Headache
© 2020 The Authors. Headache: The Journal of Head and Face Pain
published by Wiley Periodicals, Inc. on behalf of American Headache Society

ISSN 0017-8748
doi: 10.1111/head.13777
Published by Wiley Periodicals, Inc.

Research Submissions

Digital Cognitive Behavioral Therapy for Insomnia in Women With Chronic Migraines

Megan R. Crawford, PhD ; Annemarie I. Luik, PhD; Colin A. Espie, PhD; Hannah L. Taylor, PhD; Helen J. Burgess, PhD; Alex L. Jones, PhD; Rush University Sleep Research Team; Jason C. Ong, PhD

Objective/Background.—Insomnia commonly co-occurs with chronic migraines (CM). Non-pharmacological treatments for insomnia in CM patients remain understudied. This is a proof-of-concept study, which aims to evaluate the feasibility, acceptability, and preliminary efficacy of a digital cognitive behavioral therapy for insomnia (dCBT-I) for individuals with CM and insomnia (CM-I) in the United States.

Methods.—We recruited 42 females with CM-I symptoms from a U.S.-based observational cohort and from the general population via advertisements. Within a multiple baseline design, participants were randomized to receive dCBT-I after 2, 4, or 6 weeks of completing baseline sleep diaries. DCBT-I was scrutinized against benchmarks for completion rates (≥90% to complete dCBT-I), acceptability (≥80% to find dCBT-I acceptable), and posttreatment changes in insomnia symptoms (≥50% indicating a clinically relevant improvement in their insomnia symptoms). As a secondary measure, we also reported percentage of individuals reverting to episodic migraines.

Results.—Out of 42 randomized, 35 (83.3%) completed dCBT-I within the 12 weeks provided. Of these completers, 33 (94.3%) reported being satisfied (n = 16) or very satisfied (n = 17) with treatment. Additionally, 65.7% of completers responded to treatment as per universally accepted criteria for insomnia. Lastly, 34% of completers reverted from CM to episodic migraine.

Conclusion.—This study provides evidence for the feasibility and acceptability of dCBT-I in patients with CM-I complaints. Effects of improving insomnia and migraines were suggested. These results indicate that a randomized controlled trial is needed to determine the efficacy of dCBT-I in CM patients.

Key words: insomnia, migraine, cognitive behavior therapy, digital

Abbreviations: CBT-I Cognitive Behavioral Therapy for insomnia, CM chronic migraine, CM-I chronic migraines and insomnia, dCBT-I digital Cognitive Behavioral Therapy for insomnia, ITT intention to treat, MBD multiple baseline design, MIDAS Migraine Disability Assessment, PP per protocol, PSQSF Patient Satisfaction Questionnaire Short Form, RCT randomized controlled trial

(*Headache* 2020;0:1-14)

From the School of Psychological Science and Health, University of Strathclyde, Glasgow, UK (M.R. Crawford); Psychology Department, Swansea University, Glasgow, UK (M.R. Crawford and A.L. Jones); Department of Epidemiology, Erasmus MC University Medical Centre, Rotterdam, Netherlands (A.I. Luik); Sleep & Circadian Neuroscience Institute (SCNi), University of Oxford, Oxford, UK (C.A. Espie); The Maine Sleep Center, Chest Medicine Associates, Portland, ME, USA (H.L. Taylor); Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA (H.J. Burgess); Rush University Medical Center, Chicago, IL, USA (Rush University Sleep Research Team); Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA (J.C. Ong).

Address all correspondence to M.R. Crawford, School of Psychological Science and Health, University of Strathclyde, Glasgow, UK, email: megan.crawford@strath.ac.uk

Accepted for publication January 27, 2020.

INTRODUCTION

Insomnia symptoms such as difficulties initiating or maintaining sleep are a frequent complaint in patients with chronic migraines (CM).[1-9] A bidirectional relationship between CM and insomnia (CM-I) has been proposed[10,11] and explanations have varied from common pathophysiological mechanisms[12,13] to biobehavioral processes.[14] Ong and Park published a conceptual model describing the potential mechanisms underlying this bidirectional relationship.[14] The behaviors adopted to cope with migraine attacks (napping, oversleeping, caffeine, and medication intake) are known to reduce the likelihood of rapid sleep onset at night,[15] reduce sleep homeostasis, and disrupt circadian rhythms.[16,17] These changes in turn can lead to an increased propensity to future headache attacks.[1,18-25] This increased propensity leads to further engagement in coping behaviors, which triggers a vicious cycle between headache attacks and chronic insomnia.

Treatment of insomnia might offer an opportunity to interrupt this vicious cycle and there are a number of convincing arguments why cognitive behavior therapy for insomnia (CBT-I) should be the treatment of choice. First, insomnia is a treatable condition,[26,27] and CBT-I is recommended as first line treatment,[28] even when it occurs in the context of a medical condition such as chronic pain.[29,30] Second, the coping strategies outlined in the biobehavioral model,[14] are behaviors that can be modified through CBT-I.[31] Third, CM patients are often less open to polypharmacological options,[32] leading to patients being potentially more accepting of non-pharmacological treatments for insomnia.

To our knowledge, only 2 studies have tested cognitive and behavioral interventions for insomnia in adults with CM.[33,34] Smitherman and colleagues[34] evaluated a 3-sesion face-to-face behavioral treatment for insomnia for patients with CM and comorbid insomnia, which included stimulus control and sleep restriction instructions. The intervention was associated with significantly greater improvement in sleep efficiency and sleep quality. Calhoun and Ford[33] randomized 43 women with CM to a sleep hygiene intervention or placebo control group with the aim to revert chronicity by improving sleep. After 6 weeks of the intervention, remission to episodic migraine was substantially greater in the treatment than in a placebo control condition (35 vs 0%). Six weeks after completing the behavioral treatments for insomnia, the authors reported a reduction in headache frequency twice the effect seen in the placebo control condition, which included lifestyle changes only (48% reduction vs 25% reduction). Both of these clinical trials used face-to-face behavioral interventions. Unfortunately, such face-to-face interventions are time intensive and costly. CBT-I sessions usually last between 60 and 90 minutes, with 4-8 sessions needed to cover all components of the treatment. The inaccessibility of CBT-I has also been highlighted,[35,36] thus, many patients with CM will not have access to face-to-face CBT-I. A final challenge is the debilitating nature and unpredictability of migraines, which might make regular attendance and engagement with a face-to-face CBT-I program difficult.

Fortunately, over the last few decades, so-called minimal contact therapies have been developed, limiting the amount of additional burden of migraine treatments.[37,38] Digital therapies are a type of minimal contact therapy, because individuals are able to access the intervention content in their own home and complete it at their own pace. In the last decade, there has been an explosion of available digital CBT-I (dCBT-I) programs that have proven effective, with effect sizes comparable to that of face-to-face therapy.[39-41] The unique aspects of dCBT-I could make it very suitable for individuals with CM.[42] DCBT-I is flexible, scalable, and accessible; the patient can access it at their own convenience, in their own home, or when away. Furthermore, migraine patients could avoid the exposure to the clinical environment with bright lights and noise that can exacerbate a migraine attack. Most likely a result of the

Conflict of Interest: HB is paid as a consultant on the scientific advisory board for Natrol, LLC that manufacture supplements, including melatonin. During part of this work AIL was employed in a position at the University of Oxford funded by Big Health Inc., San Francisco & London. CAE is cofounder and chief medical director of Big Health Ltd. Big Health is the health app company behind Sleepio (the digital intervention evaluated here). All other authors do not have any potential conflicts of interests to disclose (MC, JO, HT, AJ).
Funding: This research project was made possible by an award from the American Sleep Medicine Foundation, a foundation of the American Academy of Sleep Medicine. Recruitment was facilitated by the National Headache Foundation.

debilitating nature of CM,[32,43-48] individuals with headaches are more likely to miss health appointments than other pain disorders.[49] Digital forms of therapy could thus facilitate engagement in this population.

