Behavioral Weight Loss Intervention for Migraine: A Randomized Controlled Trial

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Objective: The objective of this study was to test whether behavioral weight loss (BWL) intervention decreases headaches in women with comorbid migraine and overweight or obesity.

Methods: This randomized, single-blind trial allocated women 18 to 50 years old with 4 to 20 migraine days per month and a BMI = 25.0-49.9 kg/m² to 16 weeks of BWL (n = 54), which targeted exercise and eating behaviors for weight loss, or to migraine education control (ME, n = 56), which delivered didactic instruction on migraine and treatments. Participants completed a 4-week smartphone headache diary at baseline, posttreatment (16-20 wk), and follow-up (32-36 wk). The primary outcome was posttreatment change in migraine days per month, analyzed via linear mixed effects models.

Results: Of 110 participants randomly assigned, 85 (78%) and 80 (73%) completed posttreatment and follow-up. Although the BWL group achieved greater weight loss (mean [95% CI] in kilograms) than the ME group at posttreatment (−3.8 [−2.5 to −5.0] vs. +0.9 [−0.4 to 2.2], P < 0.001) and follow-up (−3.2 [−2.0 to −4.5] vs. +1.1 [−0.2 to 2.4], P < 0.001), there were no significant group (BWL vs. ME) differences (mean [95% CI]) in migraine days per month at posttreatment (−3.0 [−2.0 to −4.0] vs. −4.0 [−2.9 to −5.0], P = 0.185) or follow-up (−3.8 [−2.7 to −4.8] vs. −4.4 [−3.4 to −5.5], P = 0.378).

Conclusions: Contrary to hypotheses, BWL and ME yielded similar, sustained reductions in migraine headaches. Future research should evaluate whether adding BWL to standard pharmacological and/or nonpharmacological migraine treatment approaches yields greater benefits.

Introduction

Migraine is a neurological disease characterized by moderate-to-severe headache and accompanying autonomic, affective, and sensory features that affects 1 billion people worldwide (1-3). Migraine is also comorbid with several diseases, including obesity (4). As per current evidence, obesity contributes to increased migraine risk and severity, especially in reproductive-aged women (5,6). A recent meta-analysis comprising data from nearly 300,000 participants found that risk of migraine was increased by 27% in adults with obesity (7), whereas other studies showed that migraine headache frequency, severity, and clinical features increased with greater degree of overweight (8). These data are corroborated by overlapping physiological (e.g., inflammatory processes), psychological...
Given that obesity is a modifiable risk factor for migraine and weight loss has favorable effects on many of the putative mechanisms underlying the migraine-obesity link (9), the question of whether weight loss intervention holds efficacy for reducing migraine headache frequency is important (10). Yet few intervention studies have been conducted. Two studies showed reductions of approximately 1.5 to 3 migraine days per month after bariatric surgery (11,12). Another study in adolescents showed an average reduction of 3.1 migraine days per month after a 12-month behavioral weight loss (BWL) intervention (13). To date, only one randomized trial has been conducted (14). Findings showed differences in mean reduction of monthly migraine days in favor of bariatric surgery (10.9) compared with monthly BWL therapy (4.7), but only after controlling for weight loss and several demographic characteristics. Although findings from these studies are promising, all are limited by one or more of the following factors that undermine rigor and robust, clearly interpretable findings: uncontrolled design, retrospective headache measurement, unstandardized BWL intervention, and lack of an appropriate non–weight-loss-producing control condition.

The Women’s Health and Migraine study is the first randomized controlled trial (RCT) to test the impact of a standardized BWL intervention on migraine headache frequency (15). Women 18 to 50 years old with overweight or obesity (BMI = 25-49.9 kg/m²) who expressed interest in an intervention that used a smartphone diary for 28 days. Following the headache monitoring period, participants returned the smartphone equipped with a diary application to record headache activity for 28 days. The protocol was approved by The Miriam Hospital Institutional Review Board. All participants provided signed informed consent before enrollment.

