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Treatment Adherence in Child and Adolescent Chronic Migraine Patients: Results from the Cognitive Behavioral Therapy and Amitriptyline Trial

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Abstract

Objectives—To examine treatment adherence among children and adolescents with chronic migraine who volunteered to be in a clinical trial using three measures: treatment session attendance, therapy homework completion, and preventive medication use via daily diary.

Methods—Analyses are secondary from a trial of 135 youth aged 10 to 17 years diagnosed with chronic migraine and with a Pediatric Migraine Disability score over 20. Participants were randomly assigned to cognitive behavioral therapy plus amitriptyline (CBT+A, N = 64) or headache education plus amitriptyline (HE+A, N = 71). Therapists recorded session attendance. Completion of homework/practice between sessions was reported to therapists by patients. Patients reported preventive medication adherence using a daily headache diary.

Results—Mean session attendance adherence out of 10 treatment sessions was 95% for CBT+A and 99% for HE+A. CBT+A participants reported completing a mean of 90% of home practice of CBT skills between the 10 sessions. Participants reported taking amitriptyline daily at a mean level of 90% when missing diaries were excluded and 79% when missing diaries were considered as missed doses of medication.

Discussion—Our findings demonstrate that youth with chronic migraine who agree to be a part of a clinical trial do quite well at attending therapy sessions, and report that they are adherent to

completing home/practice between sessions and taking medication. These results lend further support to consideration of CBT+A as a first-line treatment for youth with chronic migraine and suggest that measurement of adherence when this treatment is provided in practice will be important.

Keywords

headache; pain; pediatrics

Introduction

Chronic migraine is defined as 15 or more days with headache per month with at least 8 episodes including migraine features such as moderate to severe intensity, pulsating quality, and associated symptoms of nausea, vomiting, phonophobia, and photophobia.¹ Approximately 1.75% of adolescents are affected by chronic migraine, and the majority of these adolescents experience severe burden due to their condition.² Cognitive behavioral therapy (CBT), a psychological, “mind and body” intervention including active learning and implementation of coping skills to manage pain related to headache, is one form of treatment for youth with chronic pain.³ CBT specifically focuses on the development of behavioral coping skills, including diaphragmatic breathing, progressive muscle relaxation, and guided imagery, and cognitive coping skills such as problem solving and cognitive restructuring (i.e., changing maladaptive thoughts, beliefs, attitudes) for addressing pain management. A recent randomized clinical trial demonstrated the efficacy of cognitive behavioral therapy plus amitriptyline (CBT+A) in reducing days with headache per month and migraine-related disability for children and adolescents with chronic migraine.⁴ Specifically, number of headache days per month decreased by 11.5 days for the youth with migraine receiving CBT +A while youth receiving headache education plus amitriptyline (HE+A) showed a 6.8 day decrease. Similarly, headache disability assessed by the Pediatric Migraine Disability Score (PedMIDAS) decreased by 52.7 points for the CBT+A group versus 38.6 points for the HE +A group.⁴

Medication and behavioral treatments such as CBT are only effective in reducing headache frequency and improving daily functioning when youth with chronic migraine engage in treatment and follow through with recommendations. Treatment nonadherence is a significant behavioral health problem and public health concern in pediatric populations. Approximately 50% of children⁵ and 65–90% of adolescents^{6,7} are non-adherent across pediatric conditions. Poor adherence is a concern in the context of a research study such as a clinical trial as well as in typical clinical practice.^{4,7} Specifically, nonadherence can lead to a variety of consequences, including poorer treatment outcomes, misleading results from research studies, drug resistance, poorer health-related quality of life (HRQOL), increased health care utilization resulting in health care costs in excess of \$300 billion, and increased morbidity and mortality.^{5,8–10} Importantly, no published studies have simultaneously examined adherence to treatment session attendance, skills/home practice, and medication in youth with chronic migraine, or compared rates of adherence to these variables between treatment and control groups in a randomized clinical trial.