However, it is equally important to consider the potential challenges of dCBT-I for CM patients. For example, increased screen time could lead to an increase in headaches or migraines, as reported in other studies.[50] Furthermore, CBT-I includes temporary sleep deprivation as part of sleep restriction therapy, which in itself may increase headaches/migraines.[21] Indeed, in participants without migraine, an increase in headaches and/or migraines have been reported as a side effect of dCBT-I.[51,52] Completing a fully automated, digital treatment without guidance from a health care provider might prove challenging and lead to increased dropout rates. These are real concerns for the implementation of digital therapy in this population, and with this proof-of-concept study, we are able to evaluate whether these concerns would prevent users from engaging in the program. The aims of this proof-of-concept study were to establish feasibility and acceptability of dCBT-I in patients with CM and preliminary efficacy of this treatment in improving insomnia symptoms and migraines. We set benchmarks to inform future refinement of dCBT-I for patients with CM-I.

METHODS

Participants.—Participants were recruited from 2 sources. The first subset included a pool of participants who completed a case-control observational study;[53] that included an assessment of sleep and circadian phase in women with migraines. The second subset of participants were individuals with CM-I, who were prospectively recruited through (1) referrals from patients who presented to the Department of Neurological Sciences at Rush University Medical Center; (2) referrals from other health care providers; (3) advertisements posted around the medical Centre where the research was conducted, on public transportation (eg, buses and trains), and on community bulletin boards (online and physical); (4) research listservs; (5) newsletters; and (6) word of mouth. We recruited until May 2016 toward our minimum target sample size of 20. While no formal power calculation was conducted, this sample size was expected to be meaningful to evaluate feasibility and acceptability of the treatment.[54] We included women 18 years or above, who had endorsed symptoms of insomnia, defined as a total score ≥11 on the Insomnia Severity Index (ISI).[55] This validated cutoff score is recommended for clinical trials on insomnia.[55] Furthermore, individuals had to meet criteria for CM, which was defined as ≥15 headache days per month for ≥3 months with ≥8 of those days characterized as migraines days[56] and assessed through the Structured Diagnostic Interview and Headache checklist (SDIH-R,[57]). We only included females because of the high prevalence of women in both CM and insomnia disorder.

We excluded any females with an unstable medical condition (including other sleep disorders) which required immediate treatment according to the study physician, or was judged to interfere with the protocol. Similarly, individuals with any psychiatric condition (self-reported or assessed by clinical interview) judged to interfere with the study protocol including substance abuse, psychotic disorder, cognitive disorder, current suicidal ideation, or any uncontrolled psychiatric conditions that required immediate treatment were excluded from this study. Regular users of illegal substances or medications known to affect sleep as well as women who were pregnant or nursing were excluded.

Study Design.—We used a multiple baseline design (MBD) where the introduction of the intervention phase is staggered across different groups of individuals (tiers) in a time-lagged manner (see Fig. 1). Effects

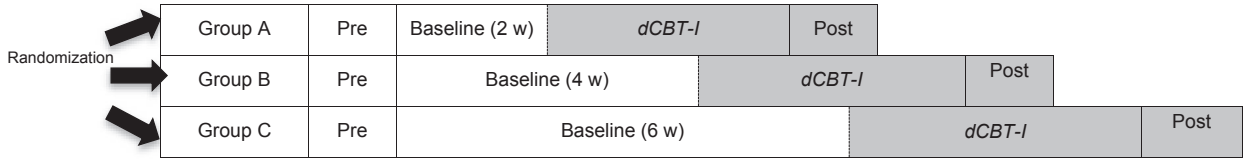

Fig. 1.—Study design. Eligible participants were randomised to one of three different groups, differing in length of baseline prior to the start of the intervention (dCBT-I). Pre-treatment assessment (Pre), post-treatment assessment (Post), weeks (W).

related to the intervention are inferred when a change in the dependent variable coincides with the introduction of the intervention, and this relationship is replicated across the subsequent tiers. MBD was selected for this study to efficiently inform feasibility, while simultaneously assessing potential treatment effects of dCBT-I in CM-I. MBD has been used to test interventions for both migraine[58] and insomnia.[59]

Procedures.—The study was approved by the Rush University Medical Center Institutional Review Board. Upon expressing interest in participating in this study, individuals were asked to provide informed consent and were assessed for eligibility. Informed consent was gathered in writing or by email for those living out of travel distance. All participants completed the ISI to confirm the presence of insomnia symptoms. Participants who were recruited from the case-controlled observational study underwent a brief interview to confirm eligibility. Those individuals recruited prospectively were evaluated through a medical and psychiatric screening interview. Once eligibility was ascertained, all participants completed a baseline questionnaire packet sent via an online survey tool (Survey Monkey®). The questionnaire packet consisted of several measures assessing sleep and headaches. Participants were then randomly assigned to 1 of 3 baselines (see Fig. 1): Group A, consisted of a 2-week baseline, Group B, consisted of a 4-week baseline, and Group C, consisted of a 6-week baseline. A statistician at Rush University Medical Center not involved in the research study, generated a block-stratified randomization schedule using the "rand()" function in excel. To avoid bias, the schedule was concealed for the research staff members (MRC, HLT) that were involved in the screening process until the participant was deemed eligible and had to be notified of their randomization. Each participant began the baseline assessment by completing an electronic sleep diary, which was specifically created for the case-controlled observational study.[53] After completion of the baseline period, individuals started the 6-week dCBT-I program. We chose 2 weeks for the baseline length in Group A and a 2-week time lag for each subsequent tier, because MBDs require a stable baseline pattern prior to the intervention and 2 weeks of sleep diary data is often cited in the literature as the minimum requirement to record a stable sleep pattern.[60] After completing the baseline period, individuals were sent an access code for the dCBT-I program (see details below). During the trial, participants were instructed to continue with treatment as usual, and consult with their health care provider about any changes to their medication regime. About 1 week following completion of the dCBT-I program, all participants were sent an email with a link to complete posttreatment assessments via Survey Monkey. The assessment consisted of several patient-reported measures assessing insomnia, headaches, and treatment satisfaction (see below for details). Participants received USD 100 for completing all study activities.

