Randomized Controlled Pilot Trial of Behavioral Insomnia Treatment for Chronic Migraine With Comorbid Insomnia

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Background.—Migraine frequently co-occurs with and is triggered by sleep disturbance, particularly insomnia, and the large majority of patients with chronic migraine (CM) have comorbid insomnia. Limited evidence suggests that behavioral regulation of sleep may reduce migraine frequency, but studies to date have not assessed the viability of stimulus control and sleep restriction interventions or included objective measurement of sleep parameters. The aim of this study, thus, was to pilot-test the efficacy of a brief behavioral insomnia intervention for adults with CM and comorbid insomnia; headache diaries and actigraphy were included to assess outcomes throughout the trial.

Methods.—This randomized parallel-arm pilot trial recruited adults with both CM and comorbid insomnia. Participants were randomly assigned to three 30-minute biweekly sessions of cognitive-behavioral therapy for insomnia (CBTi) or control treatment. Participants were blinded to treatment and control conditions to control for outcome expectations. Each treatment condition involved training in and daily practice in 5 instructions/skills. The CBTi group learned and practiced skills pertaining to stimulus control and sleep restriction. The control intervention was the same as used by Calhoun and Ford (2007) and involved training in and daily practice of skills pertaining to keeping a consistent food/liquid intake, range of motion exercises, and acupressure. Participants provided outcome data via daily headache diaries, actigraphy, and self-report measures. The primary outcome was reduction in headache frequency at 2 weeks post-treatment and 6-week follow-up; secondary outcomes included other headache parameters, objective actigraphic and subjective changes in sleep, and treatment effect sizes and perceived credibility. Generalized estimating equations with a binomial logit link and inverse probability weights were used to assess the primary outcome among the intent-to-treat sample, and repeated measures generalized linear models were used to assess changes in secondary outcomes after controlling for baseline values.

Results.—The intent-to-treat analyses included 31 adults (M age = 30.8 [12.9] years; 90.3% female; 80.6% white) with CM and comorbid insomnia. Both interventions yielded reductions in headache frequency at post-treatment (26.9% reduction for CBTi vs 36.2% for control) and follow-up (48.9% for CBTi vs 25.0% for control). At follow-up the odds of experiencing headache were 60% lower for CBTi than for control treatment, indicative of a large effect size that did not reach...
statistical significance after Bonferroni correction for assessing two primary endpoints (odds ratio: 0.40; 95% CI: 0.17, 0.91; \(P = .028\)). CBTi produced significantly larger increases than control treatment in total sleep time and sleep efficiency as quantified by actigraphy, as well as in self-reported insomnia severity. Adherence was high and treatments were perceived as credible without differences between groups, but the control group experienced a higher rate of dropouts. No adverse events were reported.

Conclusions.—Behavioral treatment of comorbid insomnia in individuals with CM produced large reductions in headache frequency, though some improvement in headache occurred with a behavioral intervention not focused on modifying sleep. Among the CBTi group only, both headache frequency and sleep parameters continued to improve after treatment, suggesting the presence of enduring effects over time. Directly treating insomnia using components of stimulus control and sleep restriction holds promise for reducing comorbid migraine. Development of and comparison to a truly inert pseudotherapy control presents unique challenges that future studies should address.

Key words: migraine, chronic migraine, insomnia, behavioral treatment, randomized controlled trial, sleep

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INTRODUCTION

Migraine affects 1 out of every 7 individuals annually and is the third most common medical condition worldwide, negatively affecting patient functioning, quality of life, and societal health care burden. The impairment associated with migraine is compounded by the presence of comorbid psychiatric conditions such as major depression and anxiety spectrum disorders, which affect migraineurs 2-5 times more often than those without migraine. These disorders are most prevalent among those with chronic (CM; \(\geq 15\) headache days per month for \(>3\) months) vs episodic (EM; \(<15\) days per month) migraine. Identification and management of these comorbidities is important because they compound migraine-related disability, portend a poorer response to headache treatment and are associated with progression of headache over time.

A growing body of literature has explored relations between migraine and disturbances in sleep. Existing data converge around the notion that the co-occurrence of sleep disturbances and migraine likely results from shared pathophysiology, such as deficiencies in serotonergic bioavailability from the dorsal raphe nucleus and decreased concentrations of melatonin, both of which are affected by fluctuations in circadian biorhythms as a function of hypothalamic activity. Although sleep disturbances such as somnambulism, nightmares, snoring, restless legs syndrome, and obstructive sleep apnea are common in migraine, insomnia is the most prevalent sleep disorder in migraineurs, occurring in one-half to two-thirds of individuals who present to community headache clinics. Insomnia is diagnosed when recurrent difficulties with initiation, maintenance, duration, or quality of sleep are present and contribute to daytime functional impairment.