The goal of this study was to examine rates of adherence to migraine treatment among children and adolescents with chronic migraine. Secondary analyses were conducted using data from a randomized controlled trial comparing the effectiveness of CBT+A versus HE+A in reducing headache frequency and disability.⁴ Adherence to migraine treatment was evaluated using three measures: proportion of 10 treatment sessions attended, proportion of home practice completion of CBT skills between the treatment sessions per self-report to the therapist, and proportion of days in which prescribed migraine preventive medication (amitriptyline) was taken as self-reported on a daily headache diary. The two groups were analyzed separately on adherence to session attendance given that content was significantly different between the CBT+A and HE+A groups, allowing for group comparisons on this variable. Only the CBT+A group was assessed for home practice between sessions because the control group, while given a homework task, was not asked to do any skills practice between sessions. This study fills a critical gap in the migraine literature in several ways: 1) it documents daily self-reported medication adherence rate in youth with migraine across a 140-day clinical trial period, 2) a checklist was utilized by trained therapists to systematically determine behavioral recommendation homework adherence, and 3) we document session attendance in addition to outside of session medication and behavioral recommendation adherence. Our aim was to describe adherence rates using multiple measurement approaches in the context of a randomized clinical trial that has the potential to change current clinical practice.^{11,12}

Materials and Methods

Participants

Approval was obtained from the institutional review board at Cincinnati Children's Hospital Medical Center prior to beginning the study. Parents or legal guardians provided written consent for all adolescents, and assent was obtained from participants older than 11 years of age. Study participants for the clinical trial were recruited from the Cincinnati Children's Headache Center and included 135 children and adolescents with chronic migraine meeting intent to treat criteria (attending at least one treatment session). Inclusion criteria required participants to be between the ages of 10 and 17 years, inclusive. All participants were also required to have a prior diagnosis of chronic migraine from a board-certified headache specialist using the International Classification of Headache Disorders, 2nd Edition (ICHD-II) criteria,^{1,13} 15 or more days with headache per month using a prospective headache diary, and PedMIDAS¹⁴ score of greater than 20 points but less than 140 points, indicating at least moderate disability.

Participants were excluded from the study on the basis of the following criteria: medication overuse as defined by ICHD-II; current use of amitriptyline or other preventive migraine medication within a period equivalent to less than 5 half-lives before study screening; other chronic pain conditions; abnormal electrocardiogram; severe orthostatic intolerance or dysregulation; developmental delay or impairment; severe psychiatric comorbidity such as psychosis, bipolar disorder, or major depressive disorder; PedMIDAS score over 140 points indicating excessive functional disability; pregnancy or being sexually active without use of medically approved forms of contraception; and use of disallowed medications including

opioids, antipsychotics, antimanics, barbiturates, benzodiazepines, muscle relaxants, sedatives, tramadol, or herbal supplements.

Procedure

Eligible subjects were randomized into one of the two treatment conditions (CBT+A or HE +A) using block randomization (block sizes varied between 4 to 10). Participants were also stratified by age (10–13 and 14–17 years). Treatment consisted of 8 weekly 1 hour sessions followed by 2 monthly “booster” sessions, and a post-treatment assessment at 20 weeks. The CBT intervention was based on a pediatric pain coping skills protocol¹⁵ modified with a biofeedback component including thermal and electromyographic monitoring of response to relaxation strategies (e.g., deep breathing, progressive muscle relaxation, guided imagery). The HE+A group served as an attention control group, which emulates placebo in behavioral treatment research.^{16–18} The HE+A group received generalized headache education from a trained therapist on the same schedule as the CBT+A group. As part of the study protocol, participants who failed to arrive for or needed to cancel a scheduled appointment were able to reschedule that appointment within a week. Subjects completed headache disability and frequency assessments at baseline and post-intervention (20 weeks). Treatment was provided based on structured treatment manuals by postdoctoral psychology fellows trained and supervised by a licensed clinical psychologist with specialized experience in pain management. Powers and colleagues describe the study design and treatments in further detail.⁴ Adherence to attending treatment sessions was measured for both CBT+A and HE +A groups. Adherence to completing therapy homework practice was measured for the CBT +A group only, as the HE+A group were not asked to complete skills-based practice between headache education sessions. Medication adherence was measured in both groups using a self-report daily diary. Participants were called by a nurse every two weeks to remind them to complete their daily diaries. All participants were prescribed amitriptyline at a dose of 1 mg/kg. Participants were instructed at the beginning of the study to take their medication the next day as scheduled if a dose was missed, per typical standards of treatment. All participants were on the same type and approximate dosage of medication, so the participants were examined as one group. Families were reimbursed for time and travel for attending treatment sessions (\$20 for each treatment session attended) and completing self-report daily diaries (up to \$3.00/week for diaries completed and returned).

