

# Enhanced mindfulness-based stress reduction in episodic migraine—effects on sleep quality, anxiety, stress, and depression: a secondary analysis of a randomized clinical trial

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## Abstract

Patients with migraine suffer from high morbidity related to the repeated headache attacks, characteristic of the disorder, poor sleep, and a high prevalence of comorbid psychosocial disorders. Current pharmacological therapies do not address these aspects of migraine, but nonpharmacological treatments such as mindfulness-based stress reduction (MBSR) have been shown to improve both pain and psychological well-being. In this secondary analysis, we examined the change over time in sleep quality and psychosocial outcomes from the magnetic resonance imaging outcomes for mindfulness meditation clinical trial and assessed how these mediated treatment response (50% reduction in headache frequency postintervention). We also examined the relationship between baseline values and treatment response. The trial (primary outcomes previously reported) included 98 patients with episodic migraine randomized to either enhanced MBSR (MBSR+) or stress management for headache. They completed psychosocial questionnaires and headache diaries at baseline (preintervention), midintervention (10 weeks after baseline), and postintervention (20 weeks after baseline). There was a significant improvement in sleep quality from baseline to postintervention ( $P = 0.0025$ ) in both groups. There were no significant changes from baseline or between groups in anxiety, depression, and stress. There was also no significant association between baseline scores and treatment response. Mediation analysis showed a significant indirect effect of 6% for sleep: In other words, small improvements in sleep may have contributed to the efficacy of MBSR+. Trial registration: NCT02133209.

**Keywords:** Headache, Multivariate mediation, Comorbidities, Chronic pain

## 1. Introduction

Migraine is a chronic, neurological disorder affecting 10% to 15% of the general population.<sup>20</sup> Anxiety and depression are more prevalent in patients with migraine compared with the general population;<sup>8</sup> stress is one of the most common migraine triggers,<sup>26,47</sup> and sleep disturbances are common in migraine.<sup>16,27,45</sup> Although the biological mechanisms associating these factors with migraine are unclear, the relationship is likely

bidirectional because patients with anxiety and depression report greater migraine frequency.<sup>17,25,27,38,49</sup>

Comorbid conditions complicate treating migraine. Current migraine therapies either reduce pain or prevent migraines from occurring.<sup>38</sup> However, relief from migraine is a combination of the physical components (eg, pain and nausea) and the affective factors, all of which may be improved by nonpharmacological interventions such as mindfulness-based stress reduction (MBSR).<sup>2,18</sup> Although some mindfulness studies in patients with

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headache report improvements in headache frequency,<sup>2,6</sup> pain intensity, and quality of life compared with usual care, findings are inconsistent. Two recent reviews found psychological therapies, including mindfulness, did not significantly improve headache frequency compared with controls.<sup>1,36</sup> Similarly, a recent clinical trial for MBSR compared with headache education showed no treatment group differences.<sup>46</sup> Although evidence for the efficacy of mindfulness for migraine is mixed, heterogeneity in results might be due to small sample sizes and differences in study design, including a lack of an active control arm.<sup>11,21,22,29,44</sup>

Considering psychological end points, MBSR is associated with reductions of stress, anxiety, and depression in healthy populations, patients with pain, and patients with cancer,<sup>13,35,41</sup> but there is variability and small to moderate effect sizes depending on the pain population.<sup>10,29</sup> In migraine, Wells et al. found that patients who received MBSR had greater improvement in depression compared with headache education.<sup>46</sup> Others have shown improved anxiety in patients with migraine but lack of statistical power limits interpretation.<sup>37,47</sup> Mindfulness-based stress reduction shows only moderate evidence for sleep improvement and only in studies with nonspecific active controls.<sup>30</sup> Evidence in other populations shows that individual differences in these psychological factors can play a role in the treatment success of MBSR.<sup>9,14,15,24</sup> Distress tolerance and social anxiety have been shown to be moderators of MBSR.<sup>9,15</sup> Given that MBSR may improve psychosocial factors and increased stress, anxiety, depression, and sleep can trigger migraines, it is plausible that MBSR operates through one or several of these pathways to reduce headache frequency. Neither treatment moderating factors nor potential mediators of treatment response have been examined in the headache literature on mindfulness.

In this study, we leverage the sample size, the use of an active control arm, and a more targeted intervention, we call enhanced MBSR (MBSR+),<sup>32</sup> which we previously reported has efficacy for migraine.<sup>32</sup> We hypothesized the following: (1) compared with stress management for headache (SMH), patients randomized to MBSR+ have greater improvement in sleep quality, anxiety, depression, and stress symptoms over time; (2) higher values (ie, poor sleep, worse anxiety, etc.) of baseline sleep quality, anxiety, depression, and stress symptoms are associated with treatment response to MBSR+; and (3) sleep quality, anxiety, depression, and stress symptoms mediate the MBSR+ treatment response.

## 2. Methods

### 2.1. Clinical trial design

This secondary analysis used data from the magnetic resonance imaging outcomes of mindfulness meditation for migraine clinical trial (NCT02133209).<sup>32</sup> Participants were enrolled from June 2014 to February 2017. The primary objective of the clinical trial was to determine the short-term and long-term efficacy of MBSR+ on headache frequency and brain structure and function. This was a randomized placebo-controlled trial with single masking. Participants were excluded if they reported severe or unstable psychiatric conditions, but patients with anxiety and/or depression were eligible for inclusion. All patients with migraine had episodic migraine and were randomly assigned to receive either MBSR+ or SMH. Patients were randomized 1:1 to either treatment in prespecified blocks, using a web-based randomization system. Randomization was stratified by the presence or absence of another chronic pain disorder and by headache frequency: 4 to 8 (low frequency) or 9 to 14 (high

frequency) headache days per 28 days. The clinical trial also enrolled 30 healthy pain-free controls, matched to the patients with migraine on age ( $\pm 5$  years), sex, body mass index (BMI) ( $\pm 5$ ), education (college and no college), and race. Data from healthy controls were not used in these analyses. Each treatment was administered weekly for 8 weeks with an additional half day retreat for the MBSR+ arm, and then, both treatments were administered for an additional 4 sessions over 8 weeks. Full inclusion and exclusion criteria have been previously reported.<sup>32</sup>

