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Research Submissions

Does Mindfulness-Based Cognitive Therapy for Migraine Reduce Migraine-Related Disability in People with Episodic and Chronic Migraine? A Phase 2b Pilot Randomized Clinical Trial

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Objective.—The current Phase 2b study aimed to evaluate the efficacy of mindfulness-based cognitive therapy for migraine (MBCT-M) to reduce migraine-related disability in people with migraine.

Background.—Mindfulness-based interventions represent a promising avenue to investigate effects in people with migraine. MBCT teaches mindfulness meditation and cognitive-behavioral skills and directly applies these skills to address disease-related cognitions.

Methods.—Participants with migraine (6-30 headache days/month) were recruited from neurology office referrals and local and online advertisements in the broader New York City area. During the 30-day baseline period, all participants completed a daily headache diary. Participants who met inclusion and exclusion criteria were randomized in a parallel design, stratified by chronic migraine status, to receive either 8 weekly individual MBCT-M sessions or 8 weeks of waitlist/treatment as usual (WL/TAU). All participants completed surveys including primary outcome evaluations at Months 0, 1, 2, and 4. All participants completed a headache diary during the 30-day posttreatment evaluation period. Primary outcomes were the change from Month 0 to Month 4 in the headache disability inventory (HDI) and the Migraine Disability Assessment (MIDAS) (total score ≥ 21 indicating severe disability); secondary outcomes (headache days/30 days, average headache attack pain intensity, and attack-level migraine-related disability [Migraine Disability Index (MIDI)]) were derived from the daily headache diary.

Results.—Sixty participants were randomized to receive MBCT-M (n = 31) or WL/TAU (n = 29). Participants (M age = 40.1, SD = 11.7) were predominantly White (n = 49/60; 81.7%) and Non-Hispanic (N = 50/60; 83.3%) women (n = 55/60; 91.7%) with a graduate degree (n = 35/60; 55.0%) who were working full-time (n = 38/60; 63.3%). At baseline, the average HDI score (51.4, SD = 19.0) indicated a moderate level of disability and the majority of participants (50/60, 83.3%) fell in the "Severe Disability" range in the MIDAS. Participants recorded an average of 16.0 (SD = 5.9) headache days/30 days, with an average headache attack pain intensity of 1.7 on a 4-point scale (SD = 0.3), indicating moderate intensity. Average levels of daily disability reported on the MIDI were 3.1/10 (SD = 1.8). For the HDI, mean scores decreased more from Month 0 to Month 4 in the MBCT-M group (−14.3) than the waitlist/treatment as an usual group (−0.2; $P < .001$). For the MIDAS, the group*month interaction was not significant when accounting for the divided alpha, $P = .027$; across all participants in both

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groups, the estimated proportion of participants falling in the "Severe Disability" category fell significantly from 88.3% at Month 0 to 66.7% at Month 4, $P < .001$. For diary-reported headache days/30 days an average headache attack pain intensity, neither the group*month interaction (Ps = .773 and .888, respectively) nor the time effect (Ps = .059 and .428, respectively) was significant. Mean MIDI scores decreased in the MBCT-M group (−0.6/10), whereas they increased in the waitlist/treatment as an usual group (+0.3/10), $P = .007$.

Conclusions.—MBCT-M demonstrated efficacy to reduce headache-related disability and attack-level migraine-related disability. MBCT-M is a promising emerging treatment for addressing migraine-related disability.

Key words: migraine, mindfulness, therapy, behavioral treatment, disability

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INTRODUCTION

Migraine is a common neurologic disease[1] estimated to affect over a billion people worldwide.[2] Migraine accounts for a disproportionate amount of disease burden, particularly among women from the age of 15 to 49.[2] Because migraine is characterized by unpredictable episodic attacks of potentially debilitating neurological symptoms and is most prevalent during the most potentially productive and childbearing years,[2,3] it has a particularly pernicious impact on work, school, and social/family functioning.[3-6]

Behavioral treatments for migraine, including cognitive-behavioral therapies, relaxation, and biofeedback, have demonstrated efficacy to reduce migraine attack frequency and migraine-related disability.[7-10] However, not every person with migraine responds to existing behavioral treatments; further, access to evidence-based behavioral migraine treatment remains a challenge to wide-scale dissemination.[10] People with migraine are increasingly turning to complementary and integrative health strategies to address migraine,[11,12] particularly when their pharmacologic choices are restricted, such as during pregnancy or due to low efficacy or lack of tolerability of pharmacologic therapies.[13] More than 50% of adults with migraine and severe headache report utilizing complementary and integrative health strategies for headache management.[14] Further, complementary and integrative health strategies are often added on to pharmacologic and other therapeutic strategies. Mindfulness-based interventions have a high level of interest in people considering nonpharmacologic therapies and have demonstrated efficacy in other disease states including chronic pain and therefore

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Trial prospectively registered at clinicaltrials.gov: NCT02443519.

represent a promising avenue to investigate effects in people with migraine.[15,16]

Mindfulness is an attention regulation technique characterized by the nonjudgmental awareness of the present moment.[17] Mindfulness exemplifies the "third-wave" treatments, which extend behavioral and cognitive treatments with mindfulness- and acceptance-based frameworks. Mindfulness is thought to alter the way patients respond to pain by making it more tolerable and by making it easier to engage in meaningful activities despite symptoms.[17] Many third-wave therapies have demonstrated empirical support for the treatment of a variety of psychiatric and medical conditions including chronic pain.[18-20] Several recent pilot studies have found that mindfulness-based interventions can achieve clinically meaningful reductions in headache-related disability among people with primary headache disorders, though these interventions tend to have minimal effects on headache days and headache attack pain intensity.[21-24] This finding is not surprising; mindfulness-based interventions are expected to primarily act on headache-related disability, rather than headache symptoms specifically.

Mindfulness-Based Cognitive Therapy (MBCT) teaches mindfulness meditation and cognitive-behavioral coping skills and directly applies these skills to address disease-related cognitions and coping. It was originally developed to prevent depression relapse[25-27] and has been modified to address a variety of chronically painful conditions.[28] MBCT targets maladaptive disease-related beliefs in addition to stress reduction and is traditionally delivered using a group format with groups of 8-10 individuals. MBCT seems to outperform simple mindfulness meditation on measures of pain-related interference in people with chronic low back pain.[29] Across medical conditions, randomized clinical trials of MBCT consistently find a reduction in stress and disease-related disability or impairment; however, changes in disease outcomes tend to be small or not statistically significant on an average.[28,30]

A pilot study with patients with both migraine and tension-type headache (n = 36) found that group-based 8-session MBCT for primary headache was associated with improvements in self-efficacy and pain acceptance compared to waitlist participants; in the completer sample (n = 24), large improvements in pain interference were more frequent in the active group than in waitlist controls ($d = -1.29$).[31] Though both groups experienced a reduction in headache frequency, the MBCT group was not significantly different than the waitlist group.

