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Treatment Effects on Pain Catastrophizing and Cutaneous Allodynia Symptoms in Women with Migraine and Overweight/Obesity

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Abstract

Objective: Pain catastrophizing and cutaneous allodynia represent two risk factors for greater headache-related disability. Yet, there is limited knowledge of the extent to which these risk factors are modifiable and whether non-pharmacological treatment-related changes are associated with migraine improvements. Using data from the Women's Health and Migraine (WHAM), a randomized controlled trial that compared effects of behavioral weight loss (BWL) and migraine education (ME) in women with migraine and overweight/obesity, we tested whether: (a) BWL v ME produced greater changes in pain catastrophizing and allodynia from baseline across post-treatment and follow-up time points and (b) whether these improvements were associated with improvements in headache disability.

Methods: Women (n = 110) were randomly assigned to 16 weeks of either BWL or ME and assessed at baseline, post-treatment, and follow-up (32 weeks). Multilevel mixed effects modeling tested: (a) for between-group differences in pain catastrophizing and allodynia changes over time, and (b) associations of changes in pain catastrophizing and allodynia with changes in headache disability, adjusting for migraine severity and weight loss.

Results: Both BWL and ME had significant reductions in pain catastrophizing and allodynia from baseline to post-treatment and follow-up, and the improvements were comparable across conditions. Reductions in pain catastrophizing and cutaneous allodynia were associated with

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significant reductions in headache disability, even when controlling for intervention-related improvements in migraine and weight loss.

Conclusions: Pain catastrophizing and allodynia are not only reduced after non-pharmacologic treatments for migraine, but greater improvements are associated with greater reductions in headache-related disability, independent of migraine severity.

Keywords

migraine; cognitive behavioral therapy; refractory pain; fear of pain; hyperalgesia; treatment outcome

Introduction

Heightened sensitivity to pain and related stimuli is a core mechanism implicated in migraine (Aguggia, Saracco, Cavallini, Bussone, & Cortelli, 2013; Russo et al., 2018; Schwedt, 2013). Pain sensitivity is likely influenced by various mechanisms, including neural factors (e.g., structural and functional abnormalities related to pain processing), biased cognitive processing (e.g., attentional bias, pain expectancies), physiological alterations (e.g., due to stress, sleep dysfunction), central nervous system dysfunction (e.g., diminished endogenous inhibition of pain), and HPA activation or inflammatory processes (Hubbard et al., 2014; Quartana, Cambell, & Edwards, 2009; Sullivan et al., 2001). Pain catastrophizing (i.e., heightened cognitive and affective response to pain; (Sullivan, Bishop, & Pivik, 1995; Sullivan et al., 2001) and cutaneous allodynia (i.e., hypersensitivity to non-noxious skin stimulation; (Lipton et al., 2008) are two factors related to pain sensitivity and amplification in migraine (Bond et al., 2015). Examination of these two constructs simultaneously provides a novel opportunity to characterize pain sensitivity in migraine from a bio-psychological perspective, by considering: (a) cognitive-affective vulnerability to pain sensitivity (i.e., pain catastrophizing) and (b) physiological vulnerability to pain sensitivity (i.e., cutaneous allodynia); both of which have been independently associated with greater migraine severity and disability as well as poorer treatment outcomes. Indeed, an integrative theoretical model of migraine progression (Buse, Greisman, Baigi, & Lipton, 2019) posits that psychological factors related to pain catastrophizing (e.g., anxiety) and comorbidities (e.g., obesity) contribute to heightened pain sensitization in migraine and that allodynia is a manifestation of this sensitization.