Measures

Background information form—Parents of patients provided information regarding demographic characteristics (ethnicity, socioeconomic status, parental educational levels and occupational background).

Headache diary—A prospective headache diary was used to obtain data on headache frequency. This diary was self-reported by youth and included documentation of headache frequency by asking patients to report which days they experienced a headache throughout the duration of the trial. The 28 days prior to randomization were used to determine baseline headache frequency and the 28-day period prior to the week 20 visit was used to determine post-intervention headache frequency. For medication, participants were asked to check

“yes” or “no” in response to the following question: “Did you take your study medication today?”.

Pediatric Migraine Disability Assessment Scale (PedMIDAS).¹⁴—The PedMIDAS is a 6-item instrument that assesses the impact of headaches on functioning in school, home, and social environments over the past three months. The PedMIDAS uses a total score grading scale of none (0–10), mild (11–30), moderate (31–50) and severe (>50). The measure shows excellent internal consistency and test-retest reliability, and has been shown to be sensitive to intervention effects. The total PedMIDAS score at baseline and post-intervention was used as an indicator of headache-related disability.

Session attendance adherence (CBT+A and HE+A)—Participants in both groups were scheduled to attend 10 sessions across a 20-week period (weekly sessions for 8 weeks, then 2 monthly “booster” sessions), with the CBT+A group receiving Cognitive Behavioral Therapy and the HE+A group receiving headache education. In order to evaluate the attendance component of adherence to treatment, therapists recorded attendance for each participant in the trial. Session attendance was calculated separately for the CBT+A and HE+A groups given that content was significantly different between the CBT+A and HE+A groups and to allow for comparison of rates of attendance between groups. Potential therapist effects were controlled for by having the same therapists conduct both CBT and headache education sessions and record session attendance for both groups.

CBT home practice adherence (CBT+A only)—Adherence to home practice of skills was assessed using a checklist at the beginning of each session by the therapist. Therapists specifically asked participants if they completed home practice of the skills between sessions, and all participant responses were recorded by the therapist. Responses were coded “yes” if they indicated engaging in home practice of skills, regardless of the frequency or duration of reported home practice between therapy sessions. Given that participants in the HE+A group were not assigned any skill-based home practice between sessions, they could not be included in measuring home practice adherence.

Medication adherence (CBT+A and HE+A)—Medication adherence was assessed using the medication question from the daily headache self-report diary. Patients were asked to complete this diary daily for the duration of the trial, and patients returned completed diaries at each treatment session. To determine the average medication adherence among all participants, the number of days medication was reported was divided by the number of days a medication diary was completed and returned and multiplied by 100. Medication adherence was calculated in two ways. First, missing diaries were not included in the first calculation of medication adherence so as to not assume that patients did not take their study medication simply because they did not complete and return a diary to their provider (i.e., we did not want to assume that medication was not taken simply because a patient failed to turn in a diary). For this measure, multiple imputation was used to calculate estimated rates of adherence if all diaries were not completed and returned. Second, missing diaries were included in the second calculation making the assumption that if participants did not complete and return a study diary, they also did not take their medication on that day. Diaries

were missing only when participants failed to complete and return a paper diary to their therapist at appointments. Difficulties with non-adherence due to negative side effects of medication were not anticipated given that amitriptyline at doses of up to 1 mg/kg/day is not typically associated with significant negative effects that may lead to avoidance of the medication.^{4,19}

Statistical Analyses

SPSS version 23.0 was used to complete all data analyses. Descriptive data on demographics, headache characteristics, and all three measures of adherence were computed for the sample. Treatment session attendance adherence were calculated separately for the CBT+A and HE+A groups. An independent samples t-test was conducted to determine if session attendance adherence differed between the two groups. CBT home practice adherence was evaluated for the CBT+A group only given that the HE+A group was not asked to complete skill-based home practice between headache education sessions. Medication adherence was calculated for the CBT+A and HE+A groups combined because all participants were taking the same study medication and were asked to complete the same daily self-report diaries of medication adherence. An independent samples t-test was conducted to determine if medication adherence differed between the groups. A p-value of < .05 was used for all analyses.