Recent work with behavioral randomized clinical trials has specified four phases:[32] Phase I studies define the treatment paradigm and refine treatment delivery including dose ranging; Phase II studies are single-arm proof-of-concept studies and two-arm controlled pilots; Phase III studies are adequately powered efficacy randomized controlled trials; and Phase IV studies are effectiveness research. Earlier research with MBCT for depression treatment and relapse prevention defined the treatment targets of mindfulness meditation skills and disease-related cognitions and refined the classic 8-week, group delivery intervention protocol.[25,33] The two-armed trial in people with primary headache disorders tailored the protocol for headache and demonstrated proof-of-concept in this population.[31,34] This treatment protocol was further refined for migraine (MBCT for Migraine; MBCT-M) in an individual format for the current trial.[35]

The current Phase 2b study aimed to evaluate the efficacy of MBCT-M to reduce migraine-related disability in people with migraine. Headache-related disability was selected as the primary outcome rather than the headache frequency because mindfulness-based treatments are primarily expected to alter the patient's experience of migraine, resulting in a reduction in migraine-related disability. We chose individual over group therapy because (1) preparatory interviews with headache providers (neurologists and psychologists) suggested that individual treatment protocols would be more readily implemented in their clinical settings and (2) to avoid the nonindependence of observations that results from group treatment paradigms. Therefore, the primary aim of the study was to evaluate whether MBCT-M was superior at reducing two measures of overall migraine-related disability compared to a waitlist/treatment as usual (WL/TAU) control. Secondary aims included evaluating whether MBCT-M reduced headache days, average headache attack pain intensity, and a daily diary measure of migraine attack disability compared to WL/TAU.

METHODS

Participants.—Participants were recruited from neurology office referrals and local and online advertisements in the broader New York City area including New York, New Jersey, and Connecticut. Inclusion criteria were (1) currently meeting International Classification of Headache Disorders (ICHD)-3 beta headache diagnosis for migraine using a semi-structured clinical interview and the validated American Migraine Study/American Migraine Prevalence and Prevention Study migraine diagnostic screener;[36] (2) self-reported and prospective diary-confirmed ≥6 headache days per month; (3) aged 18-65; (4) ability to read English; and (5) capacity to consent. Exclusion criteria were (1) continuous headache over the course of 30 days; (2) initiation of a preventative migraine treatment within four weeks of the baseline assessment or a plan to initiate preventive migraine treatment during the duration of the study, (3) severe psychiatric illness that would interfere with participation in the treatment such as active suicidality, active psychosis, or failing a cognitive screen; or (4) inability to adhere to headache diary during the baseline period (recorded fewer than 26/30 days). All participants were screened through an online portal and participated with an in-person intake evaluation including a semi-structured clinical interview for headache and psychiatric diagnosis with doctoral psychology students. Students were trained in interviewing for headache and psychiatric diagnoses and supervised by licensed psychologists who are experts in behavioral headache treatment (ES and DB). This is a single-site study in which intake assessments and intervention visits were conducted at one of the two locations in the campus of Yeshiva University (Bronx and Manhattan).

Study Design and Treatment.—This is a two-arm parallel randomized clinical trial to test the superiority of MBCT-M compared to WL/TAU to reduce headache disability. The study began enrolling patients in July 2015 and all primary outcome data were collected by September 2018. The protocol was prospectively registered at clinicaltrials.gov (NCT02443519) and received ethics approval by the Einstein IRB (2015-4684). No changes were made to the original protocol.

Participants who met initial inclusion criteria at intake were enrolled by their graduate student intake interviewer. All participants provided written informed consent. During the 30-day baseline period, all participants completed a daily headache diary (Fig. 1). Chronic migraine status was determined by the number of headache days recorded during the first 30-day period; 15 or more days per month was considered chronic migraine (following Silberstein-Lipton criteria[37]) with at least one discrete full-criteria migraine attack. Participants who met inclusion and exclusion criteria after the 30-day baseline period were randomized by a graduate student research assistant who had no further direct contact with patients in a 1:1 ratio in a parallel design, stratified by chronic migraine status, to receive either 8 weekly individual MBCT-M sessions or 8 weeks of WL/TAU. Neither participants nor researchers were blinded to the treatment group assignment.

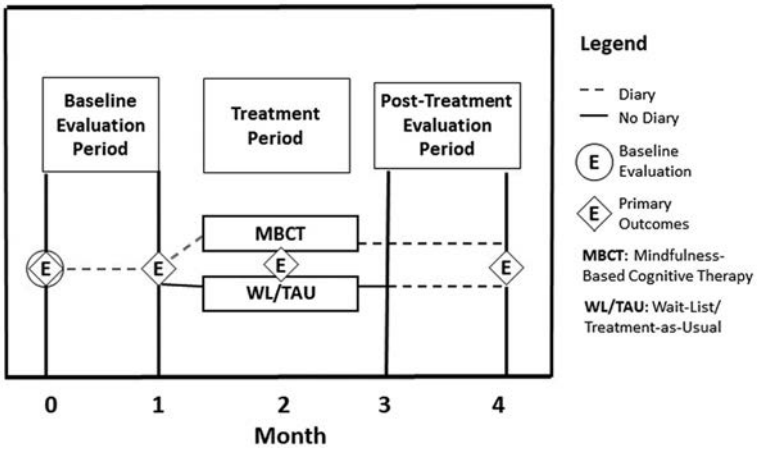

Fig. 1.—Study design.

A researcher not otherwise connected with this study used computerized stratified block randomization with random block sizes to generate the randomization sequence which was provided to a research assistant in opaque, sealed sequentially numbered envelopes.

During the 2-month treatment period, participants randomized to MBCT-M continued the daily headache diary. Participants randomized to the WL/TAU condition did not complete a daily headache diary during the treatment period as the headache diary was conceptualized as a part of the treatment. All participants completed surveys including primary outcome evaluations at Months 0, 1, 2, and 4. All participants completed a headache diary during the 30-day post-treatment evaluation period. All data were captured using REDCap, a HIPAA-compliant online data capture system; outcome data were collected automatically without direct contact with research assistants. Adverse events were captured systematically through routine contact with the research coordinator and study therapists. Participants were compensated up to $70 for the completion of study measures. Participants in the WL/TAU condition were offered the 8-week treatment program after completion of the 4-month study protocol.

MBCT-M consisted of 8 individual 75-minute sessions which occurred approximately weekly over a period of 8-10 weeks (Table 1) and a daily headache diary and mindfulness log. The treatment protocol was adapted from the MBCT for the chronic headache pain protocol created by Day and colleagues.[19,31] Adaptation largely included modifying the theoretical rationale for mindfulness training to be appropriate for migraine rather than chronic pain; in addition, the mindful movement component was modified to simple stretching and walking to avoid movements that might be particularly challenging for people with migraine. Each session included education, cognitive exercises designed to demonstrate how to think mindfully, and in-vivo mindfulness meditation practice designed to help participants systematically gain mindfulness skills throughout the course of treatment. Participants were given "homework," including formal mindfulness meditation and informal mindful awareness exercises, labeling thoughts, identifying warning signs for stress and migraine, and planning nourishing activities, in between sessions (Table 1). Most sessions were conducted in-person at research sites in the Bronx or Manhattan. Because migraine is characterized by unpredictable disabling attacks, we permitted phone sessions for up to 3 of the 8 sessions per patient to avoid extending the treatment timeframe beyond 10 weeks. Therapists were doctoral-level clinical psychology graduate students who attended two 6-hour training sessions supervised by psychologists with specific expertise in MBCT (MD) and migraine (ES and DB). Therapists were then supervised by licensed clinical psychologists who are experts in behavioral headache treatment (ES and DB) throughout the course of the study. Supervision included individual weekly meetings and monthly group supervision with all study therapists to reduce protocol deviations. All sessions were recorded and evaluated on an ongoing basis for fidelity to the protocol. A data safety monitoring committee met every other month throughout the course of the study.