Pain catastrophizing is characterized by anxious cognitive and emotional response to pain, including persistent pain-related thoughts, exaggerated worry about pain consequences, and perceived helplessness in response to pain (Sullivan et al., 1995, 2001) and is an amplifier of the subjective pain experience (Sullivan, Thorn, Rodgers, & Ward, 2004). Indeed, pain catastrophizing is posited to be a risk marker for adverse pain-related outcomes, including pain severity, pain-related disability, psychological distress, healthcare utilization, and pain medication use (Quartana et al., 2009). In migraine, clinical pain catastrophizing is common in approximately 25% of individuals with migraine (Bond et al., 2015) and is associated with more severe migraine attacks, migraine chronification, and disability (Bond et al., 2015; Drahovzal, Stewart, & Sullivan, 2006; Galioto et al., 2017; Holroyd, Drew, Cottrell, Romanek, & Heh, 2007; Thomas et al., 2016).

Cutaneous allodynia is defined as the perception of pain in response to typically innocuous stimuli to the skin, such as heat, cold, or pressure (Lipton et al., 2008), and is a marker for central sensitization and increased activation of trigeminal nociceptive neural pathways (Burstein, Yarnitsky, Goor-Aryeh, Ransil, & Bajwa, 2000). Allodynia is estimated to occur in 40%-70% of individuals with migraine during attacks (Bigal et al., 2008; Dodick et al., 2019; Kalita, Yadav, & Misra, 2009; Landy, McGinnis, & McDonald, 2007; Lipton et al., 2008; Louter et al., 2013) and is associated with more severe migraine and disability (Bigal et al., 2008; Lipton et al., 2008; Thomas et al., 2016), poor treatment response to pharmacotherapy (Burstein, Collins, & Jakubowski, 2004; Burstein et al., 2000; Kalita et al., 2009; Lipton et al., 2017, 2016) and migraine chronification (Louter et al., 2013). Indeed, multiple studies have demonstrated that allodynia indicative of refractory migraine, which is resistant to acute treatment with triptans - the most common pharmacological intervention (Dodick & Silberstein, 2006; Latremoliere & Woolf, 2009; Oshinsky, 2006). Since the efficacy of migraine treatment depends on its ability to prevent or abort central sensitization (Dodick & Silberstein, 2006), behavioral innervations, though not yet studied, could aid in attenuation of allodynia.

Based on the above, there is strong clinical and theoretical rationale to examine how pain sensitization indices (pain catastrophizing, allodynia) operate over time and respond to non-pharmacological treatment (Buse et al., 2019). Behavioral approaches to migraine treatment produce moderate reductions in migraine severity, which are roughly equal in efficacy to pharmacological treatments (Holroyd & Drew, 2006); however, there is limited understanding of how these migraine risk factors change in response to behavioral treatment. There is at least some evidence that cognitive behavioral treatments for migraine, both those that explicitly target pain catastrophizing (Thorn et al., 2007) and those that do not (Bromberg et al., 2012; Seng & Holroyd, 2014), produce significant reductions in pain catastrophizing compared to control conditions, and subsequent improvements in migraine-related disability (Seng & Holroyd, 2014).

To extend this line of inquiry, post-hoc analyses were conducted on data from the Women's Health and Migraine (WHAM) study, a randomized controlled trial that compared effects of behavioral weight loss (BWL) treatment and migraine education (ME) in women with migraine and overweight/obesity (Bond et al., 2018). Previous examination of the relationships among migraine characteristics, allodynia, and pain catastrophizing among treatment-seeking women who have migraine and obesity showed that higher pain catastrophizing is associated with more severe allodynia (Bond et al., 2015) and that both pain catastrophizing and allodynia moderate the relationship between migraine pain intensity and headache disability (Thomas et al., 2016). Given these cross-sectional associations and theoretical relevance (Buse et al., 2019), the current study sought to understand whether reductions in pain catastrophizing and allodynia during migraine treatment were related to improvements in headache disability -- the most important outcome, beyond headache frequency and pain intensity, to capture the impact of migraine. Results from the WHAM trial showed that BWL and ME produced similar reductions in migraine outcomes (frequency, intensity) after treatment that were maintained at follow-up (Bond et al., 2018). Although BWL and ME produced comparable migraine outcomes, it is possible that BWL's targeting of behavior change and self-regulation may aid in

attenuation of pain hypersensitivity. Given this, the present study aimed to test whether (a) BWL versus ME produced greater changes in pain sensitivity (i.e., pain catastrophizing and allodynia) from baseline across post-treatment and follow-up time points and (b) whether these improvements were associated with improvements in headache-related disability; after adjusting for migraine characteristics and weight loss.

