Cessation versus continuation of 6-month migraine preventive therapy with topiramate (PROMPT): a randomised, double-blind, placebo-controlled trial

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Summary

Background Use of preventive therapy for migraine is often recommended for only 6–9 months, but no randomised, placebo-controlled trials have investigated migraine frequency after the end of prophylaxis. We assessed the effects of discontinuation of topiramate after a treatment period of 6 months.

Methods 818 patients who have migraines were enrolled from 88 clinics in 21 countries. After a 4–8-week lead-in period, patients received topiramate in a 26-week open-label phase. Daily dose was increased from 25 mg to 100 mg in steps of 25 mg every week; the dose could be adjusted further in the range 50–200 mg/day, but was stable for the final 4 weeks. Patients were randomly assigned to continue this dose or switch to placebo for a 26-week double-blind phase. The primary endpoint was the difference in number of days with migraine during the last 4 weeks of the double-blind phase compared with the last 4 weeks of the open-label phase. Analysis was by intention to treat. This trial is registered with EudraCT, number 2005-000321-29.

Findings 559 patients (68·3%) completed the open-label phase; 514 entered the double-blind phase and were assigned to topiramate (n=255) or placebo (n=259). The mean increase in number of migraine days was greater in the placebo group (1·19 days in 4 weeks, 95% CI 0·71 to 1·66; p<0·0001) than in the topiramate group (0·10, –0·36 to 0·56; p=0·5756; mean difference between groups –1·09, –1·75 to –0·43). Patients in the placebo group had a greater number of days on acute medication than did those in the topiramate group (mean difference between groups –0·95, –1·49 to –0·41; p=0·0007). Quality of life, as assessed by the MIDAS questionnaire, fell in the placebo group but remained stable in the topiramate group. Patients were more satisfied with the efficacy of topiramate than with that of placebo, whereas satisfaction with tolerability was similar in both treatment groups.

Interpretation Sustained benefit was reported after discontinuation of topiramate, although number of migraine days did increase. These findings suggest that patients should be treated for 6 months, with the option to continue to 12 months in some patients.

Introduction

Migraine is a common neurological disorder, with an estimated yearly prevalence of 4·1–5·7% in men and 13·7–17·3% in women.[1] Frequent migraine attacks impair quality of life and ability to carry out daily activities, and decrease productivity as a result of days missed from work or school.[2,3] National and international guidelines for migraine therapy recommend prophylactic treatment in several categories of patient, including those who have frequent or severe attacks, those with uncommon or complicated migraine conditions, and those for whom acute medication is unsuitable or overused.[1,4–6] Most guidelines recommend that treatment is assessed after 3–12 months, although there is no evidence to support this practice,[7] and no controlled trial has investigated what happens when effective prophylactic treatment is discontinued. Theoretically, migraine frequency could return to that reported before treatment began, remain at a frequency reported during treatment, or lie somewhere in-between. A rebound phenomenon, with a steep increase in migraine frequency after the end of treatment, is also possible. We therefore investigated how migraine frequency changes after the end of preventive therapy.

Topiramate is licensed for prophylaxis of migraine, and its efficacy has been shown in several placebo-controlled trials of 6 months' duration.[8–10] In this randomised, placebo-controlled study, the Prolonged Migraine Prevention with Topiramate trial (PROMPT), we compared the effects of discontinuation of topiramate therapy after 6 months with continued treatment for a further 6 months. A secondary aim was to assess the efficacy of topiramate beyond 6 months of use in terms of number of migraine days.

Methods

Participants

Patients were enrolled from 88 neurology clinics in 21 countries in Europe and the middle east. Patients were eligible for the trial if they were 18–80 years of age and fulfilled International Headache Society criteria for migraine with or without aura.[11] All patients had a history of migraine for at least 1 year, with a mean of at least four migraine days per month during the 3 months before trial

entry. All patients needed to be able to keep trial records. Patients were excluded if they had used migraine prophylactic medication in the month before trial entry (or flunarizine in the 3 months before entry), or had experienced poor or no efficacy with more than two regimens of migraine prophylactic medication. Patients were excluded if they overused acute medication (defined as ≥10 days in every 4 weeks for opioids, ergots, triptans, or combination analgesics, and ≥15 days in every 4 weeks for other analgesics),[11] or had used topiramate regularly for more than 2 weeks before study entry. Women who were pregnant or breastfeeding were excluded, and all women of childbearing age were required to have a negative pregnancy test before enrolment and to confirm that they would use adequate contraception throughout the study.

All patients provided written informed consent. The trial was done in accordance with guidelines on good clinical practice from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and was approved by local ethics committees.

Procedures

The protocol for the trial (Janssen-Cilag trial number TOPMAT-MIG-303) had four consecutive phases. In the prospective baseline phase, patients received no study medication, and they recorded occurrence of migraine headaches and use of acute treatment in a diary for at least 4 weeks. Patients were eligible to enter the remaining phases of the study if they had at least four migraine days (defined as a calendar day during which the patient had a migraine headache at any time) over a 4-week baseline period. If patients had fewer than four migraine days in 4 weeks, the lead-in period was extended to 8 weeks; patients who had eight migraine days over the 8-week period were eligible to enter the remaining phases of the study.