Intervention.—In this study dCBT-I (Sleepio, www.sleepio.com), consisted of 6 weekly sessions delivered over the internet by an animated virtual therapist. The content included behavioral (eg, sleep restriction, stimulus control), cognitive (eg, putting the day to rest, thought restructuring, imagery, articulatory suppression, paradoxical intention, mindfulness), and relaxation strategies (progressive muscle relaxation and autogenic training) as well as advice on lifestyle and bedroom factors (sleep hygiene), see Table 1. The program was fully automated, and personally tailored using dynamic algorithms applied to the data gathered throughout the program with questionnaires and sleep diaries. More detail about the intervention can be found in the original publication.[61]

To access dCBT-I, participants were provided with a voucher access code with instructions on how to log onto the website. Sessions could be completed at

Table 1.—Outline of Intervention Sessions

Session	Description
1	Formulation, goal setting, diary keeping, motivational contract
2	Sleep hygiene (lifestyle & bedroom), Progressive relaxation, thought checker
3	Sleep hygiene (schedule), stimulus control, sleep restriction
4	Depending on priorities: Cognitive restructure,
5	autogenic training, imagery, mindfulness, paradoxical intention
6	Review goals, reinforce motivation

the individual's own pace in a maximum of 12 weeks. The shortest interval between individual sessions was 7 days; thus, the program could be completed between 5 and 12 weeks. There was no face-to-face contact throughout the intervention and all treatment sessions, support, and reminders were provided through the system. The online platform was accessible to each participant any time of the day or night. The participants were encouraged, however, to contact the research team if they were experiencing any difficulties related to the trial, and the program support team if they were experiencing any technical issues. The research team initiated contact during the intervention phase only when it was clear that the participant was approaching the deadline to complete the treatment within the 12 weeks (accounting for the need to have at least 7 days between each treatment session), or when there were concerns about the participant's safety (eg, indicating increased daytime sleepiness on their diary). The intervention was tested in its original format and no adaptations for this population were made to the intervention at this stage.

Measures.—*Patient Satisfaction Questionnaire Short Form (PSQSF).*—The PSQSF was originally created to measure patient satisfaction for sleep apnea services. The item "how satisfied are you with the care you received from the sleep center?" was amended to "how satisfied are you with the care you received from Sleepio for your insomnia?" and responses were indicated on a 5-point scale from very satisfied to very dissatisfied. Open box responses were also added to the questionnaire for participants to indicate areas they liked/disliked about the program after completing the intervention

Insomnia Severity Index.—The ISI is a brief 5-item scale that measures insomnia severity.[62,63] It has adequate internal consistency with evidence supporting concurrent, predictive, and content validity.[62] The ISI was used both as a screening tool and a postintervention measure.

Sleep Diaries.—Prospective daily sleep diaries were used to assess self-reported sleep patterns and ratings of sleep quality. Sleep diaries have been shown to be a reliable and valid index of insomnia[64] and have been used as an outcome measure in efficacy studies on insomnia (eg, Edinger et al[65]). During the baseline and intervention phases prospective self-report data were collected using online sleep diaries both based on the consensus sleep diary[66] which consisted of questions regarding bed time, sleep onset latency, wake time after sleep onset, rise time, and ratings of sleep quality. From these variables, we were able to deduce total sleep time and sleep efficiency (ratio between total sleep time and time in bed). The sleep diary for the baseline phase was provided through a portal developed specifically for the case-control observational study[53] and the sleep diary during the intervention was provided through the intervention interface.

The Migraine Disability Assessment (MIDAS)[67].—The MIDAS was used to measure migraine impairment, frequency, and severity pre- and postintervention. The 5-item questionnaire assesses the number of days of impairment in different domains (eg, work, school, household) over the previous 3 months. The psychometric properties of the scale are good.[67]

Benchmarks.—As outlined by Leon and colleagues[68] proof-of-concept studies should not test formal outcome hypotheses, but focus on gathering data needed to inform the design of a subsequent full-scale randomized controlled trial (RCT). Feasibility, acceptability, and preliminary efficacy were measured to achieve this aim.

Feasibility (Benchmark 1).—Completion of dCBT-I was used as a marker of feasibility and defined as completing all 6 sessions within the maximum 12-week period. Our benchmark for feasibility was ≥90%.

Acceptability (Benchmark 2).—A version of the Patient Satisfaction Questionnaire Short Form PSQSF adapted for use in the CM population[69] was used to assess patient's treatment satisfaction as it pertains to the treatment protocol. Treatment satisfaction was operationalized, as the percentage of participants indicating to be "satisfied" or "very satisfied" with the intervention on the PSQSF (1-item). Our benchmark for acceptability of dCBT-I was set to ≥80% of the sample reporting satisfaction with treatment. We monitored the responses in the open boxes of the PSQSF for any reported side effects associated with the treatment.

Preliminary Efficacy (Benchmark 3).—Preliminary efficacy was assessed primarily by number of individuals showing a clinically meaningful difference in insomnia severity at the end of treatment. Improvements in insomnia severity were measured using the ISI and defined as >7 points change in the ISI total score,

which has been established as a valid cutoff depicting marked clinical improvement.[70] Our benchmark for preliminary efficacy was at least 50% of participants demonstrating a clinically meaningful change in insomnia severity from baseline-to-posttreatment. The benchmark of 50% was selected based on previous studies reporting response rates between 39 and 65% after digital CBT-I.[71,72]

Data Preparation and Statistical Analysis.—For each benchmark, we calculated the percentage of participants meeting those prespecified criteria. We also calculated intention to treat (ITT) rates based on all individuals who were randomized, as well as those who started and finished the program as per protocol [PP]). Qualitative data from open-box responses on the adapted PSQF were also analyzed using content analysis[73] to capture rich data on treatment acceptability (reported in Supporting Information 1). In addition to our benchmarks, we analyzed pre-to-post change in insomnia severity and headache impairment, severity, frequency, and reported confidence intervals for the difference. Means and standard deviations are reported where appropriate. As exploratory analysis, we conducted a visual analysis of the multiple baseline data (reported in more detail in the Supporting Information 2) and a mixed model analysis to test the effects of the intervention (details reported in the Supporting Information 3). Since this was a feasibility study, no formal statistical inferences were conducted for all analyses. Instead, results focus on estimating effect sizes and confidence intervals. There was no missing data for the benchmark data (feasibility, acceptability of treatment, and improvement in insomnia) or for the migraine data (secondary analysis). For the baseline phase, there were no missing sleep diary days. For the treatment phase, the average was 2.85 days missing (SD = 9.54, max = 44). Only 3 participants had more than 5 missing days in total, and the missing days were from instances where the continuation of the intervention was temporarily interrupted for personal reasons. Missing data on individual days/nights on the diary are controlled for within the mixed model analysis.

RESULTS

Participant Characteristics.—About 193 individuals were evaluated for study eligibility; 149 did not continue past the initial telephone screening interview, see Figure 2. The most frequent reasons for exclu-