### 2.2. Outcome measures

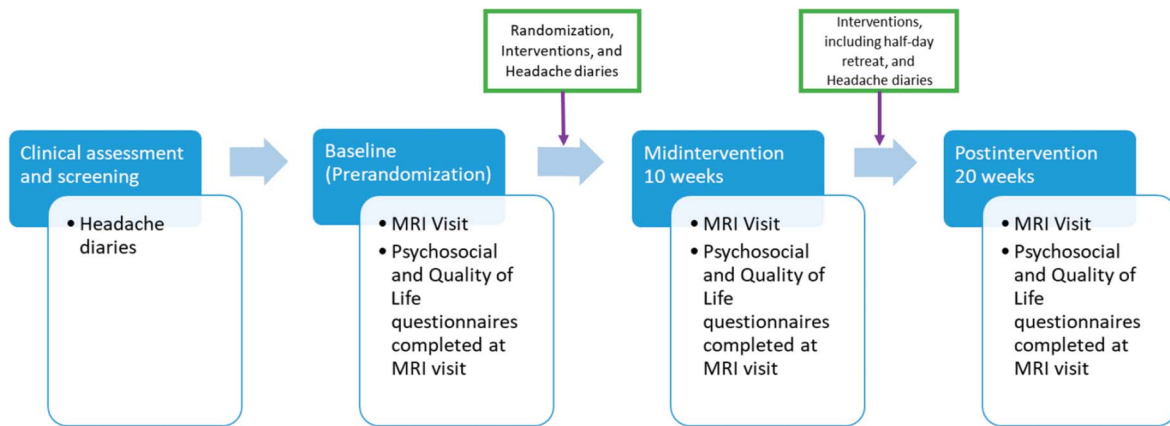
Patients were assessed at 3 time points: baseline (prerandomization), midintervention (week 10), and postintervention (week 20). The midintervention assessment occurred after the first 8 weeks of intervention, and the postintervention assessment occurred after the second 8 weeks (Fig. 1).

### 2.3. Headache frequency

Daily headache diaries were completed electronically (online through a link sent through email) and collected detailed information on headaches over a 28-day period (eg, pain intensity, headache duration, and other symptoms). Headache diaries were used to ascertain clinical end points including headache frequency at baseline and over time. Given the nature of headache diaries, not all patients completed a full 28 days. To address this, we calculated a proportion for everyone by dividing the number of headache days reported by the total number of diary days collected in that period. For any given individual, the maximum denominator was 28. In addition, we multiplied the proportion by 28 to get a continuous variable for headache days. In final models, we used treatment response as the main clinical headache end point. To calculate the treatment response in the sample, we used the above proportion and the standardized headache day variables and calculated the difference between baseline and the postintervention time point. Treatment responders were defined as achieving at least a 50% reduction in headache frequency from baseline to postintervention (week 20). This end point is consistent with several studies for migraine preventative medications such as topiramate and nonpharmacological treatments such as acupuncture.<sup>12,19,40</sup>

### 2.4. Sleep quality and psychosocial questionnaires

Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) questionnaire,<sup>3</sup> a 23-item scale that assesses the quality of sleep over the past month with possible scores ranging from 0 to 21.<sup>3</sup> Anxiety was assessed using the Generalized Anxiety Disorder (GAD-7) questionnaire,<sup>28,33</sup> a 7-item questionnaire that measures common symptoms of anxiety with scores ranging from 0 to 21. Depression was measured with the Patient Health Questionnaire-9 (PHQ-9),<sup>34</sup> a 9-item questionnaire for depressive symptom severity over the past 2 weeks with scores ranging from 0 to 27. Stress was assessed with the Perceived Stress Scale (PSS),<sup>5,23</sup> a 10-item questionnaire that measures an individual's perceived stress to everyday life situations over the past month with scores ranging from 0 to 40. Questionnaire scores were also categorized according to validated cut points. Pittsburgh Sleep Quality Index total scores  $\geq 5$  indicate poor sleep quality.<sup>3</sup> Generalized Anxiety Disorder was categorized into 4 groups: 0 to 4 (no anxiety symptoms), 5 to 9 (mild anxiety symptoms), 10 to 14 (moderate anxiety symptoms), and  $15 \leq$  (severe anxiety symptoms).<sup>28,33</sup> Similarly, PHQ-9 was separated



**Figure 1.** Flow diagram to illustrate the ordering of study activities. Blue rectangles represent the periods in the study from prebaseline when patients were enrolled to postintervention when patients had completed the last intervention session. Boxes outlined in blue at the bottom highlight activities that take place at the MRI visits at each time point. Boxes with a green outline detail activities that take place between each MRI session. All participants completed headache diaries before randomization and the commencement of intervention. Headache diaries were collected over a 28-day period before randomization. After the initial 8 weeks of intervention, participants completed their second 28-day headache diary. After the completion of the second 8 weeks of intervention, participants completed their postintervention 28-day headache diary. All participants completed an MRI visit and the associated questionnaires at baseline before the randomization and intervention. The second MRI visit was conducted after the initial 8 weeks of intervention, and the third was conducted after the second 8 weeks of intervention. MRI, magnetic resonance imaging.

into 5 categories, as follows 0-4, 5-9, 10-14, 15-19, and  $\geq 20$ , to represent no depression symptoms, mild, moderate, moderately severe, and severe depression symptoms, respectively.<sup>34</sup> Perceived Stress Scale was categorized into 3 groups where 0 to 13 is average, 14 to 26 is moderate stress, and 27 to 40 is high stress.<sup>5,23</sup> Finally, patients were assessed as either having symptoms or not for all the abovementioned questionnaires (eg, depression symptoms yes/no) using the minimum cut point for each questionnaire (eg, score of 5 on the PSQI questionnaire).

## 2.5. Statistical analysis

### 2.5.1. Demographic and clinical variables

Distributions of baseline patients' characteristics between those randomized to MBSR+ and SMH and differences between treatment responders and nonresponders were assessed using  $\chi^2$ , *t* tests, and nonparametric Wilcoxon and Kruskal–Wallis tests. Baseline characteristics included headache frequency, presence of an additional idiopathic pain condition, education, age, sex, race, and BMI. In addition to sleep quality and psychosocial factors, the following clinical headache characteristics were examined: headache days, mean headache pain, and headache impact test (HIT-6) scores. All analyses used the intention-to-treat (ITT) analysis; therefore, patients were analyzed as randomized.

