Topiramate for Migraine Prevention
A Randomized Controlled Trial

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Migraine headache is a neurologic disorder associated with significant disability and impaired quality of life,1,2 adversely affecting daily activity and work-related productivity for many persons.3,4 Approximately 11% of the US population experiences migraine,4 and a similar prevalence is evident in other industrialized countries.5,6 Many migraineurs patients do not consult a physician for treatment, and even among patients who are treated, less than one third report consistently effective results with their current pharmacologic regimens, most of which include over-the-counter analgesics.2 Furthermore, most migraine patients require bed rest in addition to medication, indicating that migraine continues to significantly affect their lives.3

The goals of managing migraine are to reduce migraine frequency, severity, and disability; reduce reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies; improve quality of life; reduce headache-related distress and psychologic symptoms; educate patients and enable them to manage their disease; and avoid dose escalation of acute medications.3 Recent studies suggest that habitual overuse of acute medications, including triptans, ergots, and other analgesics, can lead to the development of chronic daily headaches.10 Preventive medications can serve an important role in the treatment of migraine by reducing migraine frequency and by ameliorating dose escalation and the potential for overuse of acute pharmacotherapies.10

Topiramate is a broad-spectrum antiepileptic drug indicated as adjunctive therapy and monotherapy for adults

Context Small open-label and controlled trials suggest that the antiepileptic drug topiramate is effective for migraine prevention.

Objective To assess the efficacy and safety of topiramate for migraine prevention in a large controlled trial.

Design, Setting, and Patients A 26-week, randomized, double-blind, placebo-controlled study was conducted during outpatient treatment at 52 North American clinical centers. Patients were aged 12 to 65 years and had a 6-month history of migraine (International Headache Society criteria) and 3 to 12 migraines a month but no more than 15 headache days a month during a 28-day prospective baseline phase.

Interventions After a washout period, patients meeting entry criteria were randomized to topiramate (50, 100, or 200 mg/d) or placebo. Topiramate was titrated by 25 mg/wk for 8 weeks to the assigned or maximum tolerated dose, whichever was less. Patients continued receiving that dose for 18 weeks.

Main Outcome Measures The primary efficacy measure was change from baseline in mean monthly migraine frequency. Secondary efficacy measures included responder rate (proportion of patients with ≥50% reduction in monthly migraine frequency), reductions in mean number of monthly migraine days, severity, duration, and days a month requiring rescue medication, and adverse events. The month of onset of preventive treatment action was assessed.

Results Of 483 patients randomized, 468 provided at least 1 postbaseline efficacy assessment and comprised the intent-to-treat population. Mean monthly migraine frequency decreased significantly for patients receiving topiramate at 100 mg/d (−2.1, P=.008) and topiramate at 200 mg/d (−2.4, P<.001) vs placebo (−1.1). Statistically significant reductions (P<.05) occurred within the first month with topiramate at 100 and 200 mg/d. The responder rate was significantly greater with topiramate at 50 mg/d (39%, P=.01), 100 mg/d (49%, P<.001), and 200 mg/d (47%, P<.001) vs placebo (23%). Reductions in migraine days were significant for the 100-mg/d (P=.003) and 200-mg/d (P<.001) topiramate groups. Rescue medication use was reduced in the 100-mg/d (P=.01) and 200-mg/d (P=.005) topiramate groups. Adverse events resulting in discontinuation in the topiramate groups included paresthesia, fatigue, and nausea.

Conclusion Topiramate showed significant efficacy in migraine prevention within the first month of treatment, an effect maintained for the duration of the double-blind phase.

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and pediatric patients and has shown efficacy in the treatment of several other neurologic and psychiatric diseases, including binge eating disorder,11 bulimia,12 and essential tremor.13,14

Open-label15-17 and small controlled18 studies with adult patients suggest that topiramate may be efficacious for migraine prevention. Topiramate has multiple mechanisms of action that could contribute to migraine prevention, including state-dependent inhibition of voltage-gated sodium channels, inhibition of high-voltage-activated calcium channels, inhibition of glutamate-mediated neurotransmission at α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid and kainate receptor subtypes, and enhancement of γ-aminobutyric-acidA-receptor-mediated chloride flux.19 It is unclear which of these mechanisms (or which combination) is most important in the prevention of migraine, but basic research into the pathophysiology and genetics of migraine suggests that the disorder can develop through the dysfunction of multiple systems. Recent research suggests that topiramate may modulate trigeminovascular signaling, which could affect migraine pathogenesis.20