Over one-third of migraineurs sleep less than 6 hours per night, and nearly half experience difficulty with sleep onset or sleep maintenance as compared to age- and gender-matched controls. The severity and prevalence of insomnia increases proportionally to headache frequency, such that individuals with CM experience more frequent and severe insomnia symptoms than those with EM. Prior studies indicate that the overwhelming majority (68-84%) of patients with CM suffer from symptoms of insomnia, most of whom experience insomnia on a daily basis, and that the association between insomnia and migraine is not merely a function of comorbid psychiatric disorders.

An extensive literature indicates that cognitive-behavioral interventions for insomnia, grounded in principles of learning theory and intended to alter consequences that maintain insomnia, are highly effective in reducing sleep onset latency, increasing total sleep time, and improving sleep efficiency (time asleep: time in bed). Cognitive-behavioral therapy for insomnia (CBTi) typically combines components of stimulus control and sleep restriction. Stimulus control involves techniques to reassociate the bed/bedroom with sleep (eg, limiting awake time in the bedroom, establishing a consistent sleep-wake schedule). Sleep restriction involves
restricting time in bed to an amount equal to one’s total sleep time, which is gradually increased as sleep efficiency increases. “Sleep hygiene” may be included as an adjunct psychoeducational component and focuses on promoting healthy sleep behaviors and sleep-conducive environmental conditions (eg, limiting caffeine and meals prior to bedtime, keeping a comfortable bedroom temperature). Both randomized controlled trials26–28 and reviews29,30 confirm that CBTi produces large effects at least equal to those of pharmacotherapy and that may be more durable. These interventions may be highly effective when delivered in as little as two sessions,31 making them portable and feasible to administer in the context of physician practice settings.

Most recently, CBTi has growing evidence of efficacy in improving sleep among medical patients for whom insomnia is a common comorbidity, such as those with cancer, fibromyalgia, and chronic pain.32–34 One randomized controlled trial has tested the efficacy of a brief behavioral sleep intervention in patients with CM. Calhoun and Ford35 randomly assigned 43 women with transformed migraine to receive either 5 mostly sleep hygiene instructions (eg, schedule consistent bedtime, use visualization techniques, move meals to at least 4 hours before bed and limit fluids before bed) or 5 “sham” instructions delivered in one 20-minute psychoeducational session.35 After 6 weeks, only the sleep hygiene group experienced significant reductions in both headache frequency and severity, 35% of whom had reverted to episodic migraine. Although changes in sleep parameters were not reported, this study suggests that a brief intervention to improve sleep habits holds promise for reducing the frequency and severity of headache among individuals with CM.

A multicomponent behavioral insomnia intervention similar to those validated in other medical patients has yet to be tested among individuals with CM. This is a needed area of research because systematic reviews,29 practice parameters,25 and clinical guidelines36 recommend CBTi involving stimulus control and sleep restriction over sleep hygiene alone for insomnia. A second impetus for this study was the need for objective monitoring of sleep during the trial, which can be accomplished through use of actigraphy in conjunction with daily sleep diaries.36,37 The goal of this study was thus to pilot test a brief, multicomponent behavioral insomnia intervention (including stimulus control and sleep restriction) among chronic migraneurs, using both diary and actigraphy data to quantify headache and sleep outcomes. We hypothesized that CBTi would yield significant reductions in headache frequency (primary outcome) from baseline to post-treatment and follow-up, and that these reductions would exceed those of the control group. We hypothesized also that CBTi would produce greater reductions in headache severity and disability, and improvement in total sleep time (secondary outcomes), compared to control treatment.

MATERIALS AND METHODS

Participants.—Adult participants were recruited from June 2011 to March 2013 through one of two sources: (1) as they presented for treatment of CM at a local neurology clinic or (2) were identified as having CM through their completion of an electronic headache diagnostic at a large southeastern university. A formal a priori power analysis was not conducted, but the target sample size for this pilot trial was 30 participants, consistent with previous studies of behavioral insomnia interventions that have demonstrated large effects.31,32,35

Inclusion and Exclusion Criteria.—Participants were adults meeting revised ICHD-II criteria for CM without medication overuse headache (MOH)38 and ICSD-3 criteria for insomnia39 (eg, sleep onset or maintenance insomnia or nonrefreshing sleep, plus daytime impairment). (Diagnostic criteria for CM and MOH were those in use at the time the study began.) Exclusion criteria included presence of a secondary headache disorder including MOH, pregnancy or breastfeeding, being unable to read or speak English at a 6th grade level, untreated sleep apnea, active alcohol or substance abuse or dependence, active bipolar disorder, psychiatric hospitalization within the last year, employment involving rotating shift work schedule, and recent or expected change in preventive headache pharmacotherapy (ie, starting a new preventive medication within 3 weeks of enrollment or
expecting to start a new medication during the 3-month study duration).