The second phase was a 26-week, open-label, dose-characterisation phase, in which eligible patients were given topiramate (Topamax®, Janssen-Cilag EMEA) in 25-mg tablets. Treatment was started at one tablet every evening. The dose was increased after 1 week to two tablets per day, taken morning and evening, and was increased further in steps of 25 mg/day per week to a target dose of 100 mg/day or the maximum tolerated dose, whichever was reached first. The dose could be adapted further to the patient's needs, but could not exceed 200 mg/day. Treatment twice per day was maintained if subsequent dose increases were required. The final dose of topiramate was kept stable during the last 4 weeks of the open-label phase; this period was used to obtain baseline values for comparison with the double-blind phase.

Patients who adhered to the study protocol and received a topiramate dose of 50–200 mg/day were eligible to enter the 26-week double-blind phase. In this phase, patients continued on the same topiramate dose as was received in the last 4 weeks of the open-label phase, or received a placebo equivalent of identical appearance. Patients assigned to placebo had their daily topiramate dose reduced by 100 mg per week until discontinuation.

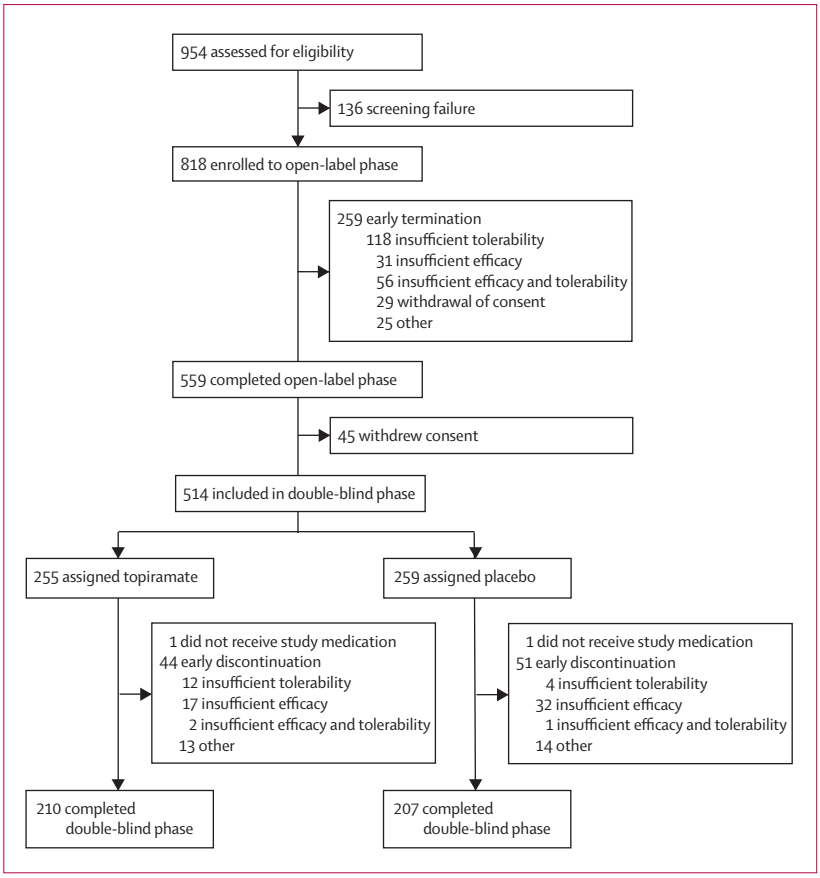

Figure 1: **Trial profile**

Patients were randomly assigned to topiramate or placebo at the end of week 26 of the open-label phase. Topiramate tablets and placebo tablets of identical appearance were packaged by Janssen-Cilag. Computer randomisation was used before the start of the study, with medication randomised in blocks of four (two topiramate and two placebo per block) and numbered. Medication blocks were provided to the study centres. When patients entered the double-blind phase, they were assigned to the next available medication number within the block. Patients were provided only with medication of this specially assigned number during the rest of the trial (at each trial visit, medication was issued to cover the period until the next visit). On completion of the double-blind phase, or after early withdrawal, treatment was discontinued by reduction of the daily dose by 100 mg per week, in accordance with the approved labelling for topiramate. Patients remained unaware of their treatment type during this discontinuation phase.

Throughout the study, use of other antiepileptic drugs, including flunarizine, resulted in mandatory

For the **ICH Good Clinical Practice: consolidated guidelines** see http://www.ich.org

withdrawal. Use of β blockers and tricyclic antidepressants was allowed for indications other than migraine prevention, with the recommendation that patients continue to take these drugs on a stable dose throughout the study.

