JAMA Internal Medicine | Original Investigation

# Effectiveness of Mindfulness Meditation vs Headache Education for Adults With Migraine
## A Randomized Clinical Trial

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**IMPORTANCE** Migraine is the second leading cause of disability worldwide. Most patients with migraine discontinue medications due to inefficacy or adverse effects. Mindfulness-based stress reduction (MBSR) may provide benefit.

**OBJECTIVE** To determine if MBSR improves migraine outcomes and affective/cognitive processes compared with headache education.

**DESIGN, SETTING, AND PARTICIPANTS** This randomized clinical trial of MBSR vs headache education included 89 adults who experienced between 4 and 20 migraine days per month. There was blinding of participants (to active vs comparator group assignments) and principal investigators/data analysts (to group assignment).

**INTERVENTIONS** Participants underwent MBSR (standardized training in mindfulness/yoga) or headache education (migraine information) delivered in groups that met for 2 hours each week for 8 weeks.

**MAIN OUTCOMES AND MEASURES** The primary outcome was change in migraine day frequency (baseline to 12 weeks). Secondary outcomes were changes in disability, quality of life, self-efficacy, pain catastrophizing, depression scores, and experimentally induced pain intensity and unpleasantness (baseline to 12, 24, and 36 weeks).

**RESULTS** Most participants were female (n = 82, 92%), with a mean (SD) age of 43.9 (13.0) years, and had a mean (SD) of 7.3 (2.7) migraine days per month and high disability (Headache Impact Test-6: 63.5 [5.7]), attended class (median attendance, 7 of 8 classes), and followed up through 36 weeks (33 of 45 [73%] of the MBSR group and 32 of 44 [73%] of the headache education group). Participants in both groups had fewer migraine days at 12 weeks (MBSR: −1.6 migraine days per month; 95% CI, −0.7 to −2.5; headache education: −2.0 migraine days per month; 95% CI, −1.1 to −2.9), without group differences ($P$ = .50). Compared with those who participated in headache education, those who participated in MBSR had improvements from baseline at all follow-up time points (reported in terms of point estimates of effect differences between groups) on measures of disability (5.92; 95% CI, 2.8-9.0; $P$ < .001), quality of life (5.1; 95% CI, 1.2-8.9; $P$ = .01), self-efficacy (8.2; 95% CI, 0.3-16.1; $P$ = .04), pain catastrophizing (5.8; 95% CI, 2.9-8.8; $P$ < .001), depression scores (1.6; 95% CI, 0.4-2.7; $P$ = .008), and decreased experimentally induced pain intensity and unpleasantness (MBSR group: 36.3% [95% CI, 12.3% to 60.3%] decrease in intensity and 30.4% [95% CI, 9.9% to 49.4%] decrease in unpleasantness; headache education group: 13.5% [95% CI, −9.9% to 36.8%] increase in intensity and an 11.2% [95% CI, −8.9% to 31.2%] increase in unpleasantness; $P$ = .004 for intensity and .005 for unpleasantness, at 36 weeks). One reported adverse event was deemed unrelated to study protocol.

**CONCLUSIONS AND RELEVANCE** Mindfulness-based stress reduction did not improve migraine frequency more than headache education, as both groups had similar decreases; however, MBSR improved disability, quality of life, self-efficacy, pain catastrophizing, and depression out to 36 weeks, with decreased experimentally induced pain suggesting a potential shift in pain appraisal. In conclusion, MBSR may help treat total migraine burden, but a larger, more definitive study is needed to further investigate these results.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: NCT02695498

*JAMA Intern Med*. doi:10.1001/jamainternmed.2020.7090
Published online December 14, 2020.

Visual Abstract
Invited Commentary
Supplemental content

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Migraine is the second leading cause of worldwide disability.[1] Two-thirds of patients with migraine discontinue medications due to inefficacy or adverse effects,[2] despite significant disability caused by migraine.[3] Although the American Headache Society recommends against opioids, with risks of opioid use disorder and the development of the refractory condition of medication overuse headache, one-third of patients turn to opioids.[4-6] A significant need exists for nonopioid, nondrug migraine treatments.[7]

Mindfulness-based stress reduction (MBSR), a standardized mind-body treatment that teaches momentary awareness with decreased sensory percept judgment, is associated with improvements in many chronic pain conditions.[8-11] Mindfulness may be particularly helpful for migraine, as it diminishes affective responses to stress,[12,13] the most common migraine trigger.[14] Furthermore, mindfulness decreases affective (ie, pain unpleasantness) and sensory (ie, pain intensity) experimental pain by engaging brain regions important for cognitive and affective pain modulation.[15,16] Affective/cognitive processes, such as depression, pain catastrophizing, and self-efficacy, can play a significant role in migraine and its associated disability.[17,18] While patients with migraine commonly use mind-body treatments,[19,20] and small studies demonstrate safety, feasibility, and preliminary benefits,[21-24] standardized, rigorous approaches evaluating both clinical benefit and mechanisms are needed.[22]

We conducted a double-blinded, randomized clinical trial of MBSR vs headache education for adults with migraine. We hypothesized that, compared with headache education, MBSR would improve migraine frequency, disability, quality of life, and affective/cognitive processes (eg, depression, pain catastrophizing, and self-efficacy). We used quantitative sensory testing (QST) to evaluate pain perception, hypothesizing that MBSR would decrease experimentally induced affective pain (unpleasantness) more than sensory (intensity) pain.

### Key Points

**Question** Does mindfulness-based stress reduction (MBSR) improve migraine outcomes and affective/cognitive processes compared with headache education?

**Findings** In this randomized clinical trial of 89 adults who experienced between 4 and 20 migraine days per month, standardized training in mindfulness and yoga through MBSR did not improve migraine frequency more than headache education about migraine, as both groups had similar decreases.

**Meaning** Mindfulness meditation may help treat the total burden of migraine, although a larger, more definitive study is needed to further investigate these results to understand the association of mindfulness with migraine outcomes.