METHODS

Inclusion Criteria

Patients were required to have an established history of migraine with or without aura, as assessed by International Headache Society (IHS) criteria, for at least 6 months before screening. Patients had to be aged 12 to 65 years and to have between 3 and 12 migraines but no more than 15 headache days (migraine or nonmigraine) per 28 days during the prospective baseline phase. A headache day was defined as a calendar day during which the patient experienced headache for at least 30 minutes. Women were required to be postmenopausal, surgically incapable of bearing children, or practicing a medically acceptable method of birth control for at least 1 month before study entry.

Exclusion Criteria

Patients were excluded from the study if they experienced headaches other than migraine, episodic tension, or sinus headaches. Although episodic tension and sinus headaches were not expected to respond to treatment, the data were tabulated to confirm that these allowable headaches were accurately captured. Patients were also excluded if their headaches failed to respond to more than 2 adequate previous regimens of migraine-preventive medications, if their onset of migraine occurred after age 50 years, or if they overused analgesics or specific agents for the acute treatment of migraine episodes. Examples of analgesic overuse included the following: more than 8 treatment episodes (episode defined as any calendar day of usage) of ergot-containing medications a month; more than 8 treatment episodes of triptans a month; or more than 6 treatment episodes of potent opioids a month. The final decision about analgesic use constituting overuse rested with the study investigators.

Patients also were excluded if they required continued use of the following medications for any medical reason during the study: β-blockers, tricyclic antidepressants, antiepileptics, calcium channel blockers, monoamine oxidase inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs) daily, magnesium supplements at high doses (eg, 600 mg/d), riboflavin at high doses (eg, 100 mg/d), corticosteroids, local anesthetics, botulinum toxin, or herbal preparations such as feverfew or St John’s wort. Nonpharmacologic prophylactic approaches started at least 1 month before the prospective baseline phase could be continued throughout the study. Patients with a history of nephrolithiasis were excluded, as were patients who had participated in a topiramate study or had taken topiramate for more than 2 weeks. Patients who had received an experimental drug or used an experimental device within 30 days of screening also were excluded.

Randomization and Blinding

Eligible patients were assigned to 1 of 4 treatment groups according to a computer-generated randomization schedule. Study medication was packaged and labeled according to a medication code schedule generated before the trial. Each bottle had a 2-part tear-off label; study medication identification was concealed and could be revealed only in case of emergency. An interactive voice response system was used to assign randomization numbers to patients, and treatment assignments were not revealed to study patients, investigators, clinical staff, or study monitors until all patients had completed therapy and the database had been finalized.

The trial was conducted with full approval by the institutional review boards at the respective sites. Each patient signed an informed consent form, which conformed to the current revision of the Declaration of Helsinki.

Study Design

After evaluation for inclusion and exclusion criteria, eligible patients 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 headache and medication record information completed by patients was reviewed. During the baseline phase, patients were permitted to take rescue medication. Patients who completed the prospective baseline phase and met all entry criteria were randomized to 1 of 4 treatment groups: placebo or topiramate at 50 mg/d, 100 mg/d, or 200 mg/d.

Randomization was balanced by using permuted blocks of 4 and stratified by center. Patients and clinicians were blinded to study medication. Patients randomized to topiramate started at a dose of 25 mg/d; the daily dose was increased by 25 mg weekly (for a total of 8 weeks) until patients reached either their assigned dose or maximum tolerated dose, whichever was less. Patients then continued receiving that amount for 18 weeks in 2 divided doses.
(morning and evening). Patients who completed the 18-week maintenance period or who exited the double-blind phase for lack of efficacy were eligible to enter an open-label extension after a blinded transition period of 7 weeks. In the event of tolerability problems, patients were given the opportunity to reduce study medication by a maximum of 2 dose levels during the entire 26-week treatment phase.