### 2.6. Change in sleep quality and psychosocial symptom scores over time

Exploratory data analysis examined the distributions of baseline continuous scores and the change in scores over time (baseline, 10 weeks, and 20 weeks) of all questionnaires (Supplementary Table 1, available at <http://links.lww.com/PAIN/B409>). Wilcoxon test, analysis of variance, and repeated measures analysis of variance were used to assess differences in group, time, and group-by-time interactions. Several regression diagnostic measures were used to examine the linearity of variables as outcomes and to assess the correlation of these variables as predictors. Using the variance inflation factor and Cook D plots of both the raw and scaled residuals and predicted values, we examined the

assumptions of normality, linearity, and independence of these variables as both outcome and predictive measures. Given the skewed nature of PSQI, GAD-7, and PHQ-9, we also assessed the utility of log transformation on these factors. Using the mixed-effects model diagnostics, it was determined to use the untransformed continuous scores in all final models.

All final analyses used mixed-effect models, and a random intercept was included in the final model for depression alone because this was the only outcome where this approach improved the model fit. All models were corrected for multiple comparisons; used an unstructured covariance; and assessed differences between MBSR+ and SMH groups, change from baseline, and group-by-time interactions. Models were assessed using the Akaike information criterion (AIC) as well as the impact of additional variables on the standard error.

### 2.7. Baseline sleep quality and psychosocial scores and the relationship with treatment response

Pittsburgh Sleep Quality Index, GAD-7, PHQ-9, and PSS scores are known to be related, and initial analyses assessed the statistical correlation using Spearman rho as well as their impact on each other by examining collinearity diagnostics. Rho values equal to or more than 0.5 as well as a *P* value  $\leq 0.05$  were assessed further. We assessed condition index, variance inflation factor, tolerance, and proportion of variance values. It was determined that each predictor would be modeled separately to assess their individual association with treatment response.

Individual models assessed continuous baseline sleep and psychosocial variables as the predictors, adjusting for the treatment group. We assessed interactions between the treatment group and baseline values for sleep and psychosocial factors, but there were none and thus final models do not stratify by group. Confounders of interest at baseline were BMI, education, race, sex, age, idiopathic pain condition, and HIT-6. We also assessed the role of baseline mindfulness and pain catastrophizing as potential confounders, but inclusion did not significantly affect the model or change the size of the estimates for the psychosocial variables of interest. Final models were

assessed as described above. All statistical analyses were conducted using SAS (v.9.4, SAS Institute Inc, Cary, NC). Testing was two sided and performed at the 0.05 level of significance.

### 2.8. Mediation of treatment response by change in sleep quality over time

We examined the mediation of treatment effects (MBSR+ vs SMH) on treatment response through changes in sleep. To assess the presence of mediation, we used the mediation analysis methods for binary outcomes and multiple mediators as outlined by VanderWeele<sup>42</sup> and VanderWeele and Vansteelandt.<sup>43</sup> Figure 2 depicts the directed acyclic graph that guided the development of the final models. The weighting method developed by VanderWeele and Vansteelandt uses an inverse probability of treatment weighting approach to estimate the direct and indirect effects even when mediators affect each other.<sup>43</sup>

This approach estimates 3-weighted averages which correspond to the following counterfactuals:  $E[\text{Treatment response } a^*Ma^*]$ ,  $E[\text{Treatment response } aMa]$ , and  $E[\text{Treatment response } aMa^*]$  where  $a = \text{MBSR+}$ ,  $a^* = \text{SMH}$ , and  $M = \text{mediator vector}$ . Each response is calculated in a 3-step process. For  $E[\text{Treatment response } a^*Ma^*]$ , the first step fits a logistic regression model using a mediator vector (this included sleep and headache frequency reported at 10 weeks) and baseline covariates to estimate predicted probabilities of  $P(\text{SMH}|\text{ci})$ . Second, a weighted average of the predicted values for subjects is calculated by  $P(A = \text{SMH})/P(A = \text{SMH}|\text{ci})$ . The final step uses the weight in a regression model to estimate the value of  $E[\text{Treatment response } a^*Ma^*]$ . The process is repeated for each counterfactual component. The direct effect is given by  $E[\text{Treatment response } aMa^*] - E[\text{Treatment response } a^*Ma^*]$ , and the indirect effect is given by  $E[\text{Treatment response } aMa] - E[\text{Treatment response } aMa^*]$ .

We adjusted for the baseline values of the anxiety, stress, and depression. To account for mediator–outcome confounding, headache frequency at midintervention is included in the mediator vector. Exposure–mediator (treatment group\*sleep) interactions and interactions between sleep and other psychosocial factors were assessed; however, these models did not differ significantly from those without interaction. Given that no interactions existed, the natural direct effect is assumed equivalent to the controlled direct effect. To calculate standard errors and 95% confidence intervals (CIs) for each estimate, a bootstrapping approach was used. This process generated 1000 samples with replacement after which counterfactual estimates and CIs were generated for all samples. Confidence intervals that did not include the null were significant. Analyses were conducted using SAS (v.9.4, SAS Institute Inc).

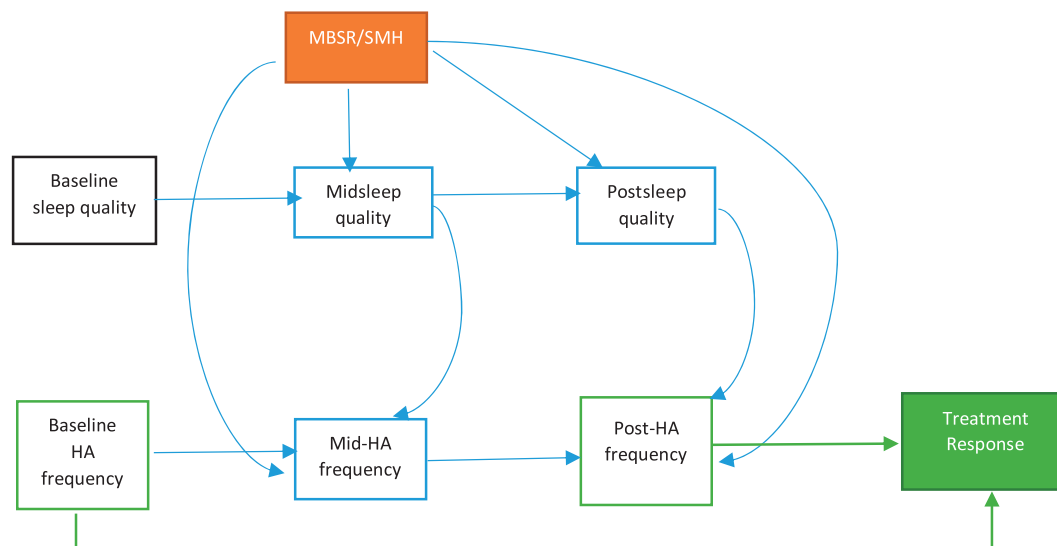
Power for this analysis was calculated using the powerMediation package in R for dichotomous outcomes. Assuming a sample size of 98 (49 per group), power 0.8, standard deviation of the mediator 0.4, correlation between the predictor and mediator 0.3, alpha 0.05%, and 30% marginal prevalence of the outcome, the minimal detectable difference attributable to the mediator will be an OR of 1.62.

