all entry criteria were randomised to one of the treatment groups in the core double-blind phase, which consisted of two periods: titration (8 weeks) and maintenance (18 weeks); clinic visits were scheduled every 4 weeks \((28 ± 3\) days). The treatment groups were 50 mg/day topiramate in the MIGR-001 and MIGR-002 trials, 100 mg/day topiramate, 200 mg/day topiramate, and placebo in all 3 trials and propranolol 160 mg/day in MIGR-003. Patients assigned to topiramate started at a dose of 25 mg/day; the daily dose was increased by 25 mg weekly until patients reached either their assigned dose or maximum tolerated dose, whichever was lower. The maintenance dose was continued for 18 weeks. Study drug was administered daily in equally divided twice daily doses. At the end of treatment, the study medication was tapered during an exit phase lasting up to 7 weeks. In the event of tolerability problems, subjects could reduce study medication by a maximum of two dose levels during the entire 26-week treatment phase. Also, during the double-blind study, patients were also permitted to take medication to treat acute migraine attacks or headaches as needed (aspirin, paracetamol, NSAIDs, ergot derivatives, triptans and opioids).

DATA COLLECTION AND ANALYSIS

Patients recorded in a diary the frequency, severity and symptoms of all headaches or auras, as well as the times at which the symptoms started and stopped. Patient diary information was reviewed on days 1, 29, 57, 85, 113, 141 and 183 of the study. Across all treatment groups, headaches were classified using the subjects’ own judgement. Patients also recorded the type and amount of rescue medication used. Adverse events were collected by interviewing subjects in a nondirected
manner at each visit and followed until resolved or until a clinically stable endpoint was achieved.

Monthly migraine frequency was assessed threefold: 1) number of migraine periods, 2) number of migraine attacks and 3) number of migraine days. The primary efficacy measure was the comparison of the reduction in mean monthly migraine periods from the baseline phase through the entire double-blind phase between the groups treated with topiramate and placebo. A migraine period was defined as any occurrence of migraine headache that started, ended or recurred within 24 h. Any pain lasting for more than 24 h after its initial onset constituted a new, distinct migraine period. Aura was not considered a migraine headache unless acute treatment was utilised during aura symptoms.

Secondary efficacy measures included the mean changes in monthly migraine attacks, monthly migraine days and migraine duration, as well as the change in number of days per month requiring rescue medication. For the assessment of migraine attacks, headache information was classified according to an algorithm based on IHS criteria for the diagnosis of migraine (episode lasting 4–72 h) (12). A migraine day was defined as any calendar day during which a patient had a migraine headache of at least 30-min duration. In addition, for the monthly migraine periods, the monthly migraine attacks, the monthly migraine days and the migraine duration, responder rates were calculated at three levels: the proportion of patients achieving at least 50% reduction, 75% reduction or migraine freedom for the respective parameter. Tolerability was assessed by the reports of adverse events.

Table 1 Demographic and baseline characteristics

|                         | Placebo (n = 372) | Topiramate (100 mg/day) (n = 386) |
|-------------------------|-------------------|----------------------------------|
| Age                     |                   |                                  |
| Mean ± SD (years)       | 39.8 ± 11.1       | 39.8 ± 11.5                      |
| Range (years)           | 12–70             | 12–65                            |
| Gender                  |                   |                                  |
| Male (percentage of patients) | 17.7         | 13.8                             |
| Female (percentage of patients) | 82.3        | 86.2                             |
| Body weight             |                   |                                  |
| Mean ± SD (kg)          | 76.0 ± 18.9       | 73.6 ± 17.6                      |
| Body mass index         |                   |                                  |
| Mean ± SD (kg/m²)       | 27.4 ± 6.4        | 26.6 ± 5.6                       |
| Range (kg/m²)           | 14–50             | 17–49                            |
| Normal (<25 kg/m²), percentage of patients | 44.9       | 48.9                             |
| Overweight (25 < <30 kg/m²), percentage of patients | 27.5       | 29.0                             |
| Obese (≥30 kg/m²), percentage of patients | 27.5       | 22.1                             |
| Concomitant medication, percentage of patients | 74.5       | 74.9                             |
| Monthly migraine period rate, mean ± SE | 5.4 ± 0.12 | 5.4 ± 0.12                      |
| Monthly migraine attack rate, mean ± SE | 4.2 ± 0.12 | 4.4 ± 0.13                      |
| Monthly migraine days, mean ± SE | 6.4 ± 0.14 | 6.3 ± 0.14                      |
| Monthly migraine duration, mean ± SE (h) | 2.4 ± 0.09 | 2.3 ± 0.08                      |
| Monthly days of medication use to treat acute migraine attacks, mean (%) ± SE* | 20.2 ± 0.51 | 20.0 ± 0.50                      |

*Days with medication to treat acute attacks (aspirin, paracetamol, NSAIDs, ergot derivatives, triptans and opioids) relative to the duration of the baseline period.