The frequency, severity, and symptoms of all headaches or auras were recorded by each patient in a diary, which was then transcribed into the patient's case record form at each clinic visit. The transcription of each patient's diary into the case record form was performed on days 1, 29, 57, 85, 113, 141, and 183 of the study. Across all treatment groups, headaches were classified by using the patient's own judgment. Patients were permitted to take rescue medication for headaches during the study, including during the baseline phase. Each patient recorded the type and amount of rescue medication used. Allowable medications included aspirin, acetaminophen, NSAIDs, ergot derivatives, triptans, and opioids.

Hematologic (red blood cell count, white blood cell count, platelet count, and hemoglobin and hematocrit levels), serum chemistry (including glucose, sodium, potassium, serum urea nitrogen, and total protein levels), and liver function tests (alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and bilirubin levels) were performed for all patients at specific intervals throughout the study, and physical examinations were performed at the beginning and end of the study. Hematologic and serum chemistry tests were performed at the first, third, and final visits of the double-blind phase. Liver function tests were performed each clinic visit. A urinalysis was performed at baseline only. Vital signs and weight were recorded at each clinic visit. Adverse events during the study were recorded and followed up until resolved or until a clinically stable end point was achieved.

**Outcomes**

The primary efficacy measure was a comparison of the reduction in mean 28-day monthly migraine frequency from the baseline phase through the entire double-blind phase between the groups treated with topiramate and placebo. Patients recorded the times and dates on which migraine symptoms started and stopped. Migraine frequency was assessed by the number of migraine periods. A migraine period was defined as any occurrence of migraine headache that started, ended, or occurred within 24 hours. Pain persisting more than 24 hours after its initial onset was considered to be a new, distinct migraine period. Aura was not counted as a migraine headache unless acute treatment was used during aura symptoms.

Secondary efficacy measures included proportion of patients responding to treatment (as measured by a 50% or more reduction in monthly migraine frequency); the mean change in monthly migraine days, severity, and duration; and the change in number of days requiring rescue medication per month. A migraine day was defined as any calendar day during which a patient had a migraine headache lasting at least 30 minutes.

The month of onset of action for each topiramate dose was assessed. Analyses were performed to identify the first cumulative monthly period (ie, month 1, months 1 and 2, up to months 1 through 6) during which there was a statistically significant reduction in the monthly migraine frequency for that topiramate group compared with placebo. In addition, this difference was required to be maintained for all subsequent cumulative periods. This month would then be identified as the onset of action.

Safety was assessed by reports of adverse events, physical and neurologic examinations, and clinical laboratory tests.

**Statistical Analyses**

According to pilot placebo-controlled studies, a sample size of 120 patients per treatment group was calculated to give a 95% power to detect a difference of 1.19 in change from baseline in mean monthly migraine frequency between dose group and placebo at the 5% 2-sided significance level, assuming 2.50 as the common SD. Efficacy analyses were conducted on the intent-to-treat population, which was defined as randomized patients who had at least 1 post-baseline efficacy assessment. For patients discontinuing early, the mean monthly migraine frequency during the entire double-blind treatment phase and the cumulative monthly periods were computed according to the migraine periods observed before discontinuation.

The primary efficacy measure was assessed with a linear model, with treatment and analysis center as factors and the baseline value as a covariate. As is done in the Tukey-Ciminera-Heyse trend test, secondary treatment groups were compared by using equally spaced contrasts of treatment effects within the linear model. To control the type I error, linear contrasts were implemented with a step-down procedure. The hypothesis of a trend in dose response among all doses and placebo was tested by the corresponding equally spaced contrast at the first step at the .05 level. If the first step was statistically significant, then the 200-mg/d group would be declared different from placebo and the procedure would proceed to the second step, in which the hypotheses of a trend among placebo, the mid dose, and the low dose would be similarly tested. Finally, the low dose would be compared with placebo only if the second step test was statistically significant.

For all secondary variables and migraine frequencies during cumulative monthly periods, comparisons of each topiramate group with placebo were analyzed with pairwise comparisons, and nominal P values are given. The proportions of patients responding to treatment were analyzed with the Cochran-Mantel-Haenszel test stratified by analysis center. All other secondary variables, as well as the analyses for onset of action, were based on linear models corresponding to the model used for the primary efficacy measure. Estimates of various treatment effects and
their graphical depictions are based on the treatments’ least squares means, which are the means adjusted for the variables in the statistical model. Analyses were done with SAS (version 6.12; SAS Institute Inc, Cary, NC) at a significance level of .05.