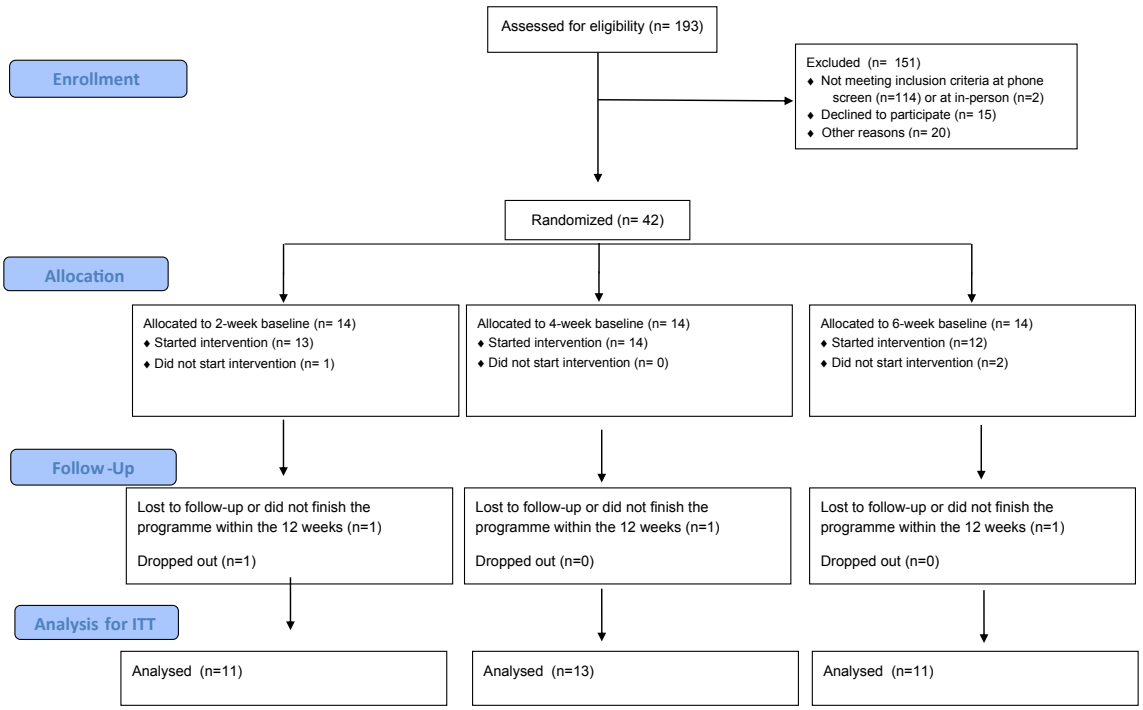

Fig. 2.—CONSORT 2010 flow diagram.

sion (n = 114) at the telephone stage were not meeting criteria for CM (n = 73, 64%), or insomnia (n = 22, 19.3%), or presenting with an unstable medical condition (n = 5, 4.4%). A total of 44 participants completed the in-person screening, after which 2 were excluded. These 2 individuals were excluded because of not meeting criteria for CM (n = 1) and suspicion of delayed sleep phase disorder (n = 1). Participant characteristics are reported in Table 2.

Primary Analysis: Benchmarks.—*Benchmark 1-Feasibility*.—Out of 42 randomized participants, only 39 participants started the program. In total, 35 completed the program within the 12 weeks provided, thus, the PP completion rate was 89.7% (35/39). Based on intention-to-treat (ITT) analysis, 35 of the initial 42 who were randomized completed dCBT-I, thus, the ITT completion rate was 83.3%, see Table 3. Both rates were somewhat under our benchmark of ≥90% completion rate. Reasons for not completing the program were inability to complete because of time commitments, and misunderstanding of requirement to complete all 6 sessions.

Benchmark 2-Acceptability.—Out of the 35, who completed dCBT-I and rated their satisfaction with the treatment, 33 (94.3%) reported being satisfied (n = 15) or very satisfied (n = 18) with treatment, thus, our benchmark for acceptability (≥80% satisfied with treatment) was met, see Table 2. The remaining 2 individuals rated that they felt neutral about the program. We were not able to collect satisfaction from data from non-completers. The ITT acceptability rate (% satisfied of those randomized) was 78.6% (33/42). The PSQSF questionnaire also provided participants with the opportunity to detail specific likes and dislikes, which are reported in detail in Supporting Information 1. Briefly, 2 raters (MRC and HLT) reviewed the content and independently assigned a code to each data point. Content analysis revealed that the majority of individuals liked the content of the program and there was no overwhelming dislike of the program. The three most frequently rated likes were "content of the program" (n = 17), "efficacy of the treatment" (n = 12), and "accessibility/convenience/ease" (n = 12). The most frequently noted dislike was "configurations of the interface/computer program/app" (n = 10)). This included comments such as "get an app for android," or "the constant motion of the animation."

Table 2.—Participant Characteristics of 42 Randomised Participants

	N(%)/Mean (Range or SD)
Age	42.0 (range 22-80)
Race	
Black or African American	6 (14.3%)
White	36 (85.7%)
Ethnicity	
Hispanic	1 (2.4%)
Non-Hispanic	41 (97.6%)
Employment	
Full-time employment (≥32 hours/week)	15 (35.7%)
Part-time employment (<32 hours/week)	12 (28.6%)
Unemployed	0
Full-time caregiver	1 (2.4%)
Retired	5 (11.9%)
Student	2 (4.8%)
Disabled/too ill to work	7 (16.7%)
Education (years)	16.6 (SD 2.7)
Marital status	
Single	8 (19.0%)
In relationship but not cohabiting	6 (14.3%)
Living with spouse/life partner	25 (59.5%)
Divorced or separated	2 (4.8%)
Widowed	1 (2.4%)
Insomnia Severity Index score at baseline	18.4 (SD 3.7)
Duration of chronic migraines in years	8.1 (SD 8.0)

Table 3.—Benchmarks and Results

	Benchmark	Result
Feasibility	≥90%	89.7% for PP (83.3% for ITT)
Acceptability	≥80%	94.3% for PP (78.6% for ITT)
Clinical improvement, ISI change >7	≥50%	65.7% for PP (54.8 for ITT)

ISI = Insomnia Severity Index; ITT = intention to treat; PP = per protocol.

We recorded spontaneous reporting of adverse events through the information in the open-response text box on the posttreatment (eg, feeling nauseous from the motion in the animation). No serious adverse events deemed related to the intervention were reported by the participants.

Benchmark 3-Efficacy.—Of the 35 individuals who completed the treatment program (per protocol), 23

(65.7%) showed a clinically meaningful difference as indicated by a change from baseline >7 points on the ISI (responders). The ITT response rate was 54.8% (23/42). Both values (per protocol [PP] and ITT) were higher than our target benchmark of 50% response rate, see Table 3. Additionally, 16 (45.7%) were classified as remitters, which was defined as an ISI posttreatment score <8.

Secondary Analysis: Improvements in Sleep and Migraines.—Insomnia severity was reduced at posttreatment (ISI mean = 7.7, SD = 4.1) compared to baseline (ISI mean = 17.6, SD = 4.0, mean difference = −9.9; 95% CI = −11.7; −8). At baseline, the average total MIDAS score was 28.7 (SD = 19.5) and at posttreatment this reduced to 22.4 (SD = 17.8), mean difference = −6.3 (95% CI = −12.3; −0.02). We used the frequency and severity items from the MIDAS to report changes in frequency and severity. The migraine frequency was reduced from 21 (SD = 7.0) to 18.4 (SD = 8.7) headache days per month at posttreatment (mean difference = −2.6, 95% CI: −4.58; −0.7). At posttreatment, the severity of migraines had reduced (on a scale of 0-10) from 6.5 (SD 1.4) to 5.4 (SD 1.3), mean difference = 1.1, 95% CI: −1.5; −0.6) with lower scores indicating less severe migraines. At posttreatment, 12 individuals of the 35 who had completed the treatment had reverted to episodic migraine (34.3% of the sample; ITT = 12/42 = 28.6%) and no longer met the duration criteria for CM.

