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Original Article

Objective sleep disturbance is associated with poor response to cognitive and behavioral treatments for insomnia in postmenopausal women

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ABSTRACT

Study objectives: To determine whether insomnia patients with objective sleep disturbance are less responsive to cognitive and behavioral treatments than those without objective sleep disturbance, characterize effects of insomnia therapy on objective sleep, and determine whether reductions in nocturnal cognitive arousal correspond to changes in objective sleep.

Methods: Secondary analysis of a single-site, randomized controlled trial. 113 postmenopausal women (56.40 ± 5.34 years) with menopause-related insomnia disorder were randomized to three treatment conditions: cognitive-behavioral therapy for insomnia (CBTI), sleep restriction therapy (SRT), or sleep education control. Primary outcomes were the Insomnia Severity Index (ISI) and polysomnography (PSG) sleep parameters and were collected at pretreatment, posttreatment, and six-month follow-up.

Results: Patients with lower pretreatment PSG sleep efficiency had lower rates of insomnia remission after active treatment relative to those with higher sleep efficiency (37.8% vs 61.8%). Neither CBTI and SRT produced clinically meaningful effects on PSG sleep. Exploratory analyses revealed that reductions in nocturnal cognitive arousal were associated with decreases in PSG sleep latency, but not wake after sleep onset.

Conclusions: Our findings support an emerging literature suggesting that insomnia patients with objective sleep disturbance may have blunted response to insomnia therapy. Research is needed to enhance treatments to better improve insomnia in patients with objective sleep disturbance. A lack of observed CBTI and SRT effects on PSG sleep suggests that these therapies may be presently ill-designed to improve objective sleep. Nocturnal cognitive arousal may represent an entry point to improve objective sleep latency in insomnia.

Name: Behavioral Treatment of Menopausal Insomnia: Sleep and Daytime Outcomes. **URL**: clinicaltrials.gov. **Registration**: NCT01933295.

1. Introduction

Polysomnography (PSG) is the gold standard tool for the objective quantification of sleep and assessing most sleep disorders [1]. Yet, PSG has a complex history with insomnia in regard to its usefulness for evaluating, treating, and understanding the etiology of the disorder. This is reflected in diagnostic systems for sleep disorders (current and prior iterations of Diagnostic and Statistical Manual of Mental Disorders [2] [DSM] and International Classification of Sleep Disorders [3] [ICSD]) that define insomnia disorder as a symptom-based condition without PSG criteria. Weak empirical support for the diagnostic utility of PSG for insomnia led to recommendations against its use in routine evaluations, except to assess for other sleep disorders that can co-occur with or contribute to sleep complaints (eg, sleep apnea) [4–6]. Evidence casting doubt on the utility of PSG in insomnia includes discrepancy between patient-reported sleep and objective sleep findings, little or no reliable difference in objective sleep between insomnia patients

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and healthy sleepers, and data suggesting that changes in objective sleep are unnecessary for successful alleviation of insomnia with therapy [7–9]. Clinicians and researchers have thus considered patient-reported symptoms as a better indicator of the clinical experience of insomnia. Consequently, objective sleep assessment in insomnia has largely fallen by the wayside.

Although the insomnia patient population as a whole does not reliably exhibit objective sleep disturbances, a subset of the population does. Accumulating evidence suggests that insomnia disorder may be comprised of two broad phenotypes: insomnia with and without objective sleep disturbance [8,10,11]. Even so, there is no universal consensus on how objective sleep disturbance should be operationalized in insomnia (eg, total sleep time < 6 h, sleep latency or wake after sleep onset > 30 min, etc.). Nevertheless, the distinction is important as insomnia patients with objective sleep disturbances have poorer stress regulation, more comorbidities, and poorer long-term prognoses relative to those with normal objective sleep [10,11]. As insomnia with objective sleep disturbance may have a different etiology and stronger biological basis than insomnia without objective sleep findings [10], researchers have taken interest in potential differences in treatment responsivity by phenotype.

These clinical trials focused on insomnia with vs without objective short sleep (<6 h total sleep time on PSG or actigraphy) and have produced mixed results. In two trials, insomnia patients with objective short sleep, relative to those with normal sleep duration, had blunted response to cognitive behavioral therapy for insomnia (CBTI) [12,13], which is gold standard treatment for insomnia [14]. In contrast, three other trials showed no difference in treatment response between the normal sleep duration and short sleep insomnia phenotypes [15–17]. As no clear patterns in methodology distinguish studies that support vs refute differential treatment response, it is unclear why such a degree of inconclusion with markedly opposing findings was produced. Although all studies used the total sleep time < 6 h operationalization for objective sleep disturbance, it is possible that a lack of established criteria for an objective sleep disturbance phenotype contributed in part to these mixed results; particularly as objective sleep disturbance may manifest in ways other than total sleep time < 6 h.

Further complicating the matter of objective sleep disturbance and insomnia therapy, overwhelming evidence suggests that cognitive and behavioral interventions have minimal or no effect on objective sleep disturbance [9]. As clinical trials of cognitive and behavioral treatments for insomnia have traditionally focused on patient-reported sleep symptoms, the lack of improvement in objective sleep and the potential importance of such effects has been downplayed. A recent review identified only five high quality CBTI trials that reported PSG outcomes, none of which required objective sleep criteria for trial entry [9]. In-line with recent interest in objective sleep disturbance as an indicator of insomnia morbidity, mortality, and treatment-resistance [8,10–13], there has been renewed emphasis to better understand the effects of insomnia therapies on objective sleep and identifying how objective sleep outcomes can be improved [18].

The present report was a secondary analysis of a single-site RCT comparing CBTI, sleep restriction therapy (SRT; a single component of CBTI and effective standalone treatment), and sleep hygiene education control (SHE) for the treatment of menopause-related DSM-5[2]/ICSD-3[3] insomnia disorder in a sample of 150 postmenopausal women. See reports by Drake et al., and Kalmbach et al., for outcome data pertaining to insomnia, sleep diaries, depression, and daytime function [19–21]. In this secondary analysis, we (1) tested pretreatment objective sleep disturbance as a potential moderator of treatment response, and (2) tested effects of cogitative-behavioral therapy for insomnia (CBTI) and SRT on objective sleep disturbance relative to control. Based on proposals that insomnia with objective findings represents a more severe and biologically-based phenotype of the disorder, we hypothesized that patients with lower PSG sleep efficiency before treatment would report greater insomnia symptoms after CBTI and SRT relative to those with higher pretreatment sleep efficiency. We predicted no such pattern would be observed in the control condition. Importantly, we chose to test sleep efficiency as a moderator as it captures all manifestations of objective nocturnal wakefulness (sleep latency, wake after sleep onset, short sleep duration) and because no universally accepted cutoff defining objective sleep disturbance in insomnia exists.

Second, a lack of objective sleep criteria for clinical trial entry has been identified as a limitation of prior RCTs evaluating CBTI effects on objective sleep due to restricted range and potential insufficient statistical power to detect effects. The present RCT required objective sleep disturbance for entry. When this study was initially proposed, our team hypothesized that CBTI and SRT would improve objective sleep. However, meta-analytic data published in the interim [9] changed our expectations, thus we predicted that neither CBTI nor SRT would improve objective sleep relative to control, despite our PSG inclusion criteria.

