Original Investigation

Cognitive Behavioral Therapy Plus Amitriptyline for Chronic Migraine in Children and Adolescents
A Randomized Clinical Trial

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IMPORTANCE Early, safe, effective, and durable evidence-based interventions for children and adolescents with chronic migraine do not exist.

OBJECTIVE To determine the benefits of cognitive behavioral therapy (CBT) when combined with amitriptyline vs headache education plus amitriptyline.

DESIGN, SETTING, AND PARTICIPANTS A randomized clinical trial of 135 youth (79% female) aged 10 to 17 years diagnosed with chronic migraine (≥15 days with headache/month) and a Pediatric Migraine Disability Assessment Score (PedMIDAS) greater than 20 points were assigned to the CBT plus amitriptyline group (n = 64) or the headache education plus amitriptyline group (n = 71). The study was conducted in the Headache Center at Cincinnati Children's Hospital between October 2006 and September 2012; 129 completed 20-week follow-up and 124 completed 12-month follow-up.

INTERVENTIONS Ten CBT vs 10 headache education sessions involving equivalent time and therapist attention. Each group received 1 mg/kg/d of amitriptyline and a 20-week end point visit. In addition, follow-up visits were conducted at 3, 6, 9, and 12 months.

MAIN OUTCOMES AND MEASURES The primary end point was days with headache and the secondary end point was PedMIDAS (disability score range: 0-240 points; 0-10 for little to none, 11-30 for mild, 31-50 for moderate, >50 for severe); both end points were determined at 20 weeks. Durability was examined over the 12-month follow-up period. Clinical significance was measured by a 50% or greater reduction in days with headache and a disability score in the mild to none range (<20 points).

RESULTS At baseline, there were a mean (SD) of 21 (5) days with headache per 28 days and the mean (SD) PedMIDAS was 68 (32) points. At the 20-week end point, days with headache were reduced by 11.5 for the CBT plus amitriptyline group vs 6.8 for the headache education plus amitriptyline group (difference, 4.7 [95% CI, 1.7-7.7] days; $P = .002$). The PedMIDAS decreased by 52.7 points for the CBT group vs 38.6 points for the headache education group (difference, 14.1 [95% CI, 3.3-24.9] points; $P = .01$). In the CBT group, 66% had a 50% or greater reduction in headache days vs 36% in the headache education group (odds ratio, 3.5 [95% CI, 1.7-7.2]; $P < .001$). At 12-month follow-up, 86% of the CBT group had a 50% or greater reduction in headache days vs 69% of the headache education group; 88% of the CBT group had a PedMIDAS of less than 20 points vs 76% of the headache education group. Measured treatment credibility and integrity was high for both groups.

CONCLUSIONS AND RELEVANCE Among young persons with chronic migraine, the use of CBT plus amitriptyline resulted in greater reductions in days with headache and migraine-related disability compared with use of headache education plus amitriptyline. These findings support the efficacy of CBT in the treatment of chronic migraine in children and adolescents.

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Migraine is a neurological disorder that is ranked in the 2010 Global Burden of Disease study as the eighth leading cause of years lived with disability.[1] When migraines become frequent, there is a significant effect on work or school, home, and social activities.[2-4] Chronic migraine is defined as having at least 15 days of headache per month with a majority having migraine features such as moderate to severe intensity, pulsating quality, and associated symptoms of nausea, vomiting, phonophobia, and photophobia.[5] In adults, more than 2% of the population has chronic migraine and in children and adolescents the prevalence is up to 1.75%.[6] In pediatric patients who seek care in headache specialty clinics, up to 69% have chronic migraine[6,7]; however, there are no interventions approved by the US Food and Drug Administration for the treatment of chronic migraine in young persons. As a result, current clinical practice is not evidence-based and quite variable.[8]

Psychological intervention, in particular, cognitive behavioral therapy (CBT) focused on coping skills training and including biofeedback-assisted relaxation training, has shown good evidence for the management of chronic and recurrent pain in children and adolescents.[9,10] Amitriptyline, a tricyclic antidepressant medication, is 1 of 2 main drugs used worldwide in children and adults for the prevention of headache, is a recommended prophylactic medication based on national practice parameters and a recent meta-analysis, and has been shown in an open-label study to reduce days with headache and disability specifically in patients with chronic headache seen in a pediatric headache center.[11-14] A high priority research need in headache medicine is the testing of multimodal treatments (eg, behavioral therapy and medication) against pharmacotherapy alone.[15]

The objective of this randomized clinical trial was to test whether treatment with CBT plus amitriptyline was superior to headache education plus amitriptyline in youth aged 10 to 17 years diagnosed with chronic migraine. It was hypothesized that CBT plus amitriptyline would lead to greater reductions in days with headache and migraine-related disability than headache education plus amitriptyline.