Exploratory Analysis: Visual Analysis and Interrupted Time Series Linear Mixed Model Analysis of the Multiple Baseline Data.—We visually analyzed the sleep efficiency data across the baseline and treatment phases, in order to determine whether a change in sleep efficiency was associated with the start of the intervention. To accomplish this, 2 raters (HT and AL) reviewed graphical representation of sleep efficiency changes across the baseline and the intervention phases for each participant (see Fig. 3 as an example). Each

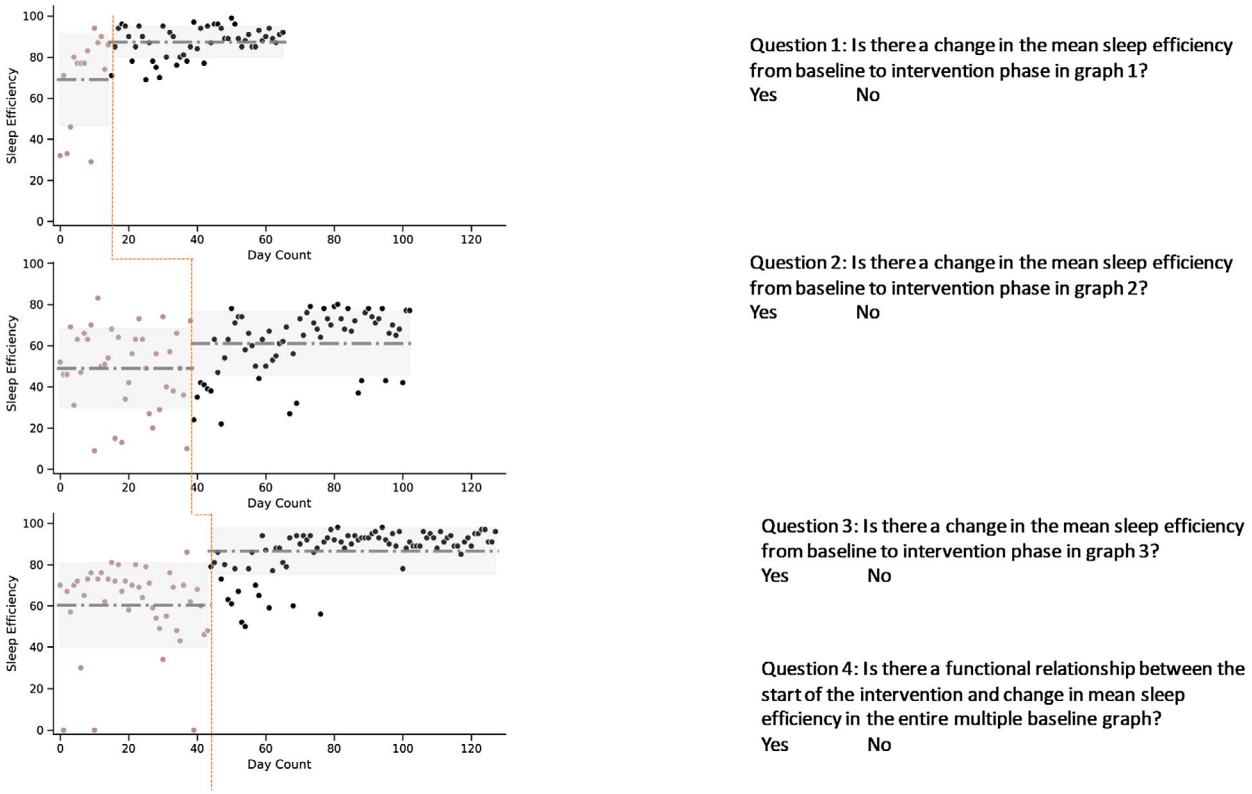

Fig. 3.—Example multiple baseline graph, where the change in mean sleep efficiency (dashed line) in all graphs increased with the start of the intervention (according to both raters). The individual in the top graph was randomized to 2-weeks baseline, the individual in the middle graph to 4-weeks baseline (note, this participant started the intervention with a slight delay), the individual in the bottom graph was randomized to the 6-week baseline.

rater evaluated whether there was a change in the mean, trajectory and night-to-night variability of sleep efficiency that coincided with the start of the intervention. Inter-rater reliability (IRR) was evaluated by calculating kappa values for each variable. The IRR varied between 0.5 and 0.8, indicating a moderate to substantial agreement between the 2 raters. The raters agreed that there was a change in the mean sleep efficiency associated with the start of the intervention in 83% of participants; a change in the sleep efficiency trajectory in 33% of participants; and a change in the night-to-night variability in 41% of the participants (further details on the visual analysis and results are provided in the Supporting Information 2).

In addition to the visual analysis, we also conducted a time series linear mixed model. The linear mixed model allowed us to estimate the effect of the intervention for each participant in an interrupted time series context, taking into account individual differences in sleep efficiency and responses to the intervention. Our model was:

$$Y_{is} = (\beta_0 + S_{0s}) + \beta_1 T_i + (S_{1s} + \beta_2 I)_i + \beta_3 TI_i + \beta_4 TI_i^2$$

where Y_{is} is the ith sleep efficiency score for participant S, S_{0s} represents the random intercept for each participant, S, and S_{1s} is the random slope indicating the individual response to the immediate introduction of the intervention. The other terms represent the fixed effects described for a standard interrupted time series analysis. Although the data are a MBD, the continuous time covariate accounts for different baseline lengths.

The time series linear mixed model revealed an influence of Time (b = 0.12, 95% CI [0.05, 0.18], SE = 0.04), indicating an increase in sleep efficiency with time. There was also an effect of intervention, (b = −4.57, [−9.06, −0.08], SE = 2.29), which showed a decrease in sleep efficiency with immediate introduction of the intervention. The interaction between time and the intervention, however, showed an increase in sleep efficiency with time after the intervention (b = 0.20, [0.07, 0.33], SE = 0.07). Finally, the quadratic interaction term did not show a large influence on sleep efficiency, (b = −0.001, [−0.002, −0.001], SE = 0.00). Additional information about the model is presented in Supporting Information 3.

DISCUSSION

This proof-of concept study has highlighted that dCBT-I could be an appropriate treatment for individuals with CM-I. The results demonstrate that the majority of our benchmarks were met (2 out of 3, and 1 just marginally under the benchmark for our PP rates). While our ITT results were less promising (according to the ITT rates 1 out of 3 benchmarks met), however, this was because of the higher dropout rates *prior* to treatment. We, therefore, still conclude that dCBT-I is a feasible treatment for females with CM-I. A follow-up RCT is appropriate needed to determine the efficacy.

The majority of the participants (89.7%) were able to complete the program within the designated timeframe. The ITT completion rate was lower (83%), however, these dropouts occurred prior to the start of the intervention, so we believe there is no need to refine the intervention for this population. The reasons for non-completion did not seem to be related to any specific aspect of the dCBT-I program. The number of individuals who did not complete the program (n = 4, 10%) is lower than those reported in the Smitherman et al. study (n = 7, 22%), in which the authors tested a 3-session face-to-face intervention for insomnia which included stimulus control and sleep restriction. This is surprising, considering digital therapies are typically associated with higher dropout rates (around 24%[39]). The reason for our lower dropout rates might be the increased contact with participants during the baseline phase prior to treatment initiation.