Method

Participants

Participants (N = 110) were 18–50 year old women with both migraine (including ≥ 3 migraine headache attacks and 4–20 migraine headache days during each of the past three months) and overweight/obesity. Participants were enrolled in the Women's Health and Migraine (WHAM) randomized trial at the Weight Control and Diabetes Research Center (WCDRC) of The Miriam Hospital. Detailed inclusion and exclusion criteria were previously reported (Bond et al., 2013, 2018). Of note, 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 psychotropic medications and oral contraception.

Measures

Headache Characteristics.—A smartphone-delivered headache diary was used daily prior to bedtime during a 28-day baseline period to self-report presence of headaches (*yes*/*no*), maximum intensity of pain (0 = *no pain* to 10 = *pain as bad as you can imagine*), and duration of migraine attack.(Bond et al., 2013)

Anthropometric Measurement.—Height was measured in millimeters using a wall-mounted Harpenden stadiometer (Holtain Ltd., Crosswell, Crymyh, Pembs, UK). Weight was measured in light street clothing, without shoes, and to the nearest 0.1 kg using a calibrated digital scale (Tanita BWB 800; Tanita Corporation of America, Inc., Arlington Heights, IL, USA). BMI was calculated from these measures using the formula: BMI (kg/m^2) = weight(kg) / (height[m])^2.

Headache Disability.—The Headache Impact Test-6 (HIT-6) (Kosinski et al., 2003) a validated global measure of adverse headache impact, was used to assess severity of headache pain and migraine impact on daily functioning and psychological distress. The HIT-6 is an ideal measure of disability in these analyses because it encompasses a wide spectrum of factors contributing to the burden of headache (i.e. vitality, cognitive functioning, and psychological distress) that are directly relevant to the focus on pain catastrophizing and allodynia. Additionally, the HIT-6 appears to be influenced more by headache intensity than headache frequency; this is relevant given that the relationship between pain catastrophizing and headache disability is mediated by pain intensity (Nasiri, Pakdaman, Dehghani, & Togha, 2017). Respondents answer according to how frequently each item applies to them (*never* = 6 points, *always* = 12 points), and points for all 6 items are summed. Scores on the HIT-6 range from 36 to 78 and are divided into 4 categories with higher scores indicating greater impact on daily life and functional ability (49 or less =

little or no impact, 50–55 = some impact, 56–59 = substantial impact, 60 or greater = very severe impact). The HIT-6 has good reliability and internal consistency and demonstrates discriminant validity for levels of migraine frequency and severity (Shin, Park, Kim, & Lee, 2008; Yang, Rendas-Baum, Varon, & Kosinski, 2011).

Pain Catastrophizing.—The Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995) is a well-validated 13-item self-report assessment of catastrophic thinking in relation to pain experience, including pain rumination ("*I can't stop thinking about how much it hurts*"), magnification ("*I worry that something serious may happen*"), and helplessness ("*It's awful and I feel that it overwhelms me*"). Respondents rate the extent to which they have experienced various thoughts and emotions in response to pain on a scale from 0 (*not at all*) to 4 (*all the time*), and responses are summed to create a total score (possible range 0–52). The PCS items have good internal consistency and concurrent and discriminant validity (Osman et al., 1997; Sullivan et al., 1995).