Methods

Participants

The trial was approved by the Cincinnati Children's Hospital Medical Center institutional review board and was conducted at the Cincinnati Children's Headache Center between October 2006 and September 2012. All parents or legal guardians provided written informed consent and youth older than 11 years provided assent. Inclusion criteria included a diagnosis of chronic migraine made by a board-certified headache specialist using the *International Classification of Headache Disorders*, 2nd Edition (*ICHD-II*) criteria,[5,16] 15 or more days with headache per month measured by a prospective 28-day headache diary, and Pediatric Migraine Disability Assessment Score (PedMIDAS) of greater than 20 points, indicating at least moderate disability.

Exclusion criteria were (1) medication overuse (*ICHD-II* criteria[5,16]), (2) current use of amitriptyline or other prophylactic antimigraine medication within a period equivalent to less than 5 half-lives before study screening, (3) other chronic pain condition such as fibromyalgia or complex regional pain syndrome II, (4) abnormal electrocardiogram, (5) severe orthostatic intolerance or dysregulation, (6) documented developmental delay or impairment, (7) severe psychiatric comorbidity (eg, psychosis, bipolar disorder, major depressive disorder), (8) PedMIDAS of greater than 140 points (indicating excessive disability and need for multisystemic therapies), (9) pregnancy or being sexually active without use of medically accepted form of contraception (barrier or hormonal methods), and (10) use of disallowed medications including opioids, antipsychotics, antimanics, barbiturates, benzodiazepines, muscle relaxants, sedatives, tramadol, or herbal products.

Study Design and Treatments

All participants completed a baseline assessment that included a medical and psychosocial screening and prospective 28-day headache diary. An eFigure summarizing the study protocol appears in the Supplement. Information about participant race and ethnicity was self-reported using a multiple-choice format consistent with the categories used for reporting study findings to the National Institutes of Health. These data were included to assist in understanding the potential generalizability of the trial results in the clinical care context. Participants were randomly assigned to either CBT plus amitriptyline or headache education plus amitriptyline with a 1:1 allocation.

Cognitive behavioral therapy plus amitriptyline was defined as the experimental or treatment group and headache education plus amitriptyline was defined as the control group. Block randomization (with varying block sizes of 4-10) was used, and participants were stratified by age (10-13 years and 14-17 years). Randomization was computer generated and supplied via secure e-mail to the study therapist when a participant had met entry criteria. Families were informed that there were 2 behavioral or educational conditions and that all participants would receive amitriptyline.

To achieve participant blinding, families were aware that there were 2 different psychological interventions, but were unaware of the differences or the specific components of each intervention. Outcome assessments were conducted by blinded study personnel; the therapists who delivered CBT plus amitriptyline and headache education plus amitriptyline were the only unblinded members of the study team. Trained study therapists delivered both interventions.

The CBT intervention was based on an evidence-based coping skills protocol for pediatric pain,[10] modified to include a biofeedback component that included thermal and electromyographic monitoring of the relaxation response. The headache education intervention consisted of discussion of headache-related education topics. It also included nonspecific support along with equal time and attention from a trained therapist. Details of the CBT and headache education treatments are presented in the eTable in the Supplement.

Participants in each treatment group received 8 weekly, 1-hour individual sessions, followed by monthly booster sessions of similar duration at weeks 12 and 16, and at the 3-, 6-, and 9-month follow-up points. The blind was retained through the 12-month follow-up assessment. With this design, non-

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specific treatment elements, such as number of treatment sessions, therapist contact time and support, and demand characteristics across treatments were controlled. In behavioral trials, this approach mirrors the purpose of pill placebo.[17-19]

For all participants, amitriptyline was titrated to a goal dose of 1 mg/kg/d, taken at dinner time, in a standardized protocol over the first 8 weeks, then held at this maintenance dose from week 8 to week 20. The dose was increased by 0.25 mg/kg at weeks 0, 2, 4, and 6. Participants who experienced adverse effects were instructed to contact the research staff immediately. Adverse events were assessed at each time point and weekly therapy visit. Adverse events were coded by body system and categorized as regular level adverse events and upper level events. Regular level adverse events included any reported event regardless of intensity, relationship, or action. Upper level events were defined by either intensity at level 3 or above (severe or life threatening), relationship at level 4 or above (probable or definite), and/or action at level 4 or above (medication discontinued or dose reduction).

During the 1-year follow-up, participants returned to routine multidisciplinary care with prevention medication adjusted as clinically indicated.[8,20] Use of medications for acute pain (usually nonsteroidal anti-inflammatory drugs and/or triptans) was allowed and documented. Participants were instructed not to use acute medications more than 3 times per week. Those who required use of an exclusionary medication were withdrawn. Participants were asked not to begin any new therapies after study enrollment so that no other psychological intervention was provided.

