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SCIENTIFIC INVESTIGATIONS

Effects of trazodone versus cognitive behavioral therapy in the insomnia with short sleep duration phenotype: a preliminary study

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Study Objectives: The insomnia with objective short sleep duration phenotype is associated with increased risk for adverse health outcomes, physiological hyperarousal, and a blunted response to cognitive behavioral therapy for insomnia (CBT-I). Whether insomnia with objective short sleep duration responds better to pharmacological treatment compared to CBT-I has not been examined.

Methods: Participants included 15 patients with chronic insomnia (86.7% female), aged 45.3 ± 8.1 years. Eight patients were randomized to CBT-I and 7 to trazodone. Patients were examined with 2 weeks of actigraphy, salivary cortisol, and the insomnia severity index at 3 time points (pretreatment, 3-month posttreatment, and 6-month follow-up). Mixed between-within-subjects analysis of variance and univariate analysis of covariance were conducted to assess the impact of trazodone and CBT-I on patients' total sleep time, salivary cortisol, and insomnia severity index scores across the 3 time points.

Results: Trazodone, but not CBT-I, significantly lengthened total sleep time (when measured with actigraphy) both at posttreatment (51.01 minutes vs –11.73 minutes; $P = .051$; Cohen's $d = 1.383$) and at follow-up (50.35 minutes vs –7.56 minutes; $P = .012$; Cohen's $d = 1.725$), respectively. In addition, trazodone, but not CBT-I, showed a clinically meaningful decrease in salivary cortisol from pretreatment to posttreatment (–36.07% vs –11.70%; Cohen's $d = 0.793$) and from pretreatment to follow-up (–21.37% vs –5.79%; Cohen's $d = 0.284$), respectively. Finally, there were no differences on insomnia severity index scores between the trazodone and the CBT-I groups.

Conclusions: The current preliminary, open-label, randomized trial suggests that trazodone, but not CBT-I, significantly improves objective sleep duration and reduces hypothalamic-pituitary-adrenal axis activation, suggesting a differential treatment response in the insomnia with objective short sleep duration phenotype.

Clinical Trial Registration: Registry: ClinicalTrials.gov; Name: Study of Trazodone & Cognitive Behavioral Therapy to Treat Insomnia ; URL: https://clinicaltrials.gov/ct2/show/NCT01348542 ; Identifier: NCT01348542.

Keywords: insomnia, trazodone, cognitive-behavioral therapy for insomnia, total sleep time, cortisol, insomnia short sleep duration phenotype

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Individuals who have insomnia with short sleep duration differ from individuals who have insomnia with normal sleep duration in terms of health risks and treatment response. Insomnia with short sleep duration is associated with increased risk of adverse health outcomes, greater physiological hyperarousal as indicated by hypothalamic-pituitary-adrenal axis activation, and worse response to cognitive behavioral therapy for insomnia.

Study Impact: This study explored whether patients with insomnia with short sleep duration show a differential response to 2 common insomnia treatments, cognitive behavioral therapy for insomnia and trazodone. The current randomized trial suggests that trazodone, but not CBT-I, significantly improves objective sleep duration and reduces hypothalamic-pituitary-adrenal axis activation, which has been shown to be a mediator of morbidity and mortality associated with this insomnia phenotype.

INTRODUCTION

Insomnia is the most common sleep disorder and is associated with significant morbidity and mortality.[1,2] However, its pathophysiology remains poorly understood, and most commonly available treatments for this disorder are associated with good outcomes in self-reported sleep quality but have no effect in objective sleep duration.[3] Previous research has attempted to define subgroups within insomnia based on etiology (ie, primary vs secondary), age of onset (ie, childhood vs adult), and objective sleep findings.[4] However, these subtypes have shown poor reliability and validity and have not shown utility for guiding insomnia treatment decisions.[5] Therefore, current diagnoses of insomnia are based solely on self-reported complaints.[4]