## Methods

### Study Design, Setting, and Participants

Participants were recruited by targeting patients and health care professionals from widespread community advertising and a large tertiary care academic medical center in Winston-Salem, North Carolina (detailed recruiting efforts described in eMethods in Supplement 1). Enrollment occurred from August 26, 2016, through October 1, 2018, over 7 cohorts (cohort details in eTable 1 in Supplement 1). Eligibility was assessed with (1) phone screens (eMethods in Supplement 1); (2) in-person evaluation by a neurologist/United Council of Neurological Subspecialties–certified headache specialist including the Structured Diagnostic Interview for Headache[25,26]; and (3) 4-week baseline headache log (**Figure 1**). Inclusion criteria were diagnosis of migraine (*International Classification of Headache Disorders-2 [ICHD-2]*, the edition in effect at the time the study began); between 4 and 20 migraine days per month; history of migraine for at least 1 year; at least 18 years old; and availability for 8 weekly classes. For each cohort, 1 day/time class option was available; if the participant was not available on that day/time, they were not eligible for that cohort but could be notified for future cohort eligibility. Exclusion criteria were regular mind-body practice; unstable medical or psychiatric illness; severe clinical depression (Patient Health Questionnaire, PHQ-9, > 20); nonmigraine chronic pain; medication overuse headache (MOH by *ICHD-2*); current or planned pregnancy; use of new migraine medication within 4 weeks; inability to maintain stable medications for study duration; incomplete baseline headache log; and absence of pain ratings to noxious (49 °C) stimuli. While the study targeted episodic migraine, headache frequency up to 20 per month was included given significant monthly headache variability[27]; the MOH exclusion limited chronic migraine (see eTable 2 in Supplement 1 for eligibility criteria justification). This study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, the Declaration of Helsinski,[28] and migraine pharmacological and behavioral research guidelines.[29,30] All participants provided written informed consent at the screening visit with a study team member. This study was approved by the Wake Forest Baptist Institutional Review Board (study protocol in Supplement 2) and followed Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines. A National Institutes of Health certificate of confidentiality was obtained to protect research participant identity.

### Masking and Randomization

To blind participants to active vs comparator group randomization, recruitment materials described the study as "classes to learn information that may help headaches without medications" without course content details. This avoided (1) group assignment dissatisfaction/dropouts; (2) group expectation differences; and (3) selection bias with only participants interested in mindfulness. The principal investigator, coinvestigators, data analysts, and QST administrators were blinded to group assignment.

Treatment assignments were generated with SAS PROC PLAN statement by a study biostatistician (who did not conduct data analyses) using permuted blocks with randomly varying block size and sealed in numbered, opaque envelopes and given to the research coordinator. After eligibility was confirmed, a research coordinator opened each sequentially numbered sealed envelope to inform participants of group assign-



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ment. Participants were randomized (1:1) to receive MBSR or headache education, stratified by baseline headache log frequency (4-9 per month, low, vs 10-20 per month, high).

## Interventions

Participants could continue current acute and preventive migraine medications and were requested to maintain stable medications for study duration. The MBSR and headache education interventions were comparable in duration (2 hours/week for 8 weeks, with optional retreat day), format (group), and participants per group. The MBSR instructor followed the standardized curriculum[31] to teach mindfulness meditation/yoga without migraine modifications. The headache education group received instruction on headaches, pathophysiology, triggers, stress, and treatment approaches (eTable 3 in Supplement 1 for course content). The MBSR participants received electronic audio files for home practice and were encouraged to practice at home 30 minutes per day.

## Treatment Fidelity, Expectations, and Satisfaction

We implemented a detailed treatment fidelity plan according to the National Institutes of Health Behavior Change Consortium[32,33] and Template for Intervention Description and Replication Checklist[34] for mindfulness-based research[35] (eTable 4 in Supplement 1). Participants were considered "completers" with attendance of at least 5 of 8 classes. The following instruments (and time points) were assessed: Credibility/Expectancy Questionnaire[36] (at baseline, after second class, and at 36 weeks); patient-centered communication skills[37] (PCC, 12 weeks); Working Alliance Inventory (WAI, after the second class, 12 weeks); and client satisfaction questionnaire (CSQ, 12 weeks).

## Follow-up

Participants completed follow-up study visits at 12, 24, and 36 weeks. The QST assessments were in-person, while follow-up Research Electronic Data Capture (REDCap) surveys could be completed remotely.

## Measures

National Institute of Neurological Disorders and Stroke Common Data Elements for Headache informed the sociodemographic information obtained at the screening visit (**Table 1**). Outcome data were captured using REDCap, hosted at Wake Forest School of Medicine.[38]

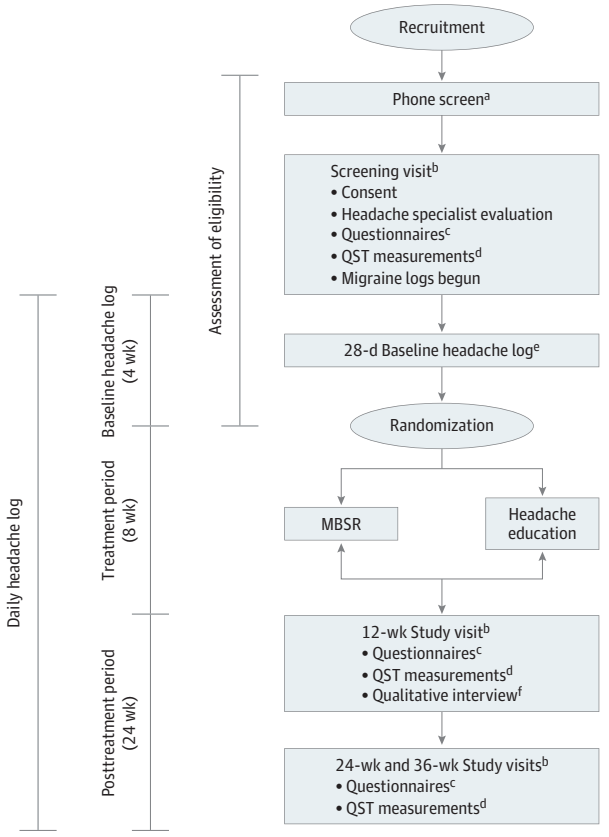
### Primary Outcome

The primary outcome was a change in monthly migraine day frequency from baseline to 12 weeks, defined as a calendar day with moderate to severe headache (6-10 on 0-10 scale) lasting more than 4 hours, or treated with acute medication. Participants maintained daily REDCap headache logs for study duration, capturing presence, duration, intensity, unpleasantness, symptoms, and medication use.