Outcome Measures

Primary End Point

The 28-day paper and pencil prospective headache diary included (1) use of any headache abortive medication, (2) headache occurrence, (3) headache intensity rated as average pain intensity for that day using a 0- to 10-point scale, (4) headache duration, and (5) associated symptoms for migraine. Number of days with headache recorded was used as the primary outcome measure. The clinical significance outcome measure of a 50% or greater reduction in days with headache was also computed based on published guidelines from the International Headache Society and the American Headache Society.[17-19,21]

Secondary End Point

The PedMIDAS[3] scale evaluated the perceived effect of headaches and migraines on school, home, play, and social activities over a 3-month period. Six developmentally appropriate questions included (1) number of complete school days missed due to headache, (2) number of partial school days missed due to headache, (3) number of school days in which the youth functioned at less than 50% of their abilities due to headache, (4) number of days the youth was unable to do homework or chores due to headache, (5) number of days the youth was unable to participate in play, sports, or social activities due to headache, and (6) number of days the youth participated at less than 50% of full ability in play, sports, or social activities (more information is available at http://www.cincinnatichildrens.org/service/h/headache-center/pedmidas). The questions were answered by the youth in consultation with their parents, and confirmed via clinical interview with medical research staff. The measure has excellent psychometric properties.[3] Scores can range from 0 to 240 points and disability is graded as 0 to 10 (little to none), 11 to 30 (mild), 31 to 50 (moderate), and greater than 50 (severe).[22] Total PedMIDAS was used as the secondary outcome measure, and clinical significance was defined as a reduction of disability to a score of less than 20 points, indicating mild to no disability.[3,22]

Other Measures

Treatment Integrity | Postdoctoral psychology fellows (trained and supervised by a licensed clinical psychologist with specialized experience in pain management) conducted the CBT and headache education sessions based on structured treatment manuals. In addition to regular therapist supervision, a trained doctoral-level independent evaluator reviewed a random 20% of the session audiotapes for each participant to assess treatment integrity and adherence. The evaluator used a checklist of required session topics to obtain a percentage accuracy score. Therapist drift was prevented by reinstruction of staff if quarterly review showed less than 80% accuracy for any given session.

Treatment Credibility | Participants and parents each completed a 9-item measure of treatment credibility after 4 sessions (at week 5) and again at the 20-week end point. The purpose of gathering this information was to document whether each of the treatment groups had equivalent credibility. Each item was scored on a scale of 0 (not confident at all, not logical at all, makes no sense) to 8 (very confident, very logical, makes a lot of sense). Questions pertained to whether the medication and therapy seemed logical, confidence in success of decreasing headache frequency, helping to deal with headaches, and recommending the treatment to someone else with headaches. The overall credibility score was an average (total score/9 items) on a 0 to 8 scale.

Statistical Analysis

The primary goals of this trial were to determine if CBT plus amitriptyline was significantly superior to headache education plus amitriptyline in reducing (1) number of headache days per month (primary end point) and (2) migraine-related disability (secondary end point) from baseline to the 20-week posttreatment assessment via testing a null hypothesis of no difference. We also examined group differences in the proportion of participants in each group who achieved the clinically meaningful end points of a 50% or greater reduction in days with headache per month and PedMIDAS of less than 20 points.

Based on an a priori power analysis with a standardized group mean difference of 0.6 for change in number of days with headache per month (corresponding to a clinically meaningful group difference of 4 headache days per month [see, eg[23]] and a SD of 6.7), a sample size of 60 per group yielded power of 0.90. The same standardized mean difference and power were obtained for migraine-related disability. Proportions of 75% and 50% in the CBT plus amitriptyline and headache education plus amitriptyline groups, respectively, on the clinically meaningful end point of a 50% or greater reduction in days with headache per month yielded power of 0.81 for 60 participants.

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Table 1. Baseline Demographics, Headache Frequency, and Migraine-Related Disability

	No. (%) of Patients[a]		
		Amitriptyline Plus	
	Total (N = 135)	Cognitive Behavioral Therapy (n = 64)	Headache Education (n = 71)
Sex			
Male	28 (21)	13 (20)	15 (21)
Female	107 (79)	51 (80)	56 (79)
Race			
White	120 (89)	59 (92)	61 (86)
Black	13 (10)	4 (6)	9 (13)
Asian	1 (1)	1 (2)	0
American Indian or Alaskan Native	1 (1)	0	1 (1)
Education level of parent			
Mother			
High school graduate	33 (24)	12 (19)	21 (30)
Some college or technical school	33 (24)	19 (30)	14 (20)
College graduate	49 (36)	22 (34)	27 (38)
Graduate degree	20 (15)	11 (17)	9 (13)
Father			
High school graduate	40 (31)	16 (25)	24 (37)
Some college or technical school	30 (23)	17 (27)	13 (20)
College graduate	43 (33)	22 (34)	21 (32)
Graduate degree	16 (12)	9 (14)	7 (11)
Age, mean (SD), y	14.4 (2.0)	14.4 (1.9)	14.4 (2.1)
Baseline values for primary and secondary end points, mean (SD)			
Headache frequency/28 d, d	21.3 (5.2)	21.4 (5.4)	21.2 (5.1)
Headache disability, points[b]	68.3 (31.9)	67.3 (29.8)	69.2 (33.8)

[a] Unless otherwise indicated.