Cutaneous Allodynia.—The Allodynia Symptom Checklist (ASC-12) (Lipton et al., 2008) is a validated self-report assessment used to evaluate the frequency of various allodynia symptoms in association with migraine headache attacks: "How often do you experience increased pain or an unpleasant sensation on your skin during your most severe type of headache when you engage in the following?" in reference to twelve non-noxious stimuli (e.g., *wearing a ponytail*, *shaving the face*). Scores on the ASC-12 range from 0 to 24 and indicate the respondent's level of cutaneous allodynia: none (0–2), mild (3–5), moderate (6–8), or severe (9 or greater). Items have good internal consistency and the measure has been validated for use in individuals with migraine (Jakubowski, Silberstein, Ashkenazi, & Burstein, 2005; Lipton et al., 2008). Measure concurrence with "gold standard" quantitative sensory testing (QST) has been established, with the self-report questionnaire correctly labeling more than three-fourths of participants whose allodynia status was confirmed by QST (Jakubowski et al., 2005). Moreover, the prevalence of allodynia per the ASC-12 in a large migraine population sample ($n > 11{,}000$) was highly consistent with prevalence rates previously clinically detected by QST (Lipton et al., 2008). Because of its demonstrated utility for predicting differential response to pharmacological treatment, as well as superior feasibility for clinical use, self-report of allodynia, rather than QST, has been recommended for broad use (Landy et al., 2007; Mathew, Kailasam, & Seifert, 2004).

Procedures

Women who responded to advertisements were initially screened by phone. Eligibility was confirmed at an orientation visit which included informed consent, examination by a neurologist to confirm diagnosis of migraine, objective measurement of height and weight, completion of study questionnaires, and receipt of a smartphone with a headache diary application to record headache characteristics. After the baseline headache monitoring period, participants returned to the clinic and were randomly assigned to 16 weeks of either Behavioral Weight Loss (BWL, $n = 54$) or Migraine Education (ME, $n = 56$). BWL involved a standard fat-and calorie-restricted diet, weekly home-based exercise goals, and behavior modification strategies such as self-monitoring, problem solving, and stimulus control in service of changes to eating and physical activity habits. ME included time-matched lectures

about migraine symptoms, risk factors, pathophysiology, treatments, and evidence-based self-management strategies. Both conditions were delivered by the same interventionists to control for therapist effects, but special care was taken to prevent content cross-over, such that weight loss benefits and skills were not discussed in ME, and content on migraine and its management was not provided to BWL participants. Measures of headache disability, pain catastrophizing and cutaneous allodynia were administered at baseline, post-treatment, and 6-months post-treatment. As previously reported,(Bond et al., 2018) overall retention was 78% (n = 85) at post-treatment and 73% (n = 80) at follow-up. This study is a post hoc analysis of data from the WHAM randomized trial, which was approved by the Miriam Hospital Institutional Review Board.

Statistical analysis

Analyses were conducted using IBM SPSS Statistics v25. Descriptive statistics were used to characterize the sample in terms of anthropometrics, headache characteristics, pain catastrophizing and allodynia. Pearson's correlations were used to evaluate bivariate associations between pain catastrophizing and allodynia in relationship to headache characteristics. Linear and nonlinear mixed modeling methods were used to examine (a) the effect of treatment condition on changes in pain catastrophizing and allodynia and (b) whether changes in pain catastrophizing and allodynia were associated with improvements in headache-related disability.

Model Building—In the first set of analyses, change in pain catastrophizing and allodynia were modeled as the dependent variables. Initial unconditional models were used to determine whether a linear or nonlinear trend best fit the longitudinal trajectory of the outcomes, and to evaluate the variance components associated with the slope of time to determine assignment as fixed versus random effects. Quadratic time was a better fit for both pain catastrophizing and allodynia. Intercepts and slopes were treated as random effects in all models. Then, treatment condition was added to the model as the independent variable, in addition to the condition x time to account for variability in the trajectory of outcomes. Model covariates included demographic characteristics (age, non-Hispanic status [no/yes]), pre-treatment factors (BMI, headache-related disability, migraine severity [migraine days, duration, average pain severity]), and pre-treatment value of the outcome variable. Pre-treatment anxiety and depression were also controlled for given the known effects of psychological distress on migraine outcomes. Treatment-related changes in migraine severity were also controlled for isolate the treatment effects on changes in pain catastrophizing and allodynia, beyond improvement in migraine severity. Estimated marginal means for change in pain catastrophizing and allodynia by treatment condition were examined at both post-treatment and follow-up.

