American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 18, No 6 (June), 2017: pp 637-644
Available online at www.jpain.org and www.sciencedirect.com

Trajectory of Improvement in Children and Adolescents With Chronic Migraine: Results From the Cognitive-Behavioral Therapy and Amitriptyline Trial

John W. Kroner,* James Peugh,*,† Susmita M. Kashikar-Zuck,*,† Susan L. LeCates,‡,§ Janelle R. Allen,*,§ Shalonda K. Slater,*,†,§ Marium Zafar,* Marielle A. Kabbouche,†,‡,§ Hope L. O'Brien,†,‡,§ Chad E. Shenk,*,† Ashley M. Kroon Van Diest,* Andrew D. Hershey,†,‡,§ and Scott W. Powers*,†,§

**Division of Behavioral Medicine and Clinical Psychology, ‡Division of Neurology, §Headache Center, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio.*
†Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio.

Abstract: **We compared headache frequency trajectories between clinical trial participants who received cognitive-behavioral therapy (CBT) and amitriptyline (CBT+A) or headache education (HE) and amitriptyline (HE+A) to determine if there was a differential time course of treatment response between the groups. One hundred thirty-five patients (age 10–17 years) diagnosed with chronic migraine participated, attending 8 one-hour one-on-one CBT or HE sessions with a trained psychologist for 8 weekly sessions, 2 sessions at weeks 12 and 16, and a post-treatment visit at week 20. Participants kept daily headache diaries and completed take-home assignments between visits. Data from daily headache diaries are presented for each day and according to 28-day periods. Trajectories of improvement indicate initial decrease in headache days began during the first month of treatment, for both groups, and continued to decrease throughout treatment. The CBT+A group had greater daily improvement than the HE+A group. A significantly greater proportion of the CBT+A group had a ≥50% reduction in headache days each month, and a significantly greater proportion of the CBT+A group had ≤4 headache days per month in months 3 through 5. Results indicate the trajectory of decrease in headache days is significantly better for patients receiving CBT+A versus HE+A.**

Perspective: ***This article presents daily information about headache frequency over a 20-week clinical trial. Youth with chronic migraine who received CBT+A improved faster than those in the control group. Findings provide clinicians with evidence-based expectations for treatment response over time and ways of monitoring treatment success.***

Trial registration: clinicaltrials.gov **identifier NCT00389038.**

Key words: *Pain, pediatrics, clinical trial, headache, treatment.*

Chronic migraine has an estimated prevalence of 1.75% in children and adolescents.[17] Up to 69% of children and adolescents who seek care in headache specialty clinics meet diagnostic criteria for chronic migraine (which include 15 or more headache days per month, with most having migraine features).[4,17] Youth with chronic migraine experience severe disability as a result of the condition, including decreased functioning in home, academic, and social settings.[11] Because of the level of disability associated with chronic migraine among youth, understanding effective treatments for the condition is a clinical priority. Cognitive-behavioral therapy (CBT), a form of nonpharmacological treatment, has been shown to be effective in treating chronic pain among children and adolescents by modifying behavioral responses to pain using active coping skills, such as relaxation techniques and cognitive strategies.[5-8,14] The effectiveness of CBT for treating chronic migraine

Received July 20, 2016; Revised November 7, 2016; Accepted January 4, 2017.
This work was supported by the National Institutes of Health (grant numbers R01NS050536; T32DK063929; UL1TR000077).
The authors have no conflicts of interest to declare.
Address reprint requests to Scott W. Powers, PhD, ABPP, FAHS, Cincinnati Children's Hospital Medical Center, Division of Behavioral Medicine and Clinical Psychology, MLC: 7039, 3333 Burnet Avenue, Cincinnati, OH 45229-3039. E-mail: Scott.Powers@cchmc.org
1526-5900/$36.00

http://dx.doi.org/10.1016/j.jpain.2017.01.002

among youth was shown in a clinical trial comparing CBT combined with amitriptyline (CBT+A), a standard headache medication,[10] with an attention control group receiving headache education (HE) and amitriptyline (HE+A).[21] Primary results from the trial indicated that CBT+A led to better outcomes in headache frequency and disability compared with HE+A at the 20-week end point and over the course of a 1-year follow-up period.

