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# Trial of Amitriptyline, Topiramate, and Placebo for Pediatric Migraine

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## Abstract

**BACKGROUND—**Which, medication, if any, to use to prevent the headache of pediatric migraine has not been established.

**METHODS—**We conducted a randomized, double-blind, placebo-controlled trial of amitriptyline (1 mg per kilogram of body weight per day), topiramate (2 mg per kilogram per day), and placebo in children and adolescents 8 to 17 years of age with migraine. Patients were randomly assigned in a 2:2:1 ratio to receive one of the medications or placebo. The primary outcome was a relative reduction of 50% or more in the number of headache days in the comparison of the 28-day baseline period with the last 28 days of a 24-week trial. Secondary outcomes were headache-related disability, headache days, number of trial completers, and serious adverse events that emerged during treatment.

**RESULTS—**A total of 361 patients underwent randomization, and 328 were included in the primary efficacy analysis (132 in the amitriptyline group, 130 in the topiramate group, and 66 in the placebo group). The trial was concluded early for futility after a planned interim analysis. There were no significant between-group differences in the primary outcome, which occurred in 52% of the patients in the amitriptyline group, 55% of those in the topiramate group, and 61% of those in the placebo group (amitriptyline vs. placebo, P = 0.26; topiramate vs. placebo, P = 0.48; amitriptyline vs. topiramate, P = 0.49). There were also no significant between-group differences in headache-related disability, headache days, or the percentage of patients who completed the 24-week treatment period. Patients who received amitriptyline or topiramate had higher rates of

*A complete list of investigators in the Childhood and Adolescent Migraine Prevention (CHAMP) trial is provided in the Supplementary Appendix, available at NEJM.org.

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several adverse events than those receiving placebo, including fatigue (30% vs. 14%) and dry mouth (25% vs. 12%) in the amitriptyline group and paresthesia (31% vs. 8%) and weight loss (8% vs. 0%) in the topiramate group. Three patients in the amitriptyline group had serious adverse events of altered mood, and one patient in the topiramate group had a suicide attempt.

**CONCLUSIONS—**There were no significant differences in reduction in headache frequency or headache-related disability in childhood and adolescent migraine with amitriptyline, topiramate, or placebo over a period of 24 weeks. The active drugs were associated with higher rates of adverse events. (Funded by the National Institutes of Health; CHAMP ClinicalTrials.gov number, NCT01581281).

More than 6 million children and adolescents in the United States have migraines.[1–3] The majority continue to have headaches into adulthood, taking a toll on the U.S. economy of approximately $36 billion and resulting in substantial effects on quality of life.[4–7] Pediatric clinical practice guidelines for migraine treatment are consensus based rather than evidence based,[8,9] with no Food and Drug Administration (FDA)–approved migraine prevention medication for children younger than 12 years of age.

The Childhood and Adolescent Migraine Prevention (CHAMP) trial tested the effects of amitriptyline and topiramate in comparison with each other and with placebo in pediatric migraine. Previous studies of this disorder have shown high placebo response rates (up to 50 to 60%).[10–14] The two medications were chosen on the basis of a survey of pediatric headache specialists, who indicated that these drugs were the most commonly used preventive medications.[8,9] Both the International Headache Society Clinical Trial Guidelines[15] and respondents to the same survey indicated that a clinically meaningful end point is a reduction of 50% or more in days on which a patient had headache. The CHAMP trial involved three hypotheses related to the primary end point of a relative reduction of 50% or more in the number of headache days from the 28-day baseline period to the final 28 days of the 24-week trial: that amitriptyline would provide greater relief than placebo, that topiramate would provide greater relief than placebo, and that one of the active treatments would provide greater relief than the other active treatment.

## METHODS

### TRIAL DESIGN AND OVERSIGHT

The CHAMP trial was a phase 3, multicenter, double-blind, placebo-controlled trial funded by the National Institutes of Health.[16] An independent data and safety monitoring board that was appointed by the National Institute of Neurological Disorders and Stroke (NINDS) participated in the protocol review and provided trial oversight in collaboration with the NINDS. The trial was conducted under an investigational new drug application with the FDA. Patients were enrolled from 31 sites in the United States. Written permission from a parent or guardian and, when appropriate, child assent were obtained.[17] Randomization was stratified according to age (8 to 12 years vs. 13 to 17 years) and the number of headache days on the basis of the diary kept during the 28-day baseline period (4 to 14 [episodic] vs. ≥15 [chronic]).