[b] According to the Pediatric Migraine Disability Assessment Score.

All analyses were performed on the full intention-to-treat sample, with missing data handled via maximum likelihood estimation within the PROC MIXED procedure (SAS Institute Inc) for continuous outcomes and generalized estimating equations within the GENMOD procedure (SAS Institute Inc) for dichotomous outcomes. All analyses were conducted using SAS version 9.3. Two-sided *P* values of less than .05 were considered statistically significant.

Group differences on the primary and secondary outcome measures were tested via the time × treatment group interaction within a repeated-measures mixed-effects model. The clinically meaningful dichotomous end points were tested via χ^2 analyses.

In addition to the primary goal of assessing immediate posttreatment effects, we explored whether group differences in outcomes were maintained during a 12-month follow-up period (assessments at 3, 6, 9, and 12 months after the 20-week posttreatment evaluation) via post hoc analyses. These hypotheses were examined using longitudinal data analysis methods via a random coefficients model within the PROC MIXED procedure. Specifically, we first examined the time × treatment group interaction during follow-up for each outcome. If this interaction was not statistically significant, the interaction term was removed from the model and the statistical significance of the main effect for treatment group was examined during the follow-up period. Similar models were examined for the clinically meaningful dichotomous end points with the important exception that a generalized linear model with a logit link function was used within the GENMOD procedure.

Results

Participant Characteristics

Demographic and clinical characteristics for the 135 participants appear in **Table 1**. Participants were predominantly female (79%), and on average, reported 21 days with headache per 28 days at baseline. The PedMIDAS averaged 68 points at baseline, indicating a severe grade of disability. The flow of participants through the trial appears in **Figure 1**. Of the 398 patients approached, 197 agreed to be screened for the trial. Of these, 135 met all eligibility criteria and were randomized to CBT plus amitriptyline or headache education plus amitriptyline. Retention was excellent with 92% of patients completing the trial and follow-up visits.

Safety and Tolerability

There were a total of 199 adverse events of all grades reported during the trial (90 in the CBT plus amitriptyline group vs 109 in headache education plus amitriptyline group). The headache education group reported more regular level adverse events for central nervous system and respiratory categories than the CBT group. A total of 23 upper level events were reported. There were no differences between the CBT and head-

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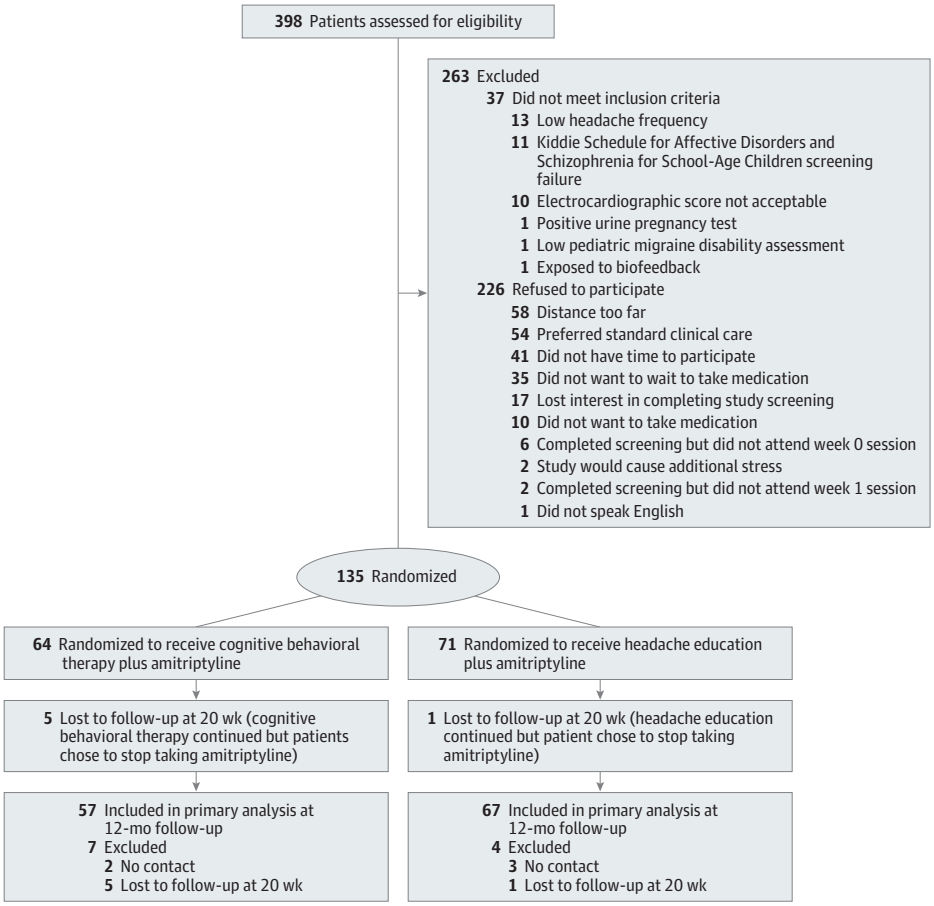
Figure 1. Flow of Participants Through the Trial