**Materials and Measures.**—**Actiwatch II** (Philips Respironics, Murrysville, PA, USA). The Actiwatch II actigraph is an ambulatory digital monitoring device that uses a piezo-electric accelerometer and silicon photodiode light sensor to quantify 3-dimensional movement and ambient light. This waterproof, wrist-worn device continually samples ambulatory movement and ambient light to quantify sleep/wake cycle parameters using validated algorithms calculated by vendor-supplied software (Actiware). Total sleep time and sleep efficiency were the variables of interest. Thirty-second epochs were sampled for periods of 14 consecutive days (during baseline, post-treatment, and follow-up).

**Headache and Sleep Diary.**—Participants completed daily headache self-monitoring diaries throughout the trial. At bedtime they reported whether they experienced a headache that day and the corresponding duration, severity, and symptoms. Participants in the CBTi group each morning also recorded their bedtime, wake time, sleep onset latency, and total sleep time from the prior night; these data were used to calculate sleep restriction times.

**Structured Diagnostic Interview for Headache-Revised.**—The Structured Diagnostic Interview for Headache-Revised was administered to potential young adult student participants and is computerized version of the validated Structured Diagnostic Interview for Headache that was modified to comport with diagnostic criteria of the 2nd edition of the International Classification of Headache Disorders. This measure was used to verify CM and exclude secondary headache disorders among the young adult study candidates; participants from the neurology clinic were assessed for both CM and insomnia by the treating neurologist in accordance with aforementioned diagnostic criteria.

**Migraine Disability Assessment Questionnaire.**—The Migraine Disability Assessment questionnaire (MIDAS) is a 5-item measure of headache-related disability that quantifies the number of days during the prior 3 months that migraine has impaired one’s ability to function at work/school, perform household duties, and participate in leisure activities. Scores range from 0 to 270, with higher scores indicative of greater functional impairment. Scores >20 are indicative of severe headache-related disability. The MIDAS has good internal consistency, test–retest reliability, and validity with daily diary data.

**Headache Impact Test-6.**—The Headache Impact Test-6 (HIT-6) is a 6-item measure of headache-related disability, incorporating ratings of activity impairment, pain severity, and impact on emotional and cognitive functioning. Total scores indicate the overall impact of headache and range from 36 to 78; higher scores are indicative of greater impairment. Scores >55 are indicative of substantial impact of headache on functioning. The HIT-6 is a reliable and valid measure of disability among episodic and chronic headache sufferers and was used in conjunction with the MIDAS because they quantify disability in different and complementary ways.

**Pittsburgh Sleep Quality Index.**—The Pittsburgh Sleep Quality Index (PSQI) is a 24-item Likert-type measure that assesses insomnia severity as a function of sleep quality, sleep latency, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Items are rated on a 0-3 scale and collapsed into 7 component scores, for a possible range of 0-21. Higher scores are indicative of greater insomnia severity, and scores above 5 are considered clinically significant. The PSQI is a highly sensitive measure for assessing sleep disturbance among individuals with primary insomnia and was used to assess insomnia severity.

**Epworth Sleepiness Scale.**—The Epworth Sleepiness Scale (ESS) is a widely used 8-item measure of daytime sleepiness that accords well with polysomnographic data of both sleep-disordered and non-clinical samples. Respondents rate on a 0–3 scale the likelihood of falling asleep during 8 everyday activities. Scores greater than 10 are considered clinically significant.

**Patient Health Questionnaire-Depression Scale and Generalized Anxiety Disorder 7-item Scale.**—The Patient Health Questionnaire-Depression scale (PHQ-9) and Generalized Anxiety Disorder
7-item scale (GAD-7) are brief, reliable, and well-validated measures used to assess symptoms of depression and anxiety, respectively. They query the frequency of experiencing psychiatric symptomatology over the last two weeks using 9 (PHQ-9) or 7 (GAD-7) items with 0–3 Likert-type response options (0 = not at all; 3 = nearly every day). Scores of 10 or higher are indicative of moderate or greater symptomatology.

Credibility/Expectancy Questionnaire.—The Credibility/Expectancy Questionnaire (CEQ) is a 6-item self-report measure used to assess perceived credibility of behavioral interventions. The first four items are rated on a 1-9 Likert-type scale (eg, “At this point, how logical does the treatment offered to you seem?”), and the last two items pertain to expectations regarding treatment outcomes rated on a 0-100% scale (eg, “By the end of the treatment period, how much improvement in your symptoms do you think will occur?”). Higher ratings reflect higher perceived treatment credibility and expectations for improvement. For the present study, the word “migraine” was added to the instructions and into questions referencing “symptoms” so that the participant would answer in reference to expectations for improvement in headache specifically. Factor analytic data indicate that the first 3 items reflect treatment credibility, and the mean score of these 3 items (1-9) was thus used to index credibility.