Measures.—*Baseline Characteristics*.—Participants reported age, gender (male and female), ethnicity (Hispanic and Non-Hispanic), race (White, Black/African American, Native American, Asian, Pacific Islander, and Other), employment status (employed full-time [35 or more hours/week] and employed part-time [less than 35 hours/week], student, self-employed, homemaker, on medical or maternity leave, unemployed, disabled, retired, volunteer, or other), education (Grade 8 or less, high school graduate or GED, some high school, some college or technical school, college graduate/bachelor's degree, and graduate degree), and marital status (single, married, separated/divorced, widowed, and live with a domestic partner) at baseline. Participants reported all medications used at baseline. Participants also reported baseline psychiatric symptoms on the 8-item Patient-Reported Outcomes Measurement Information System Depression (PROMIS-D) and Anxiety (PROMIS-A) Short Forms;[38] scores are reported as population normed *T*-scores.

Primary Outcomes.—The primary outcomes were changes in headache-related disability from Month 0 to Month 4; two measures were utilized to capture different components of headache-related disability.

The Henry Ford hospital headache disability inventory (HDI)[39] is a 25-item survey designed to assess the perceived impact of headache. Items include, "Because

Table 1.—Overview of Mindfulness-Based Cognitive Therapy for Migraine

Theme	Teach a Concept	Practice a Skill	Homework
1: Automatic pilot	Automatic pilot involves lacking awareness and habitual responding to one's environment. Mindfulness can improve living with migraine through intentional awareness	▪ Body scan ▪ Mindful eating	▪ Body scan
2: Awareness of appraisals and stress	Mindfulness allows you to observe how you feel and think. How we appraise a situation is more important than the objective situation itself. How you appraise migraine and other life stressors can impact the stress response, which in turn influences your likelihood of having a migraine attack	▪ Body scan ▪ Awareness of appraisals ▪ Awareness of thoughts arising during breathing meditation	▪ Body scan ▪ Mindfulness of breath ▪ Awareness of thoughts ▪ Stressful events calendar
3: Mindfulness of the breath	Practicing mindfulness throughout the day can break automatic pilot patterns and disrupt the stress response. The breath is always with you and can anchors you to the present moment	▪ Breathing space ▪ Labeling automatic thoughts	▪ Sitting meditation and body scan ▪ Breathing space
4: Recognizing aversion	Aversion is an automatic response to avoid unpleasant experiences. Mindfulness helps us to inquire about the multiple responses we can have to stressors, such as migraine	▪ Mindful movement (walking and stretching)	▪ Sitting meditation and mindful movement ▪ Breathing space
5: Allowing/letting be	Mindfulness, as opposed to aversion, can help us experience stressors without judging them (acceptance) and thoughtfully choose how to react to any given situation	▪ Identifying automatic thoughts ▪ Sitting meditation with acceptance	▪ Sitting meditation ▪ Breathing space
6: Thoughts are not facts	Thoughts are not facts. Mindfulness teaches us how to observe our thoughts and consider the context in which our thoughts are occurring	▪ Sitting meditation ▪ Mindful observation of cognitions and considering alternatives ▪ Awareness of pleasant events	▪ Choose your own meditation ▪ Breathing space for coping ▪ Pleasant events calendar
7: How can I best take care of myself?	When you notice your life becoming unbalanced, stressors emerging, or begin to feel migraine symptoms, you can use "warning signs" to mindfully consider the best course of action	▪ Sitting meditation ▪ Linking activity and mood/stress/migraine ▪ Identifying warning signs for stress and migraine ▪ Making a plan for nourishing activities	▪ Develop a routine to practice mindfulness ▪ Dealing with stress and migraine
8: Using mindfulness to cope with migraine	Maintaining and extending the gains you have made during MBCT-M requires planning and intentional action	▪ Body scan ▪ Relapse prevention ▪ Focused meditation	

of my headaches I feel handicapped," with total scores ranging from 0 to 100, with higher scores indicating higher levels of disability. The HDI has demonstrated reliability and validity,[39,40] and excellent internal consistency in this study, $\alpha = .90$.

The Migraine Disability Assessment (MIDAS)[41,42] is a 5-item survey designed to assess the functional impact of migraine on occupational/academic work, household work, and social/leisure activities. Items include, "On how many days in the last 3 months did you miss work or school because of your headaches," with total scores interpreted as 0-5: "Little or No Disability," 6-10: "Mild Disability," 11-20: "Moderate Disability," and ≥21: "Severe Disability." For the purposes of analysis, the MIDAS total score was dichotomized at 21. The MIDAS has demonstrated reliability and validity

in previous studies;[40] in this study, it demonstrated adequate internal consistency, $\alpha = .76$.

Secondary Outcomes.—Participants recorded headache activity daily in an electronic headache diary using status/post,[43,44] a secure ecological momentary assessment application which interacts with the REDCap data capture system. The app is available for iOS devices; participants used either their personal device or a device provided to them by the study team if they did not have a compatible personal device. Secondary outcomes included: headache days/30 days, average headache attack pain intensity/30 days (scored as 0 = None, 1 = Mild, 2 = Moderate, and 3 = Severe), and Migraine Disability Index (MIDI) score. The MIDI is a 4-item scale designed to assess the extent to which the headache attack interfered with family/home, recreation, social, and occupational functioning on each headache attack day,[45] with response options for each domain ranging from 0, "not at all," to 10, "totally." Responses to the four items are averaged to obtain a day-level score. The MIDI has demonstrated good reliability and validity in previous studies;[45,46] in this study, it demonstrated excellent internal consistency, $\alpha = .91$.

MIDAS questions A and B were also used to evaluate headache days/90 days and average headache attack intensity/90 days. Results are reported with MIDAS A score divided by three, such that the MIDAS A score indicates headache days/30 days.

Treatment Fidelity.—Therapist fidelity to the treatment protocol was assessed with Mindfulness-Based Cognitive Therapy Adherence, Appropriateness, and Quality Scale,[19] a 23-item self-report instrument adapted from previous well-validated measures of fidelity to cognitive therapies[47] and used in the previous study of MBCT for chronic headache.[31] All sessions were audio recorded and 3 sessions per patient were rated by two raters on adherence (the extent to which the therapist provided the intervention per protocol), appropriateness (the extent to which the therapist provided the intervention in a manner which addressed the patient's symptoms and presentation), and quality (the overall skill with which the therapist provided the intervention). Raters were undergraduate, postbaccalaureate, and masters-level research assistants who had no other connection to the study. All raters were trained on 5 practice sessions. Every fifth session was rated by all raters monthly to maintain high levels of inter-rater reliability. Inter-rater reliability was excellent, adherence intra-class correlation = .90, appropriateness intra-class correlation = .90, and quality intra-class correlation = .91.[46]

Participant daily mindfulness practice (yes/no) was captured in the daily headache diary in the MBCT-M group during the 8-week treatment period and 30-day follow-up period.[48]

Acceptability.—Exit interviews with participants who participated in the MBCT-M protocol were conducted by a clinical psychologist (ES). Semi-structured interviews included questions about favorability toward the intervention, therapist, using mindfulness in daily life, desire to continue with the skills learned in the treatment, and whether they would recommend it to others with migraine.

Analyses.—Distributions of all study variables were inspected. Single imputation at the day-level was used to impute missing diary data points (15.5%) for headache day, attack pain intensity, and the MIDI by obtaining estimates using mixed models for repeated measures analysis with fixed effects of treatment, month, day, and all of their interactions, and random effects of intercept and day*month. Simulated clinical trial data have demonstrated that mixed models for repeated measures produce remarkably unbiased estimates when observations are both missing at random and missing not at random.[49-51] Patient characteristics and clinical outcomes described using mean and standard deviation for normally distributed variables, and number and percent for nominal variables. Differences between demographics and primary and secondary outcomes at baseline were evaluated using *t*-tests for independent samples or chi-square analyses.