## 3. Results

### 3.1. Description of baseline demographic and clinical measures in patients with episodic migraine

Of the 583 patients screened, 122 completed baseline assessments and 98 were eligible and randomized to receive either MBSR+ ( $n = 50$ ) or SMH ( $n = 48$ ). All 98 patients were included in the analyses examining changes in sleep and psychosocial metrics over time. Treatment response analyses were reduced to the 95 patients with baseline and postintervention follow-up data that were needed to assess the outcome.

Patients with migraine randomized to MBSR+ or SMH were of comparable age, race, sex, BMI, and educational attainment. Both



**Figure 2.** Causal diagram to represent plausible mediation relationship between MBSR+ and treatment response. Arrows assume direction of causal relationships. Model assumes no unmeasured confounding. Black box indicates the randomized treatment MBSR+ vs. SMH. The orange box indicates the randomized treatment MBSR+ vs. SMH. The solid green box is the outcome which is treatment response. This variable is created from baseline and post-intervention headache frequency (green outlined boxes). Blue boxes represent possible mediators of the relationship between exposure and outcome. Baseline sleep quality was measured prior to randomization and therefore is not affected by the treatment. Mid-point (10 weeks post baseline) sleep quality was measured at the scan visit directly after the completion of the first block of treatment. Headache diaries were completed for 28 days post the first block of treatment and therefore are captured after the psychosocial measurements. Post-treatment (20 weeks post baseline) psychosocial measurements were taken at the scan visit directly after the final treatment block had been completed. These visits usually occur over a two-week period post study completion. Headache diaries are completed for 28 days post treatment. HA, headache; MBSR, mindfulness-based stress reduction; MBSR+, enhanced mindfulness-based stress reduction; SMH, stress management for headache.

**Table 1**  
**Baseline clinical and demographic variables in patients with episodic migraine randomized to either enhanced mindfulness-based stress reduction or stress management for headache.**

Variable	MBSR+ (n = 50)	SMH (n = 48)	P*
Sex (%)			
Male	3 (6)	6 (12.5)	0.31
Female	47 (94)	42 (87.5)	
Age/median (range)	36 (18-65)	35.5 (21-63)	0.44
Race/n (%)			
Black	10 (20)	7 (14.58)	0.79
White	35 (70)	36 (75)	
Others	4 (8)	5 (10.42)	
Unknown	1 (2)	0	
Education/n (%)			
Some college or less	13 (26)	7 (14.58)	0.16
College and above	37 (74)	41 (85.42)	
BMI/median (range)	27.30 (15.66-47.44)	25.71 (16.63-45.45)	0.79
Migraine qualities at baseline			
Low frequency (4-8 d)/n (%)	25 (50)	25 (52.08)	0.84
High frequency (9-14 d)/n (%)	25 (50)	23 (47.92)	
Headache days/median (range)	8 (3-14)	7 (3-14)	0.83
Headache pain/mean ± SD	4.72±1.65	4.31±1.57	0.22
HIT-6 total mean ± SD	61±5.83	60.85 ± 5.586	0.52
Idiopathic pain/n (%)			
Yes	15 (30)	13 (27.08)	0.75
No	35 (70)	35 (72.92)	
Preventative migraine medication use/n (%)			
Yes	11 (22)	4 (8.33)	0.06
No	39 (78)	44 (91.67)	
Sleep quality and psychosocial measures/median (range)			
PSQI	3.5 (0-11.67)	4.67 (0-14)	0.77
GAD-7	1 (0-16)	1.5 (0-16)	0.08
PHQ-9	2 (0-13)	3 (0-7)	0.07
PSS	9 (2-32)	13 (1-26)	0.18

\* P-values calculated from t-tests,  $\chi^2$ , Wilcoxon, and Kruskal–Wallis tests. BMI, body mass index; GAD-7, Generalized Anxiety Disorder; HIT-6, Headache Impact Test; MBSR+, enhanced mindfulness-based stress reduction; SMH, stress management for headache.

groups were predominantly women, White, and college educated with a median age of 36 years (**Table 1**). Clinical characteristics, particularly those related to migraine, were also similar between the randomized groups. The proportion of headache days ranged from 0.11 to 0.5 in both groups with an average value of 0.25 in the SMH group and 0.29 in the MBSR+ group. Overall, 29% of patients reported poor sleep quality, 13% of all patients met criteria for anxiety symptoms, 20% for depression symptoms, and 39% for stress. There was no significant difference in the proportions between MBSR+ and SMH groups (Supplementary Table 2, available at <http://links.lww.com/PAIN/B409>).

**Table 2**  
**Adjusted analyses assessing effects of group and time on sleep and psychosocial factors in patients with episodic migraine.**

Variable	Mean difference (95% confidence interval)	P*
Sleep quality (PSQI)†		
Group effect		
MBSR+ vs SMH	-0.42 (-1.39 to 0.55)	0.39
Time effect		
Δ 10 wk	-0.13 (-0.70 to 0.45)	0.66
Δ 20 wk	-0.67 (-1.10 to -0.24)	<b>0.0025</b>
Anxiety (GAD-7)‡		
Group effect		
MBSR+ vs SMH	-0.13 (-0.71 to 0.46)	0.67
Time effect		
Δ 10 wk	-0.20 (-0.66 to 0.25)	0.38
Δ 20 wk	0.14 (-0.26 to 0.55)	0.48
Depression (PHQ-9)§		
Random effects variance parameter		
Intercept	2.62 (1.85 to 3.98)	
Residual	2.23 (1.83 to 2.78)	
Group effect		
MBSR+ vs SMH	-0.14 (-0.88 to 0.61)	0.72
Time effect		
Δ 10 wk	0.35 (-0.09 to 0.80)	0.12
Δ 20 wk	-0.11 (-0.57 to 0.35)	0.64
Stress (PSS)¶		
Group effect		
MBSR+ vs SMH	-0.93 (-2.49 to 0.62)	0.24
Time effect		
Δ 10 wk	0.09 (-0.84 to 1.03)	0.85
Δ 20 wk	-0.49 (-1.65 to 0.67)	0.40

\* P-value from linear mixed model. † Model adjusted for stress, body mass index, and headache pain. ‡ Model adjusted for stress and depression. § Model adjusted for anxiety, headache impact score, and additional idiopathic pain condition. Model includes random intercept. ¶ Model adjusted for depression, anxiety, sleep, and headache days. Significant effects are shown in bold. GAD-7, Generalized Anxiety Disorder; MBSR+, enhanced mindfulness-based stress reduction; PSS, Perceived Stress Score; PHQ-9, Patient Healthy Questionnaire; PSQI, Pittsburgh Sleep Quality Index; SMH, stress management for headache.