### Secondary Outcomes

Headache day frequency, intensity, unpleasantness, and duration were also assessed. Reliable, well-validated survey instruments were completed at each study visit to assess headache-related disability, quality of life, and well-being measures. Headache-related disability was assessed with the Migraine Disability Assessment (MIDAS)-1 month[39,40] and the Headache Impact Test-6 (HIT-6).[41-43] Quality of life was assessed with the Migraine-Specific Quality of Life Questionnaire, version 2.1 (MSQv2.1),[44,45] depression with the Patient Health Questionnaire-9 (PHQ-9),[46] anxiety with the Generalized Anxiety Disorder-7 (GAD-7),[47] pain catastrophizing with the Pain Catastrophizing Scale (PCS),[48,49] self-efficacy with the Headache Management Self-Efficacy Scale,[50] and trait mindfulness with the Five-Facet Mindfulness Questionnaire.[51,52] Each

Figure 1. Overview of Study Design, Conducted for Each Cohort




MBSR indicates mindfulness-based stress reduction.

[a] Trained study team members conducted the phone screens, including the principal investigator, master's-level students, and undergraduate students.

[b] Participants were initially required to be migraine-free for 48 hours prior to each study visit, but to complete the study, this was changed (after cohort 1's 12-week study visit) to migraine-free the day of study visits (given that participants' headache frequencies could be up to 20 days per month). See details in Supplement 2.

[c] Questionnaires were completed in-person at the screening visit and in-person or remotely for follow-up visits (when headache-free).

[d] All quantitative sensory testing (QST) assessments were in-person, with confirmation of no pain relieving medications taken within 12 hours.

[e] This run-in period confirmed ability to maintain daily headache log and confirmed eligibility criteria (assessment of migraine frequency and exclusion for medication overuse headache).

[f] Qualitative interview results will be reported elsewhere.



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Table 1. Baseline Characteristics of Study Participants

| Baseline characteristic | No. (%)[a] MBSR (n = 45) | Headache education (n = 44) |
|---|---|---|
| **Sociodemographics** | | |
| Age, mean (SD), y | 44 (12) | 44 (14) |
| Sex | | |
| Female | 42 (93) | 40 (91) |
| Male | 3 (7) | 4 (9) |
| Race | | |
| White | 40 (89) | 39 (89) |
| Black or African American | 5 (11) | 5 (11) |
| Ethnicity | | |
| Hispanic or Latino | 2 (4) | 4 (9) |
| Not Hispanic or Latino | 43 (96) | 40 (91) |
| Primary health insurance | | |
| Private | 40 (89) | 33 (75) |
| Medicare/Medicaid/other public | 5 (11) | 9 (20) |
| None | 0 | 2 (5) |
| Marital status | | |
| Married/living with partner | 31 (69) | 26 (59) |
| Divorced/separated/widowed | 6 (13) | 8 (18) |
| Single, never married | 8 (18) | 10 (23) |
| Household income[b] | | |
| <$15 000 | 4 (9) | 4 (9) |
| $15 000-49 999 | 9 (20) | 13 (30) |
| $50 000-149 999 | 23 (51) | 22 (50) |
| >$150 000 | 9 (20) | 4 (9) |
| Current employment status[c] | | |
| Employed/self-employed full time (>30 h/wk) | 30 (67) | 25 (57) |
| Employed part time | 4 (9) | 5 (11) |
| Student, homemaker, volunteer | 7 (16) | 3 (7) |
| Unemployed, retired | 2 (4) | 7 (16) |
| Education | | |
| ≤High school | 3 (7) | 2 (5) |
| College | 28 (62) | 30 (68) |
| Graduate degree | 14 (31) | 12 (27) |
| Recruitment source | | |
| Academic medical center/clinician referral[d] | 20 (44) | 23 (52) |
| Community[e] | 25 (56) | 21 (48) |
| Baseline physiology, mean (SD)[f] | | |
| Body mass index | 27 (8) | 29 (7) |
| Systolic blood pressure, mm Hg | 120 (16.5) | 122 (12.9) |
| Diastolic blood pressure, mm Hg | 73 (11.4) | 73 (8.8) |
| Heart rate, beats/min | 73 (13) | 78 (13) |
| **Headache features** | | |
| Years with migraine, mean (SD) | 24 (13) | 24 (14) |
| Migraine with aura | 16 (36) | 18 (41) |
| Family history of headache | 31 (69) | 28 (64) |
| Headache days during 28-d baseline, mean (SD) | 9.5 (3.4) | 9.8 (3.6) |
| Migraine days during 28-d baseline, mean (SD) | 7.2 (2.5) | 7.4 (3.0) |
| Use of treatments | | |
| Current use of prophylactic treatment[g] | 18 (40) | 31 (71) |
| Daily medication | 11 (24) | 22 (50) |
| No. of daily prophylactic medications, mean (SD) | 1.3 (0.6) | 1.5 (0.6) |
| Procedures (Botox/occipital nerve blocks) | 5 (11) | 5 (11) |
| Supplement | 10 (22) | 14 (32) |
| Current use of acute medication[g] | 41 (91) | 36 (82) |
| Triptan | 25 (56) | 31 (70) |
| Nonsteroidal anti-inflammatory | 28 (62) | 19 (44) |
| Antinausea | 8 (18) | 7 (16) |
| No. of previously tried daily prophylactic medications, mean (SD) | 2.8 (1.7) | 3.2 (2.4) |
| No. of previously tried acute medications, mean (SD) | 4.9 (3.1) | 4.9 (3.2) |
| No. of previously tried integrative treatments, mean (SD)[h] | 3.6 (2.5) | 4.3 (2.9) |
| Experienced headache medication side effect | 25 (56) | 31 (71) |
| Of those with triggers, No. of triggers, mean (SD)[i] | 7.2 (2.7) | 6.4 (3.3) |
| Stress or let-down stress as a trigger | 35 (78) | 31 (71) |
| **Comorbid conditions** | | |
| Current or past diagnosis of depression | 19 (42) | 19 (43) |
| Current or past diagnosis of anxiety | 15 (33) | 19 (43) |

Abbreviation: MBSR, mindfulness-based stress reduction.

[a] No. (%) reported unless otherwise specified.

[b] Based on n = 43 for headache education (n = 1 [2%] of data missing).

[c] Based on n = 43 for MBSR (n = 2 [4%] of data missing); based on n = 40 for headache education (n = 4 [9%] of data missing).

[d] Clinician recruitment included direct referrals, referrals through electronic medical record, through the Wake Forest Be Involved clinical trial registry, through the electronic medical record, or from prior headache research recruitment. See Supplement 1 for further details.

[e] Community recruitment included flyers, social media (Facebook/Twitter), email listservs from local organizations, television advertising, magazines, online advertisements, and friends/family referrals. See Supplement 1 for further details.

[f] Blood pressure and heart rate measurements are from baseline visit.