In an exploratory analysis based on data from our lab and others showing that cognitive arousal and rumination is associated with objective sleep disturbance [22–27], we conducted *posthoc* analyses to investigate whether changes in nocturnal cognitive arousal were associated with changes in PSG sleep latency and wake after sleep onset, irrespective of treatment condition (as we hypothesized no treatment effects). This exploratory analysis was conducted in attempt to identify therapeutic targets associated with changes in objective sleep.

2. Methods

2.1. Subjects and setting

This trial was conducted in a six-hospital health system in metro Detroit, Michigan, USA. Patients were recruited from the health system in primary care and sleep medicine clinics, from the community via newspaper advertisements, and from a database of prior sleep center studies. Inclusionary criteria included having 12 consecutive months without menses and self-reported wake after sleep onset $\geq$ 1 h per night at least three nights per week, as well as meeting criteria for DSM-5 insomnia disorder that onset or exacerbated during the peri- or postmenopausal period per clinical interview with a registered nurse with specialty training in behavioral sleep medicine. Inclusionary criteria regarding objective sleep disturbance required women exhibit mean wake after sleep onset of 45 min or more on two overnight PSG studies (adaptation night + baseline night, neither of which could have wake after sleep onset < 30 min). Exclusionary criteria included prior or current DSM-5 major depression per diagnostic interview, sleep-wake disorders other than insomnia (examined on PSG adaptation night and per patient report), and medications influencing sleep. Women receiving hormone replacement therapy were eligible to participate.

Participants were randomized to one of three conditions: SHE, SRT, and CBTI. Randomization was conducted using 150 allocations (50 per group) that were ordered randomly and concealed in envelopes. Group allocation for each participant was then assigned using the order of concealed envelopes. While double-blind could not be achieved given the nature of the behavioral interventions, subjects were not informed which treatments were considered control versus active, or of the specific hypotheses. Assessments of self-reported insomnia symptoms (via online surveys) and

objective sleep parameters (via in-lab overnight PSG were collected prior to treatment, at posttreatment (within two weeks of completing treatment), and six months after treatment completion.

2.2. Polysomnography assessments and schedule

The study protocol included four overnight laboratory PSG studies. Night 1: Subjects who passed the in-person screening interview then underwent a PSG adaptation/screening night with a montage routinely used to rule out sleep disorders other than insomnia disorder such as obstructive sleep apnea and periodic limb movement disorder (apnea-hypopnea index > 10, periodic limb movement index with arousal > 10). Night 2: A week later, patients underwent a second PSG night, which was used to help determine eligibility (see *Subjects and setting* section above) and served as the pretreatment baseline night to which posttreatment and follow-up data would be compared. Night 3: Within two weeks of completing treatment, subjects underwent a third PSG study to record posttreatment objective sleep disturbance. Night 4: Six months later, subjects underwent the final PSG study to record longer-term objective sleep. For all subjects, overnight PSG study bedtimes were scheduled in accordance with self-reported habitual bedtimes and ended 8 h after lights out.

2.3. Treatment conditions

Sleep hygiene education (SHE), ie, minimal intervention control condition. Women randomized to the online sleep hygiene education condition received six weekly emails including general, non-personalized information on the following topics: the basics of endogenous sleep regulation; the impact of sleep on health problems such as obesity, diabetes, and hypertension; the effects of stimulants and other sleep-disruptive substances; the relationship between sleep, diet, and exercise; and tips on creating a sleep-conducive bedroom environment. Sleep hygiene is neither the primary cause nor a sufficient therapeutic target in insomnia disorder and therefore served as an ideal minimal intervention control condition and real-world comparator [28].

Cognitive-behavioral therapy for insomnia (CBTI) was one of two active treatments in this RCT. Women randomized to CBTI completed six face-to-face sleep therapy sessions with a registered nurse who specializes in behavioral sleep medicine. CBTI is a structured, multi-modal treatment that targets sleep-disruptive behaviors and beliefs (see Ref. [29]). Data from clinical trials consistently show that CBTI is as efficacious as pharmacological treatment in the short-term, but produces superior treatment response in the long-term [14,30]. CBTI patients received six weekly sessions, which covered behavioral (sleep restriction and stimulus control) and cognitive (eg, cognitive restructuring) components, as well as relaxation strategies (eg, progressive muscle relaxation and autogenic training) and sleep hygiene education.

Sleep restriction therapy (SRT) was the second active treatment in this RCT and is considered an effective standalone behavioral treatment for insomnia [31]. Although SRT actually predates CBTI, SRT is now commonly packaged as part of CBTI and is considered a critical element. As CBTI consists of SRT plus multiple other components, SRT is the briefer of the two interventions. Here, SRT was delivered as a two-week intervention. Specifically, the initial face-to-face session consisted of reviewing patient sleep history, education and rationale for sleep restriction practices, and behavioral homework. Then four follow-up sessions (three phone contacts, each 3–4 days apart, followed by a second face-to-face session) were delivered across the following two weeks and were used to titrate sleep schedules based on sleep diary data. SRT as delivered in this RCT was the same as the sleep restriction component in CBTI, except that sessions were spaced more closely together (every 3–4 days rather than approximately weekly), and thus prescribed sleep schedules were based on fewer days of sleep diary data.

2.4. Measures

PSG data were scored by a certified sleep technician according to standard procedures by the American Academy of Sleep Medicine's 2012 guidelines [32]. PSG scorers were blind to group. Sleep measures included sleep latency (minutes from lights out to first epoch of sleep), wake after sleep onset (minutes awake post onset), sleep efficiency (proportion of time in bed asleep), and total sleep time (sleep duration).

All self-report measures were collected via online surveys hosted by Qualtrics, LLC. Prior to treatment, patients reported sociodemographic and health history information.

The Insomnia severity index (ISI) is a seven-item self-report measure of insomnia symptom severity [33]. Scores range from 0 to 28 with higher scores indicating greater symptom severity. The ISI was administered at pretreatment, posttreatment, and six-month follow-up. Recommendations for clinical trials research include detecting positive insomnia cases based on ISI scores $\geq$ 11, whereas remission is indicated by ISI scores $\leq$ 7 [34].

The Presleep Arousal Scale's Cognitive factor (PSAS-C) [35] was used to measure cognitive arousal during the presleep period, ie, when individuals are in bed attempting to fall asleep. The PSAS Cognitive scale consists of eight items (eg, 'review or ponder events of the day' and 'can't shut off your thoughts') and possible scores range from 8 to 40 with higher scores indicating greater presleep cognitive arousal.

Presleep somatic arousal was measured using the Presleep Arousal Scale's Somatic factor (PSAS-S) [35]. The PSAS Somatic scale consists of eight items (eg, 'heart racing, pounding, or beating irregularly' and 'a tight, tense feeling in your muscles') and possible scores range from 8 to 40 with higher scores indicating greater presleep cognitive arousal.