When determining if treatments are effective in managing chronic migraine, response to treatment is typically measured by comparing baseline headache characteristics with those experienced post-treatment, in accordance with International Headache Society (IHS) clinical trial guidelines.[24] These IHS guidelines specifically recommend using an absolute reduction in headache days and a ≥50% reduction in headache frequency per month when determining if a treatment was effective in managing the condition. Although these guidelines are useful in determining the significance of treatment outcomes in clinical trials research, they lack an accurate reflection of clinical significance, particularly for patients suffering from chronic migraine (ie, 15 or more headache days per month before treatment). Previous work by this team has expanded upon research on guidelines for successful treatment outcomes by identifying a benchmark of a reduction in headache days to ≤4 headache days per month post-treatment.[16] This benchmark is a more clinically meaningful outcome within the context of a clinical trial exploring the effectiveness of CBT; however, there is currently little information about the trajectory of improvement from the first day of treatment to the end of treatment within existing interventions for chronic migraine, including CBT.

Exploring the trajectory of improvement in response to CBT in a longitudinal fashion is necessary for a determination to be made as to when optimal treatment effects occur within the course of treatment, particularly because of the demonstrated effectiveness of CBT in treating youth with chronic migraine.[21] It is important for CBT clinicians treating youth with chronic migraine to have an understanding of time points at which most patients are likely to show a clinically meaningful reduction in headache frequency within the course of treatment. In addition, importance lies in monitoring if patients are likely to maintain treatment gains, when achieved, to effectively monitor patient outcomes and discuss expectations for treatment gains with patients and families. Thus, the aim of this study was to conduct new analyses from a National Institutes of Health-funded clinical trial to examine the trajectory of daily headache frequency over 20 weeks of treatment and determine if patterns of change in improvement differ between CBT+A and HE+A groups.

Methods

Participants

Patients were randomized as part of a clinical trial conducted at the Cincinnati Children's Headache Center between October 2006 and September 2012 with approval from the Cincinnati Children's Hospital Medical Center institutional review board. Written informed consent was obtained from parents or legal guardians for all subjects enrolled in the study, and informed assent was obtained for all youth age 11 years or older. Inclusion criteria for the study included a diagnosis of chronic migraine by a board-certified headache specialist according to *International Classification of Headache Disorders, Second Edition* criteria,[9] 15 or more headache days per month, age 10-17 years, and a Pediatric Migraine Disability[12] score >20 (indicating moderate disruption of daily activities). Exclusion criteria were medication overuse, continuous head pain throughout the 28-day baseline assessment period, current use of amitriptyline or other prophylactic migraine medication within a period equivalent to less than 5 half-lives before study screening, other chronic pain condition, such as fibromyalgia or complex regional pain syndrome II, abnormal electrocardiogram, severe orthostatic intolerance or dysregulation, documented developmental delay or impairment, severe psychiatric comorbidity, Pediatric Migraine Disability score >140 points (indicating very severe disability), pregnancy, or being sexually active without the use of a medically acceptable form of contraception, and use of disallowed medications, including opioid, antipsychotic, antimanic, barbiturates, benzodiazepines, muscle relaxants, sedatives, tramadol, or herbal products.

Study Design

Enrolled study participants completed a baseline assessment and were instructed to keep a prospective headache diary during a 28-day screening period. Those who met the enrollment criteria after the screening period were randomized into the experimental CBT+A group or the HE+A attention control group. Treatment assignment was blinded, and both groups received the same amount of therapist contact, with only the therapist being unblinded to treatment assignment. Controlling for therapist contact emulates the purpose of pill placebo in the HE+A group.[1,13,19] Participants attended 8 one-hour sessions during weeks 1 through 8, 2 "booster" sessions at weeks 12 and 16, and a post-treatment visit at week 20. Sessions were conducted one-on-one. Participants who received at least 1 dose of treatment (completion of the first week of treatment) were considered the intent-to-treat sample and were included in the final analysis. Both groups were prescribed amitriptyline and titrated to a goal dose of 1 mg/kg/d over the initial 8 weeks of the trial. Participants were returned to standard clinical care after week 20 for medication management, and continued to receive CBT or HE booster sessions once every 3 months for a 1-year follow-up period. Fig 1 shows the study phases and the timing of treatment interventions.

Outcome Measures

Subjects kept a daily headache diary throughout the screening, treatment, and follow-up phases of the study (only the last 28 days of each 3-month period for follow-up). Daily diaries included documentation of acute