The authors were responsible for all elements of the trial, including design, data collection, analysis, and interpretation. Data were collected by the site investigators and site trial staff and were transmitted electronically to a data coordinating center for analysis: all data remained confidential and blinded during the trial. All the authors were involved in each stage of the manuscript development and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol and statistical analysis plan, which are available with the full text of this article at NEJM.org. The data and safety monitoring board and the NINDS reviewed and provided feedback on the manuscript to the authors, who had full editorial control of the manuscript.

The investigational pharmacy at Cincinnati Children's Hospital Medical Center purchased generic drugs for this trial with the use of grant funds. Trial drugs and placebo were enclosed in capsules to maintain blinding.

## TRIAL POPULATION

Children and adolescents 8 to 17 years of age were eligible for participation. Inclusion criteria[16,17] included a diagnosis of migraine with or without aura or chronic migraine without continuous headache, as defined by the International Classification of Headache Disorders, 2nd Edition[18]; a score on the Pediatric Migraine Disability Assessment Scale (PedMIDAS) of 11 to 139 (range, 0 to 240, with a score of 0 to 10 indicating no disability, 11 to 30 mild disability, 31 to 50 moderate disability, and >50 severe disability)[19]; and a headache frequency of 4 or more days from a prospective headache diary over a baseline period of 28 days.

## TRIAL INTERVENTION

After the baseline period, eligible patients were randomly assigned in a 2:2:1 ratio to receive oral amitriptyline, topiramate, or placebo, administered in a divided dose of 1 capsule twice daily. The target dose was 1 mg per kilogram of body weight per day for amitriptyline and 2 mg per kilogram per day for topiramate. Dose escalation occurred every 2 weeks over a period of 8 weeks, with dose modification based on side effects. A 16-week constant-dose (maintenance) phase followed at the highest dosage achieved. Site investigators ended drug treatment for patients with severe side effects occurring during the maintenance period of the trial, but these patients were followed for safety monitoring. Decisions regarding cessation of medication and withdrawal from the trial were made with input from the family, site-investigator judgment, and medical-monitor recommendations. After the 24-week treatment period, a 2-week weaning period and a 4-week follow-up occurred. Details of the trial protocol were published previously.[16,17]

## TRIAL ASSESSMENTS

Patients completed a daily headache diary, in accordance with the NINDS Common Data Elements.[20] A headache day was defined as any day during which a headache occurred within a 24-hour period starting at midnight. The PedMIDAS, which assesses the effect of migraines on school, home, play, and social activities, was used to determine the change in headache-related disability between baseline and the end of the trial. Safety was assessed with the use of adverse-event reports that were collected from parents and patients by means

of a structured interview. Weight, height, vital signs, clinical laboratory tests, and physical and neurologic examinations were serially monitored, according to the protocol. Serious adverse events were reported by site investigators, then reviewed on an urgent basis by the medical safety monitor, who determined the potential relationship to treatment. Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities*, version 11.0. The Child Depression Inventory (with raw scores ranging from 0 to 54 and higher scores indicating more severe depression),[21] Behavior Rating Inventory of Executive Function (BRIEF),[22] and electrocardiographic (ECG) measures were used in conjunction with the review of adverse events by the medical monitor on a quarterly basis to further assess safety. Adherence was assessed by means of central analysis of blood levels of amitriptyline or topiramate, depending on the treatment assignment.

## TRIAL OUTCOMES

The primary outcome was a relative reduction of 50% or more in the number of headache days in the comparison of the 28-day baseline period with the last 28 days of the 24-week trial. Four secondary outcomes were headache disability, as measured by absolute change in the PedMIDAS score; the absolute reduction in the number of headache days, from the 28-day baseline period to the final 28-day period of treatment; number of trial completers, as assessed by the percentage of patients who completed the 24-week treatment period; and serious adverse events that emerged during treatment.

## STATISTICAL ANALYSIS

We chose the sample size to ensure adequate power, assuming that 50% of the patients receiving placebo versus 70% of those receiving amitriptyline or topiramate would have a reduction in the number of headache days of 50% or more, with a 15% dropout rate. We planned to enroll 675 patients (270 in the amitriptyline group, 270 in the topiramate group, and 135 in the placebo group) to provide at least 85% power to detect all differences between active treatment and placebo and 90% power to detect a difference of 15 percentage points between the two active treatments. Interim assessments for futility as well as efficacy were planned when 225 and 450 patients had completed their 24-week visit. Stopping for futility was to occur if the conditional power based on the prespecified effect for both treatments compared with placebo fell below 20 percentage points.