**3.2. Change over time in enhanced mindfulness-based stress reduction and stress management for headache groups**

**3.2.1. Sleep quality**

Sleep quality results show that although patients randomized to MBSR+ on average had lower scores (better sleep quality) than those randomized to SMH, the difference between the groups was not significant (**Table 2**). However, the change in sleep quality across groups over time was significant. Patients reported improved sleep quality from baseline to week 10 because impairment was reduced by -0.13 (95% CI: -0.70 to 0.45) and further at 20 weeks (-0.67, 95% CI: -1.10 to -0.24) (**Table 2**). (See Supplementary Tables 1 and 2, available at <http://links.lww.com/PAIN/B409>).

**3.2.2. Psychosocial factors**

Although patients randomized to MBSR+ had lower scores across all metrics, the difference between groups was not statistically significant (**Table 2**). With the exception of anxiety symptoms (an increase at 20 weeks), the scores for all other metrics had declined at 20 weeks. However, these were not

**Table 3****Baseline clinical and demographic variables in patients with episodic migraine by treatment responder status.**

Variable	Treatment responder		P*
	Yes (n = 37)	No (n = 58)	
Sex (%)			
Male	2 (5.41)	6 (10.34)	0.48
Female	35 (94.59)	52 (89.66)	
Age/median (range)	35 (22-65)	37 (18-63)	0.77
Race/n (%)			
Black	22 (59.46)	47 (81.03)	0.06
White	8 (21.62)	8 (13.79)	
Others	6 (16.22)	3 (5.17)	
Unknown	1 (2.7)	0	
Education/n (%)			
Some college or less	11 (29.73)	8 (13.79)	0.06
College and above	26 (70.27)	50 (86.21)	
BMI/median (range)	28.64 (16.75-47.44)	25.03 (15.66-45.45)	0.05
Migraine qualities at baseline			
Low frequency (4-8 d)/n (%)	16 (43.24)	32 (55.17)	0.26
High frequency (9-14 d)/n (%)	21 (56.76)	26 (44.83)	
Headache days/median (range)	9 (5-13)	8 (3-14)	0.15
Baseline headache Pain/mean ± SD	4.74 ± 1.38	4.35 ± 1.59	0.22
HIT-6 total mean ± SD	60.59 ± 5.86	61 ± 5.40	0.73
Idiopathic pain/n (%)			
Yes	15 (40.54)	12 (20.69)	<b>0.04</b>
No	22 (59.46)	46 (79.31)	
Preventative migraine medication use†/n (%)			
Yes	8 (21.62)	6 (10.34)	0.13
No	29 (73.38)	52 (89.66)	
Sleep quality and psychosocial measures/ median (range)			
PSQI	4.67 (1.17-11.67)	3.5 (0-14)	0.07
GAD-7	1 (0-16)	1 (0-16)	0.63
PHQ-9	3 (0-13)	2 (0-10)	0.38
PSS	12 (2-28)	11.5 (1-32)	0.28

\* p values calculated from t tests,  $\chi^2$ , Wilcoxon, and Kruskal–Wallis tests.

† Preventative medications cover 4 categories of medications, which have been combined in this table.

Significant effects are shown in bold.

GAD-7, Generalized Anxiety Disorder; HIT-6, Headache Impact Test; PSS, Perceived Stress Score; PHQ-9, Patient Healthy Questionnaire; PSQI, Pittsburgh Sleep Quality Index.

significant (**Table 2**). (See Supplementary Tables 1 and 2, available at <http://links.lww.com/PAIN/B409>).

### 3.2.3. Baseline sleep quality, anxiety, depression, and stress symptom scores and the association with treatment response

**Table 3** provides a description of the patients included in this analysis. There was no significant association between any baseline symptom score and treatment response (**Table 4**). There was no interaction between intervention arm and baseline psychosocial score. Therefore, results are not stratified by intervention arm.

### 3.2.4. Mediation of treatment response by change in sleep quality over time

Results from the preceding analyses indicate that there was no significant change in anxiety, depression, or stress and that baseline values were not associated with treatment response. Thus, mediation analyses were restricted to sleep quality, which showed a significant change over time. The total causal effect, that is, the total difference in treatment response between those randomized to MBSR+ and SMH, is 25%

(Supplementary Table 3, available at <http://links.lww.com/PAIN/B409>). The direct effect of MBSR+, that is, the effect of MBSR+ independent of sleep was 0.19 (95% CI 0.18-0.2), indicating that 19% of the effect of MBSR+ is through pathways which do not include sleep. The indirect effect, the effect of MBSR+ mediated through pathways that included sleep, was 0.06 (95% CI: 0.05-0.08). This shows that 6% of the effect of MBSR+ was through the improvement of sleep. This suggests that an additional 6% in treatment response could be seen in those randomized to SMH if their sleep quality had been set to that of those who received MBSR+ (**Table 5**).

## 4. Discussion

We examined the longitudinal relationship between MBSR+ treatment, sleep quality, and psychosocial symptoms in the context of a randomized trial using an active control for headache management. We found that sleep quality was significantly improved in both treatment groups at 20 weeks. There was no significant association between baseline sleep disturbance, anxiety, depression or stress, and treatment response regardless

**Table 4**  
**Adjusted models to examine the association between continuous values of baseline sleep quality, psychosocial scores, and treatment response.**

Variable	Odds ratio (95% CI)*	P*
Sleep quality† PSQI	1.10 (0.94, 1.30)	0.24
Anxiety‡ GAD-7	1.11 (0.95, 1.30)	0.19
Depression‡ PHQ-9	1.13 (0.92, 1.38)	0.25
Stress‡ PSS	1.03 (0.96, 1.11)	0.39

\* P-value from the adjusted logistic regression model.

† Model adjusted for randomization group (MBSR+ vs SMH), race, and body mass index

‡ Models adjusted for randomization group (MBSR+ vs SMH), additional idiopathic pain condition, and body mass index.