Results

Demographic Information

Of the 398 participants approached to participate in the original trial, 197 agreed to be screened for eligibility, and the final sample included 135 children and adolescents (CBT+A N = 64, HE+A N = 71) meeting all eligibility criteria. The majority of these participants (92%) completed the study, including follow-up visits. The average age of participants was 14.4 (SD = 2.0). The majority of the participants were female (79%), White (89%), and had at least one parent with an undergraduate college degree (49% of mothers, 43% of fathers). No differences on demographic variables were found between the two groups. See Table 1 for detailed demographic information.

Headache characteristics—The average headache frequency of the sample at baseline was 21.3 headaches per 28-day period (SD = 5.2). Participants in the sample reported their average headache disability as 68.3 (SD = 31.9) on the PedMIDAS, indicating severe disability related to chronic migraine. No significant age-related differences, or differences between CBT+A and HE+A were observed in baseline headache frequency (21.2 for CBT +A and 21.0 for HE+A) or PedMIDAS disability scores (67.3 for both).

At post-treatment, the CBT+A group had a reduction in headaches by 11.5 days compared to a 6.8 day reduction for the HE+A group ($p = .002$). Disability measured by the PedMIDAS decreased by 52.7 points for the CBT+A group compared to 38.6 points for the HE+A group ($p = .01$).⁴

Adherence to Treatment

Session attendance adherence—Of the 64 participants in the CBT+A condition, the average number of CBT sessions attended out of 10 possible sessions was 9.53 (SD = 1.67). CBT session attendance ranged from 1 to 10 sessions attended. Almost all participants attended 8 or more of the 10 possible CBT sessions (99%).

Of the 71 participants in the HE+A condition, the average number of headache education sessions attended out of 10 possible sessions was 9.86 (SD = 0.87). Headache education session attendance ranged from 3 to 10 sessions attended. Almost all participants attended 8 or more of the 10 possible CBT sessions (99%).

A t-test indicated that there was no significant difference in session attendance adherence between the CBT+A and HE+A groups, $t(133) = 1.41$, $p = 0.16$.

CBT home practice adherence—Of the 64 participants in the CBT+A condition, the average home practice between therapy sessions reported out of 10 possible opportunities for home practice was 9.02 (SD = 2.22). Patients reported home practice of CBT skills ranged from 0 to 10 times between sessions for the trial duration. Almost all participants reported to their therapist that they practiced their CBT skills at home between therapy appointments 8 or more times between sessions (96%).

Medication adherence—Medication adherence was examined per patient self-reported daily diary for all 135 participants (both CBT+A and HE+A conditions). The overall group average percent of missing diaries for the trial duration was 12%, with no significant differences between the two groups for missing diaries ($M_{\text{CBT+A}} = 11\%$, $M_{\text{HE+A}} = 13\%$, $t(133) = -0.30$, $p = 0.77$). Based on completed diaries, participants reported taking their study medication as prescribed an average of 110.2 days (SD = 34.3) for the trial duration. Participants' reports of taking their study medication ranged from 8% to 100%.

When excluding missing diaries from analyses of medication adherence, the average percent of medication adherence was 90% based on days diaries were completed. To determine if self-reported adherence to medication would differ if all participants had returned all daily diaries, multiple imputation (MI) was used to account for missing data points; however, MI produced the same values presented above (90% rates of adherence). When calculating rates of adherence to medication including missing diaries (e.g., indicating that a participant did not take their medication on the day that a diary was missing), average rate of medication adherence was 79%.

A t-test indicated that there was no significant difference in medication adherence between the CBT+A and HE+A groups when excluding missing diaries, $t(133) = -0.56$, $p = 0.58$, and when missing diaries were included, $t(133) = -1.29$, $p = 0.20$. Post-hoc analyses revealed that 14% of children with migraine in the overall sample ($N = 19$) reported taking less than 80% of prescribed doses.