In November 2014, the first of two planned interim analyses occurred on the basis of data from 225 randomly assigned patients who had completed the trial; another 103 randomly assigned patients subsequently completed the trial, for a total of 328 patients analyzed for the primary outcome, as described below. The conditional power at the time of the interim analysis was 16 percentage points for the comparison between amitriptyline and placebo and 14 percentage points for the comparison between topiramate and placebo, and both met the threshold for futility. After considering all the evidence, including the conditional power calculated in a number of sensitivity analyses (e.g., multiple imputation and observed data only) to assess the effect of missing data, the data and safety monitoring board recommended early closure of the trial for futility. The NINDS accepted the recommendation and closed the trial.

Owing to the early stopping of the trial, the primary efficacy analyses and secondary analyses of disability, headache frequency, and drug discontinuation included all patients who either had complete headache-diary data at the end-point visit or had a date for an expected end-point visit on or before the target date for completion of the last weaning visit in the original closeout plan (February 4, 2015). All randomly assigned patients were included in the safety analyses.

The primary analysis used a logistic-regression model. The models and corresponding odds ratios were adjusted for age and for the number of headache days during the 28-day baseline period. Each was tested with the use of a Bonferroni corrected significance level of 0.017 (i.e., 0.05 ÷ 3). These analyses followed the intention-to-treat principle.

For the primary analyses, we imputed an outcome of treatment failure for any patient who either withdrew early for any reason or did not provide headache-diary data at week 24. We used a series of sensitivity analyses to assess the effect of missing data on the primary analysis results. In alternative imputation approaches, we assumed that all patients who withdrew owing to side effects had treatment failures. For all other patients, end points were imputed with the use of a series of sensitivity analyses.

Secondary end points were analyzed with the use of linear regression for continuous variables and binary data methods for categorical variables. These models were adjusted for age and the number of headache days during the baseline period. In the analysis of headache-related disability, we also adjusted for the baseline PedMIDAS score. A multiple-comparisons adjustment similar to that used for the primary analysis was implemented for the secondary comparison of the difference in the change in mean headache days over the 24-week treatment period but not for any of the other secondary comparisons.

Continuous variables were summarized by means, standard deviations, and minimum and maximum variables. Categorical variables were summarized by percentages. Comparisons of baseline variables between trial groups were performed with the use of t-tests for continuous variables and Fisher’s exact test for categorical variables. No adjustments were made for baseline comparisons.

The mean T score from the Child Depression Inventory and the mean BRIEF global composite score (with the raw score converted to a T score of 0 to 100 and higher scores indicating more [or more severe] symptoms for both inventories) were calculated and compared among trial groups at baseline, visit 5, and visit 8. Binary indicators of a Child Depression Inventory T score greater than 80 and an answer of “yes” to the item on suicidal intent or ideation were also compared with the use of Fisher’s exact test among the groups.

## RESULTS

### PATIENTS

From July 16, 2012, through November 24, 2014, a total of 488 children and adolescents agreed to participate in the trial and were assessed for eligibility. Of those patients, 361 underwent randomization (Fig. 1) to receive amitriptyline (144 patients), topiramate (145

patients), or placebo (72 patients) in a 2:2:1 ratio. The baseline characteristics of the patients were similar across the three groups (Table 1). The mean (±SD) age was 14.2±2.4 years, and the trial population was predominantly female (68%) and white (70%). The mean number of headache days in the first 28 days of diary recordings for all patients was 11.4±6.1. Additional baseline data have been published previously.[17] The final average dose was 0.99±0.18 mg per kilogram for amitriptyline and 1.93±0.40 mg per kilogram for topiramate.

## PRIMARY OUTCOME

In the intention-to-treat analysis of 328 patients included before trial closure, the percentage of patients who had a relative reduction of 50% or more in the number of headache days was 52% in the amitriptyline group, 55% in the topiramate group, and 61% in the placebo group, in the comparison of the 28-day baseline period with the last 28 days of the 24-week trial (Table 2 and Fig. 2). The adjusted odds ratio for the primary outcome was 0.71 (98.3% confidence interval [CI], 0.34 to 1.48; P = 0.26) for amitriptyline versus placebo and 0.81 (98.3% CI, 0.39 to 1.68; P = 0.48) for topiramate versus placebo. There was no significant difference in effect when the two active drugs were compared with each other (odds ratio for amitriptyline vs. topiramate, 0.88; 98.3% CI, 0.49 to 1.59; P = 0.49).