[g] Percentages do not add to 100 as individuals may be on more than 1 treatment. Prophylactic treatment options included daily migraine medication, regular onabotulinum toxin A or occipital nerve blocks, or daily use of a migraine supplement. Calcitonin gene-related peptide medications were not yet US Food and Drug Administration approved at study initiation; we screened out participants with medication overuse headache, excluding patients who may have been taking opioids.

[h] Integrative treatments included acupuncture/acupressure, physical therapy, stress reduction, ice/cold compresses, yoga, meditation, deep breathing, massage, chiropractic, biofeedback, supplements (including magnesium, riboflavin, coenzyme Q10, feverfew, butterbur, melatonin), or other.

[i] Triggers included menses, caffeine, weather changes, alcohol, too little sleep, too much sleep, hunger, missed meals, psychological stress, "let down" after stressful period, food additives, light glare, odors, altitude, exercise, certain food, sex, other.



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outcome assessed changes from baseline to 12, 24, and 36 weeks. Additional assessments (eg, capturing hope, optimism, sleep) were completed and will be reported separately.

The QST assessments were only conducted when participants were migraine-free using a 16 × 16-mm thermal probe with the MEDOC TSA-II; all temperatures were lower than 50 °C to prevent tissue damage. Using a 15 cm sliding visual analogue scale,[53,54] participants quantified intensity (from "no pain sensation" to "most intense imaginable") and unpleasantness (from "not at all unpleasant" to "most unpleasant imaginable"). Participants were familiarized with 32 (or 16 at follow-up visits) 5-second stimuli (35-49 °C) on the left arm, away from increased migraine allodynia of head region.[55,56] Thermal stimulation was then administered on the right calf, starting at 35 °C with a 6 °C rise/fall rate and 5-second plateau up to randomly administered temperatures of 43, 45, 47, and 49 °C; each temperature repeated 3 times; each series repeated twice, with intensity and unpleasantness rated after each temperature. To minimize sensitization, habituation, and hyperalgesia with repetitive site stimulation, all trials were separated by 30 seconds and systematically distributed over the calf.[57]

### Adverse Events

Adverse events were systematically queried and tracked at each study visit. Quarterly reports were provided to the Wake Forest School of Medicine Data Safety and Monitoring Board, which recommended continuation without modification at every evaluation.

## Sample Size and Statistical Analysis

All statistical analyses were performed using R Statistical Software,[58] with packages mice for multiple imputation[59] and lme4 for regression analyses.[60] To model headache and migraine frequencies, headache log entries were grouped into 4-week phases. For each phase, we calculated the change in migraine days from baseline using a multivariable linear mixed model to determine change scores as a function of treatment group, phase, baseline migraine rate, years with migraine diagnosis, classes attended, and cohort, controlling for within-participant variation via random intercepts, with α = .05 significance based on treatment group and phase (time) interaction. All covariates were assessed at an α = .05 level of significance and reported with point estimates and 95% CIs. Using effect sizes from our pilot trial,[21] and by analyzing the data with our mixed effects multivariable hierarchical regression models, we estimated a final sample of 44 participants per group (n = 88) would provide greater than 90% power with α = .05 to detect a difference of 1.3 migraine days per month between groups (using PASS statistical software). Accounting for potential 10% dropout, our recruitment aim was 98 participants.

We modeled secondary outcomes using a multivariable linear mixed model framework controlling for baseline value of the outcome of interest, treatment group, cohort, and within-participant variation via random effects, with significance based on the treatment group effect and phase interaction at .05 significance level. Assessments of secondary outcomes are exploratory for future research and did not control for multiple comparisons; significant results found are viewed to provide an indication of potential treatment effect for future research, not confirm one.

To assess QST results, a multivariable linear mixed model was used to model the percent change from baseline in perceived pain intensity and unpleasantness at each visit for each of 6 measures at 49 °C. Change scores were modeled as a function of treatment group and visit, controlling for baseline. To assess medication use over time, among days when a participant reported the presence of a headache, we modeled the probability of medication use (overall and for specific medication classes) using a generalized linear mixed model with logit link function, with headache log phase and treatment group as predictors. Treatment fidelity measures (PCC, WAI, CSQ, CEQ) between groups were compared using 2-sided *t* tests.

## Missing Data and Sensitivity Analysis

Our primary analysis was based on a modified intention to treat group: participants who were randomized, attended at least 1 class, and recorded at least 1 headache log entry (n = 89). For frequency analyses, we calculated the aggregated number of headaches and migraines over each 28-day period for each participant. If fewer than 50% of log entries were missing during a phase, the daily migraine rate was calculated and converted to reflect that of a 28-day period; if more than 50% of log entries were missing in a phase (>14/28), the logs were assumed missing and multiple imputation was used for headache and migraine rates[59] (missing data details in Supplement 2).

We conducted 3 sensitivity analyses of our primary analysis: (1) assuming missing data entries were simply days with no headache (modeling similar to primary analysis); (2) including only complete (nonimputed) data in a multivariable generalized linear mixed model to determine the probability of headache/migraine for a given day, then multiplying the estimated daily probability by 28 for a 28-day rate, which makes full use of the available headache data; and (3) given the baseline disproportionate use of prophylactic treatments across groups, creating an additional model adjusting for prophylactic use, including it as a covariate.

# Results

## Participant Characteristics

After 1691 phone screens and 157 in-person evaluations were completed, 96 participants were randomized and 89 participants attended at least 1 class and completed at least 1 headache log (MBSR, 45; headache education, 44) across 7 cohorts (mean [SD] size 12.7 [5.0]) (**Figure 2** and eTable 5 and eTable 6 in Supplement 1). Baseline sociodemographic characteristics were balanced across groups, as most of the 89 participants were women (n = 82, 92%), White (n = 79, 89%), mean (SD) age was 43.9 (13.0) years, with college/graduate education (n = 84, 94%) (Table 1). Participants had a mean (SD) 7.3 (2.7) migraine days per month and 9.6 (3.5) headache days per month