Previous research on the association of insomnia with objective short sleep duration (ISS) with the stress system,[6–8] the autonomic system,[9] and medical morbidity[10–13] and mortality[14] led the authors to suggest 2 phenotypes of chronic insomnia. The first phenotype, ISS, is associated with physiological hyperarousal (ie, short sleep duration and activation of the stress system[6–8]) and significant medical sequelae (eg, hypertension,[12] type 2

diabetes,[13] cardiovascular disease,[15,16] increased mortality,[14] and a persistent natural course[17]). The second phenotype, insomnia with normal sleep duration (INS), is not associated with physiological hyperarousal (ie, normal sleep duration, normal activity of the stress system,[8] and lack of significant medical sequelae[10–14]) but instead with sleep misperception, an anxious-ruminative profile with poor coping skills,[18] and an intermittent natural course.[17] Based on these findings, we have previously proposed that the ISS phenotype may respond better to treatments that primarily aim at decreasing physiological hyperarousal (eg, hypercortisolemia) and increasing sleep duration, such as medication or other biological treatments,[17] and the INS phenotype may respond better to treatments that primarily aim at decreasing cognitive-emotional hyperarousal (eg, rumination) and altering sleep misperception, such as psychological treatment (ie, cognitive behavioral therapy for insomnia [CBT-I]).

Because the ISS phenotype is associated with hypothalamic-pituitary-adrenal (HPA) axis activation, the use of medication that downregulates the HPA axis may be a promising tool for the pharmacological approach. In support of this consideration, researchers have shown that a small dose of a sedative antidepressant (doxepin) was effective in improving sleep and normalizing plasma cortisol secretion indicated with primary insomnia.[7] Other studies have also shown that doxepin is effective in increasing objective sleep duration in chronic insomnia.[7,19,20] Although trazodone does not have a U.S. Food and Drug Administration indication for insomnia, it has been the second-most prescribed pharmacological agent for insomnia management over the past few decades at doses ranging between 25 mg and 100 mg.[21] However, its use has not been supported by systematic studies including efficacy, tolerance, and adverse effects. In addition, trazodone is known to downregulate HPA arousal and may be specifically suited for the treatment of patients with ISS.[22–28] Other common medications such as the benzodiazepines and benzodiazepine receptor agonists do not have this effect and therefore would not target the HPA arousal that has been identified in patients with ISS.[29–31] Hence, we have chosen trazodone to compare to CBT-I, which is the "gold standard" of care for patients with insomnia disorder.

CBT-I is recommended as first-line treatment, with insomnia remission rates of 50%–60% and significant symptom reduction in 75%–80% of patients.[32–34] We have hypothesized that patients with the INS phenotype, which is associated with normal activity of the HPA axis, and lack of significant medical morbidity may respond better to psychological treatment. In support of this hypothesis, several studies on CBT-I effectiveness have included patients with insomnia with an average objective sleep duration of 6 hours or more and have reported improved sleep efficiency but no significant lengthening of sleep duration.[33,35,36] Furthermore, recent investigators have shown that patients with the ISS phenotype have a blunted treatment response to CBT-I relative to those with the INS phenotype.[10,37,38]

Whether the ISS phenotype responds better to pharmacological treatment than to psychological treatment has not yet been examined. Therefore, the goal of the current preliminary, open-label, randomized study was to assess the effect of trazodone compared to CBT-I in patients with the ISS phenotype on the primary outcome, objective total sleep time, and on the secondary outcomes of salivary cortisol levels and self-reported insomnia severity.