Participant Adherence.—At treatment sessions and post-treatment participants were asked to rate on a 1 to 5 scale the extent to which they followed each of their 5 treatment instructions since their prior visit (1 = “never followed”; 5 = “nearly every day”).

DESIGN

Randomization.—This was a single-site, prospective randomized controlled pilot trial using a parallel-group superiority design with a 1:1 allocation ratio for treatment condition. Consistent with CONSORT 2010 guidelines, a stratified randomization procedure was used, wherein randomization was stratified as a function of participant gender because migraine is disproportionally common among women. Randomization occurred in a 1:1 ratio using permuted blocks of four to one of two treatment conditions using PROC PLAN via SAS 9.3 and R software. The allocation sequence was generated by a statistician (TTH) who had no contact with participants and was provided to study personnel in sequentially numbered, opaque sealed envelopes to ensure allocation concealment. Participants were allocated during the baseline clinic evaluation session after confirmation of meeting all enrollment criteria, and each was assigned the next consecutive randomization number by the treating therapist. Study personnel who initially screened (TAS, MR) participants were uninvolved with the allocation sequence; therapists (ABW, RED, CEA) remained blinded to allocation until after they collected self-report data at the baseline evaluation.

Treatments.—Treatments were provided by three graduate-level therapists with backgrounds in cognitive-behavioral therapy and behavioral medicine. They were trained in administration of each treatment by the first author, and all therapists provided both treatments to control for possible therapist effects. Therapist fidelity to the treatment protocols was assessed at each treatment session via therapist self-ratings (1-5 scale for each treatment component, with 5 being excellent adherence) and confirmed to be high and equivalent across both groups (M = 4.21 [.31] for CBTi and 4.09 [.43] for control; P = .40). To equate treatment time across conditions, both conditions involved training in and assigned daily practice of 5 skills/instructions. Participants were not contacted between treatment visits unless a scheduling conflict arose. Those receiving usual medical care were allowed to continue usual care (previously prescribed acute and/or preventive medications) throughout the trial but instructed not to start any new medications during the trial.

Trials of behavioral interventions for headache cannot be double-blinded, as the treatments involve teaching and learning particular skills; thus, therapists are always aware of which intervention protocol they are delivering. However, single-blinding was accomplished insofar as participants were not informed at any point during the trial about hypotheses regarding which treatment was expected to be superior to the other (ie, which was
the “active” treatment and which was the “control” treatment). In this way, single-blinding of participants served to control for outcome expectancies, as recommended in guidelines for behavioral headache trials.\textsuperscript{51}

Behavioral Insomnia Treatment (CBTi).—The CBTi condition included four instructions in stimulus control and one in sleep restriction:

1. Go to bed only when sleepy and intending to sleep.
2. Leave the bedroom if unable to sleep after 20 minutes, and return only when sleepy.
3. Use the bedroom only for sleep and sexual activity.
4. Set an alarm and rise daily at the same time.
5. Restrict your time in the bed to your total sleep time plus 30 minutes.

Your time in bed is from _____ to _____

Bedtime and awake time for sleep restriction (item 5) were individualized based on each CBTi participant’s mean TST from their baseline sleep diaries: 30 minutes was added to mean TST, and the participant was instructed to limit her time in bed to this duration regardless of actual sleep obtained. Bedtime was derived from having the participant choose a consistent time to awake (get out of bed) and working backward by the duration of sleep restriction (eg, if the participant needed to be awake at 6:30 am and was being restricted to 6.5 hours in bed, then she was instructed to get in bed at midnight). No participant was restricted to less than 6 hours per night. At subsequent sessions, sleep diaries from the prior 2 weeks were reviewed, and bedtime was increased 30 minutes each time sleep efficiency reached 85%.

The provided therapeutic rationale was that there is a strong association between insomnia and migraine, and that treating insomnia may improve migraine. The role of classical conditioning in psychophysologic insomnia was described, and the treatment instructions were explained as means of helping the patient learn to reassociate the bed with sleep.

Sham Control (“Lifestyle Modification”).—Sham control instructions were identical to those used by Calhoun and Ford.\textsuperscript{35}

1. Eat dinner at a consistent time every evening.
2. Do acupressure (as instructed) for at least 2 minutes twice daily, once on awakening and once before going to bed.
3. Record all liquids consumed for 3 consecutive “typical” days (identity of liquid, quantity, and time of day) and thereafter keep a consistent liquid intake each day.
4. Do 5 minutes of stretching/range of motion exercises upon awakening.
5. Consume at least one serving of protein within one hour of arising in the morning (eg, egg, cheese, cottage cheese, and tofu).