In sensitivity analyses using headache data obtained at baseline and week 24, there were 264 patients available for analysis. The percentage of patients with a relative reduction of 50% or more in the number of headache days was 66% with amitriptyline, 71% with topiramate, and 68% with placebo. Adjusted odds ratios were 0.94 for amitriptyline versus placebo (P = 0.86), 1.18 for topiramate versus placebo (P = 0.64), and 0.80 for amitriptyline versus topiramate (P= 0.45). The results of an additional sensitivity analysis involving multiple imputation are shown in Figure 2. By combining these approaches, we estimated that 52 to 66% of the patients in the amitriptyline group, 55 to 71% of the patients in the topiramate group, and 61 to 68% of the patients in the placebo group had a relative reduction of 50% or more in the number of headache days. Owing to the consistency of results across all the sensitivity analyses examining the effect of missing data, the results described below are from the subgroup of patients with data at both baseline and the end-point visit (visit 8).

## SECONDARY OUTCOMES

**Headache-Related Disability—**The baseline PedMIDAS score did not differ significantly among the three trial groups (P = 0.77). The absolute change in the score was −22.5 (95% CI, −27.6 to −17.4) with amitriptyline, −26.8 (95% CI, −32.2 to −21.5) with topiramate, and −22.6 (95% CI, −30.2 to −15.0) with placebo (Table 2). There were no significant model- adjusted differences between groups: amitripty-line versus placebo, −0.4 (95% CI, −6.6 to 6.0; P = 0.91); topiramate versus placebo, −4.8 (95% CI, −11.2 to 1.5; P = 0.13); and amitriptyline versus topiramate, 4.5 (95% CI, −0.9 to 9.9; P = 0.10).

**Headache Days—**In the comparison of the number of days on which patients had a headache in the 28-day baseline period and the 28 days preceding week 24, patients with both measurements showed an absolute change of −6.7 days (95% CI, −7.9 to −5.5) with amitriptyline, −6.7 days (95% CI, −7.6 to −5.7) with topiramate, and −5.9 days (95% CI, −7.7 to −4.1) with placebo (Table 2). There were no significant model-adjusted differences

between groups: amitriptyline versus placebo, −0.7 days (98.3% CI, −2.6 to 1.2; P = 0.36); topiramate versus placebo, −0.6 days (98.3% CI, −2.5 to 1.2; P = 0.41); and amitriptyline versus topiramate, −0.1 days (98.3% CI, −1.7 to 1.5; P = 0.90).

**Trial Discontinuation—**The percentage of randomly assigned patients who completed the 24-week treatment phase was 80% with amitriptyline, 78% with topira-mate, and 89% with placebo (Table 2). There were no significant differences in dropout rates between trial groups (amitriptyline vs. placebo, P = 0.16; topiramate vs. placebo, P = 0.08; and amitriptyline vs. topiramate, P = 0.76).

**Serious Adverse Events—**A total of 12 serious adverse events that emerged during treatment were reported (6 in the amitriptyline group, 4 in the topiramate group, and 2 in the placebo group), occurring in 11 patients. Investigators who were unaware of treatment assignments determined that 5 serious adverse events were treatment-related: 3 instances of altered mood (in the amitriptyline group) and 1 incidence each of a suicide attempt (in the topiramate group) and syncope (in the amitripty-line group). No significant trends were observed in serious adverse events that emerged during treatment across the three groups.

## SAFETY

A total of 852 adverse events were reported (301 with amitriptyline, 419 with topiramate, and 132 with placebo), in 272 patients (Table 3). There were no deaths in the trial.

Adverse events that occurred significantly more often in the amitriptyline group than in the placebo group were fatigue (30% vs. 14%, P = 0.01) and dry mouth (25% vs. 12%, P = 0.03). Adverse events that occurred significantly more often in the topiramate group than in the placebo group were paresthesia (31% vs. 8%, P <0.001) and decreased weight (8% vs. 0%, P = 0.02). Other commonly occurring adverse events with topiramate were fatigue (25%), dry mouth (18%), memory impairment (17%), aphasia (16%), cognitive disorder (16%), and upper respiratory tract infection (12%).

There were no observed differences in any of the Child Depression Inventory characteristics (mean score, percentage of patients with a T score >80, or percentage of patients with an answer of “yes” to the item on suicidal intent or ideation), the mean BRIEF T score, or results of the ECG readings at baseline, visit 5, or visit 8.