The intent-to-treat analysis used linear (HDI, MIDI/30 days, headache days/30 days, headache attack pain intensity/30 days) and logistic (MIDAS severe disability) mixed models for repeated measures to estimate missing values and evaluate changes in primary outcomes. For HDI and MIDAS, month was a 4-level variable (Month 0, 1, 2, and 4); for diary data, month was a two-level variable (baseline monitoring period vs posttreatment evaluation period). Fixed effects were group, month, and their interaction. A significant interaction indicated that the slope of the MBCT-M group differed from the slope of the WL/TAU

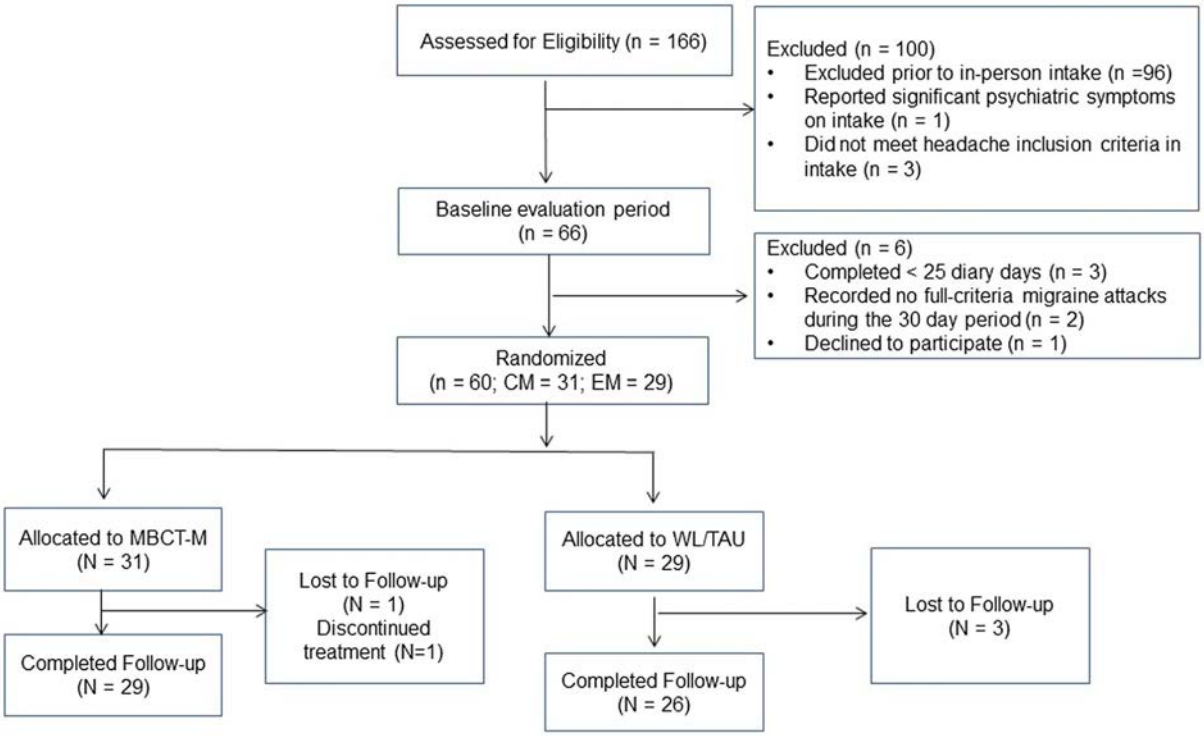

Fig. 2.—Study flow. [Color figure can be viewed at wileyonlinelibrary.com]

group. Nonsignificant group*month interactions were removed from final models. Random effects were intercept and time. Visual inspection and Akaike's information criterion indicated month be modeled using a first-order autoregressive covariance structure. All models were also evaluated 1) adjusting significant patient demographics and 2) using only completers (participants who provided outcome assessment data through Month 4).

A priori power analysis suggested that based on the large observed effect sizes on primary outcomes from previous studies of mindfulness-based treatment in headache disorders ($d = -1.29$)[21,31] with alpha set at .05, a power of .80 would require an n of 62, whereas a power of .90 would require an n of 70; therefore, we intended to enroll 80 participants. Alpha (.05, two-tailed) was divided equally between the two primary outcome analyses. Alpha was set at .05 for all other analyses. SPSS version 25.0 was used to analyze the data.

RESULTS

Participant Characteristics.—One-hundred sixty-six participants were assessed for eligibility; 100 did not meet inclusion criteria upon screening (Fig. 2). Sixty-six participants began the baseline evaluation period; 5 were excluded due to poor diary adherence (n = 3), not meeting ICHD-3b migraine criteria within a one-month monitoring period (n = 2), and one declined to continue to participate in the study after the baseline evaluation period. Therefore, 60 participants (CM = 31, EM = 29) were randomized to receive MBCT-M (n = 31; CM = 16, EM = 15) or WL/TAU (n = 29; CM = 15, EM = 14). Two people in the MBCT-M group dropped out of treatment (1 lost to follow-up and 1 discontinued) and three people in the WL/TAU group were lost to follow-up; attrition did not significantly differ across groups, $P = .938$. The study was halted prior to reaching its target enrollment of 80 due to slow recruitment; the investigators were elected to halt the study rather than to introduce bias by changing recruitment protocol or inclusion criteria.

Participants were predominantly White (n = 49/60; 81.7%), Non-Hispanic (N = 50/60; 83.3%) women (n = 55/60; 91.7%) with a graduate degree (n = 35/60; 55.0%) who were working full-time (n = 38/60; 63.3%)

Table 2.—Baseline Demographic Characteristics

Demographic	Total (N = 60) M(SD) or N (%)	MBCT-M (N = 31) M(SD) or N (%)	WL/TAU (N = 29) M(SD) or N (%)	Significance
Age	40.1 (11.7)	36.2 (10.6)	44.2 (11.5)	.007
Gender				
Female	55 (91.7%)	29 (93.5%)	26 (89.7%)	.938
Male	5 (8.3%)	2 (6.5%)	3 (10.3%)	
Ethnicity				
Hispanic	10 (16.7%)	5 (16.1%)	5 (17.2%)	.908
Non-Hispanic	50 (83.3%)	26 (83.9%)	24 (82.8%)	
Race				
White	49 (81.7%)	26 (83.9%)	23 (79.3%)	.903
Black/African American, Asian, Other	11 (18.3%)	5 (16.1%)	6 (20.7%)	
Employment				
Full-time	38 (63.3%)	21 (67.7%)	17 (58.6%)	.642
Not full-time	22 (36.7%)	10 (32.3%)	12 (41.4%)	
Education				
Some college or less	6 (10.0%)	3 (9.7%)	3 (10.3%)	.775
College graduate	21 (35.0%)	12 (38.7%)	9 (31.0%)	
Graduate degree	33 (55.0%)	16 (51.6%)	17 (58.6%)	
Marital status				
Single	28 (46.7%)	17 (54.8%)	11 (37.9%)	.821
Separated/divorced	6 (10.0%)	1 (3.2%)	5 (17.2%)	
Married/living with domestic partner	26 (43.3%)	13 (41.9%)	13 (44.8%)	

MBCT-M = mindfulness-based cognitive therapy for migraine; WL/TAU = waitlist/treatment as usual; education was divided by college graduates or less vs graduate degree; marital status was divided by single, separated or divorced vs married/living with a domestic partner.

(Table 2). MBCT-M participants (M age = 36.2, SD = 10.6) were significantly younger than WL/TAU participants (M age = 44.2, SD = 11.5), $P = .007$; no other demographic characteristics significantly differed between groups (Table 2).