In the second set of analyses, changes in headache disability was modeled as the dependent variable. Linear time was the best fit. Change in pain catastrophizing and allodynia were the independent variables, and model covariates included the abovementioned demographic characteristics, pre-treatment BMI, treatment-related changes in BMI and migraine severity, and pre-treatment value of the outcome variable. Treatment condition was also included as a model covariate; the interaction term of treatment condition x time was removed from the

model due to the fact that there were no differences between treatment groups on changes in pain catastrophizing and allodynia. For all analyses, model covariates were selected based on their theoretical relevance to migraine pain sensitivity and/or to reflect the most conservative approach to testing incremental effects of pain catastrophizing and allodynia on migraine-related disability while controlling for pre-treatment levels of the outcome variable as well as treatment target outcomes of interest (BMI, weight loss, migraine severity). The bivariate correlations between predictors were all r's < .50, ruling out issues of multicollinearity. Full information maximum likelihood was used, by making use of all available data from all randomized participants. All significance tests were two-tailed, with alpha set to .05.

Results

Sample characteristics at baseline are presented in Table 1. Pain catastrophizing and allodynia were significantly correlated at pre-treatment (r = .24, p = .010). Pre-treatment pain catastrophizing was significantly correlated with average attack duration (r = .29, p = .002) and headache disability (r = .30, p = .002) but not migraine days or pain severity. Pre-treatment allodynia was significantly correlated with more frequent migraine days (r = .24, p = .011) and headache disability (r = .34, p < .001).

Between-Group Change in Pain Catastrophizing and Allodynia

Results of the intent-to-treat mixed effects models for changes in pain catastrophizing and allodynia are presented in Tables 2 and 3, respectively. For pain catastrophizing, there were significant effects of linear time (coefficient = −14.07, p < .001) and quadratic time (coefficient = 5.09, p < .001), indicating significant initial reductions in pain catastrophizing followed by slight increases during follow-up. Means±SD on the PCS were as follows: baseline (21.44±10.21), post-treatment (13.06±7.941), and follow-up (13.72±7.79), which corresponded to a mean change of 8.4 points (CI95% = 6.2–10.6 points; Cohen's d = 0.92, p < .001) from baseline to post-treatment, and a mean change of 7.7 points (CI95% = 5.6–9.8 points; Cohen's d = 0.85, p < .001) from baseline to follow-up. The mean change from post-treatment to follow-up was non-significant (Cohen's d = .08, p = .480). Model results indicated that BWL and ME groups did not differ in (adjusted) means in pain catastrophizing at post-treatment (12.02 vs. 13.46, respectively; p = .332) or follow-up (13.21 vs. 14.31, respectively; p = .570).

For allodynia, there were significant effects of linear time (coefficient = −2.15, p < .001) and quadratic time (coefficient = 0.82, p = .003), indicating significant initial reductions in pain catastrophizing followed by slight increases during follow-up. Means±SD on the ASC were as follows: baseline (4.73±3.85), post-treatment (3.02±3.20), and follow-up (3.51±3.66), which corresponded to a mean change of 1.71 points (CI95% = 0.96–2.46 points; Cohen's d = 0.48, p < .001) from baseline to post-treatment, and a mean change of 1.23 points ($CI_{95\%}$ = 0.37–2.10 points; Cohen's d = 0.33, p = .010) from baseline to follow-up. The mean change from post-treatment to follow-up was non-significant (Cohen's d = .14, p = .120). Model result indicated that BWL and ME groups did not differ in (adjusted) means in

allodynia at post-treatment (3.23 vs. 2.90, respectively; $p = .558$) or follow-up (3.49 vs. 3.70, respectively; $p = .816$).

Association Between Change in Pain Catastrophizing and Allodynia with Change in Headache Disability

Model results are presented in Table 4. When controlling for baseline levels and change in migraine characteristics, change in pain catastrophizing was significantly associated with change in headache disability (coefficient = 0.18, $p = .001$). Additionally, change in allodynia was significantly associated with change in headache disability (coefficient = 0.50, $p < .001$).