ache education groups for upper level events. The majority of central nervous system adverse events involved status migranosus or worsening of migraine, and others included expected adverse effects of amitriptyline (fatigue or drowsiness and dizziness). Respiratory adverse events included influenza, pneumonia, seasonal allergies, and upper respiratory infections. A summary of adverse events (including the subset of upper level events) by body system and treatment group appear in **Table 2**.

The intention-to-treat group included all participants who began taking amitriptyline and attended at least 1 CBT or headache education session (N = 135). Using this definition, 8 participants enrolled but dropped out prior to meeting intention-to-treat criteria (Figure 1). During the first 20 weeks of treatment, 6 participants stopped taking amitriptyline due to concerns with adverse events, but they continued to receive CBT or headache education therapy. The CBT group attended more than 95% of therapy sessions and the headache education group attendance was more than 98%. For the overall sample, the final mean (SD) maintenance dose of amitriptyline was 1.01 (0.02) mg/kg/d. The 2 groups did not differ on final dose (1.01 vs 1.01; $P = .26$). These results indicate that the 2 treatments were well tolerated in this sample.

Outcomes

Completion of headache diaries by participants was excellent, with 100% of baseline data and 77% of all data collected prospectively verified. Retrospective report of headache frequency at posttreatment and at 3-, 6-, 9-, and 12-month follow-up was included if the correlation between the verified diaries and retrospective reports was high ($r = 0.90$, $P < .001$). The inclusion of retrospective reporting reduced missing data to 5%. Complete PedMIDAS data for 93% of participants was available at all time points. The PROC MIXED maximum likelihood estimation was used to account for missing data. In addition to this primary analysis, an analysis that discarded the retrospective data and a completer analysis both yielded similar results.

From pretreatment to posttreatment, CBT resulted in a decrease of 11.5 days with headache vs 6.8 days with headache education (change score difference, 4.7 [95% CI, 1.7-7.7] days; $P = .002$). The PedMIDAS decreased by 52.7 points with CBT vs 38.6 points with headache education (change score difference, 14.1 [95% CI, 3.3-24.9] points; $P = .01$). Sixty-six percent of the CBT group had a 50% or greater reduction in headache days vs 36% of the headache education group (odds ratio, 3.45 [95% CI, 1.66-7.15]; $P < .001$). Seventy-five percent of the CBT

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Table 2. Adverse Events and Upper-Level Events by Treatment Group

Body System	No. of Adverse Events in Patients Receiving Amitriptyline Plus		No. of Upper-Level Events in Patients Receiving Amitriptyline Plus[a]	
	Cognitive Behavioral Therapy (n = 64)	Headache Education (n =71)	Cognitive Behavioral Therapy (n = 64)	Headache Education (n = 71)
Head, eye, ear, nose, and throat	30	25	0	1
Central nervous system[b]	13[c]	28[c]	1	4
Gastrointestinal	10	11	0	0
Musculoskeletal	6	9	0	0
Cardiovascular	8	6	2	2
Behavioral	6	6	3	6
Dermatological	4	6	0	1
Respiratory[b]	1[c]	8[c]	0	0
Hematopoietic or lymphatic	5	4	1	1
Genitourinary	4	4	0	0
Other	2	1	0	1
Endocrine or metabolic	1	1	0	0
Total events	90	109	7	16

[a] Upper level events defined by either intensity at level 3 or above (severe or life threatening), relationship at level 4 or above (probable or definite), and action at level 4 or above (medication discontinued or dose reduction).

[b] The majority of central nervous system adverse events involved status migranosus or worsening of migraine, and others included expected adverse effects of amitriptyline (fatigue or drowsiness and dizziness). Respiratory adverse events included expected events for youth, including influenza, pneumonia, seasonal allergies, asthma exacerbations, and upper respiratory infections.

[c] Each of these group comparisons yielded a *P* value of .02; however, use of the χ^2 test for respiratory events may not be valid because expected cell frequencies are less than 5.