At baseline, the average HDI score (51.4, SD = 19.0) indicated a moderate level of disability (Table 3). The majority of participants (50/60, 83.3%) fell in the "Severe Disability" range on the MIDAS. On the MIDAS A, participants reported an average of 10.4 (SD = 5.1) headache days/30 days. On the MIDAS B, participants reported an average headache attack intensity of 6.2 on a 10-point scale (SD = 1.8). Participants reported average levels of both depressive (PROMIS-D M = 53.5, SD = 6.8) and anxious symptoms (PROMIS-A M = 56.5, SD = 7.3) within the normal range. Approximately half of the participants (31/60, 51.7%) were taking preventive migraine medication. No survey outcomes differed significantly across treatment groups (Table 3).

Approximately half (n = 31/60; 51.7%) of the participants were classified with chronic migraine based on ≥15 headache days in the baseline 30-day monitoring period as recorded in the headache diary (Table 3). Participants recorded an average of 16.0 (SD = 5.9) headache days/30 days, with an average headache attack pain intensity of 1.7 on a 3-point scale (SD = 0.3), indicating moderate intensity. Average levels of daily disability reported on the MIDI were 3.1/10 (SD = 1.8). No diary measures differed across treatment groups (Table 3).

Treatment Fidelity, Adherence, and Acceptability.— Preliminary analysis demonstrates that the ratings of acceptance (M = 6.1/7, SD = 0.8), appropriateness (M = 6.0/7, SD = 1.2), and quality (M = 6.2/7, SD = 0.9) were indicative of high levels of therapist fidelity to the treatment protocol. Overall, participants in the MBCT-M group practiced mindfulness on 980/1327 (73.9%) of recorded diary days during the treatment period. Of the 31 participants who were randomized

Table 3.—Baseline Clinical Characteristics

Clinical Characteristic	Total (N = 60) M(SD) or N (%)	MBCT-M (N = 31) M(SD) or N (%)	WL/TAU (N = 29) M(SD) or N (%)	Significance
Baseline surveys				
HDI	51.4 (19.0)	52.5 (21.2)	50.2 (16.2)	.644
MIDAS grade				
Severe (≥21)	50 (83.3%)	24 (77.4%)	26 (89.7%)	.355
Not severe (<21)	10 (16.7%)	7 (22.6%)	3 (10.3%)	
MIDAS A	10.4 (5.1)	10.5 (5.2)	10.3 (5.1)	.863
MIDAS B	6.2 (1.8)	5.8 (1.8)	6.6 (1.8)	.128
PROMIS-D	53.5 (6.8)	54.0 (6.2)	53.1 (7.4)	.629
PROMIS-A	56.5 (7.3)	56.7 (8.2)	56.2 (6.2)	.804
Preventive medication				
Yes	29 (48.3%)	11 (35.5%)	18 (62.1%)	.070
No	31 (51.7%)	20 (64.5%)	11 (37.9%)	
Baseline headache diary				
Headache day frequency				
≥15 days/month	31 (51.7%)	16 (51.6%)	15 (51.7%)	.993
<15 days per month	29 (48.3%)	15 (48.4%)	14 (48.3%)	
Headache days/30 days	16.0 (5.9)	16.5 (6.0)	15.5 (5.9)	.490
Average attack Intensity/30 days	1.7 (0.3)	1.8 (0.3)	1.7 (0.3)	.241
Average MIDI/30 days	3.1 (1.8)	2.8 (1.6)	3.4 (2.0)	.198

HDI = Henry Ford hospital headache disability inventory; MBCT-M = mindfulness-based cognitive therapy for migraine; MIDAS = Migraine Disability Assessment; MIDAS A = self-reported headache days over a 90 days period, divided by 3; MIDAS *B* = self-reported average headache attack intensity over a 90 days period (1-10); average attack intensity/30 days (1-3); MIDI = Migraine Disability Index (0-10); education was divided by college graduates or less vs graduate degree; marital status was divided by single, separated or divorced vs married/living with a domestic partner; PROMIS-A = patient-reported outcome measurement information system, anxiety short-form; PROMIS-D = patient-reported outcome measurement information system, depression short-form; WL/TAU = waitlist/treatment as usual.

to receive MBCT-M, 2 (6.5%) never recorded a mindfulness practice. On an average, participants practiced approximately half of the days during the treatment period (M = 31.2/60 days, 52%; SD = 14.3) and during the posttreatment evaluation period (M = 14.9/30 days, 50.0%; SD = 9.7).

Twenty-one participants provided exit interviews. Eighteen (18/21, 85.7%) reported that they felt they had derived benefit from the intervention and would recommend it to others with migraine. Participants perceived using brief mindfulness exercises throughout their days as particularly beneficial. The two participants who reported that they would not recommend the intervention to others were particularly dissatisfied with the daily diary component; both had ceased using the daily diary during the treatment period after a few weeks. Approximately half of the participants interviewed (10/21, 47.6%) requested referrals to continue mindfulness-based treatment after the study treatment protocol had concluded.

Primary Outcomes.—For the HDI, the group*month interaction was significant, $F(3, 95.9) = 4.72$, $P = .004$. From Month 0 to Month 4, mean scores on the HDI decreased more in the MBCT-M group (−14.3) than the WL/TAU group (−0.2) (Month 0 vs 4 $B = 14.1$, 95% CI = 0.8, 13.6; Fig. 3A). Sensitivity analyses found the results did not differ when evaluated adjusting for age (group*month $F[3, 95.6] = 4.79$, $P = .004$; group*Month 0 vs 4 $B = 14.3$, 95% CI = 6.6, 22.0) or only in completers (group*month $F[3, 81.2] = 4.48$, $P = .006$; group*Month 0 vs 4 $B = 14.3$, 95% CI = 6.1, 22.6).

For the MIDAS Severe Disability (Scores ≥ 21), the group*month interaction was not significant when accounting for the divided alpha, $F(3, 213) = 3.12$, $P = .027$ (group*Month 0 vs 4 $B = 1.6$, 95% CI = −0.7, 3.9; Fig. 3B). Sensitivity analyses found the results did not differ when evaluated adjusting for age (group*month $F[3, 212] = 3.10$, $P = .028$; group*Month 0 vs 4 $B = 1.6$, 95% CI = −.1, 4.0). In completers, the group*month