	All patients	Assigned to topiramate	Assigned to placebo
Sex			
Male	110 (13%)	39 (15%)	28 (11%)
Female	708 (87%)	215 (85%)	230 (89%)
Age (years)			
Mean	39·8 (10·9)	40·1 (10·6)	40·1 (10·7)
Median	40 (18–69)	40 (18–67)	40 (18–69)
Height (cm)			
Mean	166·0 (7·8)	166·0 (8·0)	165·6 (7·4)
Median	165 (140–194)	165 (146–194)	165 (140–187)
Weight (kg)			
Mean	69·8 (14·8)	71·7 (16·1)	69·6 (13·3)
Median	67·0 (45·0–151·7)	69·3 (46·6–150·7)	66·9 (45·2–125·0)
Body mass index (kg/m²)			
Mean	25·3 (4·8)	25·9 (5·1)	25·4 (4·3)
Median	24·5 (16·4–52·5)	25·2 (16·6–52·1)	24·5 (17·3–46·5)
Migraine occurrence (days/month)			
Mean	8·9 (4·3)	8·4 (3·6)	9·0 (4·5)
Median	8·0 (0–28·0)	8·0 (3·5–28·0)	8·0 (3·3–28·0)
Migraine duration (h)			
Mean	13·2 (12·3)	14·0 (14·4)	13·3 (11·4)
Median	9·8 (1·0–139·0)	10·4 (1·0–139·0)	10·1 (1·0–84·3)
Migraine severity score			
Mean	2·1 (0·5)	2·2 (0·4)	2·1 (0·5)
Median	2·1 (1·0–3·0)	2·2 (1·0–3·0)	2·1 (1·0–3·0)
Acute medication intake (days/month)			
Mean	6·1 (3·1)	5·9 (3·1)	5·9 (3·0)
Median	6·0 (0–17·6)	6·0 (0–17·0)	5·8 (0–14·0)
MIDAS score			
Patients assessed	515 (63%)	151 (59%)	155 (60%)
Mean	38·6 (42·7)	37·7 (41·0)	35·2 (41·4)
Median	26·0 (0–332·0)	27·0 (0–332·0)	25·0 (0–255·0)
HIT-6 score			
Patients assessed	781 (95%)	242 (95%)	243 (94%)
Mean	64·5 (4·8)	64·5 (4·7)	64·4 (5·0)
Median	64·5 (42·0–78·0)	65·0 (48·0–76·0)	64·0 (44·0–76·0)
SF-12 MCS score			
Patients assessed	726 (89%)	230 (91%)	225 (87%)
Mean	43·8 (10·7)	43·4 (11·3)	44·9 (9·8)
Median	44·6 (14·0–69·2)	44·4 (18·1–63·1)	45·7 (15·0–62·7)
SF-12 PCS score			
Patients assessed	726 (89%)	230 (91%)	225 (87%)
Mean	40·0 (8·7)	40·2 (8·6)	39·9 (8·5)
Median	40·0 (11·7–63·8)	40·4 (14·6–63·8)	39·6 (17·6–60·0)

Data are number (%), mean (SD), or median (range). Unless otherwise stated, data are for 818 patients from the 'all patients' group, for 254 patients assigned to topiramate, and for 258 patients assigned to placebo. MIDAS=migraine disability assessment test. HIT-6=six-item headache impact test. SF-12=short-form 12 general health status questionnaire. MCS=mental component summary. PCS=physical component summary.

Table 1: **Baseline characteristics of all patients who entered the open-label phase and all patients who entered the double-blind phase**

Follow-up visits were made at 4, 8, 16, and 26 weeks after the start of the open-label and double-blind phases. The primary endpoint was the change in number of migraine days during the last 4 weeks of the double-blind phase relative to the last 4 weeks of the open-label phase. Secondary efficacy parameters were number of withdrawals, change in the duration and severity of migraines, change in the number of days with intake of triptans, ergots, opiates, and other analgesics, change in quality-of-life questionnaire scores, and patient satisfaction and its change over the double-blind phase. The preferred topiramate dose was also recorded.

To assess frequency of migraine headaches and use of acute medication, patients continued to keep diary records throughout the open-label, double-blind, and discontinuation phases. At every follow-up visit, diaries were collected for review, and patients were issued with new diaries. Patients were responsible for recording of the type, maximum severity, dates, and start and end times of the migraines, when acute medication was used, and how many units of acute medication were taken. Investigators were responsible for checking the drug name and unit strength of acute medication.

The number of days with intake of acute medication was analysed as a measure of failing efficacy of the trial medication in prevention of migraine headaches. Duration of a migraine headache was defined as the time from the beginning to the end of a continuous episode. Severity was recorded using a three-point scale (1=mild, 2=moderate, and 3=severe). Health-related quality of life was assessed with three patient-administered questionaires: the migraine disability assessment test (MIDAS)[12] and the short-form 12 (SF-12) general health status questionnaire[13] were completed at the start and end of the open-label phase and at the end of the double-blind phase; the six-item headache impact test (HIT-6)[14] was completed during weeks 0, 8, and 26 of the open-label phase, and weeks 8 and 26 of the double-blind phase. Only questionnaires validated in the patients' local language were used. When local language versions of the questionnaires were not available, patients were excluded from the questionnaire analysis. Patients' satisfaction with the efficacy and tolerability of study medication was assessed at the end of the open-label and double-blind phases with a scale of very good, good, reasonable, moderate, or poor. Safety and tolerability were assessed by monitoring of adverse events at each visit, by physical examination and laboratory measurements when the investigator felt this to be necessary (and in weeks 8 and 26 of the open-label phase for measurements of sodium, potassium, chloride, and bicarbonate), and by assessment of vital signs at the end of the baseline, open-label and double-blind phases. Weight was assessed in weeks 8 and 26 of the open-label and double-blind phases.