## ADHERENCE AND CROSSOVER

A total of 205 patients in the active-treatment groups had end-point data, and treatment adherence was assessed for 202 patients (103 in the amitriptyline group and 99 in the topiramate group). Of these patients, 81% of those who received amitriptyline and 74% of those who received topiramate had detectable drug levels in their blood samples. Crossover between trial groups occurred in only 1 patient, who was assigned to amitriptyline but who took topiramate 3 weeks before the end of the trial; this patient was imputed to have had a treatment failure owing to a lack of end-point headache data. Because all the patients who did not provide trial data at the final visit were imputed to have had treatment failures in the

primary analysis, it is unlikely that crossover or adherence had any meaningful effect on the overall trial results.

## DISCUSSION

This trial, which was stopped early owing to futility, showed that neither of two preventive medications for pediatric migraine was more effective than placebo in reducing the number of headache days over a period of 24 weeks. Patients who received amitriptyline or topiramate had higher rates of adverse events than those who received placebo. During the trial, the FDA approved topiramate for the treatment of episodic migraine in adolescents 12 to 17 years of age. Although our trial included patients outside this age range and included those with either episodic or chronic migraine, the trial results suggest that prevention medication for pediatric migraine might be reexamined.

In this trial, we found a high placebo response rate that was similar to the rate reported in previous headache and pain trials.[10–14,23,24] It is possible that this effect can be advantageous for children and adolescents with migraine.[12] In planning for the CHAMP trial, statistical simulations[16] included the possibility of a placebo effect of 40 to 55% and medication response rates of 50 to 95%. Results indicated a probability of more than 95% that we would find no significant differences when a high placebo response rate and a low drug response rate occurred. In this trial, we did not find age-related contributions to the placebo or drug response. It is possible that the percentage of patients who completed the 24-week treatment period might have differed significantly between the medication groups and the placebo group if the trial had continued to enroll the full anticipated sample.

Given the null outcome in this trial and the adverse events and serious adverse events reported in the amitriptyline and topiramate groups, the data do not show a favorable risk–benefit profile for the use of these therapies in pediatric migraine prevention, at least over the 24-week duration of the trial. Our findings also suggest that the adult model of headache treatment, in which amitriptyline and topiramate have been effective, may not apply to pediatric patients.[25]

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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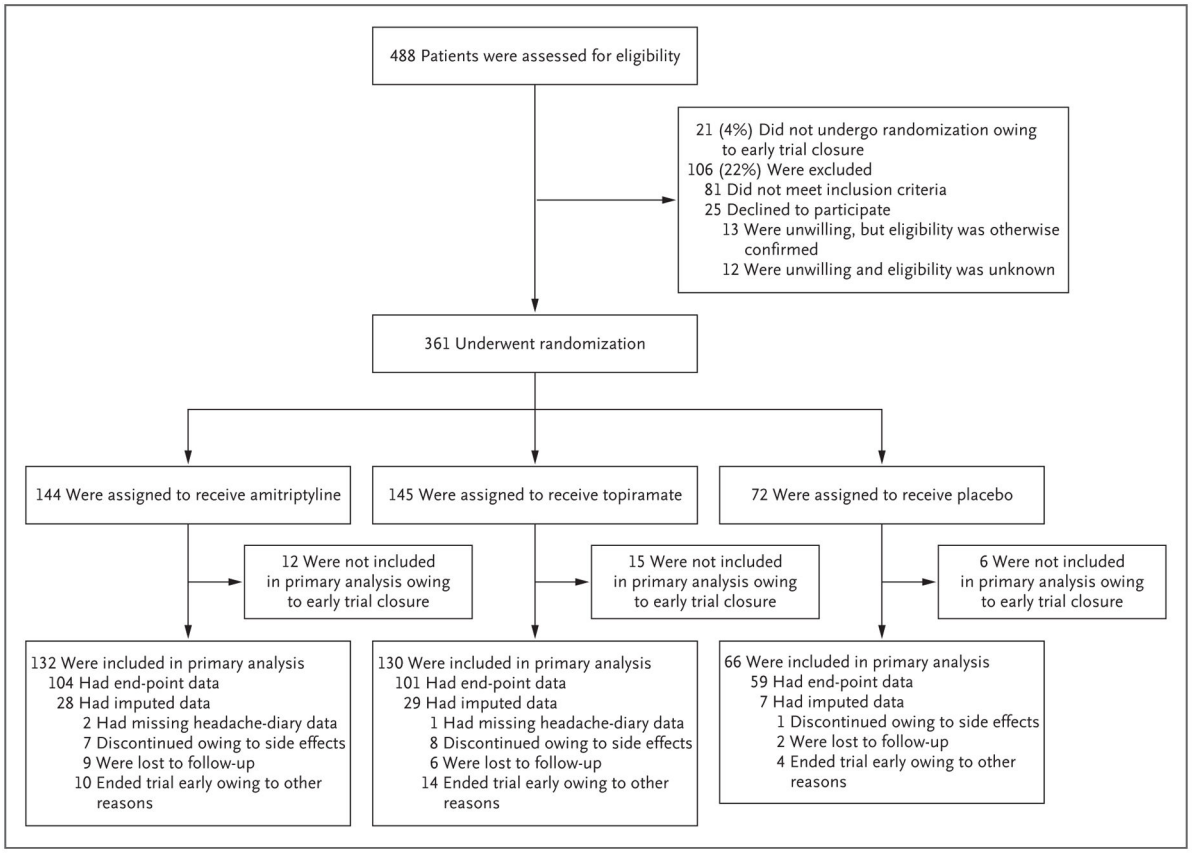