2.5. Analysis plan

Analyses were conducted using SPSS version 25. Age, menopause-related characteristics, and pretreatment PSG sleep parameters were first presented and cross-sectionally compared across the three treatment conditions to identify group differences before treatment. Next, we examined whether pretreatment objective sleep disturbance as measured by PSG sleep efficiency moderated treatment response. Specifically, we ran repeated measures analysis of covariance (ANCOVA) models to test changes in ISI from pre to posttreatment/follow-up with Treatment (active treatment [CBTI and SRT] vs control) as a between group factor and pretreatment sleep efficiency as a covariate. Notably, CBTI and SRT were combined into a single group, because our previously published findings show that they are both efficacious treatments [36] and our primary focus here is on PSG Sleep Efficiency as a moderator of treatment response, irrespective of modality. Thus, results from this model showed interactions for Treatment X Time (to demonstrate that active treatment reduced ISI greater than control, which we have reported in greater detail elsewhere [36]) and for PSG sleep efficiency X Time to evaluate whether pretreatment objective sleep disturbance altered trajectory of symptoms over time, irrespective of condition. Significant interactions were then deconstructed with *posthoc* independent samples and paired samples t-tests to describe the observed effects in relation to active treatment vs control.

We then tested treatment effects on objective sleep disturbance (ie, PSG-determined sleep latency, wake after sleep onset, sleep efficiency, and total sleep time). We first ran 3 × 2 repeated measures ANOVA models to examine Treatment × Time interactions for changes in PSG sleep parameters from pretreatment to posttreatment/follow-up. Any significant Treatment × Time interactions were followed by paired samples t-tests within each condition to test for potential simple effects. In addition, a cross-sectional one-way ANOVA was used to compare mean levels for each treatment outcome to determine differences in symptom levels across groups at posttreatment and six-month follow-up. Lastly, we used multivariate linear regression models to explore whether changes in presleep cognitive and somatic arousal were associated with acute changes in objective sleep. Specifically, we regressed changes in PSG sleep parameters between pre and posttreatment on changes in presleep cognitive and somatic arousal.

3. Results

3.1. Participant enrollment and attrition

Refer to Fig. 1 flow chart of study enrollment and participation. A total of 317 postmenopausal women were screened for eligibility. Of these individuals, 107 women were ineligible and another 56 declined to participate or had scheduling conflicts. 154 postmenopausal women were randomized to treatment: SHE: N = 50, SRT: N = 52, and CBTI: N = 52. Two subjects in both the SRT and CBTI conditions were disqualified during treatment for changes in medication or new onset comorbid sleep disorder. Thus, recruitment included two more individuals to replace those who were disqualified. This resulted in 50 subjects completing treatment in each of the three conditions. All 150 subjects provided self-reported posttreatment outcome data, whereas 16% of treatment completers did not provide follow-up data six months later (Fig. 1). Regarding PSG data, 147 women completed all three overnight PSGs (pretreatment, posttreatment, follow-up). However, data from several subjects were lost due to a shared network server failure, thus PSG data from 113 subjects were available for analysis. Because the present study focused on objective sleep disturbance, all data reported herein are from the 113 patients with partial or complete PSG data.

3.2. Screening and sample characteristics

See Table 1 for sample demographics for the full sample and by treatment condition. Our sample was largely comprised of non-Hispanic White and non-Hispanic Black women. Regarding objectively estimated sleep, mean PSG sleep latency was within normal limits (11.95 ± 13.48 m), whereas mean PSG wake after sleep onset was high (78.97 ± 44.29 m), sleep efficiency was low (81.19 ± 9.98), and total sleep time was relatively short (390.59 ± 46.78 min). One-way ANOVA models revealed treatment groups did not differ on age or pretreatment ISI (Table 1). To determine whether pretreatment PSG sleep efficiency was associated with patient-reported insomnia severity, we compared patients with pretreatment PSG sleep efficiency < 85% vs ≥ 85%, which did not differ in pretreatment ISI scores (14.60 ± 3.58 vs 15.51 ± 4.78, t[110] = 1.15, p = 0.25).

3.3. Pretreatment objective sleep disturbance buffers treatment response to insomnia therapy

3.3.1. Acute treatment response

We first ran a repeated measures ANCOVA model examining changes in ISI from pre to posttreatment with Treatment (active treatments, ie, CBTI and SRT, vs control) as a between group factor and baseline PSG sleep efficiency as a covariate. The Treatment × Time interaction was significant (F[1,108) = 51.43, p < 0.001 and a *posthoc* paired-samples t-test showed that patients who received active treatment reported a mean decrease of 7.5 points on the ISI (t[70] = -12.24, p < 0.001), whereas mean ISI decreased by just 1.2 points for controls.

The Treatment X PSG Sleep Efficiency interaction was also significant (F[1,108] = 10.64, p = 0.001) such that patients with lower pretreatment sleep efficiency exhibited smaller improvements in ISI by the end of treatment. An independent samples t-test showed that posttreatment ISI scores were lower for patients with low pretreatment sleep efficiency compared to those with high sleep efficiency (8.47 ± 5.53 vs 10.98 ± 4.73, t[111]=−2.60, p=.01).

We then evaluated treatment outcomes related to objective sleep disturbance within active treatment and then within the control condition. Among patients receiving active treatment, pretreatment sleep efficiency was negatively correlated with change scores in ISI such that lower sleep efficiency was associated with smaller decreases in symptoms (Table 2). Notably, mean ISI scores did not differ before treatment between patients with high vs low sleep efficiency (Table 3). However, after active treatment, *posthoc* descriptive comparisons showed that patients with high pretreatment sleep efficiency, relative to those with low sleep efficiency, reported lower insomnia symptom severity and higher rates of remission (Table 3). Specifically, patients in active treatment with high pretreatment sleep efficiency had a mean reduction of 9.2 points on the ISI, whereas patients with low efficiency only reported an ISI reduction of 5.9 points, (t[70] = 2.79, p = 0.007, Cohen's d = 0.68). This suggests that response to insomnia therapies for patients with objective sleep disturbance is ~33% lower than response for patients without objective sleep findings. This pattern was not replicated in the control condition (Tables 2 and 3). See Supplementary Table 1 for pre and posttreatment mean ISI scores for patients with high and low sleep efficiency across all three conditions.

3.3.2. Long-term treatment response

A repeated measures ANCOVA examining changes in ISI from pretreatment to six-month follow-up again showed that the Treatment × Time interaction was significant (F[1,109) = 54.25, p < 0.001. In addition, the Treatment X Sleep Efficiency interaction was also significant (F[1,99] = 5.14, p = 0.02) such that lower pretreatment sleep efficiency predicted smaller gains in insomnia improvement through six-month follow-up.