Discussion

A paucity of treatment adherence research for children and adolescents with migraine exists, with only six studies examining adherence to behavioral treatment recommendations and very few studies reporting medication adherence. Existing studies demonstrate 52–86% adherence to behavioral recommendations (e.g., biofeedback, progressive muscle relaxation) for children with migraine.^{20–24} These studies have utilized homework completion to signify adherence and have determined adherence based on a variety of measurements including: 1) patient reported diary,²¹ 2) therapist rating of homework completion using 80% cut-point,²⁴ 3) combination of patient/parent verbal report with “hidden watch” that calculated the amount of practice time,²⁰ 4) combination of self-reported practice time and the reporting of a “relaxation password of the day” hidden within the child’s relaxation tape.²² Several additional studies examining the efficacy of behavioral and/or medication treatments for migraine in children and adolescents have reported broad, general adherence findings such as “participants appeared adherent”^{23,25} or “adherence was good”²⁶ without reporting how adherence was assessed. No studies have provided quantitative, multi-method data regarding adherence to treatment session attendance, skills practice between sessions, and medication simultaneously for children or adolescents with migraine participating in a clinical trial. Given the lack of research in this area and the methodological limitations within the existing studies, it is necessary for adherence to be examined in children and adolescents with migraine in a systematic way.

To our knowledge, this is the first study that has presented multi-method data on adherence to treatment for pediatric chronic migraine that was assessed in a systematic way. The current study utilized secondary analyses from a larger randomized clinical trial to assess three aspects of adherence to treatment: treatment session attendance was measured using therapist report, CBT skills/home practice between sessions was reported from patients directly to the therapist, and medication adherence was measured using self-reported daily diaries. Results indicate that all patients, regardless of condition, demonstrated high rates of treatment session attendance. Patients in the CBT+A condition also reported to their therapists having high levels of adherence to recommended home practice of CBT skills between therapy sessions. Self-reported medication adherence was lower than adherence to the behavioral treatment recommendations, regardless of how medication adherence was calculated. Specifically, rates of medication adherence were 90% when excluding missing diaries, and 79% when including missing diaries as days when medication was missed. Furthermore, diary completion rates were high during the 20 weeks of treatment. Results also indicate that headache frequency and disability decreased for both groups from baseline to post-treatment, but the CBT+A group showed significantly greater reductions in headache frequency and disability than the HE+A group. Given this and previously published information on reduction of headache characteristics following CBT+A treatment,^{4,27} and the reported adherence rates found in this study, we are confident that CBT+A is an effective and potentially practical treatment for chronic migraine among pediatric patients. Medication adherence, specifically in the subset of children with adherence less than 80% may be one area for further examination and a potential area for improvement.

Overall, adherence to behavioral and medication recommendations was higher than what might be expected based on the current pediatric adherence literature.^{5,20,21,23,28} Given the high rates of adherence, there was a ceiling effect for adherence variables, preventing patients from being grouped as “adherent” versus “non-adherent”. Previous studies on adherence to migraine treatment, although quite limited, have not clearly defined a way to designate patients as “adherent” versus “non-adherent”. Although the use of a medication adherence cut-point can provide descriptive information about the adherence of this sample,²⁴ often the selection of a specific percentage cut point to distinguish between “adherent” and “non-adherent” patients is arbitrary and are accompanied by their own limitations. Thus, we chose not to include an arbitrary cut-point for adherence versus non-adherence in this study. Ceiling effects on adherence variables also limited associations between adherence and study outcome variables such as headache frequency and disability. Thus, no significant correlations exist between the three measures of adherence and any outcome variables within the current study.

It is important to note that this assessment of adherence to treatment for pediatric migraine was conducted within the context of a research study, limiting generalizability of the findings to clinical practice. Patient reports of adherence when receiving standard clinical care (outside of the context of a research protocol) for pediatric migraine may be different. Perhaps the regular contact and follow-up appointments, and reimbursements for time and travel, that are necessary within a clinical trial study may increase adherence and make estimates provided in this novel study less generalizable, at least until data on adherence (using self-report as well as electronic monitoring) within the context of regular care is available. Further, rates of adherence to daily diary completion of taking medication could have been higher than typical given that participants were given a reminder call from nurses every two weeks to promote diary completion as part of the research design. It is also possible that the task of keeping a diary and answering a daily question about medication consumption increased the teens self-monitoring and thereby increasing adherence during the study period. However, a recent study using electronic monitoring of adherence to medication in pediatric migraine within the context of typical clinical practice, indicated rates of adherence to amitriptyline at 85%,²⁹ which is comparable to rates of medication adherence reported in the current study. Future studies assessing adherence to pediatric migraine treatment should continue to work to define adherence to treatment across multiple measures (e.g., session attendance, homework completion, medication), as well as assess adherence within standard clinical care rather than within a clinical trial. Future studies should also explore rates of adherence to medication and CBT among more diverse samples, as results from this study may not be generalizable to other populations because the current sample included primarily White families with higher education levels.