GAD-7, Generalized Anxiety Disorder; MBSR+, enhanced mindfulness-based stress reduction; PSQI, Pittsburgh Sleep Quality Index; PHQ-9, Patient Healthy Questionnaire; PSS, Perceived Stress Score; SMH, stress management for headache.

of treatment condition. The total effect of MBSR+ on treatment response, operationalized as a 50% reduction in headaches at 20 weeks, included the indirect effect of improved sleep quality, in addition to direct effects of MBSR+.

The impact of MBSR on psychological well-being is inconsistent and, at best, modest. A meta-analysis of mindfulness studies with specific and nonspecific control arms, across several patient groups, reported an effect size of mindfulness on anxiety of 0.38 (95% CI 0.12-0.64) and 0.30 (95% CI 0.00-0.59) for depression at 8 weeks, both of which declined by 6 months.<sup>10</sup> Within pain populations (fibromyalgia and chronic back pain), these effects on depression and anxiety were not significant.<sup>10</sup> When compared with active treatments, such as acceptance-based therapy, the effects of MBSR in patients with chronic pain on anxiety and depression are small and not significant.<sup>44</sup> In patients with chronic lower back pain randomized to MBSR, cognitive behavioral therapy, or usual care, Cherkin and colleagues reported significant improvements in depression and anxiety up to 26 weeks postintervention.<sup>4</sup> Effects were seen at 8 weeks postintervention, and group differences were most notable comparing MBSR with usual care. In our study, although not significant, group differences in the GAD-7 score between MBSR+ and SMH were -0.13 in our patients with migraine, which is similar to that observed comparing MBSR and CBT in patients with chronic lower back pain at 8-week follow-up (-0.18).<sup>4</sup> A recent study by Wells et al. reported that patients with migraine who received a standard MBSR had greater improvement in depression but not anxiety compared with education.<sup>46</sup> Although this differs from our findings, patients in our study had baseline values for PHQ-9 and GAD-7 that were much lower than in the study by Wells. This would suggest that there was less room

**Table 5**  
**Direct and indirect effects of enhanced mindfulness-based stress reduction on treatment response.**

Effect*	Estimate	95% CI†
Direct effect of MBSR	0.19	0.18-0.20
Indirect effect through sleep	0.06	0.05-0.08

\* Model adjusted for baseline values of sleep, anxiety, stress, and depression. Models include headache frequency at midintervention in the mediator matrix to account for mediator-outcome confounding.

† Confidence intervals are highlighted in bold to identify that direct and indirect effects are significant.

CI, confidence interval; MBSR, mindfulness-based stress reduction.

for improvement and may explain why anxiety and depression showed no significant improvements over time in our study.

We do, however, see effects of treatment on sleep quality, yet no differential benefit of MBSR+ over SMH in reducing sleep disturbance. As with indices of psychological well-being, the impact of MBSR on sleep quality is varied. A systematic review assessing the effects of MBSR on sleep disturbance reported significant improvements in sleep quality in several clinical populations, including fibromyalgia.<sup>48</sup> Importantly, significant improvements were only observed in uncontrolled studies but were absent in those with an active control arm.<sup>31,48</sup> Similarly, we observed significant improvements in sleep quality, but there was no difference between our 2 active arms at 20 weeks, indicating that both treatments improved sleep quality. One possibility is that the improvement in sleep quality we observed was related to the reduction in headache frequency, rather than a direct effect of intervention. Findings from the main outcomes article show that although patients with MBSR+ had a significantly greater decrease in headache frequency, those in the SMH arm also saw long-term improvements.<sup>32</sup> Studies suggest that preventative migraine treatments and behavioral interventions such as CBT and relaxation training also improve sleep in patients with migraine.<sup>39</sup> Although patients in the SMH arm did not learn any specific mindfulness techniques, the program did provide discussions about lifestyle factors that can help modify stress and migraine triggers such as the importance of diet, exercise, and sleep hygiene. The causal relationship between sleep and migraine continues to be investigated and although research suggests that it might be bidirectional, active behavioral interventions likely share components that improve both.

We observed an indirect effect of 6%, suggesting that some of the effect of MBSR+ in reducing headache frequency may be mediated through pathways that include improvements in sleep quality. Other studies that have explored the mechanisms involved in mindfulness-based cognitive therapy (MBCT) and the effect on depressive disorder found that the main predictive and mediating components were alterations in mindfulness, rumination, worry, and self-compassion.<sup>41</sup> Patients who were more mindful saw greater improvement, and improvement in depression was mediated by other negative affect components such as rumination and worry.<sup>41</sup> In patients with headache, Day and colleagues assessed headache pain using the Brief Pain Inventory score and reported that pathways through pain acceptance were responsible for small reductions of pain scores.<sup>7</sup> These effects are comparable with our findings in that although the indirect effects were small, they still made up a significant proportion of the success of treatment. This small mediation effect and the absence of predictive value of baseline sleep and nonsignificant group differences over time are likely because our sample generally reported good sleep quality leaving little room for improvement. Previous studies have reported that, compared with patients with chronic pain with comorbid psychosocial symptomatology, patients with clinically diagnosed psychiatric disorders report greater symptom reduction after receipt of MBSR.<sup>13,35,41</sup> It is plausible that MBSR+ for migraine might be most effective in patients with high baseline levels of these comorbid factors. Although there were some patients with anxiety and depression enrolled in the study, those with unstable or uncontrolled psychological disorders were excluded.

#### 4.1. Strengths and limitations

This is the largest RCT assessing mindfulness in patients with migraine to date, providing the first comprehensive look at MBSR+ in episodic migraine. The active control treatment arm allowed us to make comparisons that are more appropriate and provided evidence that although MBSR+ does significantly reduce headache frequency, other active interventions such as SMH can be useful and likely share mechanisms of action. Stratified block randomization mitigated possible imbalances in risk factors between intervention groups, and patient retention was excellent. All analyses used ITT, preserving the benefits of randomization. Although patients randomized to SMH may have tried alternative stress management techniques or attempted MBSR on their own, the benefits of ITT outweigh the harms and the likelihood of patients trying both treatments is slim given the time burden associated.

However, our study does have some limitations. It is possible the study attracted patients with migraine who are not representative of the general migraine population given their interest in nonpharmacological therapy. We recruited patients from 2 large health systems and academic campuses and a large metropolitan community. This limited geographic scope, the demands of weekly and biweekly treatment sessions, and the requirement to complete imaging likely limit the representativeness of the patient sample.