Statistical analysis

The sample size for the study was based on the results of three previous studies of topiramate in migraine prophylaxis.[8–10] We expected that, at the end of the double-blind phase, the difference between the topiramate and placebo groups would be 1·0 migraine day per month, with an estimated SD for the difference in number of migraine days between open-label and double-blind phases of 2·5. Under these assumptions, two treatment groups of 142 patients each would be needed in the double-blind phase to show a significant difference between topiramate and placebo with a power of 0·90 and α=0·05 (two sided). We also assumed that the number of patients in the trial would fall by 25% because of screening failures, by 35% because of withdrawals in the open-label phase, and by 20% because of discontinuation between the open-label and double-blind phases. Thus, we aimed to enrol 730 patients.

Start and end dates for migraines as provided by patients were used to calculate the difference in number of migraine days between the last 4 weeks in the open-label phase and the last 4 weeks of participation in the double-blind phase. For each patient, the mean migraine headache duration and the mean severity of migraine episodes were calculated for a predefined period. In all cases, the number of migraines in a certain period was normalised to a 28-day rate, to correct for deviations from the exact, protocol-defined number of days between visits. Duration and severity in a specific period were analysed only for patients who had a migraine in that period. We compared treatment groups by use of the Wilcoxon two-sample test for ordinal and continuous data, and interpreted differences at the 5% statistical significance level (two-tailed comparison). Differences within treatment groups were tested with the Wilcoxon signed-rank test for ordinal and continuous data. Fisher's exact test was used to assess differences between nominal data. Time to discontinuation in the double-blind phase was assessed by the Kaplan-Meier method, and the log-rank test was used to test the difference between the Kaplan-Meier curves. For patients who discontinued the study prematurely, the last recorded data were carried forward to obtain the endpoint assessment. No corrections were made for multiple comparisons.

The primary efficacy analysis was by intention to treat for all patients who took at least one dose of study medication in the double-blind phase. Results from the open-label phase were compared with those from the prospective baseline phase to estimate the efficacy in prevention of migraine headaches when topiramate is titrated to the optimum dose for each patient. To investigate possible confounding effects, we did separate analyses of subsets of patients who were taking β blockers and tricyclic antidepressants, which might have migraine prophylactic effects in their own right.[5,15]

	n	Mean (SD)	Mean change from open-label baseline (95 %CI)	p*
Open-label baseline†	811	8·93 (4·29)	..	..
Weeks 0–4	800	7·33 (4·84)	–1·59 (–1·86 to –1·33)	<0·0001
Weeks 5–8	719	6·30 (4·64)	–2·68 (–2·98 to –2·38)	<0·0001
Weeks 9–16	661	5·47 (3·94)	–3·48 (–3·80 to –3·16)	<0·0001
Weeks 17–26	571	4·78 (3·60)	–4·08 (–4·44 to –3·73)	<0·0001
Last 4 weeks (endpoint)	811	5·83 (4·89)	–3·09 (–3·44 to –2·74)	<0·0001

*p values for comparison of each mean with the baseline mean, Wilcoxon's signed-rank test (two tailed). †Data from last 4 weeks of lead-in phase.

Table 2: **Mean number of migraine days per 4-week period in the open-label phase**

Role of the funding source

PROMPT was funded by Janssen-Cilag EMEA, which was responsible for protocol development, data collection, and data analysis. All authors had full access to the data. The corresponding author had final responsibility for the decision to submit the manuscript for publication.

Results

Participants were recruited between December, 2003, and February, 2005, and the last patient completed the study in May, 2006. Figure 1 shows the trial profile. Of the patients who entered the open-label phase, 68% completed the 26-week period. Two patients (one from each treatment group) did not receive trial medication in the double-blind phase and were excluded from the safety and efficacy analyses. After completion of the open-label phase, 45 eligible patients decided not to proceed to the double-blind phase. Two more patients made the same decision, but did so after a medication number had been assigned to them but before medication was issued. The most common reason for discontinuation during the open-label phase was insufficient tolerability, reported by 174 (21%) patients (including patients who cited both insufficient tolerability and insufficient efficacy as reasons for withdrawal). In the double-blind phase, insufficient efficacy (including patients who cited both insufficient tolerability and insufficient efficacy) was the most common reason for discontinuation, reported by 19 (7%) patients assigned to topiramate and 33 (13%) patients assigned to placebo (figure 1). Kaplan-Meier estimates of the time to drop-out in the double-blind phase did not differ between treatment groups (log-rank p=0·4529). Table 1 shows baseline characteristics for patients enrolled in the open-label phase and for the subset of patients who were also included in the double-blind phase.

The median modal dose of topiramate was 100 mg/day (used by 404 patients, 50%); 276 (34%) patients received a modal dose of <100 mg/day (ie, 25–75 mg/day) and 131 (16%) received a modal dose of >100 mg/day (ie, 125–200 mg/day). The number of migraine days was lower in the first 4 weeks of open-label treatment than in the prospective baseline phase, and the difference from

baseline increased as the open-label phase progressed (table 2). During the last 4 weeks of open-label topiramate therapy (endpoint analysis), the mean number of migraine days was lower than the mean during the prospective baseline phase (table 2). The mean number of days per month with intake of acute medication during patients' last 4 weeks of open-label topiramate therapy (4·16, SD 3·91) was lower than that in the prospective baseline period (table 1; mean difference from baseline –1·95, 95% CI –2·21 to –1·69; p<0·0001). For the 733 patients who had a migraine in the last 28 open-label days, the mean duration was 13·22 h (13·76; mean change in duration +0·48 h, –0·41 to 1·36; p=0·6761). For the 709 patients who supplied information on migraine severity during the same period, the mean rating was 2·02 (mean change in rating –0·11, –0·15 to –0·06; p<0·0001).