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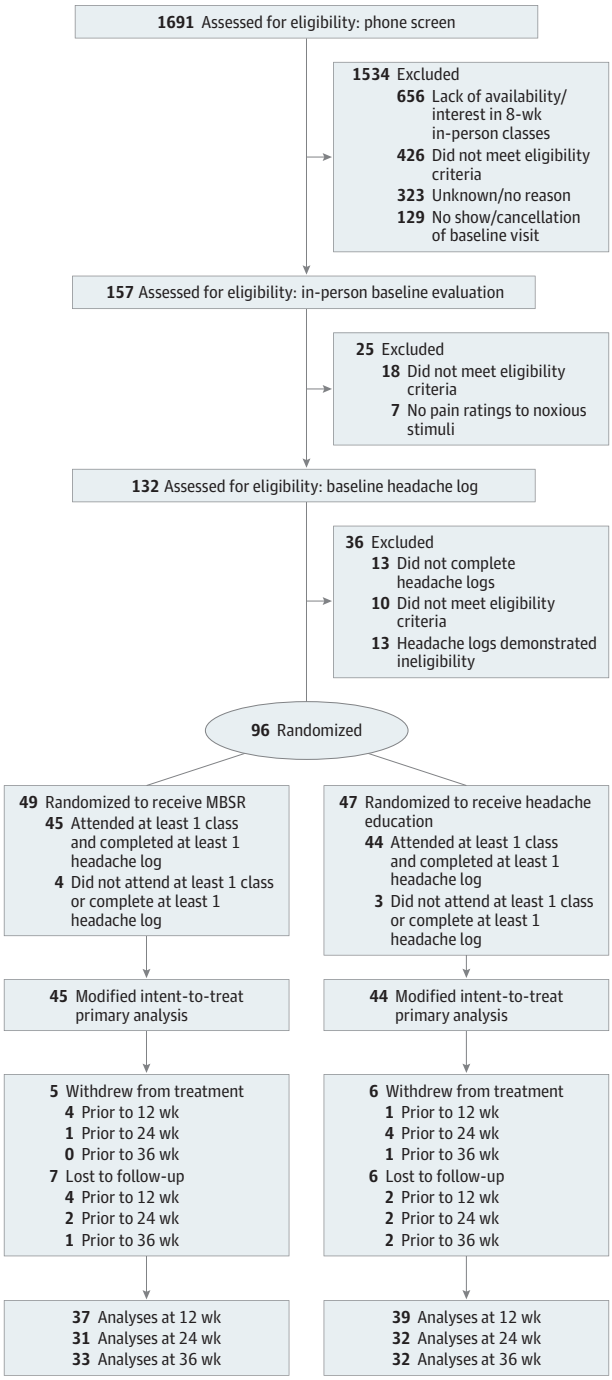
Figure 2. CONSORT Flow Diagram of Study Participation




See eTable 5 and eTable 6 in Supplement 1 for details of reasons and time points for exclusion, withdrawal, and lost to follow-up.

with high headache-related disability (mean [SD] Headache Impact Test-6 score: 63.5 [5.7]). While most participants in both groups were currently using acute medications (n = 77, 87%), 71% of headache education participants were using prophylactic treatments compared with only 40% of MBSR participants ($P$ = .01). Current or prior history of depression (n = 38, 43%) and anxiety (n = 34, 38%) was common.

## Treatment Adherence, Fidelity, Satisfaction, and Credibility

Most participants in both MBSR and headache education groups attended at least 5 of 8 classes (84% and 82%, respectively, with median attendance 7 of 8 classes for both groups) and completed the study through 36 weeks (73% for both groups). During the treatment period, participants practiced MBSR skills at home a mean (SD) 4.2 (2.5) days per week for 32.6 (14.6) minutes per day; home practice persisted during posttreatment period (2.4 [2.8] days per week for 27.2 [11.5] minutes per day). Participants in both groups demonstrated similar therapeutic relationships with the instructors (PCC: MBSR: 19.4 [1.8], headache education: 19.8 [0.6], $P$ = .26; WAI: MBSR: 73.0 [9.8], headache education: 69.6 [11.7], $P$ = .18). Program satisfaction was high (CSQ >24) in both groups, although higher in the MBSR group (MBSR: 28.4 [3.3], headache education: 25.1 [5.1], $P$ = .001). Intervention credibility and expectation were similar without group differences at baseline, after the second class, and at 36 weeks. About 50% of participants in both groups reported classes being better than expected.

## Primary Outcome

Participants in both groups demonstrated a reduction of migraine days per month from baseline at 12 weeks, without statistical differences between groups (MBSR: −1.6; 95% CI, −0.7 to −2.5; headache education: −2.0; 95% CI, −1.1 to −2.9; group differences from baseline between headache education vs MBSR, −0.5; 95% CI, −0.9 to 1.7; $P$ = .50). Sensitivity analyses did not yield different conclusions.

## Secondary Outcomes

Headache frequency (days/month) decreased from baseline at 12 weeks without group differences (MBSR, −2.0; 95% CI, −0.9 to −3.0; headache education, −2.4; 95% CI, −1.4 to −3.4; $P$ = .52). Both groups sustained reductions in frequency of migraine (MBSR, −2.2; 95% CI, −1.2 to −3.2; vs headache education, −2.7; 95% CI, −1.7, −3.8) and headache (MBSR, −3.2; 95% CI, −2.2 to −4.3; vs headache education, −3.9, 95% CI, −2.8 to −5.0]) out to 36 weeks without group differences ($P$ = .49 and .45, respectively). There were no significant changes over time or group differences on headache pain unpleasantness, intensity, or duration.

Compared to headache education, MBSR participants had statistically significant improvements from baseline at all follow-up time points in headache-related disability, quality of life, self-efficacy, pain catastrophizing, and depression scores (**Table 2**[61]), with medium to large effect sizes (**Figure 3A**[62,63]). Similar improvements for anxiety and mindfulness were seen but were not statistically significant.

Quantitative sensory testing results revealed that MBSR participants reported a greater decrease in percent change from baseline for perception of experimental pain unpleasantness and intensity, while the headache education group showed no significant change (Figure 3B). Based on the linear mixed model, the trend persisted and increased at all time points, such that by 36 weeks, the MBSR group demonstrated a 36.3% (95% CI, 12.3% to 60.3%) decrease in intensity and 30.4% (95% CI, 9.9% to 49.4%) reduction in unpleasantness while the