Statistical Analyses

Safety analysis was performed on all randomised patients for whom safety data were available during the double-blind phase (n = 372 on placebo, n = 386 on topiramate 100 mg/day). Also, medication use to treat the acute migraine attacks was assessed in this sample. All other efficacy measures were analysed on the intent-to-treat population, defined as randomised patients with at least one post-baseline efficacy assessment during the double-blind phase (n = 372 on placebo, n = 384 on topiramate 100 mg/day); 372 placebo- and 382 topiramate-treated patients had migraine information both at baseline and post-baseline. Analysis of baseline demographic and clinical features was assessed in the intent-to-treat population with the respective baseline data available. For subjects discontinuing early, the cumulative monthly periods were computed based on the migraine periods observed prior to discontinuation.

For primary and secondary efficacy parameters, the difference in changes from baseline to the full 26-week treatment period between topiramate and placebo was assessed. Ranks of the absolute changes for each study were calculated separately and subsequently analysed for treatment differences using ANCOVA. Factors included in the model were the baseline value, the original trial (or ‘protocol’), gender, treatment, treatment by protocol, and treatment by gender. The proportions of subjects responding to treatment were analysed using the Cochran–Mantel–Haenszel test, stratified by the original trial and gender. For the percent of
responders achieving at least 50%, 75% and 100% reduction in monthly migraine period rate, the homogeneity of the odds ratios was verified by the Breslow-Day test.

RESULTS

Table 1 summarises the main demographic and disease features. Baseline demographic and clinical characteristics were balanced between treatment groups. In both groups, similar proportions of patients completed the double-blind phase: 62.5% patients on topiramate 100 mg/day and 62.1% on placebo. More patients on topiramate (24.2%) withdrew because of one or more adverse events than patients on placebo (10.8%, p < 0.001). Lack of efficacy was the reason for withdrawal in 4.6% of patients on topiramate and 15.1% on placebo (p < 0.001). Other reasons for dropouts included the subject’s choice (4.4% with topiramate and 4.6% with placebo), lost to follow-up (1.6 and 3.2% respectively) and various other reasons (2.6 and 4.3% respectively).

Topiramate 100 mg/day significantly reduced the mean monthly migraine period rate throughout the entire double-blind period phase from baseline to endpoint (mean change ± SE:

![Graph showing percentage of change from baseline in monthly migraine period rate, monthly migraine attack rate, monthly migraine days and monthly migraine duration after 6 months of treatment with placebo or topiramate 100 mg/day. *p < 0.05; **p < 0.001](image)

![Graph showing response: proportion of patients achieving (A) at least 50% reduction (top) and (B) at least 75% reduction (bottom) in migraine efficacy parameters after 6 months of treatment with placebo or topiramate 100 mg/day. *p < 0.001](image)
2.0 ± 0.16 migraines for topiramate, −1.0 ± 0.13 for placebo, p < 0.001). Similarly, topiramate reduced significantly the mean monthly migraine attack frequency (−1.7 ± 0.16 versus −0.8 ± 0.13; p < 0.001), monthly migraine days (−2.4 ± 0.18 versus −1.2 ± 0.16; p < 0.001) and monthly migraine duration (−0.9 ± 0.09 h versus −0.5 ± 0.08 h; p < 0.05), when compared with placebo. The median percent changes are presented in Figure 1. Using ANCOVA, it was found that effects were significant by treatment groups, consistent through the different studies and independent of gender. At endpoint (Figure 2), about half of the topiramate patients (46.3%) achieved at least 50% reduction and one in four patients exhibited at least 75% reduction in monthly migraine period rates (p < 0.001 versus placebo). Similar response rates were found for the monthly migraine attack frequency, monthly migraine days and monthly migraine duration. With topiramate, 5.8% of patients were free of migraine periods and migraine days (p < 0.01) compared with 1.9% of placebo-treated patients. The incidence of cognitive related adverse events was 6.7% for memory difficulty (2.6% resulting in discontinuation) and 6.0% for concentration/attention

Table 2  Response rates of monthly migraine period rate according to gender

| Reduction in monthly migraine period frequency (%) | Placebo | Topiramate |
|--------------------------------------------------|---------|------------|
| All (n = 372) | Male (n = 66) | Female (n = 306) | All (n = 382) | Male (n = 53) | Female (n = 329) |
| ≥50 | 22.8 | 25.8 | 22.2 | 46.3* | 41.5† | 47.1† |
| ≥75 | 9.9 | 12.1 | 9.5 | 25.1* | 28.3† | 24.6† |
| 100 | 1.9 | 1.5 | 2.0 | 5.8** | 5.7† | 5.8† |

*p < 0.001 and **p < 0.01 for topiramate when compared with placebo. †The Breslow-Day test showed that the responder rates were homogeneous across the three original trials, the two sexes as well as the six combinations of the original trial with gender.