**Figure 1. Randomization and Follow-up**

Among the patients who did not meet the inclusion criteria, the primary reasons for ineligibility included headache frequency (38 patients), score on the Pediatric Migraine Disability Assessment Scale (23 patients), and other medical conditions (15 patients). Among the patients who declined to participate, the primary reasons included concerns about side effects (4 patients), lack of time (3), and other reasons (12 patients). The trial was stopped early for futility on the recommendation of the data and safety monitoring board.

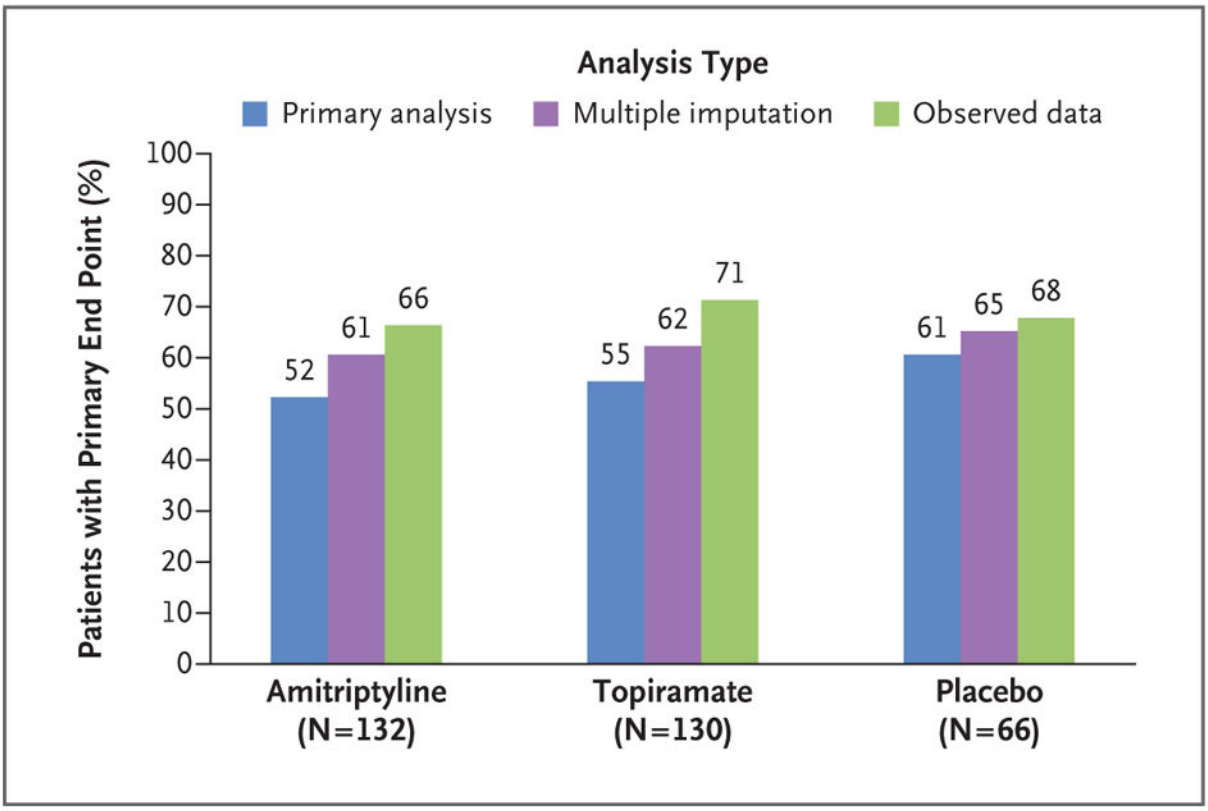


**Figure 2. Patients with a_Relative_Reduction of 50% or More in the Number of Headache Days**

Shown is the percentage of patients with a relative reduction of 50% or more in the number of headache days in the comparison of the 4-week baseline period with the last 4 weeks of a 24-week trial (primary end point). Results are shown for the primary analysis and two a priori sensitivity analyses to assess the effect of missing data. Sample sizes for the trial groups represent the primary analysis population. For observed data, the population is the subgroup with observed data at week 24.