Acupressure training entailed light but firm self-applied circular motions on the ulnar/epicondylar groove at the elbow (contralateral to the usual headache side or on the elbow of the nondominant hand) for 15-20 seconds, followed by relaxing then repeating for up to 2 minutes. Range of motion exercises included light flexion stretches predominantly of the neck (eg, slowly try to touch each ear to the corresponding shoulder, slowly twist torso to each side).

The control treatment included identical numbers of skills taught and practiced at home, similar contact time with therapists, and a credible rationale. The therapeutic rationale provided was that migraine attacks are often precipitated by deviations from routine and their resulting impact on biological rhythms, and that modifying one’s behaviors can help stabilize these rhythms. (Instructions 1, 3, and 5 were described as helping maintain consistent eating/drinking habits, and instructions 2 and 4 to facilitate somatic control and nervous system stability.) This intervention was referred to as “Lifestyle Modification” to participants to retain single-blinding and the credibility of the intervention.

Procedure.—This study received full-board ethical approval from the Institutional Review Board at the University of Mississippi and was registered prospectively with the Clinical Trials Registry (clinicaltrials.gov). All participants provided informed consent prior to randomization and baseline self-monitoring. They were compensated $100 for completing the study, which was prorated for study
Participants recruited through the university setting were offered their choice of monetary compensation or course extra credit. A CONSORT flow diagram of study procedures is shown in Figure 1. Potentially eligible patients identified at the neurology clinic or via their responses to the computerized headache interview were initially screened via telephone by the first author to confirm that they meet diagnostic criteria for CM and insomnia, as well as to rule out aforementioned exclusion criteria. Those appropriate for the study were then scheduled for the baseline evaluation, at which time they were provided a detailed overview of the study and provided informed consent. They were then administered the self-report measures and the bipolar module of the

Fig. 1.—Study flow diagram. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
Structured Clinical Interview for DSM-IV Axis I Disorders (Clinician Version)\textsuperscript{52} to confirm the absence of bipolar disorder (because mania can be triggered by sleep restriction). They were randomly assigned to treatment condition as described earlier and instructed in daily headache self-monitoring for 2 weeks; those in the CBTi group were also instructed in daily sleep self-monitoring. (Participants in the control condition did not self-monitor their sleep to minimize potential demand effects.)

At this baseline evaluation all participants were provided with and instructed in use of an actigraph, which was attached firmly but comfortably to their nondominant wrist with instructions to remove the device only when they would be immersed in water for over 30 minutes or if wearing the device caused skin irritation. To avoid demand effects, the actigraph was described as a device that quantified activity throughout the day and not as a measure of sleep specifically.

After completing 2 weeks of baseline self-monitoring and actigraphy, participants began treatment. Each treatment was administered in three 30-minute sessions, with 2 weeks between each session. Session 1 included a detailed overview and rationale of the treatment components with instructions for daily home practice. Sessions 2 and 3 entailed reviewing daily diaries and treatment adherence since the last session, reinforcing progress, and problem-solving around any obstacles to adherence. Participants continued daily self-monitoring throughout treatment and were instructed to continue practicing their 5 treatment instructions after treatment concluded.

Participants returned for two assessments, the first beginning 2 weeks after completion of treatment (post-treatment) and the second 6 weeks after completing treatment (follow-up). At both assessments patients completed all self-report measures from the intake session and subsequently engaged in 2 weeks of daily headache self-monitoring and actigraphy.

**Statistical Analyses.**—The primary analysis was conducted using generalized estimating equations (GEE) to account for the repeated diary measurements within each time period. The model was conducted using a binomial distribution with a logit link and fixed effects for treatment group (CBTi vs control) and time period. The primary outcome was defined as differences in headache frequency between groups. Monthly headache frequency was extrapolated within each time period by multiplying each participant’s observed headache probability by 30 (for a 30-day month). If imbalances between groups at baseline were observed, we planned a priori to adjust this model to include baseline values as covariates. Secondary outcomes included headache severity and disability, sleep parameters, and psychiatric symptomatology, as well as estimates of patient acceptability, treatment feasibility, and effect sizes to inform larger trials.

Statistical analyses were conducted using IBM SPSS Version 20 and R. Three GEE models were run on the primary outcome of headache frequency at post-treatment and follow-up: completer analyses, completer analyses adjusted for baseline headache frequency, and intent-to-treat analyses using inverse probability weighting. The ITT sample was defined as all randomized participants who provided baseline headache data for at least 10 days. The ITT principle was enacted using inverse probability weighting, a method that differentially weights the measurements from participants who had a high probability of dropping out of the study. This approach accounts for missing data by creating a model of which factors might predict a participant dropping out of the study, and then assigning participants who were more likely to drop out greater weights in the analysis.\textsuperscript{53} The drop-out model consisted of group assignment and baseline disability as quantified by HIT-6. Because two outcomes were assessed in the primary analysis (post-treatment and follow-up), each was interpreted at a conservative $P < .025$ level of significance.