Paraesthesia was the most common adverse event (Table 3) occurring in 50.5% of topiramate patients. Generally, paraesthesia was usually mild to moderate in severity and led to withdrawal in 8.0% of patients. Fatigue was the second most common adverse event and was seen in both groups (15.0% with topiramate and 11.8% with placebo); it led to withdrawal in 4.7% of patients on topiramate compared with 0.8% with placebo. The incidence of cognitive related adverse events was 6.7% for memory difficulty (2.6% resulting in discontinuation) and 6.0% for concentration/attention.
Table 3  Adverse events (≥5%) on topiramate in decreasing order

| WHO dictionary preferred term* | Placebo (n = 372) | Topiramate 100 mg/day (n = 386) |
|-------------------------------|------------------|---------------------------------|
|                               | Treatment-emergent | Mild/moderate | Severe | Treatment-limiting | Treatment-emergent | Mild/moderate | Severe | Treatment-limiting |
| Paraesthesia                  | 22 (5.9)          | 21 (5.6)       | 1 (0.3) | 3 (0.8)            | 195 (50.5)         | 182 (47.2)   | 13 (3.4) | 31 (8.0)          |
| Fatigue                       | 44 (11.8)         | 41 (11.0)      | 3 (0.8) | 3 (0.8)            | 58 (15.0)          | 52 (13.5)    | 6 (1.6)  | 18 (4.7)          |
| Anorexia                      | 22 (5.9)          | 22 (5.9)       | 0       | 2 (0.5)            | 56 (14.5)          | 51 (13.2)    | 5 (1.3)  | 8 (2.1)           |
| Upper respiratory tract infection | 47 (12.6)   | 43 (11.6)      | 0       | 0                 | 54 (14.0)          | 52 (13.5)    | 2 (0.5)  | 6 (1.6)           |
| Nausea                        | 33 (8.9)          | 24 (6.5)       | 9 (2.4) | 5 (1.3)            | 51 (13.22)         | 43 (11.1)    | 8 (2.1)  | 9 (2.3)           |
| Diarrhoea                     | 16 (4.3)          | 13 (3.5)       | 3 (0.8) | 2 (0.5)            | 43 (11.1)          | 41 (10.6)    | 2 (0.5)  | 6 (1.6)           |
| Weight decrease               | 5 (1.3)           | 4 (1.1)        | 1 (0.3) | 0                 | 35 (0.9)           | 33 (8.5)     | 2 (0.5)  | 4 (1.0)           |
| Dizziness                     | 36 (9.7)          | 31 (8.3)       | 5 (1.3) | 6 (1.6)            | 33 (8.5)           | 31 (8.0)     | 2 (0.5)  | 8 (2.1)           |
| Taste perversion              | 4 (1.1)           | 3 (0.8)        | 1 (0.3) | 0                 | 30 (7.8)           | 28 (7.3)     | 2 (0.5)  | 4 (1.0)           |
| Hypoaesthesia                 | 5 (1.3)           | 5 (1.3)        | 0       | 0                 | 28 (7.3)           | 27 (7.0)     | 1 (0.3)  | 7 (1.8)           |
| Insomnia                      | 18 (4.8)          | 16 (4.3)       | 2 (0.5) | 4 (1.1)            | 27 (7.0)           | 23 (6.0)     | 4 (1.0)  | 13 (3.4)          |
| Difficulty with memory NOS    | 9 (2.4)           | 9 (2.4)        | 0       | 2 (0.5)            | 26 (6.7)           | 23 (6.0)     | 3 (0.8)  | 10 (2.6)          |
| Somnolence                    | 20 (5.4)          | 16 (4.3)       | 4 (1.1) | 7 (1.9)            | 26 (6.7)           | 24 (6.2)     | 2 (0.5)  | 7 (1.8)           |
| Abdominal pain                | 20 (5.4)          | 17 (4.6)       | 3 (0.8) | 4 (1.1)            | 25 (6.5)           | 22 (5.7)     | 3 (0.8)  | 3 (0.8)           |
| Injury                        | 27 (7.3)          | 25 (6.7)       | 2 (0.5) | 0                 | 25 (6.5)           | 17 (4.4)     | 8 (2.1)  | 1 (0.3)           |
| Language problems             | 8 (2.2)           | 7 (1.9)        | 1 (0.3) | 2 (0.5)            | 25 (6.5)           | 25 (6.5)     | 0       | 6 (1.6)           |
| Sinusitis                     | 24 (6.5)          | 24 (6.5)       | 0       | 0                 | 25 (6.5)           | 21 (5.4)     | 4 (1.0)  | 0                |
| Difficulty with concentration/attention | 8 (2.2)   | 8 (2.2)        | 0       | 0                 | 23 (6.0)           | 20 (5.2)     | 3 (0.8)  | 8 (2.1)          |
| Mood problems                 | 8 (2.2)           | 8 (2.2)        | 0       | 1 (0.3)            | 23 (6.0)           | 19 (4.9)     | 4 (1.0)  | 5 (1.3)           |
| Pharyngitis                   | 14 (3.8)          | 11 (3.0)       | 3 (0.8) | 0                 | 22 (5.7)           | 18 (4.7)     | 4 (1.0)  | 2 (0.5)           |
| Anxiety                       | 8 (2.2)           | 6 (1.6)        | 2 (0.5) | 1 (0.3)            | 21 (5.4)           | 17 (4.4)     | 4 (1.0)  | 8 (2.1)           |