## Table 1

Characteristics of the Patients at Baseline.*

| Characteristic | All Patients (N = 361) | Amitriptyline (N = 144) | Topiramate (N = 145) | Placebo (N = 72) |
|---|---|---|---|---|
| Age — yr | 14.2±2.4 | 14.2±2.4 | 14.2±2.5 | 14.2±2.2 |
| Female sex — no. (%) | 247 (68) | 97 (67) | 101 (70) | 49 (68) |
| Race or ethnic group — no. (%)† | | | | |
| White | 253 (70) | 107 (74) | 98 (68) | 48 (67) |
| Black | 67 (19) | 26 (18) | 24 (17) | 17 (24) |
| Asian | 6 (2) | 0 | 6 (4) | 0 |
| American Indian or Alaska Native | 27 (7) | 8 (6) | 14 (10) | 5 (7) |
| Native Hawaiian or Pacific Islander | 1 (<0.05) | 0 | 1 (1) | 0 |
| Not reported or unknown | 7 (2) | 3 (2) | 2 (1) | 2 (3) |
| Non-Hispanic ethnic group | 316 (88) | 128 (89) | 123 (85) | 65 (90) |
| PedMIDAS score‡ | 41.9±26.8 | 40.6±26.4 | 42.6±27.4 | 42.9±26.7 |
| Headache days during 28-day baseline period | 11.4±6.1 | 11.5±6.2 | 11.5±6.1 | 11.0±6.3 |

*Plus–minus values are means ±SD. There were no significant differences among the three groups.

†Race and ethnic group were reported by the patient or surrogate.

‡Scores on the Pediatric Migraine Disability Assessment Scale (PedMIDAS) range from 0 to 240, with a score of 0 to 10 indicating no disability, 11 to 30 mild disability, 31 to 50 moderate disability, and more than 50 severe disability.

## Table 2

Primary and Secondary Outcomes.*

| Outcome | Amitriptyline (N = 132) | Topiramate (N = 130) | Placebo (N = 66) |
|---|---|---|---|
| **Primary outcome**† | | | |
| ≥50% Relative reduction in headache frequency — no. (%) | 69 (52) | 72 (55) | 40 (61) |
| 98.3% CI | 42 to 63 | 45 to 66 | 45 to 75 |
| P value for pairwise comparison with placebo | 0.26 | 0.48 | — |
| **Secondary outcomes** | | | |
| PedMIDAS score‡ | | | |
| At baseline | 41.3±27.9 | 41.2±25.0 | 42.0±27.0 |
| At wk 24 | 18.8±25.3 | 14.4±17.3 | 19.4±20.8 |
| Observed absolute difference (95% CI) | −22.5 (−27.6 to −17.4) | −26.8 (−32.2 to −21.5) | −22.6 (−30.2 to −15.0) |
| P value for pairwise comparison with placebo | 0.91 | 0.13 | — |
| Headache days per 28-day period§ | | | |
| At baseline | 11.3±6.0 | 11.3±5.7 | 11.1±6.5 |
| At wk 24 | 4.6±4.6 | 4.6±5.3 | 5.2±6.5 |
| Observed absolute difference (95% CI) | −6.7 (−7.9 to −5.5) | −6.7 (−7.6 to −5.7) | −5.9 (−7.7 to −4.1) |
| P value for pairwise comparison with placebo | 0.36 | 0.41 | — |
| **Completion outcomes**¶ | | | |
| Patients who completed the trial — no. (%) | 106 (80) | 102 (78) | 59 (89) |
| 95% CI | 73 to 86 | 71 to 85 | 80 to 95 |
| Patients who withdrew owing to side effects — no. (%) | 7 (5) | 8 (6) | 1 (2) |
| 95% CI | 3 to 11 | 3 to 12 | <0.5 to 8 |

*Plus–minus values are means ±SD. No pairwise comparisons met the criteria for statistical significance. CI denotes confidence interval.

†The primary efficacy analysis population included all the patients who either had an observed end-point visit with complete headache-diary data or had a target date for an expected end-point visit on or before the target date for completion of the last weaning visit in the original closeout plan (February 4, 2015).