RESULTS

Figure 1 depicts patient disposition during the study. Of 693 patients enrolled, 210 did not meet screening criteria, although specific reasons for exclusion were not tabulated. Four hundred eighty-three patients were randomized to 4 treatment groups; 468 were in the intent-to-treat population. Fifteen patients (3%) were randomized but did not provide postbaseline efficacy data and were not included in the intent-to-treat population. Fifty-seven of 120 randomized patients (48%) in the placebo group, 59 of 122 (48%) in the topiramate at 50 mg/d group, 59 of 122 (48%) in the topiramate at 100 mg/d group, and 51 of 121 (42%) in the topiramate at 200 mg/d group withdrew during the study.

Placebo patients withdrew most often because of lack of efficacy, and topiramate patients withdrew most often because of adverse events. Twenty-one of 114 placebo-treated patients (18%) withdrew because of lack of efficacy compared with 15 of 117 (13%) in the topiramate at 50 mg/d group, 11 of 120 (9%) in the topiramate at 100 mg/d group, and 12 of 117 (10%) in the topiramate at 200 mg/d group. Fourteen of 114 (12%) patients in the placebo group withdrew because of adverse events compared with 20 of 117 (17%) in the topiramate at 50 mg/d group, 32 of 120 (27%) in the topiramate at 100 mg/d group, and 25 of 117 (21%) in the topiramate at 200 mg/d group. No patients were required to be unblinded during the study. Two hundred fifty-five patients completed the study. For patients discontinuing early, the mean monthly migraine frequency during the double-blind treatment phase was computed according to the migraine periods observed before discontinuation because no data were available beyond discontinuation.

The mean (SD) monthly migraine frequency for all patients at baseline was 5.5 (2.33; range, 1.0-14.5), and the mean monthly number of migraine days was 6.5 (2.83; range, 1.0-18.0) (TABLE 1). Eighty-seven percent (406/468) of patients were women. At baseline, patients had a mean (SD) weight of 76.5 (19.55) kg and a mean body mass index of 27.8 (6.51). Baseline clinical and demographic characteristics were balanced between treatment groups. During the 3 months before the prospective baseline phase, 15%, 18%, and 19% of patients in the topiramate treatment groups at 50 mg, 100 mg, and 200 mg, respectively, and 24% of patients in the placebo group were receiving preventive medications. However, the differences were not statistically significant. The most common preventive
Topiramate was associated with greater reductions compared with placebo at all doses assessed. Patients treated with topiramate at 50 mg/d (39%, P = .01), 100 mg/d (49%, P < .001), or 200 mg/d (47%, P < .001) exhibited a significantly better response than patients treated with placebo (23%).

Topiramate was also associated with larger reductions compared with placebo, with topiramate at 200 mg/d compared with a decrease from 5.6 (2.2) to 4.5 (2.9) for patients treated with placebo. The change from baseline (Figure 2) was statistically significant for patients treated with topiramate at any 50% reduction in monthly migraine frequency (responder rate) for patients treated with placebo (23%), and mean SD was presented as the least squares mean (SE).

Linear model P values are vs placebo. Migraine frequency was assessed in terms of migraine periods, which were defined as any occurrence of migraine headache that started, ended, or recurred within 24 hours.
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Figure 3. Change From Baseline in Cumulative Monthly Migraine Frequency

- Placebo (n = 114)
- Topiramate 100 mg/d (n = 120)
- Topiramate 50 mg/d (n = 116)
- Topiramate 200 mg/d (n = 117)

Change from baseline is the least squares mean. Linear model P values are vs placebo. Because the analysis used a “last observation carried forward” design, the number of patients is the same at each point. A linear model with treatment and analysis center as factors and the baseline value as a covariate (as was used in the primary analysis) was used at each monthly point to compare the mean change from baseline between placebo and each treatment group, with no adjustment for multiple comparisons.

\*P < .05. †P < .01. ‡P < .001.