The intervention was also rated as acceptable by the majority of the sample (94.3%). These findings replicate previous reports of high satisfaction ratings of other digital CBT-I platforms.[74-77] The treatment was rated highly by the majority of participants, and this was corroborated by qualitative reports. For example, 34% of the participants spontaneously cited accessibility/convenience/ease of the intervention as advantages. By comparison, none of the participants felt the intervention was too burdensome. This aligns with our prediction that such a minimal contact therapy would be ideal for patients who experience CM.

The intervention was also associated with clinically meaningful response to treatment (indicated by >7 point change in insomnia severity) in 65.7% of the sample. About half of the sample's insomnia remitted

to nonclinical levels (ISI posttreatment score <8). This is comparable to remission rates published from research in digital CBT-I with insomnia and other physical comorbidities.[77] Our remission rates are slightly higher than rates reported in a meta-analysis of RCTs evaluating face-to-face CBT-I trials with physical or mental comorbidities (average 36% remission rate),[29] however, it is important to note that the meta-analysis also included the PSQI remission rates, so these numbers are not entirely comparable. Our results for insomnia improvements support previous findings on treating insomnia in individuals with CM using face-to-face interventions.[33,34] In Smitherman and colleagues[34] trial, the intervention was associated with significantly greater improvement in sleep efficiency and sleep quality, which we replicated in terms of changes in insomnia severity and daily sleep efficiency (using both the visual analysis and the linear mixed model analysis). Calhoun and Ford reported remission to episodic migraine was substantially greater in the treatment than in a placebo control condition (35 vs 0%), which is comparable to our results (34%). Six weeks after completing the behavioral treatments for insomnia, the authors reported a reduction in headache frequency twice the effect seen in the placebo control condition, which included lifestyle changes only (48% reduction vs 25% reduction). DCBT-I in our study was associated with slightly less improvement in headache impairment (22% reduction in level of impairment) and frequency (12% reduction in frequency). These differences may be due to the digital medium, and less flexibility within this program to personalize the therapeutic instructions and make them relevant to the migraine patient compared to face-to-face treatment. These changes are also lower than those associated with interventions targeting migraine specifically via CBT for migraine pain,[78] Botox (OnabotulinumtoxinA Injection),[79] or other prophylactic migraine medication[80] (between 20 and 40% reduction in migraine frequency). Future, fully powered efficacy studies will need to establish more accurate rates of remission associated with dCBT-I.

Together, our results are promising; demonstrating cognitive behavioral-based strategies for insomnia is an effective strategy for improving both insomnia and potentially as an adjunct treatment for migraines in this population. Furthermore, the results support the evaluation of treatment efficacy through a larger RCT without significant adaptations to the digital program.

A larger RCT employing more scientific rigor is needed to evaluate dCBT-I against some form of control group/placebo condition. For this proof-of-concept study, we deliberately selected a MBD to provide at least some preliminary level of control. MBDs are ideal for smaller feasibility studies as groups who begin the intervention can act as a control for the group who have already started the intervention. The visual analysis and linear mixed modeling gave us some indication that dCBT-I might be effective in this population and encourages us to explore this hypothesis in a well-controlled follow-up study.

The results need to be considered alongside the study limitations. First, we measured treatment acceptability using a single item, which compared to multi-item scales is less reliable and sensitive to change. Additionally, we limited our recruitment to individuals with CM, and therefore, our data cannot be extrapolated to episodic migraines or other types of headache disorders. However, the burden of CM is greater and sleep problems are more prevalent in CM patients compared to those with episodic migraines[44] supporting a more urgent need to evaluate treatments in this group. There are speculations that poor sleep might play a role in the chronification of migraines, but unfortunately, longitudinal studies are lacking. Future studies will need to explore the possibility that dCBT-I could counteract these effects, and potentially reduce the number of transitions to CM. Another limitation of this study is the lack of a control group receiving no treatment. However, as mentioned above, the scientific rigor and control provided through the MBD was sufficient for this type of feasibility study. For changes in headaches, we used the frequency and severity items on the MIDAS, but acknowledge that a headache diary at posttreatment would have been beneficial for more accurate estimation of these variables. We also did not take a formal measure of adverse events. Our results may also not be entirely generalizable considering (1) the inclusion of only females and (2) high levels of education in our sample, however, this is typical of research samples

in general, and those including individuals with insomnia and CM. Finally, we only measured sleep patterns subjectively; future studies should include objective measurements such as wrist actigraphy or polysomnography.

In conclusion, we are encouraged by our results on feasibility, acceptability, and preliminary efficacy, and believe that dCBT-I is appropriate for this population. An RCT to demonstrate treatment efficacy in this group of patients will be needed before use in the clinical pathway for patients with CM can be recommended.

Acknowledgments: The following members are part of the Rush University Sleep Research Team: Drs Maureen Smith, Alejandra Lastra, Ellie Zouein, and James Herdegen. These members were instrumental in the data collection part of the study.

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
Megan R. Crawford, Jason C. Ong, Annemarie I. Luik, Colin A. Espie

(b) Acquisition of Data
Megan R. Crawford, Hannah L. Taylor, Helen J. Burgess, Annemarie I. Luik, Jason C. Ong

(c) Analysis and Interpretation of Data
Megan R. Crawford, Jason C. Ong, Alex L. Jones

Category 2

(a) Drafting the Manuscript
Megan R. Crawford, Jason C. Ong, Alex L. Jones

(b) Revising It for Intellectual Content
Megan R. Crawford, Annemarie I. Luik, Colin A. Espie, Hannah L. Taylor, Helen J. Burgess, Alex L. Jones, Rush University Sleep Research Team, Jason C. Ong

Category 3

(a) Final Approval of the Completed Manuscript
Megan R. Crawford, Annemarie I. Luik, Colin A. Espie, Hannah L. Taylor, Helen J. Burgess, Alex L. Jones, Rush University Sleep Research Team, Jason C. Ong

REFERENCES

1. Kelman L, Rains JC. Headache and sleep: Examination of sleep patterns and complaints in a large clinical sample of migraineurs. *Headache*. 2005;45:904-910.
2. Lateef T, Swanson S, Cui L, Nelson K, Nakamura E, Merikangas K. Headaches and sleep problems among adults in the United States: Findings from the National Comorbidity Survey-Replication study. *Cephalalgia*. 2011;31:648-653.
3. Calhoun AH, Ford S, Finkel AG, Kahn KA, Mann JD. The prevalence and spectrum of sleep problems in women with transformed migraine. *Headache*. 2006;46:604-610.
4. Guidetti V, Galli F, Fabrizi P, et al. Headache and psychiatric comorbidity: Clinical aspects and outcome in an 8-year follow-up study. *Cephalalgia*. 1998; 18:455-462.
5. Song TJ, Cho SJ, Kim WJ, Yang KI, Yun CH, Chu MK. Poor sleep quality in migraine and probable migraine: A population study. *J Headache Pain*. 2018;19:58.
6. Zhu Z, Fan X, Li X, Tan G, Chen L, Zhou J. Prevalence and predictive factors for poor sleep quality among migraineurs in a tertiary hospital headache clinic. *Acta Neurol Belg*. 2013;113:229-235.
7. Seidel S, Hartl T, Weber M, et al. Quality of sleep, fatigue and daytime sleepiness in migraine – A controlled study. *Cephalalgia*. 2009;29:662-669.
8. Karthik N, Kulkarni GB, Taly AB, Rao S, Sinha S. Sleep disturbances in 'migraine without aura' – A questionnaire based study. *J Neurol Sci*. 2012;321:73-76.
9. Begasse de Dhaem O, Seng E, Minen MT. Screening for insomnia: An observational study examining sleep disturbances, headache characteristics, and psychiatric symptoms in patients visiting a headache center. *Pain Med*. 2018;19:1067-1076.
10. Uhlig BL, Engstrom M, Odegard SS, Hagen KK, Sand T. Headache and insomnia in population-based epidemiological studies. *Cephalalgia*. 2014;34:745-751.
11. Lovati C, D'Amico D, Raimondi E, Mariani C, Bertora P. Sleep and headache: A bidirectional relationship. *Expert Rev Neurother*. 2010;10:105-117.
12. Holland PR. Headache and sleep: Shared pathophysiological mechanisms. *Cephalalgia*. 2014;34:725-744.
13. Burstein R, Noseda R, Borsook D. Migraine: Multiple processes, complex pathophysiology. *J Neurosci*. 2015; 35:6619-6629.
14. Ong JC, Park M. Chronic headaches and insomnia: Working toward a biobehavioral model. *Cephalalgia*. 2012;32:1059-1070.