Secondary outcomes were assessed at three measurement occasions and examined via repeated measures generalized linear models using last-observation carried forward (LOCF) to impute scores for participants who dropped out of the trial prematurely or missed a follow-up session. Significance for secondary outcomes was set at $P < .05$. 

**Headache**

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RESULTS

Baseline Characteristics.—Figure 1 depicts a flow diagram of the study procedures and enrollment. Thirty-two participants were randomized; one participant dropped out 4 days into the baseline period and was thus excluded. The remaining 31 (16 CBTi; 15 control) were included in the intent-to-treat analyses. Participant mean age was 30.8 years (SD = 12.9; range = 18-57), and 28/31 (90.3%) were female; 80.6% identified as white, 16.1% as black, and 3.2% as Hispanic. Eight CBTi participants and 9 control participants were recruited from the neurology clinic.

Table 1 shows the baseline characteristics of the treatment groups. Despite randomization the CBTi group experienced 2.2 more days of headache per month than the control group (22.7 days vs 20.5 days/month [unadjusted]). Treatment groups did not differ significantly at baseline on mean age, gender, race, headache-related disability (via HIT-6 or MIDAS), depression, or anxiety. Mean disability scores for the entire analyzed sample were 65.9 (3.9) on the HIT-6 and 57.2 (39.4) on the MIDAS, both indicative of severe headache-related disability. Mean scores on the PHQ-9 (11.3 [5.1]) and GAD-7 (10.2 [5.8]) were reflective of significant depressive and anxiety symptoms, respectively. As expected, both groups also endorsed clinically significant levels of insomnia (PSQI mean = 11.5 [3.7]) and daytime sleepiness (ESS mean = 10.9 [4.2]).

Primary Outcome.—Two thousand seven hundred nine person-days of diary data were collected during the trial, of which 297 (10.7%) were missing. The overwhelming majority of these missing data were due to dropouts (266 days); only 31 days (1.1%) of missing data were embedded within the collected diary data. Table 2 presents headache frequency data at post-treatment and follow-up as a function of group status, represented as odds ratios of having headache in CBTi vs control (reference) groups. Herein, we report the ITT analyses because they account for participants who dropped out of the trial or were missing values embedded within their collected data. Models including only study completers, before and after controlling for headache frequency, are included in Table 2 to afford assessment of the observed data.

Using ITT analyses, both treatment groups obtained reductions in headache frequency over the course of the trial (see Fig. 2). At post-treatment
the CBTi group evidenced a 26.9% headache frequency reduction from baseline (22.7 to 16.6 days/month; 6.1 day reduction), compared to a 36.2% reduction from baseline (19.6 days to 12.5 days/month; 7.1 day reduction) among the control group. The odds ratio of having headache for the CBTi vs control at post-treatment was 1.06 (95% CI: 0.52, 2.15), which was not statistically significant ($P = .883$).

At follow-up, however, the CBTi group had achieved a 48.9% reduction in monthly headache frequency from baseline (22.7 to 11.6 days/month; 11.1 day reduction). By comparison, the control group reduced only 25.0% (19.6 to 14.7; 4.9 day reduction). At follow-up the odds of experiencing headache were 60% lower for those receiving CBTi than control treatment, although this difference was not statistically significant using a conservative $P < .025$ criterion (OR: 0.40; 95% CI: 0.17, 0.91; $P = .028$) as we were assessing 2 endpoints of the primary outcome. Seven of the 16 CBTi participants (43.8%) achieved at least a 50% reduction in headache frequency at follow-up, compared with 5 of the 15 (33.3%) control participants.

Secondary Outcomes.—Table 3 presents data on secondary outcomes by treatment group and outcome period.

**Headache Variables.**—Both groups evidenced clinically meaningful reductions in headache-related disability at post-treatment (3.9 points on the HIT6, 14.6 points on the MIDAS) and follow-up (6.1 points on the HIT-6 and 24.0 points on the MIDAS) that did not differ by group after controlling for baseline scores. In comparison to headache disability, reductions in headache severity were modest (0.2 at post-treatment and 0.5 at follow-up), with an absence of group differences when controlling for baseline headache severity.