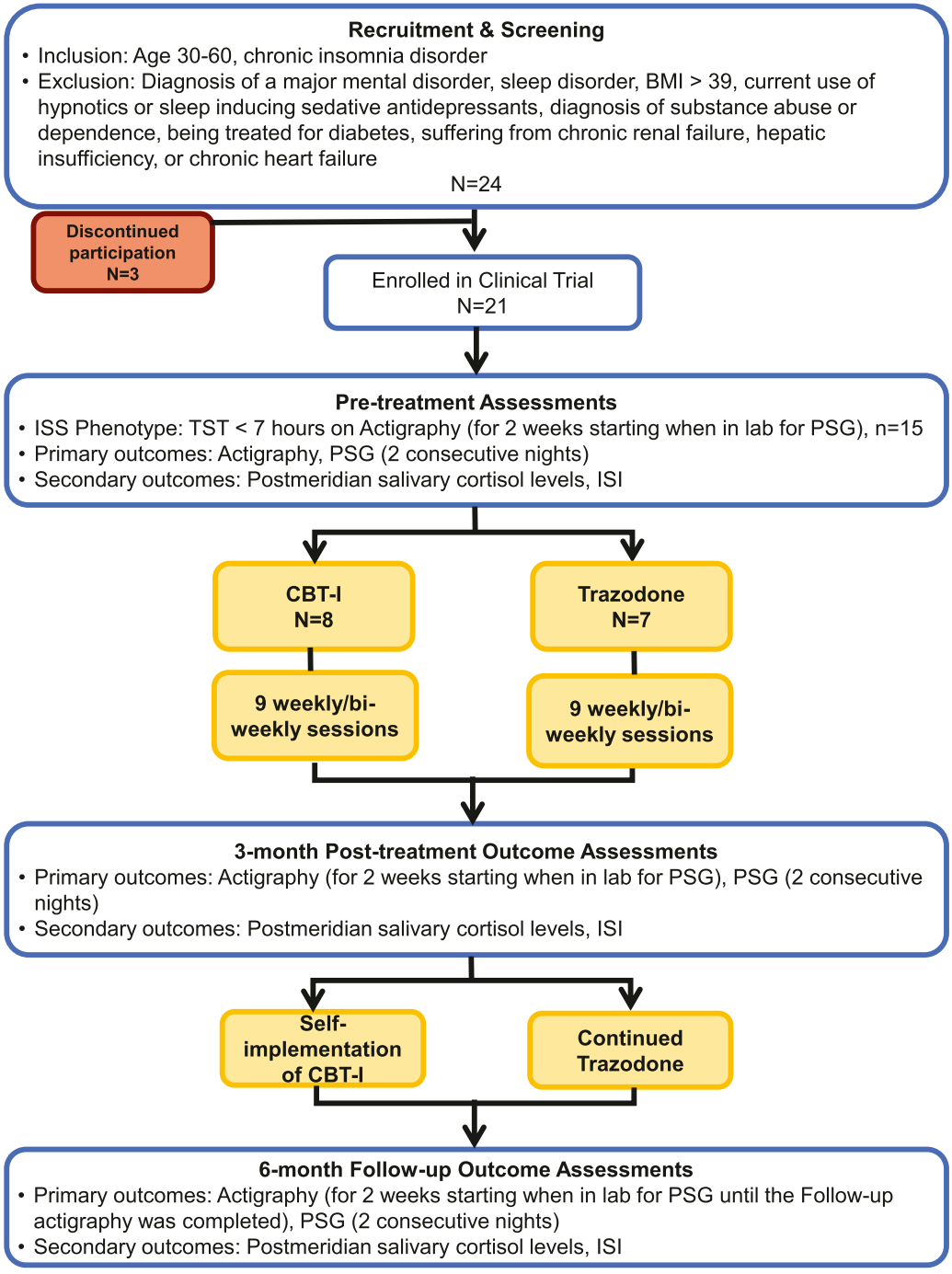
METHODS

Participants

A total of 24 patients were recruited through advertisements in the local community, were screened according to research protocols by the Sleep Research and Treatment Center at Penn State Milton S. Hershey Medical Center (Hershey, PA), and were randomized to either the CBT-I or the trazodone group. Of the 24 patients who were randomized, 3 discontinued participation after randomization had occurred but before initiation of treatment because of the time commitment required for the study, unwillingness to discontinue morphine use, and disinterest in taking trazodone. The remaining patients' diagnoses of insomnia and other sleep disorders were established with a clinical sleep history and semistructured interview conducted by a clinical psychologist who practices sleep medicine. Chronic insomnia disorder was defined as difficulties initiating and maintaining sleep, waking up too early, and being unable to return to sleep despite adequate sleep opportunity, concurrent with daytime impairment, all of which had persisted for the duration of at least 1 year. Other inclusion criteria included an age range of 30–60 years. Patients with a current diagnosis of a major mental disorder (ie, schizophrenia, major depression), sleep disorder (ie, OSA, periodic limb movement disorder, narcolepsy, circadian rhythm disorders), morbid obesity (body mass index > 39), current use of hypnotics or sleep-inducing sedative antidepressants, a diagnosis of substance abuse or dependence, treatment for diabetes, chronic renal failure, hepatic insufficiency, or chronic heart failure were excluded from the study. During the pretreatment phase, an AHI ≥ 5 events/h was used to define the presence of OSA and a periodic limb movement index ≥ 15 was used to define the presence of periodic limb movement disorder, so none of the participants that entered the trial had either elevated AHI or elevated periodic limb movement. A total of 21 patients completed the clinical trial (**Figure 1**).

Objective "short sleep" was defined based on the closest clinically meaningful cutoff (total sleep time [TST] < 7 hours) to the median value (TST < 6.8 hours) measured with actigraphy at pretreatment (mean value for 2 consecutive weeks). Previous research has used a 6-hour criterion to identify the ISS phenotype measured with polysomnography (PSG), for which 6 hours was the median of the previously studied samples (ie, primarily a general random population sample).[8,12,17] In the current study, the primary objective method to assess TST was actigraphy. Given that the median value for TST in the current sample of patients measured with actigraphy was 6.8 hours, we chose a TST cutoff of 7 hours to define clinically meaningful objective short sleep duration. It is to be expected that the median value of TST will differ based on the method used (ie, actigraphy vs PSG), population studied (ie, general random population sample vs clinical or volunteer sample), and demographics (ie, age range of the sample). Based on this criterion, 15 out of the 21 patients were categorized as having the ISS phenotype.