In patients taking β blockers (n=35), the mean number of migraine days was 7·95 (SD 3·45) at open-label baseline and 5·91 (5·04) at the end of the open-label phase (mean difference –2·03, 95% CI –3·60 to –0·46; p=0·0138). In patients taking tricyclic antidepressants (n=15), numbers of migraine days were 8·74 and 9·59 at open-label baseline and in the last 4 weeks of this phase, respectively (+0·85, –1·83 to 3·53; p=0·5611). When the 48 patients receiving a tricyclic antidepressant, a β blocker, or both were excluded from the analysis, the mean change from baseline during the open label phase was –3·20 migraine days (–3·57 to –2·84; p<0·0001).

Table 3 shows the occurrence of adverse events in the open-label and double-blind phases, and numbers of patients who discontinued the study because of these events. The most common adverse event in the open-label phase was paraesthesia. The other most common adverse events classified as nervous system disorders were disturbance in attention, dysgeusia, and dizziness (table 3). Less common nervous system adverse events included hypoaesthesia (n=33, 4% of patients), memory impairment (n=32, 4%), somnolence (n=28, 3%), non-migraine headache (n=27, 3%; seven patients judged these headaches to be severe), and aphasia (n=20, 2%). Six of the 25 reported serious adverse events were judged by investigators to be possibly (urinary calculus, dyspnoea, pyrexia, and urticaria), probably (depressed mood), or very likely to be (nephrolithiasis) related to the use of topiramate. The most common adverse event in the double-blind phase was paraesthesia in both treatment groups. Few serious adverse events were reported, with no difference between the topiramate and placebo groups (7 of 254 *vs* 10 of 258).

In patients who switched from topiramate to placebo after 26 weeks of treatment, the mean number of migraine days increased from 4·63 (SD 4·03) in the last 4 weeks of the open-label phase to 5·82 (4·36) in the last 4 weeks of the double-blind phase (mean difference from baseline +1·19, 95% CI 0·71 to 1·66; p<0·0001; figure 2). This increase was greater than the equivalent increase in the topiramate group (+0·10 days within-patient difference, –0·36 to 0·56; p=0·0011), and the difference between the increases was significant (–1·09, –1·75 to –0·43; p=0·0011). However, the number of migraine days in the placebo group did not return to the baseline value (table 1; p<0·0001 for comparison of the double-blind endpoint mean with value before open-label treatment). Number of migraine days increased sharply in the placebo group in the first 4 weeks after randomisation, with a small increase in the topiramate group (figure 3); differences between the treatment groups for the change

	Open-label phase (n=818)					Double-blind phase (n=512)	
	Patients	Event severity*			Early end of study†	Topiramate (n=254)	Placebo (n=258)
		Mild	Moderate	Severe			
Paraesthesia	411 (50%)	277	112	22	20 (2%)	77 (30%)	55 (21%)
Fatigue	102 (12%)	52	38	12	13 (2%)	18 (7%)	10 (4%)
Disturbance in attention	100 (12%)	48	44	8	15 (2%)	11 (4%)	12 (5%)
Anorexia or decreased appetite	92 (11%)	60	26	6	4 (<1%)	13 (5%)	9 (3%)
Weight decreased	74 (9%)	36	33	5	5 (<1%)	23 (9%)	18 (7%)
Nausea	71 (9%)	32	26	13	1 (<1%)	11 (4%)	10 (4%)
Dysgeusia	48 (6%)	34	11	3	1 (<1%)	8 (3%)	10 (4%)
Dizziness	47 (6%)	23	19	5	5 (<1%)	1 (<1%)	1 (<1%)
Abdominal pain	42 (5%)	17	17	8	7 (<1%)	6 (2%)	5 (2%)
Depression	39 (5%)	11	23	5	5 (<1%)	13 (5%)	13 (5%)
Any adverse event	695 (85%)	218	350	127	174 (21%)	173 (68%)	151 (59%)
Any serious adverse event‡	22 (3%)	2	9	11	5 (<1%)	7 (3%)	10 (4%)

Data are number of patients who reported the adverse event at least once during that phase (percentage of total). *In patients who reported more than one adverse event, the most severe event was included. †Number of patients in which the events led to early discontinuation of the study. ‡Serious adverse events judged by the investigator as probably or very likely to be related to topiramate treatment were depressed mood and nephrolithiasis (which each occurred in one patient in the open-label phase) and panic attack (which occurred in one patient receiving topiramate in the double-blind phase).

Table 3: **Adverse events that occurred in ≥5% of patients**

in number of migraine days compared with the double-blind baseline values were significant for all periods except weeks 9–16. Duration of migraine headaches remained the same in both treatment groups. Migraine headache severity did not change in the topiramate group between the open-label and double-blind phases (+0·01, –0·08 to 0·09), but severity increased slightly in the placebo group (+0·12, 0·04 to 0·19; p=0·0027), and this change differed from that in the topiramate group (–0·11, –0·22 to 0·003; p=0·0467).