Participants
Eligibility was limited to women 18 to 50 years old who had the following: migraine with or without aura as confirmed by the study neurologist and in accordance with International Classification of Headache Disorders 3 criteria (16), ≥ 3 migraine attacks and 4 to 20 migraine headache days during each of the past 3 months, and overweight or obesity (BMI = 25.0-49.9 kg/m²). Participants were permitted continued access to preventive and/or abortive pharmacological treatment if they were on a stable regimen for ≥ 2 months before study entry and agreed not to modify this regimen during the study. This also applied to medications used for depression and oral contraception.

Exclusion criteria included the following: headache disorder other than migraine or tension-type; previous bariatric surgery, current participation in a weight loss program, use of prescription weight loss medication, or ≥ 5% weight loss within ≤ 6 months; pregnancy, breastfeeding, or plans to become pregnant during the trial; contraindication for weight loss or unsupervised exercise; cancer diagnosis within ≤ 1 year; inability to read and/or comprehend study materials; and any condition that in the opinion of the investigators would undermine adherence to the study protocol (e.g., terminal illness, relocation outside of the geographic region of the research center, history of substance abuse, eating disorder diagnosis, or other severe psychiatric problem).

Randomization
Participants were randomly assigned to BWL or ME in a 1:1 ratio by using computer-generated randomly permuted blocks of two, four, and six. Condition assignment was not revealed to a participant and the research team until after a participant completed the baseline assessment.

Methods
Trial design
This study involved a 9-month, parallel-group, single-blinded RCT (ClinicalTrials.gov identifier NCT01197196) to compare the effects of BWL and ME interventions on migraine headache days. All procedures were conducted at a single site: the Weight Control and Diabetes Research Center (WCDRC) of The Miriam Hospital/Brown Alpert Medical School in Providence, Rhode Island. Participants were recruited from community and clinical settings via multiple methods (e.g., direct mailing of study brochures to the target demographic, newspaper advertisements, Internet/social media postings) between November 2012 and June 2016. Advertisements were targeted to women 18 to 50 years old who had migraine and obesity and sought instruction in behavioral headache management strategies. Women who contacted the WCDRC and were declared initially eligible after a telephone screening interview were invited to an in-person orientation during which the study objective (i.e., testing whether the BWL and ME interventions help alleviate migraine attacks) and procedures were explained in detail. Participants then completed informed consent, had migraine diagnosis confirmed by a study neurologist, underwent height and weight measurement, completed questionnaires, and received a smartphone equipped with a diary application to record headache activity for 28 days. Following the headache monitoring period, participants returned the smartphone to the WCDRC and received their treatment assignment. Identical procedures occurred at posttreatment (16-20 wk) and follow-up (32-36 wk). Outcomes assessors were blinded to intervention assignment. The protocol was approved by The Miriam Hospital Institutional Review Board. All participants provided signed informed consent before enrollment.

Interventions
BWL participants received a standardized intervention modeled after that used in the Diabetes Prevention Program and the Action for Health in Diabetes (Look AHEAD) trials (17,18). The structure consisted of 16 weekly group meetings led by a behavioral interventionist. The same three interventionists delivered both conditions to control for therapist effects. Participants were encouraged to lose 1 to 2 lb/wk toward a ≥ 7% weight loss goal. To achieve this goal, participants were (1) placed on a standard calorie- and fat-restricted diet, with goals of 1,200 to 1,500 kcal/d and 33 to 42 g/d of fat (25% calories from fat) (18); (2) gradually progressed to a goal of 250 min/wk of moderate-intensity, home-based exercise (50 minutes,
5 d/wk) (19); and (3) provided instruction in behavioral modification strategies such as self-monitoring (i.e., diet, exercise, weight), goal setting, stimulus control, and problem solving to modify eating and PA. BWL sessions did not include content on migraine or its treatment.

Education on migraine, pharmacological and nonpharmacological treatments, and self-management strategies is an integral component of the standard of care in headache medicine (20). Accordingly, ME participants attended 16 weeks of group lectures focused on migraine (e.g., symptoms, pathophysiology, risk factors for progression), pharmacological and nonpharmacological treatments (e.g., preventive medications, acupuncture), and evidence-based self-management strategies (e.g., cognitive restructuring, relaxation techniques, sleep hygiene). With respect to the latter, participants did not practice any strategies in group sessions, nor were they instructed to practice outside of sessions. Additionally, ME did not provide BWL-specific information or strategies to minimize potential of weight loss. The length of ME and amount of information presented exceeded that typically provided by standard care to achieve equivalent therapist contact between conditions (thereby minimizing differences in demand characteristics) and similar session attendance (15).