Figure 1—Study timeline.



BMI = body mass index, CBT-I = cognitive behavioral therapy for insomnia, ISI = Insomnia Severity Index, ISS = insomnia with objective short sleep duration, PSG = polysomnography.

Patients were randomly assigned to either a trazodone or a CBT-I group by a statistician so that the investigators remained blind to the randomization process. Data were collected at the following phases of the study: pretreatment (before initiation of treatment), posttreatment (3 months after initiation of treatment), and follow-up (6 months after termination of treatment). Patients were compensated upon completion of the study. The study and all procedures were approved by the Penn State College of Medicine institutional review board (IRB 35933) and registered with ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT01348542).

Treatment groups

CBT-I

The CBT-I protocol used in this study included evidence-based, behavioral, and cognitive techniques consisting of what is called a multimodal CBT-I treatment covering sleep hygiene,

stimulus control, sleep restriction, and cognitive therapy.[39–41] The CBT-I protocol was implemented by a clinical psychologist who practices behavioral sleep medicine (coauthor JFM) for a total of 9 months, consisting of 3 months of weekly/biweekly sessions (total of 9 consultation/therapy sessions each lasting approximately 50 minutes) plus 6 months of self-implementation of learned CBT-I techniques. Sessions 1 through 4 were held on a weekly basis, sessions 5 through 8 were held on a biweekly basis, and session 9 was held 6 months after the initiation of treatment. The treatment program utilized in the current study was based on validated protocols according to specific parameters.[39–41] Stimulus control was implemented based on standard instructions using the 15-minute rule for time awake in bed.[39–41] Sleep restriction was implemented based on sleep diary data provided by participants at each session, as follows[39]: (1) in the case of positive clinical gains (sleep efficiency ≥ 90% or sleep efficiency 85%–89% with increased sleepiness), upwardly titrate sleep opportunity by 15 minutes; (2) in the case of marginal gains (sleep efficiency 85%–89% without increased sleepiness), maintain sleep opportunity at prescribed times; and (3) in the case of negative gains (sleep efficiency < 85%), downwardly titrate sleep opportunity. Cognitive therapy was implemented in the fifth session until the end of treatment and included decatastrophizing,[39] constructive worry,[40] and cognitive restructuring[40,41] techniques. Participants in the CBT-I group were recommended to continue following the recommendations made at their last face-to-face session, through posttreatment and all follow-up data collection.