In patients who did not receive tricyclic antidepressants or β blockers, the mean changes in number of migraine days compared with the last four open-label weeks were +1·17 (95% CI 0·66 to 1·67) in the placebo group (n=239) and +0·11 (–0·37 to 0·58) in the topiramate group (n=233) (difference between groups –1·06, –1·75 to –0·37; p=0·0021).

The mean dose of topiramate used during the last 4 weeks of the open-label phase was 105·22 mg/day (SD 36·92). The mean dose used during the last 4 weeks of the double-blind phase was 103·44 mg/day (36·87) in the topiramate group, and the mean dose of placebo equivalent was 105·81 mg/day (38·45). The increase in the number of days with intake of acute medication the last 4 weeks of the double-blind phase relative to the last 4 weeks of the open-label phase was greater in the placebo group than in the topiramate group (1·13 *vs* 0·18; difference between groups –0·95, 95% CI –1·49 to –0·41; p=0·0007). Changes in the intake of triptans accounted for most of the difference, with virtually no difference in analgesic use between the two groups.

At the beginning of the double-blind phase, mean MIDAS score was 15·40 (SD 21·41; mean change from open-label baseline, –21·18, 95% CI –25·20 to –17·17; p<0·0001). At the end of the double-blind phase, the mean score had increased (ie, quality of life had deteriorated) by 6 points in the placebo group, compared with no change in the topiramate group (figure 4). SF-12 physical component score also decreased (ie, physical health was perceived to have deteriorated) in the placebo group (–3·05, –4·17 to –1·94) compared with topiramate (–0·59, –1·74 to 0·55; p=0·0007 between groups), but the change in the mental component score did not differ between groups (+0·37, –1·09 to 1·84, *vs* –0·75, –2·36 to 0·85, respectively; difference between groups –1·20, –3·37 to 0·97; p=0·2282). No significant differences between the two groups were recorded on the HIT-6 questionnaire (difference between groups –1·93, –3·44 to –0·42; p=0·1862).

At the end of the study, patients in the topiramate group were more satisfied with the efficacy of treatment than were those in the placebo group (figure 5). The groups did not differ with respect to satisfaction with the tolerability of treatment, with more than 80% of patients reporting good or very good tolerability (96 and 101, respectively, of 239 patients in the topiramate group; 116 and 101, respectively, of 247 patients in the placebo group), and only 2% of patients reporting poor tolerability (5 of 239 in the topiramate group; 6 of 247 in the placebo group).

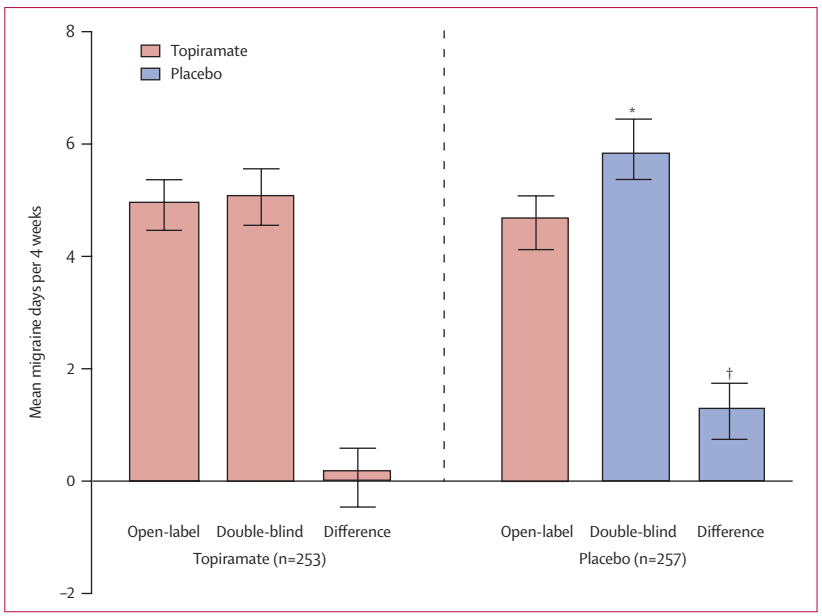

Figure 2: **Migraine days during the last 4 weeks of the open-label and double-blind phases**
Bars indicate 95% CI for means during the last 4 weeks of the open-label phase and during the last 4 weeks of the double-blind phase, and for the differences between groups. The Wilcoxon two-sample test (two tailed) was used to test significance of the differences. *p=0·0234. †p=0·0011.