Table 3. Changes in Headache Frequency and Disability at 20 Weeks' Posttreatment

	Cognitive Behavioral Therapy Plus Amitriptyline (n = 64)			Headache Education Plus Amitriptyline (n = 71)			Group Mean Difference in Change Scores (95% CI)	*t*	*P* Value
	Baseline Score	Post-treatment	Change Score	Baseline Score	Post-treatment	Change Score			
Headache frequency, d[a]									
Mean (SD)[b] [range]	21.3 (5.2) [15 to 28]	9.8 (9.8) [0 to 28]	−11.5 (8.5) [−28 to 12]	21.3 (5.2) [15 to 28]	14.5 (9.8) [0 to 28]	−6.8 (8.5) [−26 to 8]	4.7 (1.7 to 7.7)	3.13	.002
Median (IQR)	20.5 (16 to 28)	5 (3 to 17)	−13 (−17 to −5)	20 (16 to 27)	12 (7 to 25)	−7 (−13 to 0)			
Headache disability[c]									
Mean (SD)[b] [range]	68.2 (31.7) [21 to 132]	15.5 (17.4) [0 to 77]	−52.7 (36.0) [−132 to 29]	68.2 (31.7) [20 to 137]	29.6 (42.2) [0 to 216]	−38.6 (45.3) [−128 to 114]	14.1 (3.3 to 24.9)	2.58	.01
Median (IQR)	59 (47 to 90)	11 (3 to 18)	−51 (−76 to −27)	64 (41 to 98)	16.5 (3 to 36)	−37 (−66 to −13)			

[a] There was a significant reduction (≥50%) in days with headache in 42 youth (66%) in the cognitive behavioral therapy plus amitriptyline group vs 26 (36%) in the headache education plus amitriptyline group (odds ratio, 3.5 [95% CI, 1.7 to 7.2]; *P* < .001).

[b] The means and standard deviations were corrected for missing data using the maximum likelihood estimation.

[c] There was a significant reduction in headache disability (Pediatric Migraine Disability Assessment Score of <20) in 48 (75%) of the headache cognitive behavioral therapy plus amitriptyline group vs 40 (56%) of the headache education plus amitriptyline group (odds ratio, 2.4 [95% CI, 1.1 to 5.1]; *P* = .02).

group had a PedMIDAS of less than 20 points vs 56% of the headache education group (odds ratio, 2.36 [95% CI, 1.10-5.10], *P* = .02; **Table 3**).

Figure 2 presents the results from posttreatment to 12-month follow-up by treatment group for headache frequency and PedMIDAS and the proportions of patients with a 50% or greater reduction in days with headache and a PedMIDAS of less than 20 points. At 12-month follow-up, 86% of CBT participants had a 50% or greater reduction in days with headache vs 69% of the headache education group; 88% of CBT participants had a PedMIDAS of less than 20 points (mild to no disability) vs 76% of the headache education group.

Both CBT and headache education sessions were delivered with a high degree of accuracy (95.7% overall; 94.5% for CBT vs 96.9% for headache education), showing therapist adherence with the protocol. No contamination of treatment components occurred between groups.

Both parents and children reported high levels of treatment credibility for CBT and headache education at weeks 5 and 20. Overall scores ranged from 6.4 to 6.9 on a 0- to 8-point scale for both groups. The mean (SD) week 20 parent ratings were 6.8 (1.6) for CBT vs 6.5 (1.3) for headache education (*P* = .34); the mean (SD) child ratings were 6.7 (1.7) for CBT vs 6.4 (1.7) for headache education (*P* = .30).