Treatment fidelity
To ensure reliable delivery of BWL and ME, several strategies were employed: the creation of detailed patient and therapist manuals that all clinical staff were required to read and review, weekly supervision sessions with clinical staff during initial implementation, and a combination of independent review and/or rating of intervention session audio recordings and therapist completion of weekly checklists to verify inclusion of designated intervention components and minimize intervention cross contamination.

Measures
Migraine headache frequency and severity. A Web-based headache diary application, designed by the investigative team for use on smartphones provided to each participant, was used to record migraine headache occurrence (“Did you have a headache today? Yes/No”), maximum headache pain intensity (0 “no pain” to 10 “pain as bad as you can imagine”), and attack duration (in hours) prior to bedtime for 28 consecutive days (15). This ecological momentary assessment approach counters limitations of retrospective questionnaires (e.g., bias, poor ecological validity) and paper-and-pencil diaries (inability to verify compliance) by collecting date-and-time-verified data, in near real time, in participants’ natural environment (21). All electronic ratings were automatically transmitted to the research center and checked daily to ensure data completeness. If data were incomplete, research staff contacted participants by telephone to obtain missing data. Data were summarized as headache frequency (primary outcome, number of migraine days per month), average maximum pain intensity, and duration in hours.

Headache disability. The Headache Impact Test 6 (HIT-6) was used to assess the severity of headache disability (22). This measure contains six items that measure headache impact on “usual daily activities,” with higher scores reflecting more severe impact. The HIT-6 demonstrates good internal consistency and can differentiate levels of migraine frequency and severity.

Anthropometric characteristics. Height (in centimeters) and weight (in kilograms) were measured by using a wall-mounted Harpenden stadiometer (Holtain Ltd., Crymlyn, UK) and a calibrated digital scale (Tanita BWB-800; Tanita Corporation of America, Inc., Arlington Heights, Illinois). BMI was calculated by using the following formula: BMI = (weight in kilograms)/height in meters squared. Waist circumference, as a measure of abdominal fat, was measured at the midpoint between the highest point of the iliac crest and lower part of the costal margin at the midaxillary line.

Demographic characteristics. Age, marital status, race and/or ethnicity, and level of education were assessed via questionnaire at baseline.

Medications. Information about medications taken to prevent migraine attacks and treat depression were collected via the “brown bag” method. Participants were given a bag to bring all prescription and over-the-counter medications to the research center to be documented.

Statistical analysis
Baseline demographic characteristics and headache parameters were summarized by using the mean, SD, and number with percentage. Rates of retention at posttreatment and follow-up were compared by using the χ² test. Linear mixed effects models incorporating a restricted maximum likelihood approach were used to estimate and conduct between-group comparisons of the primary outcome (change in headache days per month) and secondary outcomes (change in weight and indices of migraine severity) at posttreatment and follow-up. Time was represented in the model via a binary variable coded 0 for posttreatment and 1 for follow-up. Baseline values of the outcome were entered as a covariate. In the first step of analysis, unconditional models were used to evaluate variance components associated with intercepts (change in the outcome at posttreatment) and slopes (rate of change in the outcome from posttreatment to follow-up). In the second step of analysis, intercepts were treated as random effects; treatment condition was added to the model by using a variable coded 0 for ME and 1 for BWL and to interact with the effect of time; and age, race and/or ethnicity (non-Hispanic White vs. all others), level of education (at least some post-high school education vs. all others), and marital status (married vs. not married) were entered as covariates. This intent-to-treat approach allowed all available data to be included in the analysis. Tests of significance were two tailed with alpha = 0.05. This trial was designed to detect significant between-group differences of at least three migraine days per month with 0.80 power at posttreatment, with n = 140 and ≤ 18% attrition at posttreatment. All analyses were conducted in May 2017 by using SPSS Statistics version 20.0, IBM Corp. Armonk, New York).