Through meditation analysis, we show that small changes in sleep may have contributed to treatment response. One drawback is that negative affect and stress, although highly correlated, may also affect sleep. However, in separate models (not reported), we assessed the effect of each symptom—*anxiety, depression, and stress*—separately and together and the effect was similar. This may suggest that MBSR+ works through the improvement of sleep quality; however, given the small effect size, and the fact that there were no group differences in sleep quality over time, this mediation effect is likely only partially responsible for the change that we observe. Finally, there is always the concern of unmeasured confounding especially in light of the strict assumptions that must be used with these analyses. The randomized design incorporated a rich collection of baseline covariates, diminishing this risk in this study.

#### 5. Conclusions

Enhanced mindfulness-based stress reduction may be a comprehensive therapeutic approach in patients with migraine. Benefits may differ based on a patient's baseline sleep quality, but that cannot be definitively concluded in this study. Further work incorporating a wider distribution of sleep profiles is needed. We also show that the active control arm, SMH, leads to improvement and opens the door for further exploration into the specific components of behavioral interventions that might be most effective. Importantly, MBSR+ provides patients with the opportunity to take responsibility and control over their care eliminating some of the barriers associated with traditional pharmacological options. Patients acquire lifelong skills that once maintained can improve their overall quality of life.

#### Conflict of interest statement

The authors have no conflicts of interest to declare.

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#### Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at <http://links.lww.com/PAIN/B409>.

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#### References

- [1] Anheyer D, Leach MJ, Klose P, Dobos G, Cramer H. Mindfulness-based stress reduction for treating chronic headache: a systematic review and meta-analysis. *Cephalalgia* 2019;39:544–55.
- [2] Bakhshani NM, Amirani A, Amirifard H, Shahrakipour M. The effectiveness of mindfulness-based stress reduction on perceived pain intensity and quality of life in patients with chronic headache. *Glob J Health Sci* 2015;8:142–51.
- [3] Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
- [4] Cherkin DC, Sherman KJ, Balderson BH, Cook AJ, Anderson ML, Hawkes RJ, Hansen KE, Turner JA. Effect of mindfulness-based stress reduction vs cognitive behavioral therapy or usual care on back pain and functional limitations in adults with chronic low back pain: a randomized clinical trial. *JAMA* 2016;315:1240–9.
- [5] Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* 1983;24:385–96.
- [6] Day MA, Thorn BE, Rubin NJ. Mindfulness-based cognitive therapy for the treatment of headache pain: a mixed-methods analysis comparing treatment responders and treatment non-responders. *Complement Ther Med* 2014;22:278–85.
- [7] Day MA, Thorn BE, Ward LC, Rubin N, Hickman SD, Scogin F, Kilgo GR. Mindfulness-based cognitive therapy for the treatment of headache pain: a pilot study. *Clin J Pain* 2014;30:152–61.
- [8] Fuller-Thomson E, Jayanthikumar J, Agbeyaka SK. Untangling the association between migraine, pain, and anxiety: examining migraine and generalized anxiety disorders in a canadian population based study. *Headache* 2017;57:375–90.
- [9] Gawrysiak MJ, Leong SH, Grasseti SN, Wai M, Shorey RC, Baime MJ. Dimensions of distress tolerance and the moderating effects on mindfulness-based stress reduction. *Anxiety Stress Coping* 2016;29:552–60.
- [10] Goyal M, Singh S, Sibinga EM, Gould NF, Rowland-Seymour A, Sharma R, Berger Z, Sleicher D, Maron DD, Shihab HM, Ranasinghe PD, Linn S, Saha S, Bass EB, Haythornthwaite JA. Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. *JAMA Intern Med* 2014;174:357–68.
- [11] Grossman P, Niemann L, Schmidt S, Walach H. Mindfulness-based stress reduction and health benefits. A meta-analysis. *J Psychosom Res* 2004;57:35–43.
- [12] Ha H, Gonzalez A. Migraine headache prophylaxis. *Am Fam Physician* 2019;99:17–24.
- [13] Hilton L, Hempel S, Ewing BA, Apaydin E, Xenakis L, Newberry S, Colaiaico B, Ruelaz Maher A, Shanman RM, Sorbero ME, Maglione MA. Mindfulness meditation for chronic pain: systematic review and meta-analysis. *Ann Behav Med* 2017;51:199–213.
- [14] Hsu SH, Collins SE, Marlatt GA. Examining psychometric properties of distress tolerance and its moderation of mindfulness-based relapse prevention effects on alcohol and other drug use outcomes. *Addict Behav* 2013;38:1852–8.
- [15] Jazaieri H, Lee IA, Goldin PR, Gross JJ. Pre-treatment social anxiety severity moderates the impact of mindfulness-based stress reduction and aerobic exercise. *Psychol Psychother* 2016;89:229–34.
- [16] Kim J, Cho SJ, Kim WJ, Yang KI, Yun CH, Chu MK. Insufficient sleep is prevalent among migraineurs: a population-based study. *J Headache Pain* 2017;18:50–8.
- [17] Koffel E, Kroenke K, Bair MJ, Leverty D, Polusny MA, Krebs EE. The bidirectional relationship between sleep complaints and pain: analysis of data from a randomized trial. *Health Psychol* 2016;35:41–9.
- [18] Lengacher CA, Johnson-Mallard V, Post-White J, Post-White J, Moscoso MS, Jacobsen PB, Klein TW, Widen RH, Fitzgerald SG, Shelton MM, Barta M, Goodman M, Cox CE, Kip KE. Randomized