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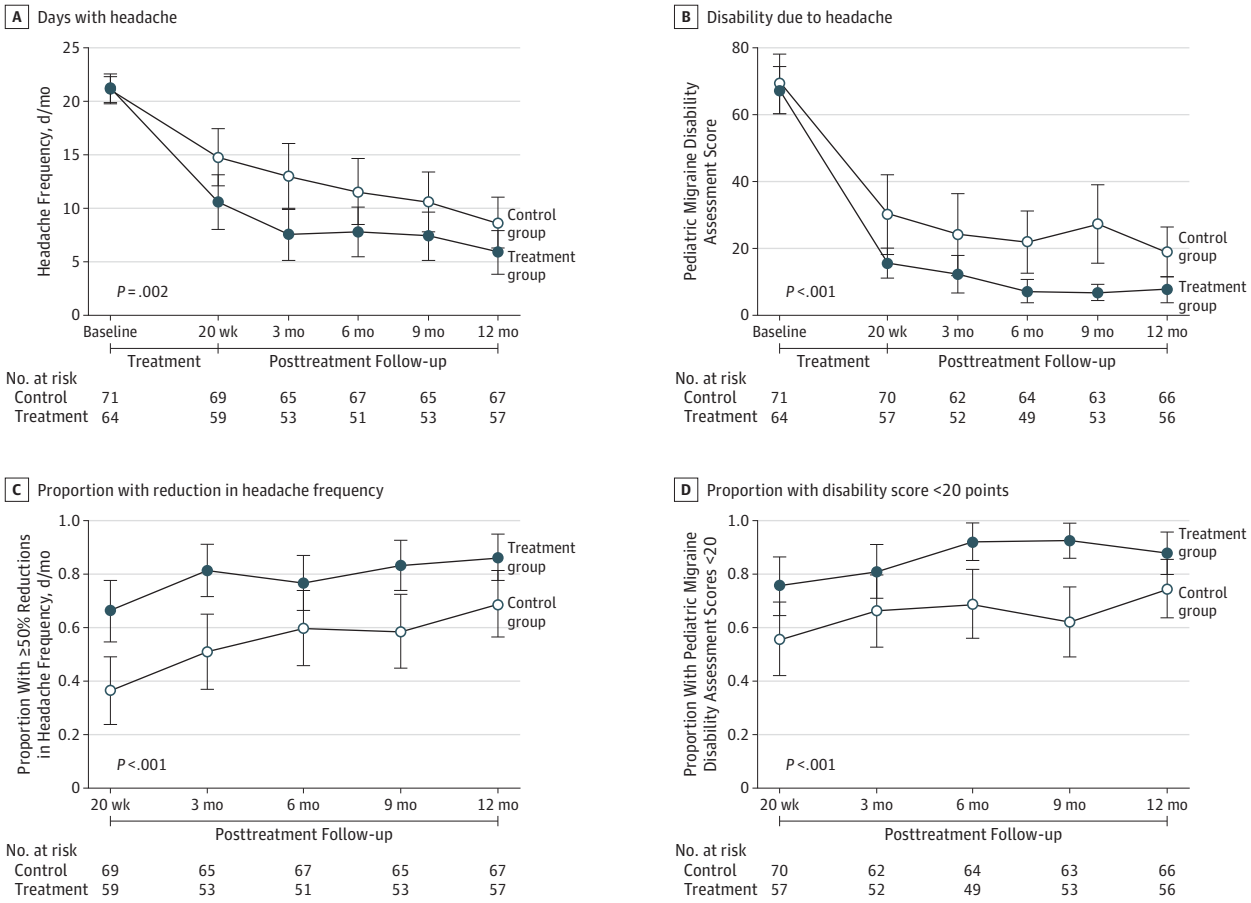
Figure 2. Results From Baseline to 12-Month Posttreatment Follow-up for Cognitive Behavioral Therapy Plus Amitriptyline (Treatment Group) and Headache Education Plus Amitriptyline (Control Group)



Error bars indicate 95% confidence intervals. The results of the pretest to posttest analyses appear in Table 3. Post hoc longitudinal analyses from posttest to follow-up were also conducted to examine change in the effect of treatment during this period. These analyses were considered post hoc because we did not have any prior expectations with respect to the pattern of results; thus, these analyses were entirely exploratory. For these analyses, PROC MIXED was used to analyze continuous outcomes with random effects for intercepts and slopes over time, whereas PROC GENMOD with a logistic link function was used to analyze longitudinal change in dichotomous outcomes. The first step in each of these analyses was to test an effect for group differences in linear change across the follow-up period. These results suggest that the treatment effects found from baseline to 20-week posttest were maintained throughout the 12-month follow-up period.

Discussion

This is the first randomized clinical trial, to our knowledge, to test interventions for children and adolescents diagnosed with chronic migraine using the *ICHD-II*[5,16] and drawn from a real-world clinical practice setting. Although at least 16 previous trials of psychological therapies have included children with headache conditions,[9] these studies were of poor to moderate quality; only 1 study[24] used standard criteria for classification of headache type and none controlled for medication use. Strengths of the current trial compared with these past studies were the use of clear diagnostic criteria, a randomized design with an education control group receiving equivalent time and attention to that of the CBT group, sample size that was fully powered to test study hypotheses, and follow-up assessments at regular intervals posttreatment to assess maintenance of treatment effects.

For all of the outcome measures proposed a priori, a combination of CBT and amitriptyline resulted in greater reductions in days with headache and migraine-related disability compared with headache education and amitriptyline. Both treatments were shown to be well tolerated and credible to both participants and families. The findings indicate that the specific features of CBT (when combined with medication) are the active change agents for youth with chronic migraine and that treatment effects are durable during 1 year. The headache education control demonstrates that improvements are not due solely to therapist support, education, or other nonspecific intervention effects.[18]

Accepted benchmarks for clinically significant outcomes were included because results of clinical trials need to be at a level of benefit to persuade clinicians to change their practice.[19,21,25] After 20 weeks, 2 of 3 participants that received CBT plus amitriptyline had a 50% or greater reduction in days with headache per month and 3 of 4 had improved from

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a disability grade considered severe to mild or no disability. At 12-month follow-up, these clinically significant indicators improved even further to almost 9 of 10 participants meeting each benchmark.