**Sleep Variables.**—Significant group differences favoring CBTi were observed in both total sleep time and sleep efficiency as quantified by actigraphy. After controlling for baseline sleep time, a significant group × time interaction was observed ($P = .049$; $\eta^2_p = .14$), owing to the greater increases in the CBTi group at follow-up (52.7 vs 5.9 min for control; $P = .068$). A significant interaction was also
observed for sleep efficiency after controlling for baseline values \((P = .001; \eta^2_p = .32)\), such that the CBTi group evidenced increased sleep efficiency at follow-up \((M \text{ increase} = 3.7)\) while the control group did not \((M \text{ decrease} = 0.3)\).

Group differences in changes in self-reported insomnia symptoms via the PSQI were also observed. After controlling for baseline PSQI scores, a significant omnibus effect for treatment group was observed, such that the CBTi group evidenced reductions in PSQI scores while the control group remained largely unchanged \((P = .009; \eta^2_p = .26)\). Headache probability at follow-up was highly correlated with PSQI scores at both post-treatment \((r = .60, P = .001)\) and follow-up \((r = .54, P = .002)\), and changes in PSQI scores were associated with changes in HIT-6 scores at post-treatment \((r = .49, P = .012)\) and follow-up \((r = .46, P = .018)\). By comparison, changes on the ESS were rather modest \((1.8 \text{ at post-treatment, } 2.0 \text{ at follow-up})\) and did not differ between groups after controlling for baseline scores.

**Psychiatric Symptomatology.**—CBTi reduced baseline depression scores \((PHQ-9)\) by 5.1 points at post-treatment and 5.7 points at follow-up, compared to reductions of 2.1 and 1.9 points in the control group. After controlling for baseline depression scores, the omnibus effect favoring CBTi was not statistically significant \((P = .054)\). On anxiety symptomatology as measured by the GAD-7, CBTi reduced baseline scores by 4.1 points at post-treatment and 4.4 points at follow-up, compared with 2.8 and 2.9 points in the control group. No significant group effect was observed after controlling for baseline GAD-7 scores \((P = .430)\).

**Treatment Credibility, Adherence, and Drop-outs.**—Participants rated both treatments as credible on the CEQ, with independent samples \(t\)-test revealing no significant difference between groups \((\text{CBTi } M = 6.9 \text{ [1.1] vs control } M = 7.0 \text{ [1.3]}\) on a 1–9 scale; \(P = .773)\). Excluding dropouts, self-reported adherence did not differ between groups or over time. Participants in both treatments reported a high mean level of adherence throughout the trial \((\text{CBTi } M = 4.3 \text{ [0.4] vs control } M = 4.4 \text{ [0.4]}, P = .650)\). Differences in dropout rates, however, were evident between groups. Two individuals in the CBTi group dropped out before treatment concluded, compared with 5 dropouts in the control group (one during baseline, two after the first treatment session, and two after post-treatment). No adverse events were reported.

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**Fig. 2.** Changes in headache frequency over time. Note: Data represent headache frequency (daily headache probability \(* 30\)) among the intent-to-treat sample using inverse probability weighting. Errors bars represent standard error.
The large majority of individuals with CM have comorbid insomnia, and a prior study found that a one-session sleep-hygiene-based intervention significantly reduced migraine. This pilot trial endeavored to assess the effects on migraine of a more intense, 3-session behavioral insomnia intervention and to generate estimates of effect sizes and treatment feasibility for future large studies. Our pilot trial provides further evidence that treating comorbid insomnia holds promise for reducing migraine.

Behavioral insomnia treatment yielded reductions in migraine frequency at both 2 weeks post-treatment and 6-week follow-up, but only at follow-up did CBTi begin to demonstrate superiority compared with control treatment. At that point CBTi participants were at 60% lower odds to experience headache, although this difference did not reach statistical significance using our conservative Bonferroni-adjusted threshold. At that point, individuals in CBTi had nearly twice the reduction in headache frequency of controls (48.9 vs 25.0%), and the magnitude of the effect of CBTi on headache frequency treatment paralleled or exceeded that observed in CM trials of both topiramate and onabotulinum. The durability of improvements associated with CBTi is consistent with prior trials that have shown continuation or maintenance of treatment gains over time. The 11-day reduction in headache frequency at follow-up among the CBTi group compares favorably to the reduction in headache frequency of controls (6.8 vs 2.4 days).

Analyses of secondary outcomes indicate that only CBTi improved insomnia, as quantified by both actigraphy and self-report, and that changes in sleep were associated with changes in headache. These results suggest not only that the CBTi intervention was effective in improving sleep but that such a brief intervention improved sleep time, sleep efficiency, and insomnia symptoms among individuals with such frequent migraine.