Discussion

This is the first study to concurrently evaluate changes in two bio-psychological factors related to pain sensitivity, pain catastrophizing and allodynia, and associated changes in headache disability following behavioral migraine treatment. Findings provide novel evidence that greater reductions in pain catastrophizing and cutaneous allodynia after behavioral interventions are associated with greater reductions in headache-related disability, independent of migraine severity. This suggests that bio-psychological processes of pain sensitivity are malleable risk factors that are uniquely linked (even after controlling for treatment-related improvements in migraine severity) to adaptive functioning in women with both migraine and obesity--who commonly present with pain catastrophizing and cutaneous allodynia (Bond et al., 2015). Moreover, this study advances our previous research indicating that pain catastrophizing and allodynia were pre-treatment factors associated with more severe migraine and disability (Bond et al., 2015) by showing these risk factors improve after migraine treatment.

Of note, reductions in pain catastrophizing and cutaneous allodynia were observed following two different *non-pharmacologic* treatments for migraine –neither of which explicitly targeted pain sensitivity. This set of findings is consistent with prior evidence that cognitive behavioral interventions for migraine provided improvements in pain catastrophizing despite not directly targeting pain catastrophizing (Bromberg et al., 2012; Seng & Holroyd, 2014). Moreover, there is evidence that pain catastrophizing is malleable through various treatments, including physical therapy and multidisciplinary treatments in other pain conditions (Quartana et al., 2009). Notably, the size of observed treatment effects in the current trial (i.e., approximately 8 point change on the PCS) appeared to be slightly larger than those observed in a cognitive-behavioral intervention that was designed to specifically target pain catastrophizing in patients with chronic headache (i.e., roughly 6.5 point change in the PCS) (Thorn et al., 2007); though patients in that study had migraine and/or tension-type headache and averaged lower PCS scores compared to the current migraine-specific sample. Particularly notable is novel evidence of malleability in the severity of cutaneous allodynia after behavioral intervention, given that allodynia is implicated in chronification of migraine (Louter et al., 2013) and risk of poor response to migraine pharmacotherapy (Lipton et al., 2017). Given the call to make further exploration of allodynia prevention and treatment a priority in migraine research (Oshinsky, 2006), these findings are especially

noteworthy. Although the mechanisms of the observed treatment effects are unknown and the near equal improvements for participants in the control condition were unanticipated, it is possible that engagement in migraine treatment, generally, can aid in the reduction of pain sensitivity, perhaps as a function of improved self-efficacy for coping, improved disease knowledge, or social-emotional factors related to the group therapy setting (e.g., sense of support, universality of suffering). The observed effects are likely not due simply to improvement in migraine severity given statistical controls. Moreover, pharmacotherapy effects can likely be ruled out as a mechanism of change given the tightly controlled rules of pharmacotherapy in this trial. Additional research is needed to determine whether interventions that specifically target these variables confer even greater reductions in migraine burden.

This study provides novel evidence of decreases in neuro-psychological aspects of pain sensitivity resulting from migraine intervention, and subsequent improvements in headache-related disability. Strengths of this study include prospective design and measurement of migraine characteristics, and large sample size that was powered to detect significant changes in migraine outcomes. However, the current findings are limited in in several ways. First, the headache disability and relevant pain sensitivity outcomes were all self-reported. Second, the generalizability of the findings may be limited given that the sample was comprised exclusively of premenopausal, predominately white females, with overweight/obesity, who were treatment-seeking; although higher levels of both pain catastrophizing and allodynia have been documented in females compared to males (Dodick et al., 2019; Edwards, Haythornthwaite, Sullivan, & Fillingim, 2004), thus these pain sensitivity factors may be particularly relevant to females with migraine. Finally, selection bias may have impacted clinical outcomes, given that a pre-treatment headache monitoring prior was required prior to treatment initiation; though this type of assessment design is consistently utilized in headache clinical trials.