Cognitive behavioral therapy plus amitriptyline exceeds the outcomes for medication alone. Although helpful, treatment effects for medications are quite modest.[26] They have typically reduced days with headache in adults with chronic migraine by 2 per month (from a baseline frequency of about 20 days[26,27]) and have produced rates of 37% to 47% for a reduction of 50% or greater days with headache.[28,29] Headache education plus amitriptyline resulted in a similar change in headache days but CBT plus amitriptyline produced 2 to 5 times the effect on this primary end point.

Children with migraine often continue to struggle with this disorder as they grow into adulthood.[30] Early, safe, and effective interventions that have lasting effects have the potential to change the course of a person's experience of migraine over time, and to reduce the disability, negative effect on overall quality of life, and health care costs (direct and indirect) associated with such a prevalent condition (10% of youth and up to 28% of young adult women).[1,4,14,20,31,32] Once early effective treatments are developed and validated, examining the benefit over time as the youth become adults will then be possible.

The current trial did not include a group that focused solely on the effect of CBT (without medication or combined with a placebo pill). The rationale for not including an inactive medication component in this trial was due to the lack of controlled studies of the effectiveness of pharmacological agents in chronic migraine in youth. Furthermore, there was the ethical concern of a null treatment for a placebo pill and behavioral placebo group in a pediatric trial as well as a concern that recruitment of participants might be challenging given the still widely prevalent preference for medication treatment in practice.[8,13,17,23,33-35] Therefore, we do not yet know if CBT plus amitriptyline is superior to CBT alone for the management of chronic pediatric migraine. Now that there is additional evidence that CBT has beneficial effects, future pediatric trials in chronic migraine and episodic migraine can be designed in a manner that would potentially allow for testing psychological therapy alone, medication therapy alone, and the combination of these therapies. Although amitriptyline is the most common preventative medication for headaches worldwide,[11] and is recommended by national practice parameters and open-label studies,[12,14] its effectiveness compared with placebo in youth remains unknown.[8,33,36] Using amitriptyline as a constant in this study allowed for a clear comparison of CBT with headache education.

The number of potential participants approached for the study who agreed to be in the trial was relatively modest, and anecdotally, due to 2 reasons: (1) not wanting to delay the start of medications while completing the screening period and (2) the time commitment required to attend the weekly sessions in-person. Due to the exclusion criteria, a small number of youth with severe psychiatric comorbidities, those with contraindications to amitriptyline, and the few youth with baseline disability in the mild to none range could not participate.[37,38] Future trials are needed to test interventions that are generalizable for all youth with chronic migraine.[38,39] Prior studies in the field of pediatric pain would suggest that CBT has additional potential generalizability to individuals with less frequent headaches, lower levels of disability, and other pain disorders in youth.[9,23,35]

Now that there is strong evidence for CBT in headache management, it should be routinely offered as a first-line treatment for chronic migraine along with medications and not only as an add-on if medications are not found to be sufficiently effective. Also, CBT should be made more accessible to patients by inclusion as a covered service by health insurance as well as testing of alternate formats of delivery, such as using online or mobile formats,[40] which can be offered as an option if in-person visits are a barrier.

Conclusions

Among young persons with chronic migraine, the use of CBT plus amitriptyline resulted in greater reductions in headache frequency and migraine-related disability compared with headache education plus amitriptyline. These findings support the efficacy of CBT in the treatment of chronic migraine in children and adolescents.

ARTICLE INFORMATION

Author Contributions: Drs Powers and Rausch had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Powers, Kashikar-Zuck, Kabbouche, Hershey.
Acquisition of data: Powers, Allen, LeCates, Slater, Zafar, Kabbouche, O'Brien, Shenk, Hershey.
Analysis and interpretation of data: Powers, Kashikar-Zuck, Allen, Shenk, Rausch, Hershey.
Drafting of the manuscript: Powers, Kashikar-Zuck, Allen, LeCates, Rausch.
Critical revision of the manuscript for important intellectual content: Kashikar-Zuck, Allen, Slater, Zafar, Kabbouche, O'Brien, Shenk, Rausch, Hershey.
Statistical analysis: Allen, Rausch.
Obtained funding: Powers, Hershey.
Administrative, technical, or material support: Powers, Allen, LeCates, Slater, O'Brien, Shenk, Hershey.
Study supervision: Powers, Kashikar-Zuck, Hershey.

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Additional Information: For more information regarding the cognitive behavioral therapy and headache education treatment manuals used in this trial, and to request copies of the manuals, please go to: http://www.cincinnatichildrens.org/research/divisions/b/psychology/labs/powers/default/.

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