Results
Recruitment and retention
The Consolidated Standards of Reporting Trials (CONSORT) diagram is depicted in Figure 1. Of 738 individuals screened by phone 110 were randomly assigned to BWL (n = 54) or ME (n = 56). Six participants (three in BWL and three in ME) were withdrawn after randomization because of family relocation (n = 1), personal or
family medical emergencies \((n = 3)\), and changes in work schedule that prevented further group attendance \((n = 2)\). Overall retention was 78\% \((n = 85)\) at posttreatment and 73\% \((n = 80)\) at follow-up, including participants who were withdrawn and whose data were included in the analysis up to the point of withdrawal. There were no significant differences in retention between the conditions at any assessment \((P > 0.50)\). Data missingness was not related to demographic characteristics, baseline headache frequency, or weight \((P > 0.10)\).

**Sample characteristics**

As shown in Table 1, participants on average were 39 years old and had obesity defined by BMI and waist circumference. One-quarter of participants identified as being a member of a racial minority group and 19\% reported having Hispanic ethnicity. Nearly all participants reported at least some post–high school education. At baseline, participants on average reported having a migraine headache on 8 of 28 days, an attack frequency that is higher than that reported by the majority \((\sim 85\%)\) of participants in population-based studies of individuals with migraine \((2,23)\). On average, these attacks produced moderate pain intensity and lasted 20 hours. Participants reported a HIT-6 score of 65, indicative of “severe” headache disability. Twelve \((9.2\%)\) participants had chronic migraine \((\geq 15\) migraine days per month). Taken together, these data indicate that the majority of the sample consisted of individuals with higher-frequency and disabling episodic migraine.

**Intervention adherence and weight loss**

BWL had a significantly greater mean weight loss \((\text{in kilograms})\) versus ME at both posttreatment \((-3.8, 95\% \text{ CI: } -2.5 \text{ to } -5.0 \text{ vs. } +0.9, 95\% \text{ CI: } -0.4 \text{ to } 0.2, P = 0.001)\) and follow-up \((-3.2, 95\% \text{ CI: } -2.0 \text{ to } -1.4 \text{ vs. } +1.1, 95\% \text{ CI: } -0.2 \text{ to } 2.4, P < 0.001)\). The mean number (SD)/percentage of weekly intervention sessions attended was similar between conditions \((\text{BWL vs. ME: } 13.3 [5.1]/83\% \text{ vs. } 12.8 [5.4]/80\%; P = 0.61)\).

**Primary outcome: change in migraine headache days**

Results of intention-to-treat analysis (Figure 2) showed that mean reductions in monthly migraine days did not differ between
conditions (BWL vs. ME) at the primary posttreatment end point (−3.0, 95% CI: −2.0 to 4.0 vs. −4.0, 95% CI: −2.9 to −5.0, P = 0.19) or follow-up (−3.8, 95% CI: −2.7 to −4.8 vs. −4.4, 95% CI: −3.4 to −5.5, P = 0.38).

**Discussion**

This study is the first to test whether a standardized behavioral intervention to reduce body weight decreases migraine headache frequency in women with comorbid overweight or obesity. Contrary to the primary hypothesis, changes in migraine headache frequency at posttreatment and follow-up were not significantly different between the BWL and ME control interventions. Rather, both BWL and ME had significant reductions in monthly migraine headache days from baseline to posttreatment and follow-up, but the improvements were comparable in the two conditions. A similar pattern of findings occurred for indices of migraine severity.

Although the BWL group lost more weight compared with the ME group, which gained weight on average, there is no evidence that this greater weight loss led to greater migraine improvements. This might owe to mean BWL weight change (−3.8 kg or 3.3% weight loss) being suboptimal (i.e., falling below the clinically relevant 5% [−5 kg] threshold) (24). It is possible that migraine and its psychological and behavioral sequelae might interfere with the ability to lose weight or adhere to behavioral prescriptions (25-28).