15. Irish LA, Kline CE, Gunn HE, Buysse DJ, Hall MH. The role of sleep hygiene in promoting public health: A review of empirical evidence. *Sleep Med Rev*. 2015;22:23-36.
16. Karacan I, Thornby JI, Anch M, Booth GH, Williams RL, Salis PJ. Dose-related sleep disturbances induced by coffee and caffeine. *Clin Pharmacol Ther*. 1976;20:682-689.
17. Salin-Pascual RJ, Valencia-Flores M, Campos RM, Castano A, Shiromani PJ. Caffeine challenge in insomniac patients after total sleep deprivation. *Sleep Med*. 2006;7:141-145.
18. Park JW, Chu MK, Kim JM, Park SG, Cho SJ. Analysis of trigger factors in episodic migraineurs using a smartphone headache diary applications. *PLoS ONE*. 2016;11:e0149577.
19. Sullivan DP, Martin PR. Sleep and headaches: Relationships between migraine and non-migraine headaches and sleep duration, sleep quality, chronotype, and obstructive sleep apnoea risk. *Aust J Psychol*. 2017;69:210-217.
20. Bokhari FA, Sami W, Shakoori TA, Ali SA, Qureshi GA. Clinical characteristics of 226 college-going female migraineurs in Lahore, Pakistan – Putting ICHD-2 to the road test. *Neuro Endocrinol Lett*. 2008;29:965-970.
21. Inamorato E, Minatti-Hannuch SN, Zukerman E. The role of sleep in migraine attacks. *Arq Neuropsiquiatr*. 1993;51:429-432.
22. Kilic K, Karatas H, Donmez-Demir B, et al. Inadequate brain glycogen or sleep increases spreading depression susceptibility. *Ann Neurol*. 2018;83:61-73.
23. Peres MF, Stiles MA, Siow HC, Dogramji K, Silberstein SD, Cipolla-neto J. Chronobiological features in episodic and chronic migraine. *Cephalalgia*. 2003;23:590-591.
24. Engstrom M, Hagen K, Bjork M, Gravdahl GB, Sand T. Sleep-related and non-sleep-related migraine: Interictal sleep quality, arousals and pain thresholds. *J Headache Pain*. 2013;14:68.
25. Bertisch SM, Li W, Buettner C, et al. Nightly sleep duration, fragmentation, and quality and daily risk of migraine. *Neurology*. 2020;94:e489-e496.
26. Trauer JM, Qian MY, Doyle JS, Rajaratnam SM, Cunnington D. Cognitive behavioral therapy for chronic insomnia: A systematic review and meta-analysis. *Ann Intern Med*. 2015;163:191-204.
27. van Straten A, van der Zweerde T, Kleiboer A, Cuijpers P, Morin CM, Lancee J. Cognitive and behavioral therapies in the treatment of insomnia: A meta-analysis. *Sleep Med Rev*. 2018;38:3-16.
28. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD, Clinical Guidelines Committee of the American College of Physicians. Management of chronic insomnia disorder in adults: A clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2016;165:125-133.
29. Wu JQ, Appleman ER, Salazar RD, Ong JC. Cognitive behavioral therapy for insomnia comorbid with psychiatric and medical conditions: A meta-analysis. *JAMA Intern Med*. 2015;175:1461-1472.
30. Geiger-Brown JM, Rogers VE, Liu W, Ludeman EM, Downton KD, Diaz-Abad M. Cognitive behavioral therapy in persons with comorbid insomnia: A meta-analysis. *Sleep Med Rev*. 2015;23:54-67.
31. Ong JC, Stepanski EJ, Gramling SE. Pain coping strategies for tension-type headache: Possible implications for insomnia? *J Clin Sleep Med*. 2009;5:52-56.
32. Palacios-Cena D, Neira-Martin B, Silva-Hernandez L, et al. Living with chronic migraine: A qualitative study on female patients' perspectives from a specialised headache clinic in Spain. *BMJ Open*. 2017;7:e017851.
33. Calhoun AH, Ford S. Behavioral sleep modification may revert transformed migraine to episodic migraine. *Headache*. 2007;47:1178-1183.
34. Smitherman TA, Walters AB, Davis RE, et al. Randomized controlled pilot trial of behavioral insomnia treatment for chronic migraine with comorbid insomnia. *Headache*. 2016;56:276-291.
35. Espie CA. "Stepped care": A health technology solution for delivering cognitive behavioral therapy as a first line insomnia treatment. *Sleep*. 2009;32:1549-1558.
36. Thomas A, Grandner M, Nowakowski S, Nesom G, Corbitt C, Perlis ML. Where are the behavioral sleep medicine providers and where are they needed? A geographic assessment. *Behav Sleep Med*. 2016;14:687-698.
37. Morgan M, Cousins S, Middleton L, Warriner-Gallyer G, Ridsdale L. Patients' experiences of a behavioural intervention for migraine headache: A qualitative study. *J Headache Pain* 2015;17:16.
38. Haddock CK, Rowan AB, Andrasik F, Wilson PG, Talcott GW, Stein RJ. Home-based behavioral treatments for chronic benign headache: A meta-analysis of controlled trials. *Cephalalgia*. 1997;17:113-118.
39. Zachariae R, Lyby MS, Ritterband LM, O'Toole MS. Efficacy of internet-delivered cognitive-behavioral