Among those in active treatment, pretreatment sleep efficiency was associated with longer-term reductions in ISI such that lower objective sleep disturbance before treatment was associated with greater reductions in ISI over the long-term (Table 2). Even so, *posthoc* descriptive comparisons showed that ISI scores did not differ between patients with high or low sleep efficiency at six-month follow-up, although remission rates approached significance (Table 3). In the control condition, pretreatment sleep efficiency was once again not associated with changes in ISI scores nor clinical outcomes at six-month follow-up (Tables 2 and 3). See Supplementary Table 1 for follow-up mean ISI scores for patients with high and low sleep efficiency across all three conditions.

3.4. CBTI vs SRT vs SHE control treatment effects on objective sleep disturbance

3.4.1. Sleep latency

See Table 4 for sleep latency means and standard deviations for all groups at posttreatment and six-month follow-up. Also see Fig. 2 for visual representation of data. When testing acute treatment

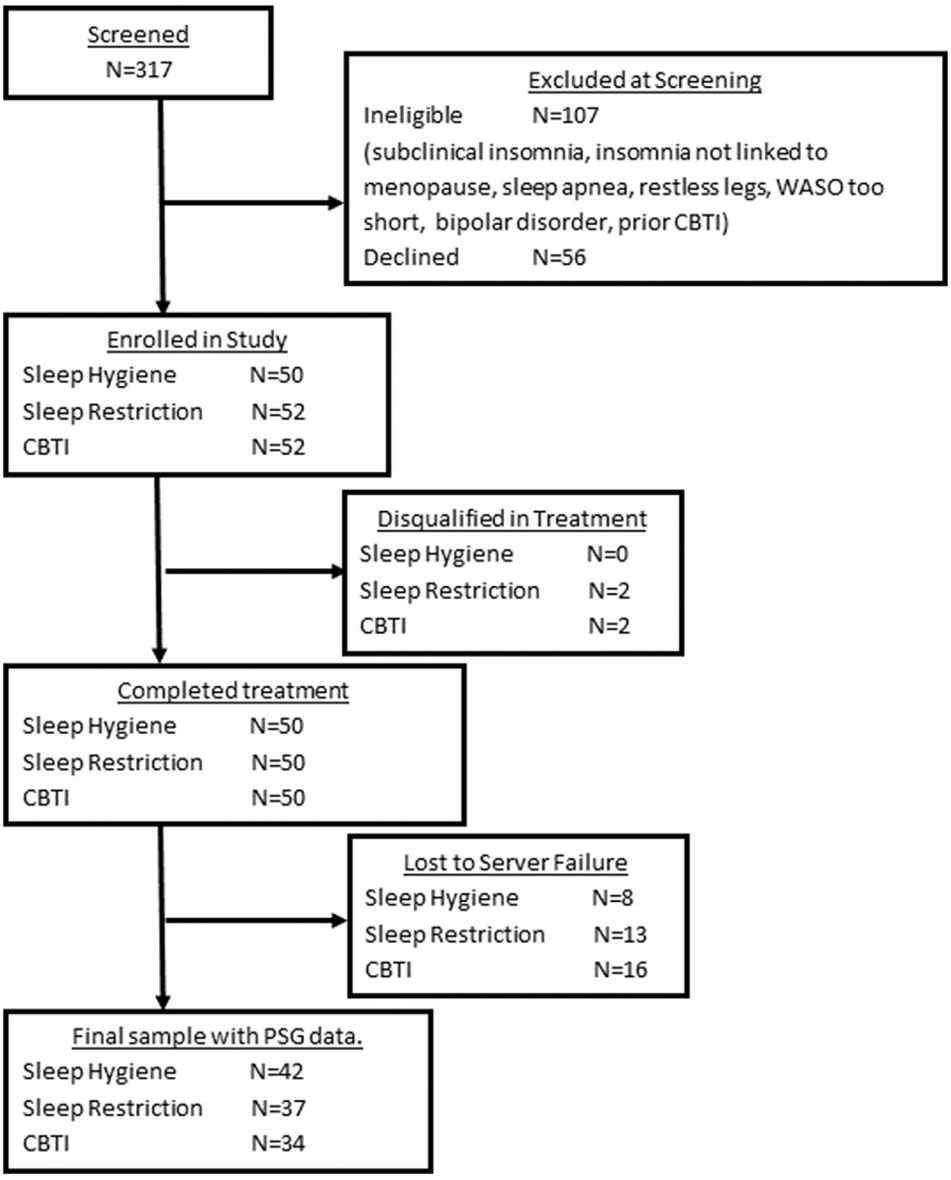

Fig. 1. Patient flowchart for recruitment and study protocol.

effects, a repeated measures ANOVA showed that sleep latency did not significantly change for the full sample between pre and posttreatment ($F[1,106] = 0.82$, $p = 0.37$). However, a significant Treatment × Time interaction was observed ($F[2,106] = 3.23$, $p = 0.04$). We then ran series of *posthoc* paired samples t-tests to identify group(s) wherein sleep latency significantly changed during treatment. In the SRT group, sleep latency significantly decreased by 5 min ($t[33] = 3.24$, $p = 0.003$). To the contrary, no significant within-group changes in sleep latency were observed for CBTI ($p = 0.27$) or SHE ($p = 0.74$). Despite the significant reduction in sleep latency in the SRT group, a one-way ANOVA revealed no posttreatment group differences in sleep latency (Table 4).

A repeated measures ANOVA also showed that PSG sleep latency did not significantly change from pretreatment to six-month follow-up ($F[1,104] = 2.26$, $p = 0.14$) nor was a Treatment × Time interaction observed ($F[2,104] = 0.85$, $p = 0.43$). Consistent with these null findings, a one-way ANOVA revealed no group differences in sleep latency six months after treatment.

3.4.2. Wake after sleep onset

See Table 4 for wake after sleep onset means and standard deviations for all groups at posttreatment and six-month follow-up. Also see Fig. 2 for visual representation of data. When exploring acute changes in sleep maintenance, a repeated measures ANOVA revealed that PSG wake after sleep onset decreased by 11 min for the full sample, which was a significant reduction ($F[1,106] = 5.86$, $p = 0.02$). Despite this acute reduction in wake after sleep onset, no Treatment × Time interaction was observed ($F[2,106] = 1.08$, $p = 0.34$). Consistent with this null interaction finding, a one-way ANOVA revealed no posttreatment group differences in PSG wake after sleep onset ($p = 0.79$; Table 4).

Findings from the six-month follow-up data were consistent with acute models. A repeated measures ANOVA again showed that wake after sleep onset decreased by 11 min from pretreatment to six-month follow-up ($F[1,104] = 4.19$, $p = 0.04$). Yet, once again, the Treatment × Time interaction was non-significant ($F[2,104] = 2.49$, $p = 0.09$) and no group differences in wake after sleep onset were observed ($p = 0.21$; Table 4).

Table 1
Sample characteristics prior to treatment (n = 113).