**Additional outcomes: change in migraine severity**

Results of intention-to-treat analysis showed that mean reductions in migraine pain intensity and attack duration (in hours) over the 28-day monitoring period did not differ between conditions (BWL vs. ME) at the primary posttreatment end point (pain intensity: −0.8, 95% CI: 0.0 to −1.5 vs. −1.0, 95% CI: −0.3 to −1.8, P = 0.59; attack duration: −1.6, 95% CI: −3.1 to −6.3 vs. −5.0, 95% CI: −0.3 to −9.6, P = 0.33) or follow-up (pain intensity: −1.5, 95% CI: −0.7 to −2.3 vs. −0.7, 95% CI: 0.1 to −1.5, P = 0.15; attack duration: −2.7, 95% CI: −2.2 to −7.5 vs. −2.2, 95% CI: −2.7 to −7.1, P = 0.89). Similarly, the groups (BWL vs. ME) did not differ on mean reductions in HIT-6 scores at posttreatment (−5.4, 95% CI: −3.7 to −7.1 vs. −4.4, 95% CI: −2.8 to −6.1, P = 0.44) or follow-up (−5.7, 95% CI: −3.9 to −7.4 vs. −5.6, 95% CI: −3.9 to −7.3, P = 0.94).

**TABLE 1 Participant characteristics at baseline**

| Demographic characteristics | Total (n = 110) | BWL (n = 54) | ME (n = 56) |
|-----------------------------|----------------|-------------|-------------|
| Age, mean (SD), y           | 39.3 (8.0)     | 38.5 (7.4)  | 40.0 (8.4)  |
| Race, n (%)                 |                |             |             |
| White                       | 86 (78.2)      | 37 (68.5)   | 49 (87.5)   |
| African American            | 12 (10.9)      | 10 (18.5)   | 2 (3.6)     |
| Other                       | 9 (8.2)        | 5 (9.3)     | 4 (7.1)     |
| Mixed                       | 3 (2.7)        | 2 (3.7)     | 1 (1.8)     |
| Ethnicity, n (%)            |                |             |             |
| Non-Hispanic                | 89 (80.9)      | 49 (90.7)   | 40 (71.4)   |
| Hispanic                    | 21 (19.1)      | 5 (9.3)     | 16 (28.6)   |
| Education, n (%)            |                |             |             |
| High school degree          | 11 (10.0)      | 6 (11.1)    | 5 (8.9)     |
| Vocational training         | 1 (0.9)        | 1 (1.9)     | 0 (0.0)     |
| Some college                | 34 (30.9)      | 15 (27.8)   | 19 (33.9)   |
| College/university degree   | 41 (37.3)      | 22 (40.7)   | 19 (33.9)   |
| Graduate/professional degree| 23 (20.9)      | 10 (18.5)   | 13 (23.2)   |
| Marital status, n (%)       |                |             |             |
| Married                     | 63 (57.3)      | 29 (53.7)   | 34 (60.7)   |
| Not married (cohabitating)  | 8 (7.3)        | 6 (11.1)    | 2 (3.6)     |
| Never married               | 26 (23.6)      | 15 (27.8)   | 11 (19.6)   |
| Separated or divorced       | 11 (10.0)      | 4 (7.4)     | 7 (12.5)    |
| Other                       | 2 (1.8)        | 0 (0.0)     | 2 (3.6)     |
| Anthropometric characteristics|               |             |             |
| BMI, mean (SD), kg/m²       | 35.6 (7.7)     | 35.8 (6.8)  | 35.4 (8.6)  |
| Waist circumference, mean (SD), cm | 105.2 (15.6) | 106.5 (15.5) | 103.8 (15.8) |
| Migraine headache characteristics|          |             |             |
| Headaches, mean (SD), n     | 5.4 (2.8)      | 5.3 (2.8)   | 5.5 (2.7)   |
| Headache days, mean (SD), n | 8.2 (4.5)      | 7.9 (4.0)   | 8.6 (4.8)   |
| Pain intensity, mean (SD), 0-10 scale | 5.7 (1.6) | 5.6 (1.5) | 5.8 (1.5) |
| Headache duration, mean (SD), h | 19.9 (15.9) | 19.9 (17.5) | 19.8 (14.4) |
| Headache impact (HIT-6), mean total (SD) | 64.7 (4.5) | 65.4 (4.6) | 63.9 (4.2) |
| Use of preventive medications, n (%) | 22 (20) | 11 (20.4) | 11 (19.6) |
intensity, regardless of pain type, is associated with poorer weight loss outcomes after BWL intervention (29). High-calorie, palatable foods might aid in pain coping, possibly undermining adherence to dietary prescriptions focused on energy intake and dietary quality (25,30,31). Migraine attacks might also reduce available time to engage in PA or contribute to avoidance of PA in general (32,33). Research to understand barriers to BWL treatment in patients with migraine is needed.