therapy for insomnia – A systematic review and meta-analysis of randomized controlled trials. *Sleep Med Rev*. 2016;30:1-10.
40. Ye YY, Zhang YF, Chen J, et al. Internet-based cognitive behavioral therapy for insomnia (ICBT-i) improves comorbid anxiety and depression-a meta-analysis of randomized controlled trials. *PLoS ONE*. 2015;10:e0142258.
41. Luik AI, Kyle SD, Espie CA. Digital cognitive behavioral therapy (dCBT) for insomnia: A state-of-the-science review. *Curr Sleep Med Rep*. 2017;3:48-56.
42. Rosenberg L, Butler N, Seng EK. Health behaviors in episodic migraine: Why behavior change matters. *Curr Pain Headache Rep*. 2018;22:65.
43. Buse DC, Silberstein SD, Manack AN, Papapetropoulos S, Lipton RB. Psychiatric comorbidities of episodic and chronic migraine. *J Neurol*. 2013;260:1960-1969.
44. Torres-Ferrus M, Quintana M, Fernandez-Morales J, Alvarez-Sabin J, Pozo-Rosich P. When does chronic migraine strike? A clinical comparison of migraine according to the headache days suffered per month. *Cephalalgia*. 2017;37:104-113.
45. Stewart WF, Wood GC, Manack A, Varon SF, Buse DC, Lipton RB. Employment and work impact of chronic migraine and episodic migraine. *J Occup Environ Med*. 2010;52:8-14.
46. Meletiche DM, Lofland JH, Young WB. Quality-of-life differences between patients with episodic and transformed migraine. *Headache*. 2001;41:573-578.
47. Peters M, Huijer Abu-Saad H, Vydelingum V, Dowson A, Murphy M. The patients' perceptions of migraine and chronic daily headache: A qualitative study. *J Headache Pain*. 2005;6:40-47.
48. Rutberg S, Ohrling K. Migraine – More than a headache: Women's experiences of living with migraine. *Disabil Rehabil*. 2012;34:329-336.
49. Odonkor CA, Christiansen S, Chen Y, et al. Factors associated with missed appointments at an academic pain treatment center: A prospective year-long longitudinal study. *Anesth Analg*. 2017;125:562-570.
50. Montagni I, Guichard E, Carpenet C, Tzourio C, Kurth T. Screen time exposure and reporting of headaches in young adults: A cross-sectional study. *Cephalalgia*. 2015;36:1020-1027.
51. Kyle SD, Morgan K, Spiegelhalder K, Espie CA. No pain, no gain: An exploratory within-subjects mixed-methods evaluation of the patient experience of sleep restriction therapy (SRT) for insomnia. *Sleep Med*. 2011;12:735-747.
52. Espie CA, Emsley R, Kyle SD, et al. Effect of digital cognitive behavioral therapy for insomnia on health, psychological well-being, and sleep-related quality of life: A randomized clinical trial. *JAMA Psychiatry*. 2019;76:21-30.
53. Ong JC, Taylor HL, Park M, et al. Can circadian dysregulation exacerbate migraines? *Headache*. 2018; 58:1040-1051.
54. Julious SA. Sample size of 12 per group rule of thumb for a pilot study. *Pharm Stat*. 2005;4:287-291.
55. Morin CM, Belleville G, Belanger L, Ivers H. The Insomnia Severity Index: Psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep*. 2011;34:601-608.
56. Headache Classification Committee, Olesen J, Bousser MG, et al. New appendix criteria open for a broader concept of chronic migraine. *Cephalalgia*. 2006;26:742-746.
57. Andrew ME, Penzien DB, Rains JC, Knowlton GE, McAnulty RD. Development of a computer application for headache diagnosis: The headache diagnostic system. *Int J Bio-Med Comput*. 1992;31:17-24.
58. Drury RL, DeRisi WJ, Liberman RP. Temperature biofeedback treatment for migraine headache: A controlled multiple baseline study. *Headache*. 1979; 19:278-284.
59. Gunning MJ, Espie CA. Psychological treatment of reported sleep disorder in adults with intellectual disability using a multiple baseline design. *J Intellect Disabil Res*. 2003;47:191-202.
60. Wohlgemuth WK, Edinger JD, Fins AI, Sullivan RJ, Jr. How many nights are enough? The short-term stability of sleep parameters in elderly insomniacs and normal sleepers. *Psychophysiology*. 1999;36:233-244.
61. Espie CA, Kyle SD, Williams C, et al. A randomized, placebo-controlled trial of online cognitive behavioral therapy for chronic insomnia disorder delivered via an automated media-rich web application. *Sleep*. 2012;35:769-781.
62. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med*. 2001;2:297-307.
63. Morin CM. *Insomnia: Psychological Assessment and Management*. New York: The Guilford Press; 1993.
64. Coates TJ, Killen JD, George J, Marchini E, Silverman S, Thoresen C. Estimating sleep parameters: A multitrait–multimethod analysis. *J Consult Clin Psychol*. 1982;50:345-352.
65. Edinger JD, Wohlgemuth WK, Radtke RA, Marsh GR, Quillian RE. Cognitive behavioral therapy for

treatment of chronic primary insomnia – A randomized controlled trial. *JAMA*. 2001;285:1856-1864.
66. Carney CE, Buysse DJ, Ancoli-Israel S, et al. The consensus sleep diary: Standardizing prospective sleep self-monitoring. *Sleep*. 2012;35:287-302.
67. Stewart WF, Lipton RB, Dowson AJ, Sawyer J. Development and testing of the Migraine Disability Assessment (MIDAS) Questionnaire to assess headache-related disability. *Neurology*. 2001;56: S20-S28.
68. Leon AC, Davis LL, Kraemer HC. The role and interpretation of pilot studies in clinical research. *J Psychiatr Res*. 2011;45:626-629.
69. Parthasarathy S, Haynes PL, Budhiraja R, Habib MP, Quan SF. A national survey of the effect of sleep medicine specialists and American Academy of Sleep Medicine Accreditation on management of obstructive sleep apnea. *J Clin Sleep Med*. 2006;2:133-142.
70. Morin CM, Vallieres A, Guay B, et al. Cognitive behavioral therapy, singly and combined with medication, for persistent insomnia: A randomized controlled trial. *JAMA*. 2009;301:2005-2015.
71. Lancee J, van Straten A, Morina N, Kaldo V, Kamphuis JH. Guided online or face-to-face cognitive behavioral treatment for insomnia: A randomized wait-list controlled trial. *Sleep*. 2016;39:183-191.
72. Cheng P, Luik AI, Fellman-Couture C, et al. Efficacy of digital CBT for insomnia to reduce depression across demographic groups: A randomized trial. *Psychol Med*. 2019;49:491-500.
73. Hsieh HF, Shannon SE. Three approaches to qualitative content analysis. *Qual Health Res*. 2005;15: 1277-1288.
74. Blom K, Tarkian Tillgren H, Wiklund T, et al. Internet-vs. group-delivered cognitive behavior therapy for insomnia: A randomized controlled non-inferiority trial. *Behav Res Ther*. 2015;70:47-55.
75. van Straten A, Emmelkamp J, de Wit J, et al. Guided Internet-delivered cognitive behavioural treatment for insomnia: A randomized trial. *Psychol Med*. 2014;44:1521-1532.
76. Strom L, Pettersson R, Andersson G. Internet-based treatment for insomnia: A controlled evaluation. *J Consult Clin Psychol*. 2004;72:113-120.
77. Ritterband LM, Bailey ET, Thorndike FP, Lord HR, Farrell-Carnahan L, Baum LD. Initial evaluation of an Internet intervention to improve the sleep of cancer survivors with insomnia. *Psychooncology*. 2012;21:695-705.
78. Basler HD, Jakle C, Kroner HB. Cognitive-behavioral therapy for chronic headache at German pain centers. *Int J Rehabil Health*. 1996;2:235-252.
79. Dodick DW, Turkel CC, DeGryse RE, et al. OnabotulinumtoxinA for treatment of chronic migraine: Pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Headache*. 2010;50:921-936.
80. Silberstein SD, Lipton RB, Dodick DW, et al. Efficacy and safety of topiramate for the treatment of chronic migraine: A randomized, double-blind, placebo-controlled trial. *Headache*. 2007;47:170-180.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site.