### Table 3—Secondary Outcomes by Group

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<td>Baseline</td>
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<tr>
<td>Disability (MIDAS)</td>
<td>59.9 (39.0)</td>
<td>44.2 (43.1)</td>
</tr>
<tr>
<td>Disability (HIT-6)</td>
<td>66.9 (3.8)</td>
<td>62.6 (5.3)</td>
</tr>
<tr>
<td>Headache Severity (0-10)</td>
<td>5.2 (0.95)</td>
<td>5.1 (1.4)</td>
</tr>
<tr>
<td>PSQI</td>
<td>11.3 (4.4)</td>
<td>7.6 (2.6)</td>
</tr>
<tr>
<td>ESS</td>
<td>11.0 (3.4)</td>
<td>9.0 (3.2)</td>
</tr>
<tr>
<td>Total Sleep Time (actigraphy)</td>
<td>7.4 hours</td>
<td>7.3 hours</td>
</tr>
<tr>
<td>Sleep Efficiency (actigraphy)</td>
<td>81.2 (7.7)</td>
<td>79.1 (8.9)</td>
</tr>
<tr>
<td>PHQ-9</td>
<td>12.1 (5.8)</td>
<td>6.9 (4.8)</td>
</tr>
<tr>
<td>GAD-7</td>
<td>10.6 (6.4)</td>
<td>6.6 (5.2)</td>
</tr>
</tbody>
</table>

Numbers represent means (SD) among the intent-to-treat sample using LOCF for missing observations.
insomnia, and these results speak to the promise of CBTi among migraineurs. Disability and psychiatric symptomatology also improved but did not differ between treatment groups.

The high response rate of our control group is notable given that the intervention was identical to that used in Calhoun and Ford,35 who failed to observe a significant control group response. Likely, this discrepancy is partly a function of a differential number of treatment sessions. Our control intervention was administered over 3 sessions, compared with only 1 session in their study, and our control group’s observed pattern of incremental headache frequency reductions until follow-up indirectly supports a dose-congruent effect. The high response rate also suggests that the control treatment was not completely inert but instead contained instructions with some effects on migraine. In particular, 3 of the 5 control instructions pertained to establishing regularity in eating/drinking habits. Missing meals or fasting is reported as a trigger of headache by 57% of migraineurs, making it one of the most common reported triggers of headache.57 Although large trials are lacking, regulating eating habits may be useful in reducing headache occurrence,58 particularly those resulting from sympathetic activity secondary to hypoglycemia.59,60 While we did not assess the effects of these control instructions on glucose regulation, it seems reasonable that establishing consistent eating habits (dinnertime consistency, protein each morning) may have resulted in some reduction in headache. The argument against the control treatment being inert is bolstered further by the high perceived credibility of and reported adherence to the control treatment, as well as our single-blinding of participants to treatment. Future studies of behavioral treatments will need to wrestle with the difficulty of establishing a truly inert pseudotherapy control.61

Strengths of this study include diagnostic verification of both CM and comorbid insomnia, a stratified randomization scheme, rigorous statistical analyses accounting for dropouts and missing data, single-blinding of treatment and control conditions to control for outcome expectancies, and inclusion of actigraphy for objective monitoring of sleep. Despite these strengths, limitations exist, the most notable of which is the small sample size, which despite randomization resulted in the CBTi group having more headache days than controls at baseline. While the sample size determination was informed by prior studies and consistent with those of other pilot trials, a larger sample likely would have established the statistical superiority of the CBTi group after correcting for multiple primary endpoints. A second limitation is that baseline and outcome assessment periods were only 2 weeks in duration, which was dictated by the time-limited nature of this pilot trial and budgetary constraints. Although a 2-week baseline can be sufficient for patients with high-frequency headache attacks,51 a 4- or 5-week period would have allowed us to take into consideration menstrual cycle influences and conduct a full run-in period. Finally, using a different control group, such as waitlist or headache education only, might have helped us establish superiority of CBTi, but we elected against this strategy in light of the prior study on this topic and our desire to rigorously control for nonspecific factors associated with attending therapy (eg, expectations for improvement, interpersonal relationship, skill practice).

The obtained effect sizes in the present study and from the other prior study on this topic35 clearly justify a need for larger trials of CBTi for patients with CM, especially in light of a need for more well-established interventions for CM. These future studies should endeavor to compare CM patients with and without medication overuse and include objective monitoring of sleep variables as was done here. If behavioral treatment of comorbid insomnia continues to show promise, head-to-head comparisons with topiramate or onabotulinum may be warranted. Finally, given the inherent limitations in making inferences using frequentist hypothesis testing, an interesting analysis would be to combine the effect sizes from this study with those from Calhoun and Ford (2007) using Bayesian analyses to inform future trials. In this approach, effect sizes from these two studies could be utilized as “information priors” to inform statistical models of future trials.
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(b) Revising It for Intellectual Content
All Authors

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(a) Final Approval of the Completed Manuscript
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