*WHO = World Health Organization; NOS = not otherwise specified.
differing body mass index (BMI) category enrolled in the trial. At the 6-month endpoint, mean weight loss was −2.5 kg for topiramate versus virtually no change on placebo (+0.1 kg). In the topiramate patients with data on BMI (n = 378), weight reduction was −1.9 kg among the patients with a normal BMI, −3.1 kg among overweight patients and −3.0 kg among obese. Figure 5 shows the distribution of the weight changes at the 6-month endpoint.

**DISCUSSION**

The findings of this pooled analysis confirm that topiramate 100 mg/day is an effective treatment for migraine prevention. Results were consistent irrespective of whether parameters were assessed by their change in absolute value or by responder rates. Findings were also consistent throughout the various assessment methods used to calculate the monthly migraine frequency (periods, attacks or migraine days). Response rates were comparable among male and female patients, with approximately half responding to topiramate 100 mg daily. The response with placebo was similar to the rate recently found by meta-analysis of various migraine prevention trials (23.5%) (13).

Treatment with topiramate was also associated with a significant reduction in the use of rescue medication to treat acute migraine attacks. Overuse of acute medications, such as triptans, ergots and simple as well as combined analgesics, can lead to an increase in migraine frequency and eventually to medication-overuse headache (3,4). In this trial, attack medication could be used as much as needed to treat acute migraine attacks.

Hence, the study design allowed evaluation of the prophylactic use of topiramate plus acute medication versus acute medication alone (placebo arm). The findings of this study indicate that preventive treatment with topiramate not only reduces the migraine frequency but also simultaneously lowers the usage of acute medication for migraine attacks.

The adverse events found in this pooled analysis are comparable with the known tolerability profile of topiramate. Most adverse events were mild to moderate and usually led to withdrawal in less than 3% of patients, with the exception of paraesthesia, fatigue and insomnia. Overall, about one fourth of patients on 100 mg of topiramate withdrew in this study. Yet, no unusual or unexpected safety risks were identified. Renal calculi were seen in three patients receiving topiramate in this study but did not lead to withdrawal from the study. This outcome is similar to that of prior reports, where patients continued treatment with topiramate once they pass the stone (8).

The incidence of paraesthesia among topiramate-treated patients was high: most of the patients characterised the paraesthesia as mild to moderate, 8% withdrew from the study because of this adverse event. Paraesthesias are most likely due to inhibition of carbonic anhydrase. In a pooled analysis evaluating the time course of paraesthesias for patients treated with topiramate for migraine prevention, most of the paraesthesias were transient, and about half of the reported cases had resolved by the end of the 26-week lasting trial (14).

Weight gain is a common problem and concern in patients receiving treatment for migraine prevention (15). The effect of topiramate on body weight was usually limited and more pronounced in patients with above normal BMI. Weight decrease led to discontinuation of topiramate treatment in only 1% of patients. The findings are similar to observations from other trials (16,17). The effect of weight can be considered a favourable outcome in overweight or obese patients or in patients on concomitant medication known to increase weight such as antidepressants or atypical antipsychotics. Several other drugs used in migraine prevention increase weight, such as valproate, flunarizine and propranolol (18,19).

With respect to contra-indications, topiramate is only contra-indicated in patients with a history of hypersensitivity to components of the medication. Most agents currently used in the prevention of migraine are contra-indicated in common conditions, such as β-blockers in patients with asthma or diabetes mellitus and valproate or divalproex sodium in hepatic disease.

In conclusion, this pooled analysis confirms the efficacy and positive benefit-risk ratio for topiramate 100 mg daily in the preventive treatment of migraine.

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