Trazodone

The trazodone group received a standard handout on sleep hygiene instructions and had a total of 9 sessions to check treatment effectiveness, adherence, and possible adverse effects and review sleep hygiene practices (eg, avoiding naps, trying to keep a consistent wake time, cutting down on all caffeine products, ensuring a comfortable and quiet bedroom). All patients in the trazodone group received a standard dose of trazodone (50 mg) in their first session and took trazodone for a total of 9 months, including 3 months of weekly/biweekly sessions (total of 9 sessions) plus 6 months of follow-up. Participants were followed up with 2 additional biweekly sessions (during sessions 2 through 3). During these biweekly sessions, dosages were adjusted according to drug effectiveness and possible adverse effects. The maximum dose used was 100 mg of trazodone, which was taken by 2 participants; 3 participants increased their dosages to 75 mg. Sessions 4 through 5 were scheduled monthly and focused on assessing treatment effectiveness, adherence, possible adverse effects, and the need to adjust medication doses. Session 6 was held 6 months after the initiation of treatment. Participants in the trazodone group were recommended to continue taking trazodone as needed until the final follow-up actigraphy was returned. All patients continued to take trazodone until the end of the final actigraphy assessment. Participants were monitored until their last pill remained and then were recommended to follow-up with their primary care provider for any further care.

Measures

Each participant completed a medical history and physical examination using a semi-structured format and a battery of clinical tests. Blood pressure was measured in the morning and in the evening using a pneumoelectric microprocessor-controlled instrument. The recorded blood pressure was the average of 3 consecutive readings during a 5-minute period after 10 minutes of rest in the supine position. Anthropometric measures included height, weight, neck size, and waist and hip measurements according to standard procedures. Specifically, neck size was measured at the superior border of the cricothyroid membrane with the patient in the upright position. The waist was measured at or 1 cm above the umbilical midline, and the hip was measured at the widest area around the buttocks.

Primary outcomes

Use of PSG

Each patient was monitored continuously for 8 hours for 3 consecutive nights (1 adaptation night and 2 consecutive nights) according to standard techniques at each phase of the study (ie, pretreatment, posttreatment, and follow-up). For analytic purposes, we excluded the adaption night and used the mean of TST for the 2 consecutive nights. Respiration was monitored throughout the night by thermocouples at the nose and mouth (Salter Labs, Lake Forest, IL), nasal cannula/pressure, and thoracic strain gauges.

Actigraphy

An actigraphy monitor (ActiGraph GT3×; ActiGraph, Pensacola FL) was placed on the wrist of patients' nondominant hand during the second night in the laboratory and worn for a 2-week period at each time point (pretreatment, posttreatment, and follow-up). Patients were asked to keep an actigraphy log for a 2-week period in which they noted daily time to bed, time out of bed, and times when the device was removed (eg, taking a bath, swimming). ActiLife Software (ActiGraph, Pensacola, FL) was used to calculate the estimated sleep variables (ie, TST, time in bed [TIB], sleep efficiency). Actigraphy logs were used to enter participant-reported bedtimes and wake-up times. Average TST values were calculated from the 2-week recording period for each phase of the study (pretreatment, posttreatment, and follow-up). TST measured with actigraphy was chosen as the main outcome in the current analyses because the ad libitum actigraphy design allowed patients in the CBT-I group to practice sleep restriction (as per recommendations from the psychologist) if necessary, compared to the fixed TIB protocol during the PSG recording, for which patients were not able to practice their sleep restriction techniques.