- controlled trial of mindfulness-based stress reduction (MBSR) for survivors of breast cancer. *Psychooncology* 2009;18:1261–72.
- [19] Linde K, Allais G, Brinkhaus B, Fei Y, Mehring M, Vertosick EA, Vickers A, White AR. Acupuncture for the prevention of episodic migraine. *Cochrane Database Syst Rev* 2016;2016:CD001218.
- [20] Lipton RB, Silberstein SD. Episodic and chronic migraine headache: breaking down barriers to optimal treatment and prevention. *Headache* 2015;55(Suppl 2):103–6.
- [21] MacCoon DG, Imel ZE, Rosenkranz MA, Sheftel JG, Weng HY, Sullivan JC, Bonus KA, Stoney CM, Salomons TV, Davidson RJ, Lutz A. The validation of an active control intervention for mindfulness based stress reduction (MBSR). *Behav Res Ther* 2012;50:3–12.
- [22] Mccubbin T, Dimidjian S, Kempe K, Glassey MS, Ross C, Beck A. Mindfulness-based stress reduction in an integrated care delivery system: one-year impacts on patient-centered outcomes and health care utilization. *Perm J* 2014;18:4–9.
- [23] Moon HJ, Seo JG, Park SP. Perceived stress in patients with migraine: a case-control study. *J Headache Pain* 2017;18:73–8.
- [24] Nyklicek I, Irmischer M. For whom does mindfulness-based stress reduction work? moderating effects of personality. *Mindfulness* 2017;8:1106–16.
- [25] Oh K, Cho SJ, Chung YK, Kim JM, Chu MK. Combination of anxiety and depression is associated with an increased headache frequency in migraineurs: a population-based study. *BMC Neurol* 2014;14:238–4.
- [26] Pancheri C, Maraone A, Roselli V, Altieri M, Di Piero V, Biondi M, Pasquini M, Tarsitani L. The role of stress and psychiatric comorbidities as targets of non-pharmacological therapeutic approaches for migraine. *Riv Psichiatr* 2020;55:262–8.
- [27] Rains JC. Sleep and migraine: assessment and treatment of comorbid sleep disorders. *Headache* 2018;58:1074–91.
- [28] Robinson CM, Klenck SC, Norton PJ. Psychometric properties of the generalized anxiety disorder questionnaire for DSM-IV among four racial groups. *Cogn Behav Ther* 2010;39:251–61.
- [29] Rosenzweig S, Greeson JM, Reibel DK, Green JS, Jasser SA, Beasley D. Mindfulness-based stress reduction for chronic pain conditions: variation in treatment outcomes and role of home meditation practice. *J Psychosom Res* 2010;68:29–36.
- [30] Rusch HL, Rosario M, Levison LM, Olivera A, Livingston WS, Wu T, Gill JM. The effect of mindfulness meditation on sleep quality: a systematic review and meta-analysis of randomized controlled trials. *Ann N Y Acad Sci* 2019;1445:5–16.
- [31] Schmidt S, Grossman P, Schwarzer B, Jena S, Naumann J, Walach H. Treating fibromyalgia with mindfulness-based stress reduction: results from a 3-armed randomized controlled trial. *PAIN* 2011;152:361–9.
- [32] Seminowicz DA, Burrowes SAB, Kearson A, Zhang J, Krimmel SR, Samawi L, Furman AJ, Keaser ML, Gould NF, Magyari T, White L, Goloubeva O, Goyal M, Peterlin BL, Haythornthwaite JA. Enhanced mindfulness-based stress reduction in episodic migraine: a randomized clinical trial with magnetic resonance imaging outcomes. *PAIN* 2020;161:1837–46.
- [33] Seo JG, Park SP. Validation of the generalized anxiety disorder-7 (GAD-7) and GAD-2 in patients with migraine. *J Headache Pain* 2015;16:97–8.
- [34] Seo JG, Park SP. Validation of the patient health questionnaire-9 (PHQ-9) and PHQ-2 in patients with migraine. *J Headache Pain* 2015;16:65–2.
- [35] Serpa JG, Taylor SL, Tillisch K. Mindfulness-based stress reduction (MBSR) reduces anxiety, depression, and suicidal ideation in veterans. *Med Care* 2014;52(12 Suppl 5):19.
- [36] Sharpe L, Dudeney J, Williams ACC, Nicholas M, McPhee I, Baillie A, Welgampola M, McGuire B. Psychological therapies for the prevention of migraine in adults. *Cochrane Database Syst Rev* 2019;7:CD012295.
- [37] Simshäuser K, Lükking M, Kaube H, Schultz C, Schmidt S. Is mindfulness-based stress reduction a promising and feasible intervention for patients suffering from migraine? A randomized controlled pilot trial. *Complement Med Res* 2020;27:19–30.
- [38] Smelt AF, Louter MA, Kies DA, Blom JW, Terwindt GM, der Heijden GJ, De Gucht V, Ferrari MD, Assendelft WJJ. What do patients consider to be the most important outcomes for effectiveness studies on migraine treatment? results of a delphi study. *PLoS One* 2014;9:e98933.
- [39] Tiseo C, Vacca A, Felbush A, Filimonova T, Gai A, Glazyrina T, Hubalek IA, Marchenko Y, Overeem LH, Piroso S, Tkachev A, Martelletti P, Sacco S, European Headache Federation School of Advanced Studies (EHF-SAS). Migraine and sleep disorders: a systematic review. *J Headache Pain* 2020;21:126.
- [40] Torres-Ferrus M, Gallardo VJ, Alpuente A, Pozo-Rosich P. Influence of headache pain intensity and frequency on migraine-related disability in chronic migraine patients treated with OnabotulinumtoxinA. *J Headache Pain* 2020;21:88–8.
- [41] van der Velden AM, Kuyken W, Watter U, Crane C, Pallesen KJ, Dahlgaard Y, Fjorback LO, Piet J. A systematic review of mechanisms of change in mindfulness-based cognitive therapy in the treatment of recurrent major depressive disorder. *Clin Psychol Rev* 2015;37:26–39.
- [42] VanderWeele TJ. Mediation analysis: a practitioner's guide. *Annu Rev Public Health* 2016;37:17–32.
- [43] VanderWeele TJ, Vansteelandt S. Mediation analysis with multiple mediators. *Epidemiol Methods* 2014;2:95–115.
- [44] Veehof MM, Trompetter HR, Bohlmeijer ET, Schreurs KM. Acceptance- and mindfulness-based interventions for the treatment of chronic pain: a meta-analytic review. *Cogn Behav Ther* 2016;45:5–31.
- [45] Vgontzas A, Pavlović J M. Sleep disorders and migraine: review of literature and potential pathophysiology mechanisms. *Headache* 2018; 58:1030–9.
- [46] Wells RE, O'Connell N, Pierce CR, Estave P, Penzien DB, Loder E, Zeidan F, Houle TT. Effectiveness of mindfulness meditation vs headache education for adults with migraine: a randomized clinical trial. *JAMA Intern Med* 2021;181:317–28.
- [47] Wells RE, Seng EK, Edwards RR, Victorson DE, Pierce CR, Rosenberg L, Napadow V, Schuman-Olivier Z. Mindfulness in migraine: a narrative review. *Expert Rev Neurother* 2020;20:207–25.
- [48] Winbush NY, Gross CR, Kreitzer MJ. The effects of mindfulness-based stress reduction on sleep disturbance: a systematic review. *Explore (NY)* 2007;3:585–91.
- [49] Zebenholzer K, Lechner A, Broessner G, Lamp C, Luthringhausen G, Wuschitz A, Obmann SM, Berek K, Wöber C. Impact of depression and anxiety on burden and management of episodic and chronic headaches—a cross-sectional multicentre study in eight austrian headache centres. *J Headache Pain* 2016;17:15–3.