Of note, rates of adherence may have been influenced by time and travel reimbursement provided to families for participation in this research, as well as a desire to appear socially acceptable to their therapists. While it is unlikely that these variables can entirely account for such high rates of adherence because participants were provided reimbursement based on diary completion regardless of their adherence rate and were not compensated for practicing skills between sessions, financial assistance may have increased the ability to attend

appointments. This is in contrast to clinical care, where families often experience costs for attending appointments because of having to pay for their own transportation.

Another limitation of this study is the use of subjective self-reported adherence. Subjective assessments, and particularly self-report, often overestimate adherence. For example, previous research has documented that parent-reported adherence (96.5%) was significantly higher than electronically monitored adherence (80%) in children with epilepsy.³⁰ Similarly, children with IBD subjectively report a median adherence level of 98.8% compared to a median adherence rate of 91.7% when electronic monitoring is used.³¹ Both of these studies established correction factors (0.83 and 0.92, respectively) which are feasible for use in clinical practice when objective data via pill counts or electronic monitoring is not available. Although no correction factor has been established for children with migraine, it is important to consider the discrepancies between subjective and objective data in other pediatric populations when interpreting these findings.

Finally, given that assessing adherence to pediatric migraine treatment was a secondary aim from this randomized clinical trial, methods of assessing adherence to treatment used in the current study were not as comprehensive as they may be for studies designed to measure rates of adherence as the primary outcome. Thus, future studies evaluating adherence to pediatric migraine treatment should include objective measures of adherence. For example, electronic medication monitoring devices or collecting serum levels of active medications³² could be used to more directly assess medication adherence. The current study attempted to utilize pill counts; however, pill counts were started late in the trial and were largely unsuccessful due to the majority of patients not returning any of their blister packs. For adherence to practicing skills between sessions, in addition to patient's self-reported practice of homework between sessions, therapists could include an embedded word within therapy home practice of relaxation skills and require patients to report this "hidden password" at the following session for a more targeted measure of adherence to home practice of therapy skills between sessions. These studies would provide more comprehensive information regarding treatment adherence beyond this initial, yet important documentation of behavioral and medication treatment recommendation adherence in the largest clinical trial to date that examined treatment efficacy in youth with chronic migraine.

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Table 1

Baseline demographics and headache frequency

	Total (N=135)	CBT+A (N=64)	HE+A (N=71)
	N (%)	N (%)	N (%)
Gender			
Male	28 (21)	13 (20)	15 (21)
Female	107 (79)	51 (80)	56 (79)
Race			
White	120 (89)	59 (92)	61 (86)
Black/African-American	13 (10)	4 (6)	9 (13)
Asian	1 (1)	1 (2)	0 (0)
American Indian or Alaskan Native	1 (1)	0 (0)	1 (1)
Parent Education			
<i>Mother</i>			
Up to high school	33 (24)	12 (19)	21 (30)
Some college/tech	33 (24)	19 (30)	14 (20)
College grad	49 (36)	22 (34)	27 (38)
Graduate degree	20 (15)	11 (17)	9 (13)
<i>Father</i>			
Up to high school	40 (31)	16 (25)	24 (37)
Some college/tech	30 (23)	17 (27)	13 (20)
College grad	43 (33)	22 (34)	21 (32)
Graduate degree	16 (12)	9 (14)	7 (11)
	Mean (SD)	Mean (SD)	Mean (SD)
Age	14.4 (2.0)	14.4 (1.9)	14.4 (2.1)
Baseline Values for Headache Frequency			
Headache Disability^a	68.3 (31.9)	67.3 (29.8)	67.3 (29.8)
Headache Days (Per 28)	21.1 (5.4)	21.2 (5.6)	21.0 (5.2)

Adapted from Powers 2013³;^aPer PedMIDAS Score