	All subjects	SHE	SRT	CBTI	
Sample size	113	42	37	34	
Age (M±SD)	56.40 ± 5.34 y	57.21 ± 5.30	56.68 ± 5.18	55.09 ± 5.46	F(2,110) = 1.58, p = 0.21
Race (n; %)					
White	56; 49.6%	20; 47.6%	21; 56.8%	15; 44.1%	
Black	51; 45.1%	20; 47.6%	13; 35.1%	18; 54.5%	
Hispanic or Latinx	1; 0.9%	–	1; 2.7%	–	
Not reported	5; 4.4%	2; 4.8%	2; 5.4%	1; 2.9%	
Years since last menses (M±SD)	7.19 ± 7.24	7.62 ± 8.01	6.42 ± 6.62	7.51 ± 7.06	F(2,110) = 0.29, p = 0.75
Hormone Replacement Therapy (n; %)	3; 2.7%	2; 4.8%	1; 2.7%	0; 0.0%	χ^2 = 1.65, p = 0.44
Medical/Surgical Menopause (n; %)	27; 23.9%	7; 16.7%	9; 24.3%	11; 32.4%	χ^2 = 2.55, p = 0.28
ISI, prior to treatment (M±SD)	15.04 ± 4.15	14.86 ± 4.45	15.16 ± 3.80	15.12 ± 4.23	F(2,110) = 0.06, p = 0.94

Note: SHE = sleep hygiene education control. SRT = sleep restriction therapy. CBTI = cognitive behavioral therapy for insomnia. PSG = polysomnography. m = minutes. Sleep latency = minutes from lights out to first epoch of sleep. Wake after sleep onset = minutes awake post sleep onset. Sleep efficiency = proportion of time in bed spent asleep X 100. Total sleep time = minutes spent asleep during total PSG recording. F = F-statistic for one-way analysis of variance to compare means across SHE, SRT, and CBTI groups. χ [2] = chi-square statistic to compare proportions across SHE, SRT, and CBTI groups. p = significance vale.

Table 2
Correlations between pretreatment sleep efficiency and changes in insomnia symptom severity among patients in active treatment and in the control condition.

	ISI_{T2-T1}	ISI_{T3-T1}
Active Treatment		
Pretreatment SE	-0.37**	-0.29*
Control Condition		
Pretreatment SE	-0.10	-0.07

Note: Active treatment includes CBTI and SRT participants. Control condition includes sleep hygiene education control participants. ISI_{T2-T1} = change in insomnia severity index score from pretreatment to posttreatment. ISI_{T3-T1} = change in insomnia severity index score from pretreatment to 6-month follow-up. SE = PSG-defined sleep efficiency.

3.4.3. Sleep efficiency

See Table 4 and Fig. 2 for PSG sleep efficiency results. Repeated measures ANOVA models revealed no acute changes in sleep efficiency (F[1,106] = 2.25, p = 0.11), whereas PSG sleep efficiency increased by ~2% for the full sample by six-month follow-up (F [1,104] = 5.63, p = 0.02). Even so, no Treatment × Time interaction was observed for acute (p = 0.11) or long-term (p = 0.09) effects. No treatment condition differences in sleep efficiency were observed at posttreatment (p = 0.54) or six months later (p = 0.24; Table 4).

3.4.4. Total sleep time

As time in bed was fixed, results for total sleep time therefore mirror sleep efficiency data (Table 4, Fig. 2). Thus, we will simply acknowledge that no Treatment × Time interactions were observed and no group differences at posttreatment or six-month follow-up were significant.

3.5. Exploring associations between presleep arousal and objective sleep disturbance

Prior to treatment, multivariate linear regression showed that PSG sleep latency was significantly associated with presleep cognitive arousal, but not with presleep somatic arousal (Table 5). Neither cognitive nor somatic arousal was associated with PSG wake after sleep onset. Posttreatment data replicated pretreatment data such that PSG sleep latency was significantly associated with presleep cognitive arousal, whereas somatic arousal was nonsignificant (Table 5). Posttreatment PSG wake after sleep onset was not associated with cognitive nor somatic arousal.

Lastly, we conducted two multivariate linear regression models to test whether acute improvements in presleep arousal were associated with improvements in objective sleep (Table 5). Consistent with pre and posttreatment models, reductions in PSG sleep latency were significantly associated with reductions in presleep cognitive arousal, but not with changes in somatic arousal. Changes in wake after sleep onset were not associated with changes in cognitive nor somatic arousal.

4. Discussion

In postmenopausal women with chronic insomnia and PSG-defined objective sleep maintenance difficulties, patients with

Table 3
Descriptive comparisons of insomnia symptom severity and remission rates across treatment between patients with and without objective sleep disturbance (Mean ± Standard Deviations presented).

	Pretreatment	Posttreatment		6-Month Follow-up	
Patients in active treatment					
ISI	Symptom Severity	Symptom Severity	Remission Rates	Symptom Severity	Remission Rates
	t(69) = -0.67, p = 0.51	t(69) = 2.64, p = .01, d = 0.63	χ^2 = 4.06, p = 0.04, RR = 1.63	t(63) = 1.55, p = 0.13	χ^2 = 3.28, p = 0.07
SE ≥ 85%	15.47 ± 4.44	6.29 ± 4.24	21/34; 61.8%	6.63 ± 4.99	22/30; 73.3%
SE < 85%	14.84 ± 3.56	8.92 ± 4.13	14/37; 37.8%	8.54 ± 4.94	18/35; 51.4%
Patients in control condition.					
ISI	Symptom Severity	Symptom Severity	Remission Rates	Symptom Severity	Remission Rates
	t(39) = -0.92, p.36	t(39) = 0.20, p = .84	χ^2 = 0.16, p = 0.69	t(35) = -0.34, p.74	χ^2 = 0.69, p = 0.41
SE ≥ 85%	15.60 ± 5.63	13.40 ± 5.01	1/26; 3.8%	13.54 ± 6.17	3/24; 12.5%
SE < 85%	14.27 ± 3.66	13.69 ± 4.07	1/15; 6.7%	12.96 ± 4.19	3/13; 23.1%

Note: Active treatment includes CBTI and SRT participants. Control condition includes sleep hygiene education control participants. ISI = insomnia severity index. t = t-statistic for independent samples t-test. p = significance value. χ^2 = chi-square. SE = sleep efficiency. SE ≥ 85% = high sleep efficiency before treatment reflecting no objective sleep disturbance. SE < 85% = low sleep efficiency before treatment reflecting objective sleep disturbance.

Table 4
Comparing CBTI vs SRT vs sleep hygiene education on objective sleep parameters.