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Table 2. Changes in Standardized Instruments Over Time in Mindfulness-Based Stress Reduction (MBSR) vs Headache Education[a]

| Instrument | Mean (95% CI) | | | | Point estimate of effect difference between groups (95% CI)[c] | *P* value |
|---|---|---|---|---|---|---|
| | Baseline | 12 weeks[b] | 24 weeks[b] | 36 weeks[b] | | |
| Migraine Disability Assessment-1 month (MIDAS)[d] | | | | | | |
| MBSR | 16.9 (12.3 to 21.5)[e] | 6.7 (4.1 to 9.2) | 6.4 (3.8 to 9.1) | 5.2 (2.6 to 7.8) | 5.9 (2.8 to 9.0) | <.001 |
| Headache education | 11.8 (9.5 to 14.4) | 12.6 (10.1 to 15.1) | 12.4 (9.8 to 15.0) | 11.1 (8.5 to 13.7) | | |
| Pain Catastrophizing Scale (PCS)[f] | | | | | | |
| MBSR | 18.5 (14.9 to 22.1) | 13.3 (10.9 to 15.6) | 13.0 (10.6 to 15.5) | 9.8 (7.4 to 12.1) | 5.8 (2.9 to 8.8) | <.001 |
| Headache education | 20.8 (16.9 to 24.6) | 19.1 (16.8 to 21.3) | 18.8 (16.5 to 21.2) | 15.6 (13.2 to 17.9) | | |
| Patient Health Questionnaire 9 Depression (PHQ-9)[g] | | | | | | |
| MBSR | 4.7 (3.3 to 6.1) | 3.9 (3.0 to 4.9) | 4.0 (3.0 to 4.9) | 3.6 (2.6 to 4.5) | 1.6 (0.4 to 2.7) | .008 |
| Headache education | 5.5 (4.2 to 6.8) | 5.5 (4.6 to 6.4) | 5.6 (4.6 to 6.5) | 5.1 (4.2 to 6.1) | | |
| Migraine Specific Quality of Life (MSQv2.1)[h] | | | | | | |
| MBSR | 44.9 (40.0 to 49.7) | 33.6 (30.5 to 36.6) | 29.9 (26.7 to 33.1) | 29.6 (26.5 to 32.8) | 5.1 (1.2 to 8.9) | .01 |
| Headache education | 43.5 (40.0 to 47.1) | 38.6 (35.6 to 41.6) | 35.0 (31.9 to 38.1) | 34.7 (31.6 to 37.8) | | |
| Headache Management Self-Efficacy (HMSE)[i] | | | | | | |
| MBSR | 110 (103 to 118) | 127 (121 to 133) | 128 (122 to 134) | 129 (123 to 135) | 8.2 (0.3 to 16.1) | .04 |
| Headache education | 114 (107 to 122) | 119 (113 to 125) | 120 (114 to 126) | 121 (115 to 127) | | |
| Generalized Anxiety Disorder (GAD-7)[j] | | | | | | |
| MBSR | 12.1 (10.8 to 13.5) | 11.0 (10.0 to 12.0) | 10.8 (9.8 to 11.8) | 10.9 (9.85 to 11.9) | 1.2 (−0.05 to 2.4) | .06 |
| Headache education | 12.7 (11.3 to 14.1) | 12.2 (11.2 to 13.1) | 12.0 (11.0 to 13.0) | 12.1 (11.06 to 13.0) | | |
| Five Facet Mindfulness (FFM)[k] | | | | | | |
| MBSR | 138 (132 to 144) | 140 (136 to 144) | 142 (138 to 147) | 143 (139 to 148) | 3.9 (−1.5 to 9.3) | .15 |
| Headache education | 134 (128 to 139) | 136 (132 to 140) | 138 (134 to 143) | 140 (135 to 144) | | |
| Headache Impact Test (HIT-6)[l] | | | | | | |
| MBSR | 63.0 (60.8 to 65.2) | 56.3 (54.4 to 58.2) | 57.9 (55.8 to 59.9) | 56.6 (54.6 to 58.6) | 5.3 (2.7 to 7.9)[m]; 0.9 (−1.9 to 3.6)[n]; 1.9 (−0.9 to 4.6)[o] | <.001[m]; .54[n]; .19[o] |
| Headache education | 63.0 (61.8 to 64.3) | 61.6 (59.8 to 63.4) | 58.7 (56.8 to 60.7) | 58.5 (56.5 to 60.4) | | |

[a] Results represent n = 78 (participants with at least 1 follow-up visit).

[b] Multivariable linear mixed regression model was used to assess instrument means by follow-up visit and treatment group, adjusted for baseline measures with random intercepts for each patient. For all but HIT-6, follow-up means are based on main-effects from the linear mixed regression model without an interaction effect between treatment group and time due to insignificant interaction effects. For HIT-6, means are based on results from a significant treatment – time interaction effect.

[c] Treatment effect measures evaluated from baseline across all 3 follow-up time points. The effect difference is in terms of a positive clinical improvement in the MBSR group relative to the headache education group (eg, a greater reduction in MIDAS or increase in FFM). Statistically significant differences between treatment groups for each time point are the same as denoted in Figure 3 (represented in the figure with Cohen *d* effect sizes).

[d] Instrument score ranges: Migraine Disability Assessment-one month (0-93), higher scores reflect greater disability, MIDAS is typically used as an average over 3 months; to facilitate interpretation of the MIDAS-1 month data presented, the mean estimate results (but not the confidence intervals) can be multiplied by 3 for conversion to the typical 3-month assessment[61]; score range for 3-month MIDAS: 0-5: little or no disability, 6-10 mild disability, 11-20 moderate disability, 21+ severe disability.

[e] There was not a statistically significant difference in baseline measures for all instruments except MIDAS. Baseline difference between treatment groups in MIDAS is statistically significant (*P* = .033). There were 3 identified outlier patients in the MBSR group with baseline MIDAS scores >50 (for reference, the maximum baseline MIDAS in the Headache Education group was 36). With these outliers removed, the mean baseline MIDAS in the MBSR group is 14.44 (11.75, 17.14) and the baseline difference between treatment groups is no longer statistically significant (*P* = .20).

[f] Pain Catastrophizing Scale (0-52), higher scores reflect greater pain catastrophizing.

[g] Patient Health Questionnaire-9 Depression (0-27), higher scores reflect greater depression, score range: 1-4: minimal depression, 5-9: mild depression, 10-14: moderate depression, 15-19: moderately severe depression, 20-27: severe depression.

[h] Migraine Specific Quality of Life (0-100), lower scores reflect greater quality of life.

[i] Headache Management Self-Efficacy (0-175), higher scores reflect more self-efficacy.

[j] Generalized Anxiety Disorder-7 (0-21), higher scores reflect greater anxiety, score range: 0-4: minimal anxiety, 5-9: mild anxiety, 10-14: moderate anxiety, 15-21 severe anxiety.

[k] Five Facet Mindfulness (0-195), higher scores reflect greater mindfulness.