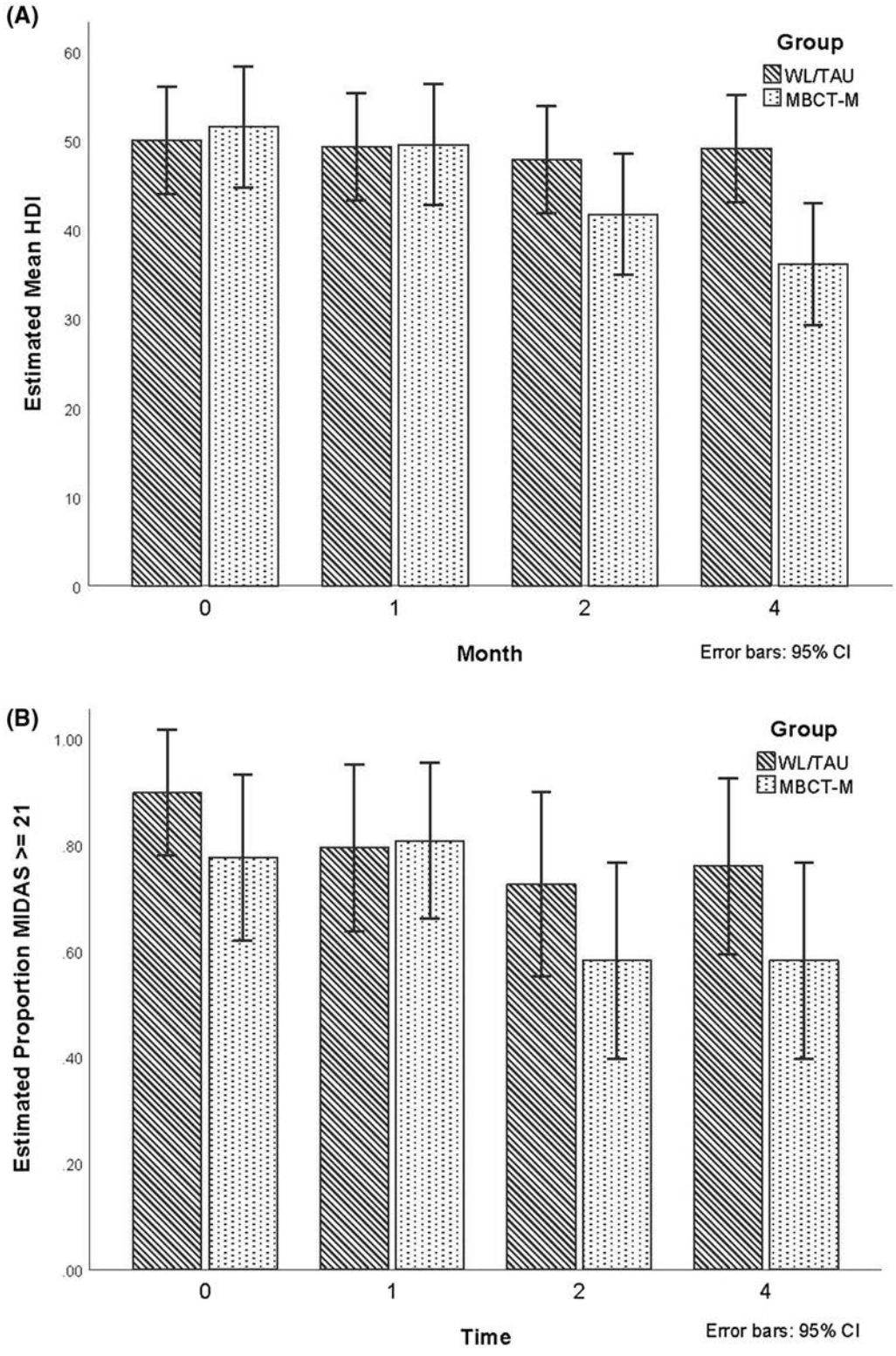

Fig. 3.—Reductions in the HDI (A) and MIDAS severe disability (B) by treatment group and month.

interaction was significant, $F(3, 200) = 3.42$, $P = .018$; however, the group*Month 0 vs 4 contrast was not significant (B = 1.9, 95% CI = −0.6, 4.5). When evaluated without the interaction in the model, the month effect was significant $F(3, 216) = 12.4$, $P < .001$; among participants in both groups, the estimated proportion of participants falling in the "Severe Disability" category fell from 88.3% at Month 0 to 66.7% at Month 4, (B = −2.4, 95% CI = −3.3, −1.4). Sensitivity analyses found the results did not differ when evaluated adjusting for age (month $F[3, 215] = 12.58$, $P < .001$; Month 0 vs 4 $B = -2.4$, 95% CI = −3.4, −1.4) or only in completers (month $F[3, 203] = 12.77$, $P < .001$; Month 0 vs 4 $B = -2.7$, 95% CI = −3.7, −1.6).

Secondary Outcomes.—For diary-reported headache days/30 days, the group*month interaction was not significant, $F(1, 53.8) = 0.08$, $P = .773$; group*month $B = -0.5$, 95% CI = −3.7, 2.8. The result did not differ when adjusted for age (group*month $F[1, 57.2] = 1.34$, $P = .251$; group*month $B = -0.5$, 95% CI = −3.7, 2.7) or among completers (group*month $F[1, 50.0] = 0.18$, $P = .678$; group*month $B = -.7$, 95% CI = −3.9, 2.6). When the interaction was removed from the model, the month effect was not significant, $F(1, 54.7) = 3.72$, $P = .059$; month $B = -1.5$, 95% CI = −3.1, 0.1); the result did not differ when adjusted for age (month $F[1, 54.7] = 3.66$, $P = .061$; month $B = 1.5$, 95% CI = −0.1, 3.1) or among completers (month $F[1, 51] = 2.36$, $P = .131$; month $B = -1.2$, 95% CI = −2.8, 0.4).

For average headache attack pain intensity, group*month interaction was not significant, $F(1, 51.8) = 0.02$, $P = .888$; group*month $B = 0.01$, 95% CI = −0.14, 0.16. The result did not differ when adjusted for age ($F[1, 51.9] = 0.01$, $P = .909$; group*month $B = 0.008$, 95% CI = −0.13, 0.16) or among completers ($F[1, 50.0] = 0.01$, $P = .917$; group*month $B = 0.008$, 95% CI = −0.14, 0.15). When the interaction was removed from the model, the month effect was not significant, ($F[1, 52.8] = 0.64$, $P = .428$; month $B = -0.03$, 95% CI = −0.10, 0.04); the result did not differ when adjusted for age (month $F[1, 52.9] = 0.63$, $P = .430$; month $B = 0.03$, 95% CI = −0.04, 0.10) or among completers (month $F[1, 50.9] = 0.31$, $P = .579$; month $B = 0.02$, 95% CI = −0.05, 0.09).

For diary-reported attack-level migraine-related disability (MIDI), the group*month interaction was significant $F(1, 51.5) = 7.7$, $P = .007$ (Fig. 4C). Mean MIDI scores decreased in the MBCT-M group (−0.6/10), whereas they increased in the WL/TAU group (+0.3/10), group*month $B = -1.0$, 95% CI = −1.6, −0.3. The result did not differ when adjusted for age (group*month $F[1, 51.5] = 7.64$, $P = .008$; group*month $B = -0.9$, 95% CI = −1.6, −0.3) or among completers (group*month $F[1, 50.0] = 7.64$, $P = .008$; group*month $B = -1.0$, 95% CI = −1.6, −0.3).

For MIDAS A, the group*month interaction was not significant, $F(3, 94.6) = 1.21$, $P = .312$ (group*Month 0 vs 4 $B = 6.3$, 95% CI = −2.0, 14.5). Results did not differ when evaluated adjusting for age (group*month $F[3, 94.3] = 1.2$, $P = .312$; group*Month 0 vs 4 $B = 1.3$, 95% CI = −2.0, 14.5) or in only completers (group*month $F[3, 79.4] = 2.00$, $P = .120$; group*month $B = 6.4$, 95% CI = −2.7, 15.5). When the interaction was removed from the model, the month effect was not significant, $F(3, 95.1) = 0.64$, $P = .590$ (Month 0 vs 4 $B = 0.5$, 95% CI = −0.9, 1.9); results did not differ when evaluated adjusting for age (month $F[3, 94.8] = 0.64$, $P = .590$; Month 0 vs 4 $B = 1.5$, 95% CI = −2.6, 5.6) or only in completers ($F[3, 80.3] = 0.33$, $P = .806$; Month 0 vs 4 $B = 1.7$, 95% CI = −2.8, 6.2).