Secondary outcomes

Salivary cortisol

Saliva was sampled at 5 time points during the day: 8:00 AM before breakfast, 12:00 PM before lunch, 3:00 PM, 6:00 PM, and 9:00 PM, for each phase of the study (ie, pretreatment, posttreatment, and follow-up). No food or exercise was allowed at least half an hour before sample collection. Each sample was collected by having participants place a cotton swab in their mouth for 2 minutes or chew it for 1 minute. The cotton swab

was then placed inside a plastic tube and kept in the refrigerator at 0°C–4°C. Salivary cortisol was extracted from the cotton by centrifuging the plastic tubes and cotton at 100g for 8 minutes to separate the saliva into the outer tube. The cotton was removed, and all samples were stored at –85°C. For the purposes of the current analyses, mean postmeridian salivary cortisol was calculated from the 12:00 PM, 3:00 PM, 6:00 PM, and 9:00 PM times, given that previous studies have shown elevated cortisol levels among patients with insomnia primarily occurring during the postmeridian period.[8]

Insomnia severity

The Insomnia Severity Index (ISI) was used for assessment of self-reported insomnia severity at pretreatment, posttreatment, and follow-up. A total ISI score from 0–7 is indicative of the absence of clinically significant insomnia, a score from 8–14 is indicative of subthreshold insomnia, and a score from 15–28 is indicative of moderate-to-severe clinically significant insomnia. In the current sample, a total of 73.3% of the participants had a clinically elevated ISI score (ie, ≥ 15) and 26.7% presented with a subthreshold ISI score (ie, 8–14).

Data analysis

All analyses were conducted among patients classified with the ISS phenotype (n = 15). Four mixed between-within-subjects analyses of variance (ANOVAs) were conducted to assess the impact of trazodone and CBT-I on patients' TST (measured with actigraphy and PSG), salivary cortisol, and ISI scores across 3 time points (pretreatment, posttreatment, and follow-up). The time and treatment condition main effects and the interaction between time and treatment condition were tested. In addition, a univariate analysis of covariance (ANCOVA) was conducted to compare the change from pretreatment to posttreatment and from pretreatment to follow-up for TST (actigraphy and PSG), salivary cortisol levels, and ISI scores between treatment groups (trazodone and CBT-I) while controlling for pretreatment levels of each outcome variable. Cohen's effect sizes were used to interpret the effect size as small ($r = 0.20$), medium ($r = 0.50$), and large ($r = 0.80$). Finally, Pearson correlations were conducted to explore the relationship between change in mean salivary cortisol levels and change in mean TST from pretreatment to posttreatment and from pretreatment to follow up.

RESULTS

Characteristics of the sample

The sample of patients with the ISS phenotype comprised 15 individuals who were predominantly female (86.7%), nonobese (86.7%), aged 45.3 ± 8.1 years, and non-Hispanic white (80.0%). From the current sample, 8 patients were randomized to the CBT-I group and 7 to the trazodone group. **Table 1** presents the demographic and clinical characteristics of the sample of patients measured at pretreatment.

Effect on objective sleep duration

A mixed between-within-subjects ANOVA was conducted to assess the impact of treatment (CBT-I, trazodone) on patients' average TST as measured with actigraphy across 3 time points (pretreatment, posttreatment, and follow-up; see **Table 2**). There was a significant interaction between treatment and time (Wilks lambda = 0.47; F [2, 12] = 6.752; $P = .011$; see **Figure 2**). Furthermore, an ANCOVA was conducted to examine the difference between groups in the change in TST from pretreatment to posttreatment and from pretreatment to follow-up while controlling for pretreatment TST. There was a marginally significant difference between treatment groups in the change in TST from pretreatment to posttreatment, with a very large magnitude of difference in the means ($P = .051$; Cohen's $d = 1.383$), and from pretreatment to follow-up, also with a very large magnitude of difference in the means ($P = .012$; Cohen's $d = 1.725$).