Figure 4. Change From Baseline in Migraine Days per Month

- Placebo (n = 114)
- Topiramate 50 mg/d (n = 116)
- Topiramate 100 mg/d (n = 120)
- Topiramate 200 mg/d (n = 117)

Change from baseline is the least squares mean (SE). Linear model P values are vs placebo.

Changes in the topiramate at 100 mg/d, 200 mg/d, and placebo groups were −2.6 (0.31), −2.9 (0.32), and −1.3 (0.32) (FIGURE 4). The mean reduction in the monthly number of days when acute rescue medication was used was also significantly greater for patients treated with topiramate at 100 mg/d (P = .01) or 200 mg/d (P = .005) compared with placebo; the respective least squares means (SEs) for the topiramate at 100 mg/d and 200 mg/d and placebo groups were −2.1 (0.29), −2.2 (0.29), and −1.0 (0.29). The mean reductions in the monthly number of migraine days and monthly number of days when acute rescue medication was used were not statistically significant for the topiramate at 50 mg/d group compared with that for the placebo group.

There was a statistically significant difference in the mean change from baseline through the double-blind phase in migraine duration between the topiramate at 200 mg/d group and placebo (P = .007) but no significant differences between placebo and the topiramate at 50 mg/d (P = .61) or 100 mg/d groups (P = .19). The respective least squares means (SEs) for the topiramate at 200 mg/d, 100 mg/d, and 50 mg/d and placebo groups were −1.2 (0.17), −0.8 (0.17), −0.6 (0.17), and −0.5 (0.18).

There was a statistically significant difference in mean migraine severity between placebo and the topiramate at 100 mg/d group (P = .04) but not between placebo and the topiramate at 50 mg/d (P = .61) or 200 mg/d (P = .46) groups (respective least squares means [SEs] for the 200 mg/d, 100 mg/d, 50 mg/d, and placebo groups were −0.1 [0.04], −0.2 [0.04], −0.1 [0.04], and −0.1 [0.04]).

Safety Measures

Treatment-emergent adverse events commonly associated with topiramate use observed to occur in 10% or more of patients treated with topiramate at 100 mg/d included paresthesia (59, 50%), fatigue (17, 14%), anorexia (16, 13%), diarrhea (13, 11%), weight loss (13, 11%), paresthesia (13, 11%), difficulty with memory (12, 10%), and nausea (12, 10%; TABLE 2). Among these, events leading to discontinuation in patients treated with topiramate at 100 mg/d included paresthesia (10, 8%), fatigue (9, 8%), diarrhea (3, 3%), paresthesia (3, 3%), difficulty with memory (4, 3%), and confusion (5, 4%) (treatment-emergent incidence, 6%).

Patients treated with topiramate lost weight compared with the placebo group. The mean (SD) in weight percentage was significantly greater for patients treated with topiramate at 50 mg/d (−2.2% [4.39%]; P < .001), 100 mg/d (−3.3% [4.19%]; P < .001), or 200 mg/d (−4.6% [4.65%]; P < .001) compared with placebo-treated patients, who gained a mean of 0.2% (3.82%) of their weight.

COMMENT

Within the first month of treatment, topiramate at doses of 100 or 200 mg/d showed significant reductions compared with placebo in the primary measure of migraine frequency, and this effect was maintained for the entire double-blind treatment phase. Treatment with topiramate at doses of 100 or 200 mg/d was associated with significant improvements during the entire double-blind treatment phase for several other migraine efficacy measures, including migraine days per month and acute rescue medication days per month, and demonstrated a significantly higher responder rate than placebo. Most treatment-emergent adverse events were mild to moderate; those occurring in 10% or more of patients and those associated with discontinuation are listed in Table 2.
The number of patients experiencing adverse events, including those resulting in study discontinuation, is acknowledged, although this outcome is not unexpected for drugs of this class and would not prevent the use of topiramate in the population of patients requiring preventive migraine treatment. In the clinical experience of the authors, slow upward titration, perhaps even slower than that used in the trial, may enhance tolerability and help to avoid many of the adverse events reported. Many of the events may also be transient or manageable. For example, paresthesia associated with topiramate therapy could be ameliorated with potassium supplements, although this claim has not been confirmed in a controlled study. The weight loss associated with topiramate therapy could be ameliorated with potassium supplements, although this outcome is not unexpected for drugs of this class and would not prevent the use of topiramate in the population of patients requiring preventive migraine treatment. The study was not sized to detect differences in adverse event rates. However, the sample size compares favorably with studies of preventive medications for migraine, including a recent trial of extended-release valproate, which had 239 randomized patients, and a small controlled trial of candesartan, which had 60 patients.