	Pretreatment	Posttreatment	6-month Follow-up
	Group Comparisons	Group Comparisons	Group Comparisons
Sleep latency	F(2,110) = 0.15, p = 0.86	F(2,108) = 1.82, p = 0.17	F(2, 108) = 1.02, p = 0.36
SHE	12.45 ± 17.33 m	11.66 ± 16.78 m	8.77 ± 6.83 m
SRT	12.35 ± 12.21 m	6.38 ± 5.30 m	10.44 ± 11.23 m
CBTI	10.88 ± 8.92 m	13.37 ± 20.91 m	12.22 ± 12.75 m
Wake after sleep onset	F(2,110) = 1.09, p = 0.34	F(2,108) = 0.24, p = 0.79	F(2, 108) = 1.58, p = 0.21
SHE	81.82 ± 42.95 m	70.80 ± 39.54 m	77.77 ± 51.04 m
SRT	84.25 ±0 .51.15 m	64.17 ± 29.83 m	58.54 ± 32.94 m
CBTI	67.97 ± 37.15 m	68.06 ± 54.26 m	68.34 ± 51.95 m
Sleep efficiency	F(2,11) = 1.02, p = 0.36	F(2,108) = 0.64, p = 0.56	F(2, 108) = 1.28, p = 0.28
SHE	80.58 ± 9.88	82.74 ± 10.16	82.01 ± 10.58
SRT	80.01 ± 10.94	85.31 ± 6.34	85.71 ± 7.15
CBTI	83.20 ± 8.94	83.08 ± 13.61	83.25 ± 11.78
Total sleep time	F(2,110) = 0.62, p = 0.54	F(2,108) = 0.62, p = 0.54	F(2, 108) = 1.43, p = 0.24
SHE	388.92 ± 45.98 m	397.46 ± 48.97 m	394.38 ± 50.65 m
SRT	385.84 ± 52.23 m	409.68 ± 30.42 m	413.25 ± 33.62 m
CBTI	397.82 ± 41.72 m	399.43 ± 65.19 m	400.74 ± 57.20 m

Note: SHE = sleep hygiene education control. SRT = sleep restriction therapy. CBTI = cognitive behavioral therapy for insomnia. PSG = polysomnography. m = minutes. Sleep latency = minutes from lights out to first epoch of sleep. Wake after sleep onset = minutes awake post sleep onset. Sleep efficiency = proportion of time in bed spent asleep X 100. Total sleep time = minutes spent asleep during total PSG recording. F = F-statistic for one-way analysis of variance to compare means across SHE, SRT, and CBTI groups. p = significance vale.

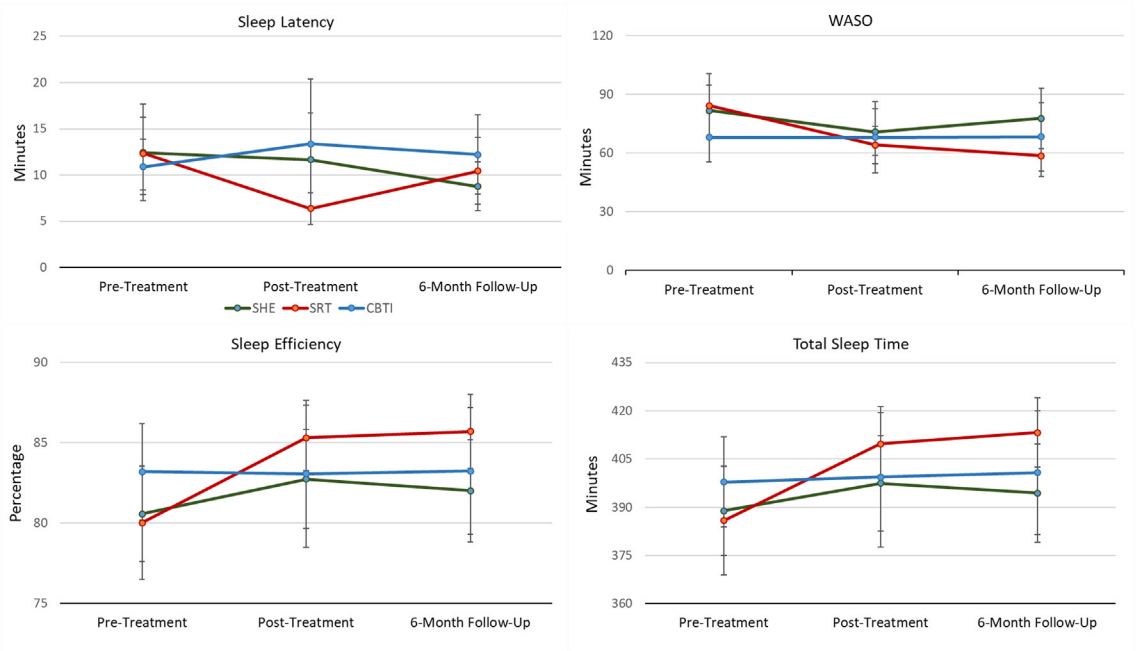

Fig. 2. Pretreatment, posttreatment, and follow-up PSG sleep latency, wake after sleep onset, sleep efficiency, and total sleep time data for CBTI, SRT, and SHE (means and standard errors presented).

greater objective sleep disturbance prior to treatment reported smaller gains on self-report measures of insomnia symptoms after therapy, relative to patients with less objective sleep disturbance. These data suggest that insomnia patients with objective sleep disturbance may respond more poorly to cognitive and behavioral insomnia treatments than patients without objective sleep findings. Not only did objective sleep disturbance appear to blunt treatment response, but CBTI and SRT exerted no therapeutically beneficial effects on objective sleep disturbance relative to control. Some evidence suggested that sleep latency could potentially be reduced with sleep restriction, but it is unclear whether this effect would be durable or clinically meaningful. Even so, patients who reported decreases in nocturnal cognitive arousal also exhibited reductions in sleep latency on PSG, which suggests that nocturnal cognitive arousal might represent an entry point for cognitive-behavioral interventions to reduce objective sleep latency in patients presenting with trouble falling asleep.

4.1. Objective sleep disturbance as a moderator of treatment response

Patients with lower PSG sleep efficiency before treatment had poorer acute and long-term self-reported insomnia outcomes relative to insomnia patients without objective findings. Important to emphasize here is that low PSG sleep efficiency before treatment was not associated with pretreatment patient-reported insomnia

Table 5
Associations of presleep cognitive and somatic arousal with objective sleep disturbance.

	b	β	p		b	β	p
Pretreatment Sleep latency				*Pretreatment Wake after sleep onset*			
Pretreatment PSAS-C	0.90	0.26	0.01	Pretreatment PSAS-C	-0.27	-0.02	0.83
Pretreatment PSAS-S	0.06	0.03	0.74	Pretreatment PSAS-S	-0.83	-0.14	0.19
Posttreatment Sleep latency				*Posttreatment Wake after sleep onset*			
Pretreatment PSAS-C	1.89	0.50	0.001	Pretreatment PSAS-C	1.37	0.12	0.42
Pretreatment PSAS-S	-0.44	-0.18	0.19	Pretreatment PSAS-S	-0.23	-0.03	0.83
Δ *Sleep latency*				Δ *Wake after sleep onset*			
Δ PSAS-C	1.34	0.28	0.04	Δ PSAS-C	0.26	0.02	0.89
Δ PSAS-S	-0.17	-0.06	0.64	Δ PSAS-S	-0.19	-0.02	0.86

Note: b = unstandardized regression coefficient. β = standardized regression coefficient. p = statistical significance. PSAS-C = presleep arousal scale, cognitive factor. PSAS-S = presleep arousal scale, somatic factor. Sleep latency = minutes from lights out to first epoch of sleep. Wake after sleep onset = minutes awake post sleep onset. Δ Sleep latency = Change in PSG-based sleep latency from pre to posttreatment. Δ Wake after sleep onset = Change in PSG-based wake after sleep onset from pre to posttreatment. Δ PSAS-C = Change in presleep arousal scale cognitive factor scores from pre to posttreatment. Δ PSAS-S = Change in presleep arousal scale somatic Factor scores from pre to posttreatment.

severity, thus pretreatment objective sleep disturbance is not merely a proxy for patient-reported illness severity. Among patients receiving CBTI or SRT, those with greater objective sleep disturbance had smaller acute and long-term insomnia improvements and lower rates of remission after therapy relative to those without objective sleep difficulties. In the control group, treatment outcomes did not differ as a function of pretreatment objective sleep disturbance. These results are consistent with prior reports suggesting that objective short sleep blunts response to CBTI [12,13], but contrary to reports that show no difference in insomnia therapy outcomes between insomnia patients with normal vs short objective sleep duration [15–17].