However, speculation that larger weight losses after BWL might have produced superior migraine improvements compared with ME is tempered when results are placed in the context of previous uncontrolled studies examining the association of weight loss and migraine improvements. For example, this investigative team has previously reported a comparatively smaller mean reduction of 1.5 migraine days per month after substantially larger mean weight losses (30.2 kg) achieved via bariatric surgery (11). Another study has reported a mean reduction of 3.1 migraine days per month (similar to the current study) in adolescents after a 12-month BWL intervention and a mean weight loss of 7 kg (13). These findings showing migraine improvements of similar or lesser magnitude after weight losses that are larger than those achieved after the BWL intervention in the current study suggest that additional mechanisms related to or apart from weight loss might also underlie BWL-related improvements.

Moreover, the fact that significant migraine improvements of a similar magnitude occurred after BWL and ME suggests that these treatments may operate through different mechanisms. Notably, special precautions were taken to ensure that migraine was not discussed during BWL and that BWL strategies were not discussed during ME. It is conceivable that BWL effects are mediated through both weight loss and related improvements in proposed physiological (e.g., inflammation), psychological (e.g., depression), and behavioral (e.g., PA) factors underlying the migraine-obesity link (9,34,35). By contrast, ME effects might be mediated by increased knowledge of migraine (i.e., causes, triggers, treatments) and related improvements in factors such as headache management self-efficacy (36). Both BWL and ME might be mediated by increased perceptions of emotional social support resulting from engagement with a group of individuals who all experience the adverse impact of migraine on daily life (37). However, it is unlikely that all of the effect can be attributed to group dynamics, given that patients who lose weight via bariatric surgery also experience reduction in migraine (9,12,14). Finally, although a significant study strength was comparison of BWL with an equally intensive ME condition, the lack of a nonintervention control group limits the ability to rule out other explanations for migraine improvements after BWL or ME, such as repeated assessments over time and regression to the mean. Given potential mechanistic differences between BWL and ME, future research should examine whether integration of these interventions produces greater migraine improvements than either intervention alone and/or no intervention.

This study involves the first RCT to test the immediate and sustained effects of BWL as a treatment for migraine in women of reproductive age, who are considered most affected by obesity-related migraine risk (5,6,38). Moreover, the inclusion of additional procedures to enhance rigor and minimize bias (e.g., near real-time, naturalistic, daily headache assessments, strategies to optimize protocol adherence and limit therapist effects) advances previous uncontrolled investigations of weight loss treatments for migraine.

This study also has certain limitations. Study participants reflect a highly selective sample. Given that the study was limited to women with migraine of a certain age who met strict headache and weight-related inclusion criteria, it is unclear whether similar outcomes would be observed in individuals who are male, are older, and have different headache frequencies or weight status. Despite substantial efforts to recruit and randomly assign the planned 140 participants, the study was terminated at the end of the funding period, with 110 participants randomly assigned, potentially limiting power to detect smaller effects as statistically significant. Although efforts were made to ensure that the BWL intervention did not address migraine, the possibility of expectancy effects regarding migraine improvements cannot be ruled out, given BWL participants’ awareness that the study was intended to test the effects of BWL on migraine frequency and severity. Finally, given previous research that has shown a relationship between obesity and risk of having migraine, studies are also needed to determine whether behavioral intervention can prevent migraine by preventing weight gain and sustaining a healthy weight (39).

**Conclusion**

This study compared the effects of BWL and ME on headache frequency in women aged 18 to 50 with comorbid migraine and overweight or obesity. Significant improvements in migraine frequency were demonstrated after both BWL and ME and sustained at follow-up, but no differences between these conditions were observed at either time point. Future research is needed to better understand treatment...
mechanisms and whether BWL can enhance the effects of standard pharmacological and/or nonpharmacological migraine therapies in patients with comorbid overweight or obesity.

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