This is 1 of 2 large North American trials that together encompass 937 patients and constitute the largest controlled trial to date of a migraine-preventive agent. The US Headache Consortium’s evidence-based guidelines classify medications for migraine prevention according to their established clinical efficacy, adverse events, and safety profile, as well as the clinical experience of US Headache Consortium participants. Drugs assigned a level I designation are supported by clinical studies with independent, blinded comparisons, accepted standards of physiology and diagnosis, and a large number of consecutive patients. Clinical efficacy is also evaluated on strength of evidence, scientific effect, and clinical impression of effect. For example, strength of clinical evidence is graded A, B, or C, where “A” designates the existence of multiple, well-designed, randomized clinical trials that yield a consistent pattern of findings. This study and a concurrently run controlled trial (Stephen Silberstein, MD, et al, unpublished data, 2003) represent remarkably consistent results encompassing more than 900 patients and fulfill the criteria for level I designation.

Patients in the 2 studies exhibited a significant reduction in migraine frequency at a topiramate dose of either 100 or 200 mg/d. This response was evident within the first month of treatment, which was also common to both studies, and the reduction in migraine frequency for patients taking topiramate at either 100 or 200 mg/d was significantly greater than that associated with placebo at each monthly assessment (Stephen Silberstein, MD, et al, unpublished data, 2003). Previous reports about the efficacy of divalproex sodium in migraine prevention cited responder rates of 44% to 48%. An extended-release formulation of divalproex was associated with a responder rate of 41% during the final 4 weeks of treatment and a mean reduction of 1.7 migraine days a month from 6.3 at baseline. A recent crossover study of candesartan, an angiotensin II receptor antagonist, used the number of headache days as a primary efficacy measure and reported a responder rate of 40%. However, these studies were considerably smaller and shorter.

Many studies assessing older drugs for migraine prevention were conducted before the IHS guidelines for clinical trials were published in 1991. Therefore, it is often difficult to place more current results in context with earlier studies because methodologic procedures have evolved. For ex-
ample, some earlier studies used a headache index or score to assess efficacy in migraine prevention. Others used a single-blind placebo run-in period before randomization, which does not necessarily diminish the appropriateness of older medications for migraine prevention; a recent report by Diener and colleagues for GlaxoSmithKline, Pfizer, Neuroscience, and Ortho-McNeil has served as a consultant to Merck, GlaxoSmithKline, Pfizer, AstraZeneca, Allergan, and Ortho-McNeil; and has received educational funding from GlaxoSmithKline. He received research grants for GlaxoSmithKline, AstraZeneca, Merck, Abbott, Allergan, Eli, Pfizer, Ortho-McNeil, and Novartis; has served on advisory boards or as a consultant for AstraZeneca, GlaxoSmithKline, Allergan, Ortho-McNeil, and Medtronic; and has served on the special scholarship and grant review boards for GlaxoSmithKline, Merck, AstraZeneca, Ortho-McNeil, and Pfizer. Dr. Couch has participated in research for, has been an advisory board member of, and served as a speaker for Ortho-McNeil.

Author Contributions: As principal investigator, Dr. Brandes had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

CONCLUSION

In previous studies, before and after the IHS guidelines, agents with class I data (including propranolol, amitriptyline, and valproate) showed an approximately 50% responder rate. The results of the current study demonstrate that topiramate is effective in migraine prevention, with results at least comparable to those of these other agents. Topiramate showed statistically significant efficacy in migraine prevention within the first month of treatment, an effect maintained for the duration of the double-blind phase. Topiramate appeared to be safe and had an acceptable tolerability profile, although pooled analyses of a larger number of patients and data on longer treatment duration should help complete the safety profile. Among several treatment-emergent adverse events was dose-dependent weight loss. According to these data, slow titration and an initial target dose of 100 mg/d in 2 divided doses appears advisable.

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