For the MIDAS B (average headache attack pain intensity), the group*month interaction was not significant, $F(3, 102.9)$ 0.65, $P = .589$ (Month 0 vs 4 $B = 0.3$, 95% CI = −0.4, 1.1). Results did not differ when evaluated adjusting for age (group*month $F[3, 102.8] = 0.65$, $P = .861$; Group*Month 0 vs 4 $B = 0.3$, 95% CI = −0.4, 1.1) or in completers (group*month $F[3, 91.0] = 0.56$, $P = .640$; group*Month 0 vs 4 $B = 0.3$, 95% CI = −0.4, 1.1). When evaluated without the interaction in the model, both the group, ($F[1, 58.2] = 4.6$, $P = .036$) and month, $F(3, 104.1) = 3.2$, $P = .028$, effects were significant. On an average, predicted average headache pain intensity was −0.77/10 points lower in the MBCT-M group compared to the WL/TAU group (B = −0.8, 95% CI = −1.5, −0.1). Predicted average headache pain intensity decreased by 0.5/10 points from Month 0 to Month 4 (Month 0 vs 4 $B = 0.5$, 95% CI = 0.2, 0.9). When evaluated adjusting for age, the month effect remained significant

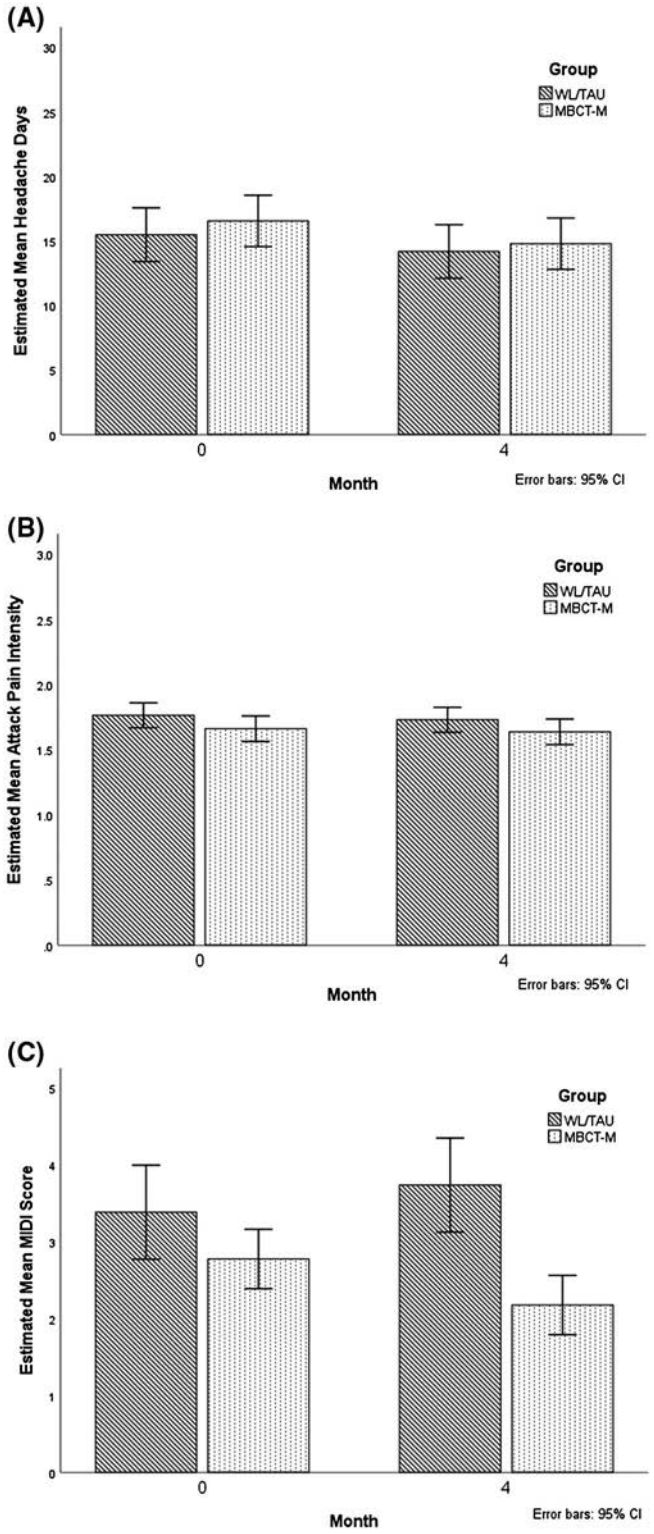

Fig. 4.—Reductions in headache days/30 days (A), average headache attack pain intensity/30 days (B), and Migraine Disability Index (MIDI) Score (C) by treatment group at baseline (Month 0) and follow-up (Month 4).

(F[3, 104.0] = 3.12, P = .028; Month 0 vs 4 B = 0.5, 95% CI = 0.2, 0.9) but the group effect was no longer significant (F[1, 57.3] = 3.70; P = .060; MBCT-M vs WL/TAU B = −0.7, 95% CI = −1.5, 0.03). When evaluated in only completers, the group effect remained significant (F[1, 50.0] = 6.85, P = .012; MBCT-M vs WL/TAU B = −1.0, 95% CI = −1.8, −0.2); the month effect omnibus test was no longer significant (F[3, 92.2] = 2.63, P = .055; Month 0 vs 4 B = 0.5, 95% CI = 0.1, .9).

Adverse Events.—Two adverse events were reported in the MBCT-M group. The first was deemed to be treatment-related: a participant experienced a vivid recollection of a traumatic event (outside of the context of posttraumatic stress disorder), while practicing mindfulness. She elected to continue with the treatment. A second participant who was taking preventive medication throughout the study experienced a severe increase in headache frequency and pain intensity; she discontinued the study as her neurologist recommended that she change her preventive pharmacologic regimen. No adverse events were reported in the WL/TAU group.

DISCUSSION

This Phase 2b randomized clinical trial found significant reductions in headache-related disability (HDI) in people with migraine who received an 8-week individual MBCT-M compared to WL/TAU. Further, MBCT-M reduced the average attack-level migraine-related disability (MIDI) reported by people with migraine, indicating that individuals who engaged in mindfulness training had improved resilience and ability to engage in functional tasks even when experiencing a migraine episode. Fewer participants reported "severe disability" on the MIDAS across both groups from Month 0 to Month 4. MBCT-M did not reduce headache days/30 days or average headache attack pain intensity compared to WL/TAU.

Mindfulness-based interventions are theoretically unique from the traditional empirically supported behavioral treatments for migraine and entail unique migraine management skills. While cognitive-behavioral therapies, relaxation, and biofeedback teach active skills to specifically reduce migraine attack frequency and associated disability, distress and comorbidities and change maladaptive thoughts related to migraine (engaging with maladaptive thoughts), mindfulness-based interventions instead teach skills to modify the person's relationship with their experience of migraine (encouraging an "observer stance"). We theoretically would expect mindfulness-based interventions to have a greater effect on headache-related disability, rather than on symptoms directly. This is borne out in this study as well as in the broader literature of mindfulness-based interventions for headache disorders.[21,24,31] Results from this study support the use of MBCT-M for participants in whom headache day reduction is not the primary goal, but rather the primary goal is reduction in the amount of disability experienced related to migraine. The results suggest that MBCT-M might be useful when combined with treatments expected to reduce monthly headache days, such as relaxation and biofeedback or preventive pharmacotherapies. Further, MBCT-M could be useful to maintain treatment gains after successful reduction in monthly headache days by preventive therapies.