There were no significant differences in sleep efficiency (as per the actigraphy data) at pretreatment for patients treated using CBT-I ($M = 83.75$; SD = 4.55) and patients treated using trazodone ($M = 85.31$; SD = 4.32; $t(13) = 0.676$; $P = .511$; 2-tailed). As per the CBT-I sleep restriction protocol, there were significant differences in sleep efficiency at posttreatment for the CBT-I group ($M = 85.32$; SD = 3.54) and the trazodone group ($M = 90.83$; SD = 3.57; $t(13) = 2.99$; $P = .010$; 2-tailed) and at follow-up for the CBT-I group ($M = 86.10$; SD = 2.28) and the trazodone group ($M = 90.44$; SD = 2.55; $t(13) = 3.50$; $P = .004$; 2-tailed). A mixed between-within-subjects ANOVA was conducted to assess the impact of treatment (CBT-I, trazodone) on patients' average TST, measured with PSG, across the 3 time points (pretreatment, posttreatment, and follow-up; see **Table 3**). There was not a significant interaction between treatment and time (Wilks lambda = 0.90; F [2, 12] = 0.662; $P = .534$), but the main effect for time was significant (Wilks lambda = 0.359; F [2, 18] = 10.732; $P = .002$). The main effect for group was not significant (F [1, 13] = 0.332, $P = 0.574$). Furthermore, an ANCOVA was conducted to examine the difference between groups on the change in TST from pretreatment to posttreatment and from pretreatment to follow-up while controlling for pretreatment TST. There was not a significant difference between groups in the change in TST from pretreatment to posttreatment, with a small magnitude of the difference in the means ($P = .301$; Cohen's $d = 0.354$). In addition, there was not a significant difference between groups in the change in TST from pretreatment to follow-up, and the magnitude of the difference in the means was small ($P = .683$; Cohen's $d = 0.345$). The correlation between pretreatment PSG and pretreatment actigraphy TST was significant ($r = 0.548$; $P = .034$).

Effect on salivary cortisol levels

A mixed between-within-subjects ANOVA was conducted to explore the impact of treatment (CBT-I, trazodone) on patients' cortisol levels at pretreatment, posttreatment, and follow-up (see **Table 4**). There was not a significant interaction between treatment and time (Wilks lambda = 0.734; F [2, 13] = 2.177; $P = .156$). However, the main effect for time was significant (Wilks lambda = 0.463; F [2, 13] = 6.964; $P = .010$). The main effect for group was not significant (F [1, 13] = 0.035; $P = .855$). In addition, an ANCOVA was conducted to examine the difference between groups on the change in cortisol levels from pretreatment to posttreatment and from pretreatment to follow-

Table 1—Demographic and clinical characteristics of the sample.

	CBT-I (n = 8)	Trazodone (n = 7)	*P* Value[a]	ES[b]
Age, y	45.87 (9.30)	44.57 (7.11)	.768	0.157
Female (%)	7 (87.5)	6 (85.7)	.919	0.026
White (%)	6 (75.0)	6 (85.7)	.387	0.465
Height, cm	168.52 (7.68)	165.08 (8.94)	.437	0.413
Weight, kg	75.55 (20.81)	70.81 (5.23)	.552	0.302
BMI	26.29 (5.25)	26.20 (3.54)	.971	0.020
SBP, mm Hg	119.45 (13.45)	115.33 (13.25)	.561	0.308
DBP, mm Hg	77.17 (8.82)	72.76 (9.31)	.364	0.487
ISI, score	15.38 (1.85)	17.57 (3.31)	.153	0.834