[l] Headache Impact Test-6 (36-78), higher scores reflect greater headache impact, score range: <49: little to no impact, 50-55: some/moderate impact, 56-59: substantial impact, 60+ severe impact. HIT-6 point estimates of effect differences between groups are displayed at three time points due to a significant treatment-visit interaction. All other instrument treatment effect measures did not significantly differ across visits (*P* > .05).

[m] 12 weeks.

[n] 24 weeks.

[o] 36 weeks.



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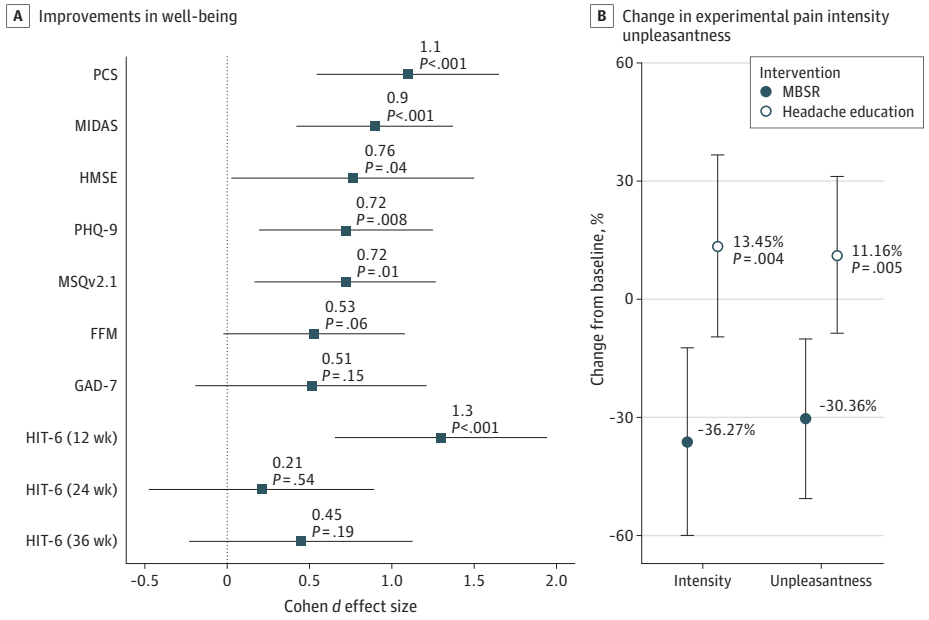
Figure 3. Changes in Well-Being and Experimental Pain Intensity and Unpleasantness Between Mindfulness-Based Stress Reduction (MBSR) and Headache Education




FFM indicates Five Facet Mindfulness; GAD-7, Generalized Anxiety Disorder 7; HIT-6, Headache Impact Test; HMSE, Headache Management Self-Efficacy; MIDAS, Migraine Disability Assessment, one month; MSQv2.1, Migraine Specific Quality of Life; PCS, Pain Catastrophizing Scale; PHQ-9, Patient Health Questionnaire-9 Depression.

A, Point estimates of Cohen *d* effect size differences between treatment groups with 95% CIs, with positive directional effect indicating an improvement in MBSR relative to headache education for each measure. HIT-6 displayed at 3 time points due to a significant treatment-visit interaction. All other instrument treatment effect measures did not significantly differ across visits ($P > .05$). Cohen *d* effect sizes of 0.2 are considered small, 0.5 medium, 0.8 large, and 1.2 very large.[62,63] B, Experimental pain measured with quantitative sensory testing, with visual analog scale range of 0-10.

headache education group demonstrated a 13.5% (95% CI, −9.9% to 36.8%) increase in intensity and an 11.2% (95% CI, −8.9% to 31.2%) increase in unpleasantness (between-group contrasts from the linear mixed model yielded $P = .004$ and .005 for intensity and unpleasantness, respectively). We found no statistically significant differences in medication use (headache specific or all medications) between treatment groups.

### Adverse Events

One MBSR participant developed squamous cell carcinoma, deemed unrelated to the study protocol.

## Discussion

In this study, MBSR was not associated with improved migraine frequency more than headache education, as both groups had decreases. Compared with headache education, MBSR participants had improvements in headache-related disability, quality of life, depression scores, self-efficacy, pain catastrophizing, and decreased experimentally induced pain intensity and unpleasantness out to 36 weeks.

Although we hypothesized that MBSR would decrease migraine frequency, we did not expect headache education would also decrease frequency, with both groups having clinically meaningful decreases.[64] A recent randomized clinical trial found that both behavioral weight loss and headache education resulted in decreased migraine frequency (3 to 4 fewer migraines per month),[65] demonstrating, consistent with the present study's results, that headache education can have meaningful effect on migraine frequency. Selecting the appropriate control for behavioral research has always been inherently challenging.[30] While headache education can serve as a time/attention control and may provide enough engagement to prevent differential group dropout, it does provide an active intervention, thus serving as a comparator group rather than a control group. The mechanisms underlying the improvements seen from this study's headache education group likely differ from mindfulness. Migraine knowledge may provide empowerment and/or lead to behavioral changes that may be associated with change in migraine frequency without change in overall well-being.[65] A recent meta-analysis of randomized clinical trials that assessed therapeutic patient education programs (where patient education was the active arm, although some programs also included active behavioral treatment strategies such as stress management, self-regulation skills, and/or relaxation) demonstrated strong to moderate evidence for improvement of headache frequency, without any evidence on self-efficacy or depression.[66]

We accurately hypothesized the association of MBSR with improved disability, quality of life, and cognitive/affective processes. Although we hypothesized that MBSR would have



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a greater effect on affective (pain unpleasantness) vs sensory (pain intensity), the improvements in both may help explain the mechanism driving the clinical improvements. Mindfulness may strengthen cognitive and affective regulation of nociceptive input by training individuals to reassess sensory percepts (including pain) in a nonjudgmental way by modifying their appraisal of, and "turning towards" pain, resulting in decreased nociception.[67,68] The changed pain perception, coupled with clinically meaningful improvements in cognitive/affective processes, both out to 36 weeks, suggests that MBSR participants learned a new way of processing pain that may have significant effect on long-term health.