Although targeted study of specific sub-populations is merited in order to explore potential mechanisms for heterogeneity in treatment outcomes, further research characterizing bio-psychological facets of pain sensitivity in diverse patients with migraine is warranted to test the generalizability of these findings that behavioral interventions seem to be beneficial for reducing pain catastrophizing and allodynia in migraine.

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Table 1.

Study variables at baseline

Variable	Baseline
Age (years)	39.25 (7.95)
Race/Ethnicity	89 (80.9%) Non-Hispanic White
Headache disability (HIT-6)	64.65 (4.46)
Pain catastrophizing (PCS)	21.44 (10.21)
Allodynia Symptoms (ASC)	4.72 (3.85)
BMI	35.17 (6.66)
MI Days	8.22 (4.46)
MI Duration (hours)	19.87 (15.93)
MI Pain severity (0–10)	5.72 (1.58)

Table 2.

Multilevel model for changes in pain catastrophizing from pre-treatment across post-treatment and follow-up.

Variable	Estimate	SE	t	p
Intercept	10.03	1.48	6.77	<.0001
Linear Time	−14.07	2.22	−6.35	<.0001
Quadratic Time	5.09	1.04	4.91	<.0001
Pre-Tx PCS	0.70	0.06	12.35	<.0001
Condition [0=ME; 1=BWL]	−1.57	1.27	−1.24	.218
Condition × Linear Time	4.67	3.13	1.49	.138
Condition × Quadratic Time	−1.67	1.47	−1.14	.258

Note: Covariates not displayed: race/ethnicity, age, baseline BMI, baseline HIT-6, baseline migraine severity, and treatment-related changes in pain severity.

Table 3.

Multilevel model for changes in allodynia from pre-treatment across post-treatment and follow-up.

Variable	Estimate	SE	t	p
Intercept	19.42	0.92	21.21	<.0001
Linear Time	−2.15	0.72	−2.99	.003
Quadratic Time	0.82	0.32	2.58	.011
Pre-Tx ASC	0.81	0.05	17.64	<.0001
Condition [0=ME; 1=BWL]	0.16	0.39	0.40	.691
Condition × Linear Time	−1.00	1.02	−0.98	.328
Condition × Quadratic Time	0.51	0.45	1.14	.257

Note: Covariates not displayed: race/ethnicity, age, baseline BMI, baseline HIT-6, baseline migraine severity, and treatment-related changes in pain severity.

Table 4.

Multilevel model for changes in headache disability (HIT-6) from pre-treatment across post-treatment and follow-up.

Variable	Estimate	SE	t	p	CI lower	CI upper
Intercept	−0.15	3.02	−0.05	.961	−6.13	5.84
Linear Time	0.90	0.68	1.33	.188	−0.45	2.25
Covariates						
Age	0.02	0.05	0.28	.778	−0.09	0.12
Race/Ethnicity	0.87	0.86	1.01	.315	−0.84	2.58
Baseline BMI	0.07	0.07	1.03	.308	−0.06	0.20
Baseline HIT-6	0.55	0.11	5.14	<.0001	0.34	0.77
Baseline PCS	−0.21	0.06	−3.61	<.0001	−0.32	−0.09
Baseline ASC	−0.19	0.14	−1.32	.189	−0.46	0.09
Baseline MI days	0.09	0.14	0.64	.525	−0.18	0.36
Baseline MI duration	−0.10	0.05	−2.21	.029	−0.19	−0.01
Baseline MI pain severity	0.08	0.35	0.23	.818	−0.61	0.77
Condition [0=ME; 1=BWL]	0.76	1.00	0.76	.448	−1.22	2.74
Variables						
PCS Δ	0.18	0.05	3.34	.001	0.07	0.29
ASC Δ	0.50	0.13	3.70	<.0001	0.23	0.76
BMI Δ	0.02	0.10	0.23	.820	−0.17	0.21
MI days Δ	0.13	0.12	1.05	.297	−0.11	0.36
MI duration Δ	−0.01	0.03	−0.24	.808	−0.06	0.05
MI pain severity Δ	0.62	0.19	3.27	.001	0.24	0.99