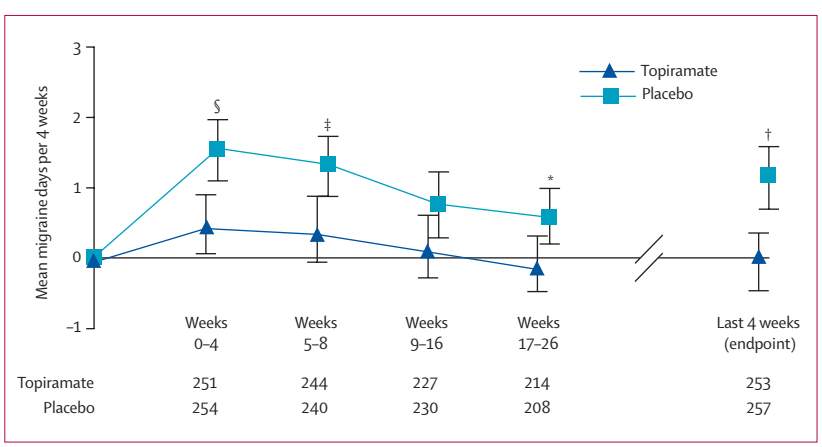

Figure 3: **Change in the number of migraine days from open-label endpoint values during the double-blind phase**
Bars indicate 95% CI for the comparison with baseline. Below the graph are numbers of patients assessed for each period. Numbers are higher for the last 4 weeks than for weeks 0–4 because patients who dropped out within the first 2 weeks were included only in the endpoint analysis. *p=0·0075. †p=0·0011. ‡p=0·0004. §p=0·0006.

Discussion

Our results show that patients who discontinued migraine preventive treatment with topiramate had an increase in the number of migraine days compared with patients who continued treatment. However, topiramate treatment had persistent benefit, because the number of migraine days did not return to pre-treatment values. This has previously

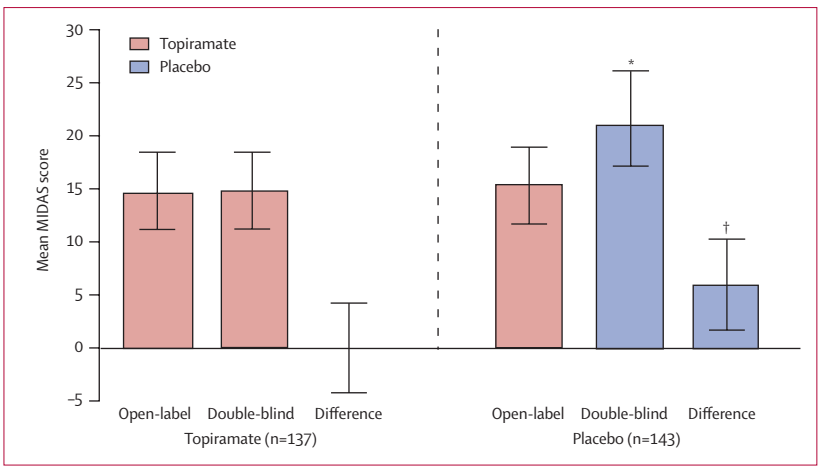

Figure 4: **Quality of life during the last 3 months of the open-label phase and during the double-blind phase**
Bars indicate 95% CI for mean MIDAS scores at the end of the open-label phase and at the end of the double-blind phase, and for the differences between these means. The Wilcoxon two-sample test (two tailed) was used to test significance of the differences. *p=0·0097. †p=0·0046.

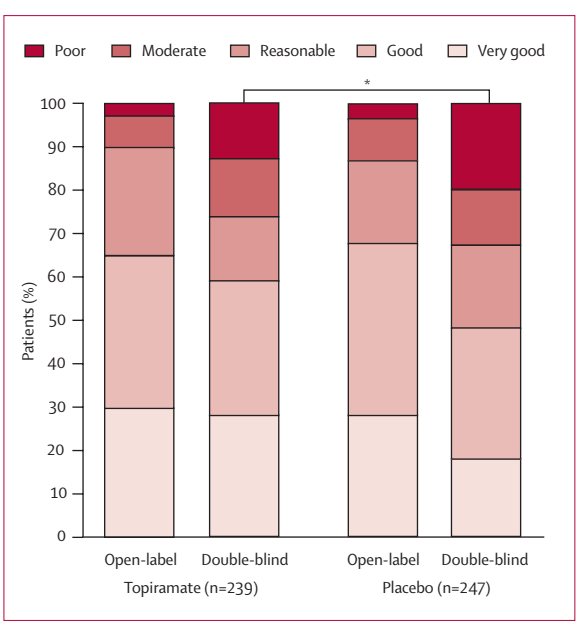

Figure 5: **Patient satisfaction with the efficacy of medication**
Satisfaction was recorded at the end of 6-month open-label treatment with topiramate and at the end of the 6-month double-blind treatment with either topiramate or placebo. The Wilcoxon two-sample test (two tailed) was used to test significance of the differences. *p=0·0052.

been suggested in studies with other migraine preventive treatments such as flunarizine or β blockers,[16,17] although a 12-month placebo-controlled study would be necessary to confirm this suggestion. The long-term effect of topiramate might be to correct the neuronal dysfunction that is thought to be a main factor in migraine pathophysiology. The results of this study therefore have implications for the understanding of migraine pathophysiology. Frequent migraine attacks might lower the threshold for future attacks and promote the progression to chronic migraine, whereas reduction in migraine frequency, either spontaneously or by treatment with topiramate (or other prophylactic drugs) has a long-term effect that outlasts the actual treatment period. Further studies will be necessary to support this hypothesis. Another possibility is that natural fluctuation in migraine course contributed to the slight worsening in the placebo group after discontinuation of topiramate therapy. There might have been regression to the mean, particularly during the open-label phase. Patients tend to agree to participate in clinical trials at times when their migraines are particularly bad.