The present study is consistent with most recent studies that demonstrate the positive effect of mindfulness on migraine disability, without improvements in headache frequency,[22,69,70] although 2 recent studies showed mindfulness impacting migraine frequency. A nonrandomized clinical trial in chronic migraine MOH[71] demonstrated that mindfulness decreased headache frequency as much as pharmacological treatment. Enhanced MBSR vs stress management showed a similar headache frequency decrease at 20 weeks with MBSR as the present study saw at 36 weeks (−3.2 headache days per month), which was more than their control group.[72] However, group differences seen at 20 weeks disappeared by 52 weeks when both groups had equivocal decreases, which was similar to results in the present study. Changes seen in their study over time (with respect to the standardized instruments) were consistent with prior findings from our pilot study.[21]

The positive direction of the many secondary outcomes is consistent with our pilot data[21] and worthy of further investigation, especially given the MIDAS-1 month improvements of 5.9 fewer days of disability per month seen in this study are clinically significant and surpass typical pharmacological effects[61,73,74] and the minimally important difference (for the 3-month MIDAS the minimally important difference is 3.7, suggesting the calculated minimally important difference for the 1-month MIDAS is 1.23).[75] For a condition with recurrent, lifelong unexpected attacks, improving a patient's pain perception and ability to function despite migraine has significant implications for overall long-term emotional and social health.[69] As recommended by migraine clinical trial guidelines available at the time of study design,[29,30] migraine frequency was chosen as the primary outcome. The additional studies evaluating mindfulness in migraine published since the present study was designed have consistently shown effect on headache-related disability,[22] demonstrating the importance of disability as a primary outcome and highlighting the need for updated migraine behavioral clinical trial guidelines to reflect this change. Additional research is underway to further understand the effect of mindfulness on migraine,[22,76] along with similar treatments such as acceptance and commitment therapy.[77]

### Strengths and Limitations

The present study's strengths include blinding participants to active vs comparator group assignment and eligibility assessment by a United Council for Neurologic Subspecialties–certified headache specialist. Community recruitment increased generalizability, as did participants' ability to continue current medications, which also increases potential adoption, as mindfulness can be combined with traditional treatments.[78] While the active comparator group is a strength, it was not an inactive control condition as the information provided may have led to meaningful behavior changes. While the 2 groups were matched on weekly class duration and frequency, daily home practices were only a part of the MBSR group. Additional limitations include the commitment and scheduling challenges for intervention participation, as only 1 day and time option was available per cohort, which limited availability and was a deterrent for many patients who were not available for or interested in 8 weekly in-person classes. This may have contributed to the lack of participant diversity, as the study was limited to those with time and availability. Given that most participants in this study were white, highly educated, and overall healthy, future studies assessing effects in more diverse populations are important to understand generalizability.

## Conclusions

At a time when opioids are still being used for migraine, finding nondrug options to prevent such use is critical. Once learned, mindfulness can be practiced anywhere at any time, a practical life skill with potential long-term effects that may have broad applicability to managing many health problems and life challenges. Mindfulness may be especially useful in light of current events. With the tremendous stress and anxiety of the COVID-19 pandemic, patients with migraine may have worsening migraine attacks,[79,80] and mindfulness may be particularly beneficial. In summary, mindfulness may help treat the total burden of migraine. A larger, more definitive study is needed to understand the impact of mindfulness on migraine.

ARTICLE INFORMATION

**Accepted for Publication:** October 2, 2020.

**Published Online:** December 14, 2020. doi:10.1001/jamainternmed.2020.7090

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**Conflict of Interest Disclosures:** Drs Wells and Zeidan reported grants from the National Institutes of Health during the conduct of the study. Dr Houle reported personal fees from GlaxoSmithKline, Eli Lilly, and StatReviewer outside the submitted work. No other disclosures were reported.

**Funding/Support:** This study was funded by an American Pain Society Grant from the Sharon S. Keller Chronic Pain Research Program, as well as the National Center for Complementary and Integrative Health K23AT008406, R21-AT010352, K99-R00 AT008238, and R01AT009693.

**Role of the Funder/Sponsor:** The American Pain Society and the National Center for Complementary and Integrative Health had no role in the collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Disclaimer:** The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

**Data Sharing Statement:** See Supplement 3.

**Additional Contributions:** This study was an extraordinary team effort, and we appreciate all the support and help of all those involved. We appreciate all the participants in this study. We are thankful for all the health care professionals who referred patients into the study, including but not limited to Lauren Strauss, DO; Laura Granetzke, MSN; Vanessa Baute Penry, MD; Cormac O'Donovan, MD; Starla Wise, DO; Sandhya Kumar, MD; Nada El-Husseini, MD, MHS; Jane Boggs, MD; Jessica Tate, MD; Heidi Munger Clary, MD, MPH; and Clark W. Pinyan, MD, MPH. We are appreciative of our MBSR instructor, Ann McCarty, PA, and our headache education instructor, Megan Irby, PhD, who were compensated for their roles in this study. We are grateful for the support of the Wake Forest Baptist Department of Neurology, Allison Brashear, MD, Charles Tegeler, MD, Kevin Shuping, and the Comprehensive Headache Program. We are grateful for the help from the Maya Angelou Center for Health Equity for help in diverse recruitment and study participation. Special thanks to Claudia Nielson, Steve Thomas, and the Creative Communications Design Team and Sarah Diamont with Marketing at Wake Forest Baptist Health. We appreciate the support of Brian Moore and the Wake Forest Institutional Review Board and Data and Safety Monitoring Board. We appreciate the support from the Wake Forest Clinical Translational Science Institute (CTSI), the Clinical Research Unit staff and support, and the Research Coordinator Pool, funded by the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through Grant Award Number UL1TR001420, who helped support the significant research coordinator support from Emily Ansusinha, Elizabeth Crenshaw, Carolyn Hedrick, Sandra Norona, Nancy Lawlor, and Brittany Briceno. We are so thankful for the additional research coordination support from Imani Randolph, MA, Jason Collier, Grace Posey, MS, and Georgeta Lester, who were compensated for their efforts. This study would not have been completed without the tremendous support of a multitude of volunteer students, including Nicole Rojas, Hudaisa Fatima, Obiageli Nwamu, MA, Vinish Kumar, Rosalia Arnolda, Paige Brabant, Danika Berman, Nicholas Contillo, Flora Chang, Geena George, Easton Howard, Caitlyn Margol, Mariam Shakir, Reid Anderson, Camden Nelson, Carson DeLong, Summerlyn Beeghly, and Anissa Berger. Several of the students received American Academy of Neurology Neuroscience is Rewarding Internship scholarship awards for their work on this project, including Nicholas Contillo, Flora Chang, Caitlyn Margo, Easton Howard, Geena George, Reid Anderson, Mariam Shakir, Anissa Berger, and Summerlyn Beeghly.

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