Reasons why our study supported objective sleep disturbance as a moderator of treatment outcomes in insomnia (as findings in the field are highly mixed) are not readily clear, but we can speculate based on notable differences in our methodology. One potential explanation is that our entry criteria included minimal requirements for objective wake after sleep onset. Prior CBTI trials with PSG outcomes have not required objective nocturnal wakefulness and may have thus suffered from restriction of range [9]. In addition, our primary analyses for examining objective sleep disturbance as a moderator centered on sleep efficiency as a continuous variable, rather than dichotomizing the sample into two subgroups. Preserving the dimensional aspect of objective sleep disturbance may have retained sufficient statistical power to detect moderating effects of objective sleep disturbance on treatment outcomes, which may have been lost if we tested our hypotheses by dichotomizing the sample into two subgroups (as observed in our posthoc descriptive comparisons between patients with high vs low sleep efficiency based on the <85% cutoff). This is especially critical in the absence of empirically supported PSG sleep efficiency-based clinical cutoff criteria for phenotypes.

4.2. Operationalizing objective sleep disturbance in insomnia: the need to identify a clinical indicator

Our reasoning behind operationalizing objective sleep disturbance as pretreatment sleep efficiency on PSG was twofold: (1) sleep efficiency is encompassing in that it captures sleep latency, wake time during sleep, and early morning awakenings, and (2) no clear cutoff defining objective sleep disturbance exists in the literature, thus examining sleep efficiency as a continuous variable at present may be preferable. Important to emphasize here is that this study's *posthoc* group comparisons based on < 85% sleep efficiency were for descriptive purposes and in alignment with clinical thresholds in behavioral sleep medicine used to guide decisions in therapy protocol, but are not intended to elucidate phenotypes.

Indeed, no consensus PSG criteria have been firmly established to classify the objective sleep disturbance phenotype. A lack of standardization is reflected by myriad operationalizations of objective sleep disturbance in insomnia research (eg, < 85% sleep efficiency, < 6.5 h total sleep time, > 30 min sleep latency, etc.) [8]. Recently, empirical support for short objective sleep duration (<6 h total sleep time, ideally assessed via PSG) as a robust indicator of objective sleep disturbance in insomnia has flourished [10,11,37–39], yet it is unclear whether other PSG criteria can also identify insomnia patients with other distinct and clinically meaningful patterns of objective sleep disturbance.

Although insomnia with short sleep duration has garnered much deserved attention, it is possible that short sleep is just one clinically meaningful indicator of objective sleep disturbance. If other indicators of significant objective sleep disturbance exist, then it is possible that a lack of consideration for these other potential manifestations of objective sleep disturbance in insomnia have contributed to mixed findings in the field. Along these lines, objective short sleep reflects physiologic hyperarousal in the context of insomnia. It is thus critical to determine whether physiologic hyperarousal underlies other forms of objective sleep disturbance (prolonged latency, extended wake after sleep onset, etc.). Future large-scale research is needed to identify valid and reliable objective criteria to differentiate between insomnia patients with and without objective findings, potentially in addition to the widely supported short sleep phenotype, and to characterize the psychological and neurobiological underpinnings, as well as characterize morbidity, mortality, and treatment-responsivity related to any indicators of objective sleep disturbance in insomnia. If objective findings are clearly established and refined, then clinical trials research will be better positioned to determine whether triage based on objective criteria can improve treatment outcomes.

4.3. Objective sleep disturbance as a treatment outcome in insomnia therapy

A notable strength of our RCT over prior trials is that we required objective sleep disturbance per PSG for study entry. Despite oversampling insomnia patients with objective findings, we did not observe any meaningful effects of CBTI or SRT on objective sleep at posttreatment or six-month follow-up, relative to control. Our findings, in combination with results from a recent meta-analysis of five high quality clinical trials [9], suggest that insomnia therapies may not exert changes to objective sleep disturbance in a clinically meaningful way. Yet, there is ample opportunity in future research

to augment CBTI and SRT to enhance treatment effects of psychological intervention on objective nocturnal wakefulness.

Although evidence suggests that insomnia and objective sleep disturbance are most toxic when co-occurring [10,11], objective sleep disturbances alone have nevertheless been linked to negative health consequences including depression and increased perceived stress, obesity and obesogenic behaviors, and cardiometabolic dysregulation [40–43]. Thus, enhancing insomnia therapies to better improve sleep in insomnia patients with these objective findings is an important endeavor for clinical sleep research, especially given growing evidence that patients with objective sleep may not experience adequate alleviation of self-reported symptoms with insomnia therapy. Research is needed to identify therapeutic targets that may serve as entry points to therapeutically and durably improve objective sleep through psychological or pharmacological interventions.

4.4. Can reducing nocturnal cognitive arousal improve objective sleep disturbance?

Prior and after treatment, nocturnal cognitive arousal levels were positively associated with PSG sleep latency, which is consistent with prior reports [22–27]. Moreover, we found that changes in nocturnal cognitive arousal were associated with changes in sleep latency such that decreases in nocturnal cognitive arousal were linked to falling asleep faster on PSG. In contrast, nocturnal cognitive arousal was not associated with sleep maintenance difficulties. Self-reported somatic arousal at night was not associated with latency or maintenance parameters on PSG.

Although our data and prior studies [9] indicate that standard CBTI and SRT may not therapeutically benefit objective wakefulness at night, identifying the connection between nocturnal cognitive arousal and objective sleep latency offers a potential entry point to improve patients' ability to fall asleep. Standard CBTI does not emphasize focus on cognitive arousal such as rumination or worry, nor is cognitive arousal considered a key therapeutic target. Unsurprisingly, CBTI has not demonstrated strong or robust effects on the tendency to ruminate or worry [20,44], although even modest reductions in cognitive-emotional arousal facilitate treatment-response in CBTI [45]. As experimental studies show that inducing rumination prolongs PSG and actigraphy-defined sleep latency [22–26], we may consider that therapeutically reducing nocturnal cognitive arousal with insomnia therapies augmented to better target these cognitive-emotional symptoms may have downstream effects on objective sleep. Future studies should determine whether enhancing CBTI (or other efficacious insomnia therapies) to defuse ruminative thought processes may improve objective sleep measures. Potential therapies and/or augmentation strategies to better improve cognitive-emotional arousal in insomnia may include cognitive therapy for insomnia [46], mindfulness-based therapy for insomnia [47], and even components of rumination-focused cognitive behavioral therapy [48] or emotion regulation therapy [49].