‡The analysis population included all the patients who had observed end-point data: 107 in the amitriptyline group, 104 in the topiramate group, and 60 in the placebo group.

§The analysis population included all the patients who had observed end-point data: 104 in the amitriptyline group, 101 in the topiramate group, and 59 in the placebo group.

¶According to the statistical analysis plan, a concern about side effects was defined as a percentage of patients who complete the 24-week treatment period for the two active-treatment groups that was significantly lower than the percentage among patients receiving placebo or a percentage that was significantly less than 65%.

**Table 3**

Adverse Events and Serious Adverse Events.*

| Adverse Event | All Patients (N = 361) | Amitriptyline (N = 144) | | Topiramate (N = 145) | | Placebo (N = 72) | |
|---|---|---|---|---|---|---|---|
| | Adverse Events | Adverse Events | Serious Adverse Events | Adverse Events | Serious Adverse Events | Adverse Events | Serious Adverse Events |
| | *number of patients (percent)* | | | | | | |
| Nervous system | | | | | | | |
| Aphasia | 43 (12) | 13 (9) | 0 | 23 (16) | 0 | 7 (10) | 0 |
| Cognitive disorder | 45 (12) | 14 (10) | 0 | 23 (16) | 0 | 8 (11) | 0 |
| Dizziness | 13 (4) | 3 (2) | 0 | 9 (6) | 0 | 1 (1) | 0 |
| Memory impairment | 42 (12) | 11 (8) | 0 | 24 (17) | 0 | 7 (10) | 0 |
| Paresthesia | 61 (17) | 10 (7) | 0 | 45 (31)† | 0 | 6 (8) | 0 |
| Syncope | 3 (1) | 3 (2) | 1 (1) | 0 | 0 | 0 | 0 |
| General: fatigue | 89 (25) | 43 (30)† | 0 | 36 (25) | 0 | 10 (14) | 0 |
| Gastrointestinal | | | | | | | |
| Dry mouth | 71 (20) | 36 (25)† | 0 | 26 (18) | 0 | 9 (12) | 0 |
| Intussusception | 1 (<0.5) | 0 | 0 | 1 (1) | 1 (1) | 0 | 0 |
| Infection | | | | | | | |
| Appendicitis | 1 (<0.5) | 0 | 0 | 0 | 0 | 1 (1) | 1 (1) |
| Streptococcal pharyngitis | 12 (3) | 7 (5) | 0 | 1 (1)† | 0 | 4 (6) | 1 (1) |
| Upper respiratory tract infection | 42 (12) | 14 (10) | 0 | 18 (12) | 0 | 10 (14) | 0 |
| Psychiatric | | | | | | | |
| Altered mood | 29 (8) | 11 (8) | 3 (2) | 14 (10) | 0 | 4 (6) | 0 |

| Adverse Event | All Patients (N = 361) | Amitriptyline (N = 144) | | Topiramate (N = 145) | | Placebo (N = 72) | |
|---|---|---|---|---|---|---|---|
| | Adverse Events | Adverse Events | Serious Adverse Events | Adverse Events | Serious Adverse Events | Adverse Events | Serious Adverse Events |
| | *number of patients (percent)* | | | | | | |
| Suicide attempt | 1 (<0.5) | 0 | 0 | 1 (1) | 1 (1) | 0 | 0 |
| Investigations: decreased weight | 11 (3) | 0 | 0 | 11 (8)† | 0 | 0 | 0 |
| Injury, poisoning, or procedural complication | | | | | | | |
| Contusion | 7 (2) | 3 (2) | 0 | 1 (1) | 1 (1) | 3 (4) | 0 |
| Hand fracture | 3 (1) | 0† | 0 | 0† | 0 | 3 (4) | 0 |
| Traumatic liver injury | 1 (<0.5) | 0 | 0 | 1 (1) | 1 (1) | 0 | 0 |
| Respiratory: bronchospasm | 5 (1) | 3 (2) | 1 (1) | 1 (1) | 0 | 1 (1) | 0 |
| Immune system: anaphylactic reaction | 1 (<0.5) | 1 (1) | 1 (1) | 0 | 0 | 0 | 0 |

*Shown are serious adverse events, adverse events occurring in more than 5% of the patients in a trial group, and adverse events that differed significantly between an active-treatment group and the placebo group. A total of four serious adverse events in the amitriptyline group (one event of syncope and three events of altered mood) and one serious adverse event in the topiramate group (one suicide attempt) were considered to be treatment-related by the medical safety monitor. No patients had more than one treatment-related serious adverse event.

†The difference in the comparison with placebo was significant in this category.