In patients who continued treatment with topiramate, there was a slight increase in migraine days after the switch from open-label to double-blind treatment, which might relate to patients' expectations about receiving a placebo. During the study, treatment with topiramate had no effect on migraine duration and little or no effect on severity. This suggests that topiramate changes the threshold for the occurrence of migraine attacks but not their intrinsic properties. Similar findings were reported in a study of valproate in patients with migraine.[18]

In the subgroup of patients who also took β blockers, topiramate was associated with a substantially lower number of migraine days compared with baseline. However, in the few patients who received tricyclic antidepressants, topiramate was associated with no significant change in the number of migraine days during the open-label phase. Exclusion of patients receiving β blockers or tricyclic antidepressants had no effect on the overall study results in either the open-label or double-blind phases. Acute migraine treatments, such as triptans, are also unlikely to have had a confounding effect on the primary endpoint, because they are taken after the onset of migraine headache.

Our result has important implications for the treatment of patients who have migraines, because there might be a sustained effect after the end of prophylaxis, and migraine frequency might not return to pre-treatment values. Continuation of topiramate therapy often depends on clinical judgment and patient preference, but the decision of whether to continue could be based on guidelines that relate the recommendation of preventive therapy to the frequency and severity of the migraines. Such guidelines could be applied again after an initial 6 months of preventive treatment.

The efficacy benefits of continued treatment were supported by patient-perceived benefits for quality of life, as assessed by both disease-specific (MIDAS) and generic (SF-12) questionnaires. In particular, the SF-12 results highlight the effect of migraine on physical health, an aspect of migraine that can be overlooked. We recorded no difference between groups in the HIT-6 questionnaire results during the double-blind phase, which is consistent with the absence of a significant effect on migraine severity and duration. The HIT-6 questionnaire might not be sensitive enough to migraine frequency to detect differences between the two groups.

Topiramate was well tolerated, with no new or unexpected adverse events. Adverse events were generally more common in the first part of the open-label phase than in the double-blind phase, and about 20% of patients discontinued treatment during the open-label phase because of poor tolerability. Patients from both the placebo and the topiramate groups who entered the double-blind phase had fewer adverse events than they did during the open-label phase, although the incidence of paraesthesia remained relatively high in the placebo group; this finding suggests at least some carry-over effect from the open-label phase. The overall prevalence of adverse events in the double-blind phase was higher in the topiramate group than in the placebo group, although the perception of tolerability did not differ between the groups. This result contrasts with the greater patient satisfaction with the efficacy of topiramate than with the efficacy of placebo.

The results of the double-blind phase are consistent with those of previous placebo-controlled topiramate studies,[8–10] a meta-analysis of these studies,[19] and open-label extensions of trials,[20] although these studies assessed the effects of initiation of topiramate rather than withdrawal. The between-group difference in migraine days reported here is similar to that in the shorter-term studies and the meta-analysis. For example, in a prospective randomised, double-blind study in 468 patients who received topiramate or placebo for 6 months, the mean change in the number of migraine days per month was more pronounced for patients who received topiramate at 100 mg/day (–2·1; p=0·008) or 200 mg/day (–2·4; p<0·001) compared with those who received placebo (–1·1).[8] Topiramate was originally licensed for prophylactic treatment of migraine on the basis of the magnitude of treatment difference in that and the other placebo-controlled topiramate studies.[9,10]

The strength of our study is its power, achieved by high patient numbers and the long observation period of 12 months, which reflects clinical reality much more closely than does the 3-month period often used in clinical trials of migraine prevention. Additionally, this study investigated migraine frequency after the end of treatment in a double-blind, placebo-controlled design. The major limitation of the study design is that patients who did not tolerate topiramate, or who did not experience a positive balance between efficacy and tolerability, were likely to drop out during the open-label phase, although this does reflect clinical practice. Expectation might also have influenced patients in both treatment groups: patients who suspected that they were receiving placebo might have had a more pronounced increase in migraine frequency.

In summary, we have shown that discontinuation of topiramate treatment in a double-blind, placebo-controlled manner after 6 months is associated with persistent benefits compared with values before treatment, although numbers of migraine days were higher and quality of life was lower in patients who discontinued topiramate use than in those who continued treatment. Patients should therefore be treated for 6 months, with the option to continue treatment to 12 months in some patients, particularly those whose migraine frequency decreased substantially with topiramate.

Contributors

H-CD, RA, GA, GB, BD, ME, ML-M, UR, MSDR, and JS participated in the study as investigators. JvO was involved in the initial study idea, drafted the protocol and case report form, was responsible for trial conduct (which included supervision and coordination of central and local trial monitoring, data management, and statistical analysis). H-CD and JvO developed the scientific question and wrote the protocol. PB did statistical analysis. All authors provided input at all stages of writing of the manuscript, and have seen and approved the final version.

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Conflicts of interest

H-CD, RA, GA, GB, BD, ME, ML-M, UR, MSDR, and JS have participated in clinical trials and advisory boards for Janssen-Cilag. PB, SS, JvO are employees of Janssen-Cilag EMEA (Europe, Middle East, and Africa). H-CD has received honoraria from Addex Pharmaceuticals,

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