4.5. Limitations and future directions

The present study should be interpreted in light of certain limitations. Our primary limitation concerns limits of generalizability related to our patient population. As these patients reported insomnia that onset or was exacerbated by the menopause transition, results from our postmenopausal sample may not generalize to men or younger women. Further, etiological processes for menopausal insomnia may differ compared to the broader adult insomnia population. Indeed, levels of nocturnal cognitive arousal were lower in this sample than what has been reported by other insomnia patient populations, which may reflect differing etiology. Given the strong association between cognitive arousal and sleep latency, it is unsurprising then that PSG sleep latencies were largely within normal limits for this sample per quantitative criteria for objective findings [50]. Thus, the nature of our sample limited our ability to detect potential CBTI and SRT treatment effects on PSG sleep latency due to restricted range. Relatedly, our study included entry criteria for PSG-based wake after sleep onset. While this is a strength for detecting improvements in objective sleep, this entry criterion limited may have contributed to our inability to testing other operationalizations of objective sleep disturbance by producing under-representation of patients with prolonged objective sleep latency and over-representation of those with objective sleep maintenance. Future studies testing treatment effects of CBTI and SRT should do so in more representative samples that allow testing different operationalizations of objective sleep disturbance, which may provide important evidence regarding clinical utility.

Notably, in the present study, all subjects were required to stay in bed for 8 h each night. Although this standardizes observation, it also creates a behavioral demand for maintaining sleep while being recorded, which itself could disrupt sleep. Along these lines, the pattern of wake after sleep onset may have been altered with CBTI or SRT. That is, if pretreatment sleep maintenance issues were widespread throughout the night, but then consolidated to early morning awakenings, this may thereby reflect consolidated sleep with early morning awakening possibly indicating that the patient does not need the full 8 h of sleep allotted to them.

It is possible or even likely that sleep restriction (as a standalone treatment or as a component of CBTI) decreases objective sleep latency, particularly before complete titration of the sleep period. Even so, acute reductions in sleep latency are not necessarily therapeutic or beneficial if (1) pretreatment sleep latency is not excessive and (2) acute gains are not durable over the long-term. Notably, posttreatment PSG in the SRT was two weeks after treatment began, whereas PSG after CBTI was conducted after ~six weeks of therapy. Therefore, it is possible that any acute sleep restriction-related changes in PSG sleep latency in the CBTI group were observable before titrating sleep schedules out. Research is needed to determine whether insomnia patients with prolonged objective sleep latency may experience a substantial and durable decrease in latency (on actigraphy or PSG) in response to sleep restriction (as standalone treatment or a component of CBTI) or whether acute movement on this index merely reflects acute sleep deprivation.

By extension, we previously reported that CBTI and SRT had no clinically meaningful effects on rumination and worry in this sample [20] and, in the present study, we showed that these therapies largely did not improve objective sleep relative to control. Despite the lack of treatment effects, we observed that decreases in nocturnal cognitive arousal were associated with decreases in PSG sleep latency. But because these treatments are ill-designed to improve ruminative cognitive processes or objective sleep, the observed effect size in the present study may be underestimated. Further, it is possible that decreases in cognitive arousal may also be associated with other changes in objective sleep, but that a lack of treatment effects on cognitive arousal and objective sleep prevented our ability to detect such effects. Finally, the small sample size and PSG data loss may have limited our ability to detect effects by reducing statistical power. Even so, null findings presented here are consistent with the extant literature.

5. Conclusions

Postmenopausal insomnia patients with objective sleep disturbance appeared to have blunted treatment response to CBTI and

SRT, whereas patients without objective sleep findings were more responsive to these insomnia therapies. In addition, cognitive and behavioral treatments for insomnia produced limited improvement in objective nocturnal wakefulness, yet alleviation of objective sleep disturbance was not necessary for insomnia remission based on patient-reported outcomes. It remains unclear, however, whether enhancing treatment effects on objective sleep could potentially improve outcomes for insomnia patients with objective sleep findings. Despite the lack of robust treatment effects, exploratory analyses suggest that reductions in nocturnal cognitive arousal are linked to reductions in objective sleep latency. This identifies cognitive arousal as a potential therapeutic target (and potential triaging variable) to facilitate improvements in objective sleep. Even so, therapeutic targets for psychological insomnia interventions to improve objective sleep maintenance remain elusive. Augmentation strategies using pharmacotherapy, possibly involving newer wake-inhibiting orexin antagonists that produce superior effects on objective total sleep time and sleep maintenance than sleep-promoting benzodiazepine receptor agonists [51,52], may enhance response to insomnia therapy in patients with objective sleep disturbance.

Disclosure statement

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CRediT authorship contribution statement

David A. Kalmbach: Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft. **Philip Cheng:** Writing - review & editing. **Thomas Roth:** Writing - review & editing, Conceptualization. **Chaewon Sagong:** Writing - review & editing. **Christopher L. Drake:** Conceptualization, Methodology, Resources, Supervision, Funding acquisition, Writing - review & editing.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2020.04.024

Appendix A. Supplemental Table 1. Mean ISI scores across treatment conditions at pretreatment, posttreatment, and 6-month follow-up for patients with high and low PSG sleep efficiency

	Pretreatment	Posttreatment	6-Month Follow-up
Patients with PSG sleep efficiency ≥ 85%			
ISI	F(2,46) = 0.19, p = 0.83	F(2,46) = 14.71, p < 0.001	F(2,40) = 8.89, p = 0.001
SHE	15.60 ± 5.63	13.40 ± 5.01[bc]	13.54 ± 6.17[c]
SRT	14.86 ± 4.62	7.71 ± 4.10[a]	8.42 ± 4.42
CBTI	15.90 ± 4.78	5.30 ± 4.14[a]	5.44 ± 5.11[a]
Patients with PSG sleep efficiency < 85%			
ISI	F(2,60) = 0.62, p = 0.54	F(2,60) = 10.33, p < 0.001	F(2,56) = 6.30, p = 0.003
SHE	14.27 ± 3.66	13.69 ± 4.07[bc]	12.96 ± 4.19[bc]
SRT	15.35 ± 3.31	9.17 ± 4.13[a]	8.52 ± 4.49[a]
CBTI	14.00 ± 3.90	8.50 ± 4.24[a]	8.58 ± 5.93[a]

Note: PSG sleep efficiency as measured on the control night prior to treatment. ISI = insomnia severity index. SHE = sleep hygiene education control. SRT = sleep restriction therapy. CBTI = cognitive behavioral therapy for insomnia. F = F-ratio for one-way analysis of variance models comparing mean ISI scores at each time-point for descriptive purposes. p = significance value. *Posthoc contrasts* were run using Bonferroni method and significant contrasts are noted as such: [a] group mean differs from SHE, [b] group mean differs from SRT, [c] group mean differs from CBTI.

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