It is notable that the HDI demonstrated significant reductions due to MBCT-M, whereas the reductions on the MIDAS did not reach significance at the .025 level (P = .027). It is possible that this difference is simply due to power: the HDI is a continuous measure, whereas the MIDAS was dichotomized, reducing power for this analysis. Further, this study was halted prior to reaching recruitment goals due to slow recruitment, which further reduced power for these analyses. It is also possible that MBCT-M, which teaches participants skills to more objectively observe their lives and to choose nourishing rather than depleting cognitive and behavioral patterns, produced a larger effect on emotional disability (assessed by the HDI only) than on functional disability (assessed by the HDI and MIDAS). However, participants in the MBCT-M group reported significant reductions in attack-level functional disability on the MIDI. The final possibility is that MBCT-M produces the largest effect on measures of disability not intrinsically linked to the number of headache days. The units of measurement for MIDAS response options are headache days. Both the HDI and MIDI produce disability scores independent from a number of headache days. Future studies of MBCT-M should consider including migraine-related disability measures that are not intrinsically linked to headache days.

Stress is commonly thought to trigger migraine attacks.[52] Multiple high-quality diary studies have demonstrated relationships between changes in stress and migraine attack onset[53-56] though the effect varies both inter- and intra-individually, and may interact with other trigger factors. Mindfulness appears to modulate the relationship between acute stressors of various types and physiological responses.[57-59] Thus, the rationale of a stress-reduction treatment to reduce migraine frequency makes intuitive sense, even though mindfulness-based interventions including MBCT-M have consistently failed to produce clinically meaningful or statistically significant improvements in headache days.[24] It is possible that typical 8-week training is insufficient to produce clinically meaningful changes in mindfulness skills, or consistent reduction in stress, to meaningfully reduce headache days. Alternatively, stress may not be as potent of a migraine trigger as is often believed. Future studies should evaluate whether achieving midtreatment increases in mindfulness and decreases in perceived stress are linked with a reduction in headache days during MBCT-M.

Migraine is a chronic disease with episodic symptom manifestations, which requires considerable in-the-moment decision making to optimize disease management.[60] Mindfulness involves the regulation of attention and active cognition, which could serve to enhance decision-making. Several randomized clinical trials evaluating mindfulness-based interventions have demonstrated cortical changes typically in insular, prefrontal, and cingulate regions.[61,62] In a secondary analysis of the previous pilot study of MBCT for headache, treatment responders were more likely to have increased adaptive pain-related cognitions (acceptance) and decreased maladaptive pain-related cognitions (catastrophizing).[63] Future studies should evaluate whether these change mechanisms mediate MBCT-related changes in outcomes. It is possible that our treatment paradigms, which were originally developed for use in chronic psychiatric illnesses, are not yet optimized for use in migraine. Future studies should use mixed qualitative and quantitative methods to understand the ways in which mindfulness can be applied migraine.

Behavioral treatments for migraine have risks. Vivid recollection of a traumatic event during meditation is a known potential side effect of meditation and relaxation exercises of all types and can occur in anyone who has experienced previous exposure to a psychologically traumatic event, even when no symptoms of posttraumatic stress disorder are present. People with migraine have been found to have experienced adverse childhood events and other traumatic events at higher rates than the general population.[64-66] Despite calls to ensure that all behavioral treatment trials evaluate adverse events,[67] these events are not well-documented in the literature. Patients should be made aware of the risks of meditation and given strategies to mitigate these risks. This is particularly important as patients are increasingly seeking out meditation options without therapist guidance. Future behavioral migraine treatment trials should evaluate previous traumatic and adverse childhood events at baseline and ensure the systematic capture of adverse events in behavioral migraine trials.

LIMITATIONS AND FUTURE DIRECTIONS

Data collected were based on patient self-report. The majority of the participants were highly educated White women which limits the generalizability of the findings to people with migraine who have lower levels of education, are members of minority groups and men. As participants over age 65 were not enrolled, findings are not generalizable to older age groups. As participants with very frequent (continuous headache) or infrequent attacks (fewer than 6 days per month) were not included, findings may not generalize to these groups. Despite significant attempts to recruit in more diverse settings, transportation was a major barrier for participants from lower income groups to participate in the study. Further, though we had relatively low rates of attrition in this study, we still encountered challenges with treatment delivery. The majority of patients required at least one telehealth session in order to complete all 8 sessions within a 10-week timeframe. However, exit interviews with patients revealed that they generally viewed these sessions favorably. In fact, participants noted the "burden" and stress of scheduling, travel and rushing to attend study sessions could sometimes outweigh the benefit of the in-session stress reduction. Migraine is most prevalent in the most potentially productive years of life, when people with

migraine are going to school, establishing their careers, and raising families.[2] Modes of administration for behavioral treatments must take this population into account. MBCT has been successfully delivered through solely telehealth delivery mechanisms in other diseases[68] and future studies should consider delivery solely via a telehealth modality. Telehealth would also remove transportation as a barrier to access care for lower income individuals.

We were unable to meet our recruitment goal of n = 80, which resulted in several analyses being underpowered, particularly given the divided alpha across two primary outcome measures. Further, the 3-month recall period of the MIDAS may have rendered it less sensitive to changes during the timeframe of the study, as the three-month recall period included the entirety of the treatment period and posttreatment evaluation period. Future studies should select measures with briefer timeframes, such as a one-month recall, to allow for the detection of treatment-related changes. Headache attack pain intensity was evaluated using a 4-point (Mild, Moderate, Severe) scale, which might have had less sensitivity than an 11-point (0-10) numeric rating scale. Future studies should consider using the 11-point numeric rating scale more common in chronic pain studies, but explicitly providing the mild (1-3), moderate (4-6), and severe (7-10) descriptors to permit translation into ICHD-3 criteria.

This study used an individual protocol for MBCT-M, which lacked the benefit of a group process to enhance the understanding and uptake of mindfulness skills. Future studies should evaluate group-delivered MBCT-M, and ideally evaluate differences in both headache-related outcomes and theoretically relevant mechanisms between individual- and group-delivered MBCT-M.

This study used a waitlist control rather than an active control. In fact, we even instructed the WL/TAU group to stop taking a headache diary during the treatment period to avoid self-monitoring effects. This was deliberate; this is an early phase trial of MBCT-M designed to detect any treatment-related signal. Now that the initial signal has been established, future trials should consider more active controls including headache diary and education controls to evaluate whether treatment effects are specific to MBCT-M. The waitlist design also precluded a longer-term follow-up of the effect of MBCT-M vs WL/TAU. Future studies that include an active control may be able to follow participants in both groups for a longer-term follow-up to evaluate the maintenance of effects.

Strengths of the study include that it was a randomized clinical trial using a manualized treatment protocol. Treatment fidelity was highly monitored and therapists were closely supervised. Outcomes were well-validated measures and migraine diagnosis was made using a validated screener; headache characteristics and patient adherence to meditation were monitored prospectively using a mobile electronic daily headache diary.

This study stratified recruitment and randomization by episodic migraine vs chronic migraine. Understanding the impact of baseline characteristics on treatment response will help clinicians tailor treatment recommendations to patients most likely to experience benefit. Future studies should evaluate the role of baseline headache attack frequency on response to MBCT-M, as well as other mindfulness-based interventions.

CONCLUSIONS

Individual MBCT-M demonstrated efficacy to reduce headache-related disability and attack-level migraine-related disability. In addition, participants generally adhered to treatment and reported a favorable attitude toward the experience. MBCT-M is a promising emerging treatment for addressing migraine-related disability. Future studies should explore avenues to increase the access to the treatment, including telehealth technology. As with other mindfulness-based interventions, MBCT-M did not reduce headache days or headache attack pain intensity. Future research should evaluate the difference in mechanisms and effect moderators between more traditional empirically supported behavioral migraine treatments and MBCT-M.

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