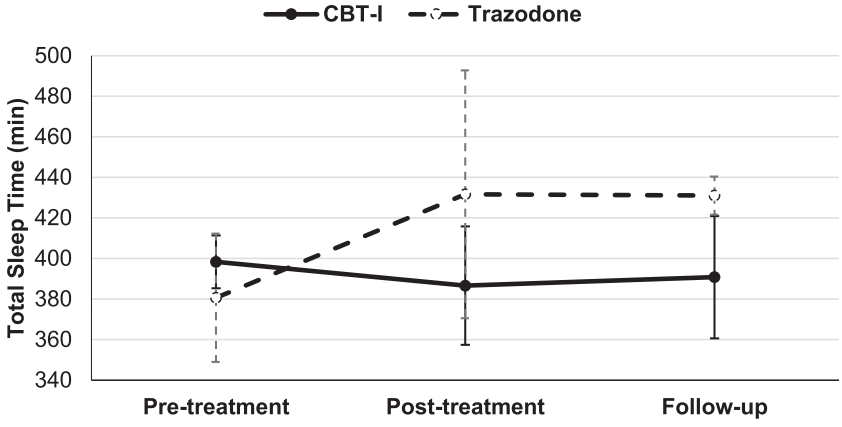
Data are means/estimated means (standard deviation).
[a]*t*-test *P* value for continuous variables, χ^2 *P* value for categorical variables. [b]Cohen's *d* for continuous variables, Cramer's *V* for categorical variables. BMI = body mass index, CBT-I = cognitive behavioral therapy for insomnia, DBP = diastolic blood pressure, ES = effect size, ISI = Insomnia Severity Index, SBP = systolic blood pressure.

Table 2—Total sleep time during 2-week actigraphy with ad libitum TIB across 3 time points.

	CBT-I (n = 8)	Trazodone (n = 7)	Treatment	*P* Values[a] Time	Interaction
Pretreatment	398.36 (13.03)	380.65 (31.64)	.066	.071	.011**
Posttreatment	386.63 (29.20)	431.66 (61.11)			
Follow-up	390.80 (30.17)	431.01 (9.41)			
			P Value[b]	ES[c]	
ΔPretreatment to posttreatment	–11.73 (31.43)	51.01 (57.50)	.051	1.383	
ΔPretreatment to follow-up	–7.56 (38.04)	50.35 (27.47)	.012*	1.725	

Data are means/estimated means (standard deviation).
[a]*P* values from repeated-measures ANOVA; data are means (standard deviation). [b]*P* values from ANCOVA; change data (Δ) are estimated marginal means (standard deviation) adjusted for pretreatment TST (measured with actigraphy). [c]Effect sizes are Cohen's d for independent samples. *$P < .05$; **$P < .01$. ANOVA = analysis of variance, ANCOVA = analysis of covariance, CBT-I = cognitive behavioral therapy for insomnia, ES = effect size, TIB = time in bed, TST = total sleep time.

Figure 2—Total sleep time during 2-week actigraphy with ad libitum TIB across 3 time points.



Data are mean and standard deviation values for TST, where the solid lines represent the CBT-I group and the dotted lines represent the trazodone group. CBT-I = cognitive behavioral therapy for insomnia, TIB = time in bed, TST = total sleep time.

up while controlling for pretreatment cortisol levels. There was a trend toward a significant difference between groups in the change in cortisol levels from pretreatment to posttreatment, with a large magnitude of difference in the means ($P = .085$; Cohen's $d = 0.793$). There was not a significant difference between groups in the change in cortisol levels from pretreatment to follow-up, and the magnitude of the difference in the means was small ($P = .967$, Cohen's $d = 0.284$). **Figure 3** shows that the largest percentage change in cortisol levels occurred from pretreatment to posttreatment among patients in the trazodone group (–36.07%) as compared with patients in the CBT-I group (–11.70%). In addition, the percentage change in

Table 3—TST during 2-night PSG with fixed TIB across 3 time points.

	CBT-I (n = 8)	Trazodone (n = 7)	Treatment	*P* Values[a] Time	Interaction
Pretreatment	373.88 (46.84)	359.96 (60.77)	.574	.002**	.534
Posttreatment	412.79 (35.45)	388.92 (52.89)			
Follow-up	406.25 (35.06)	411.75 (41.17)			
			P Value[b]	ES[c]	
ΔPretreatment to posttreatment	38.91 (24.74)	28.95 (31.70)	.301	.354	
ΔPretreatment to follow-up	32.36 (30.31)	51.78 (76.39)	.683	.345	

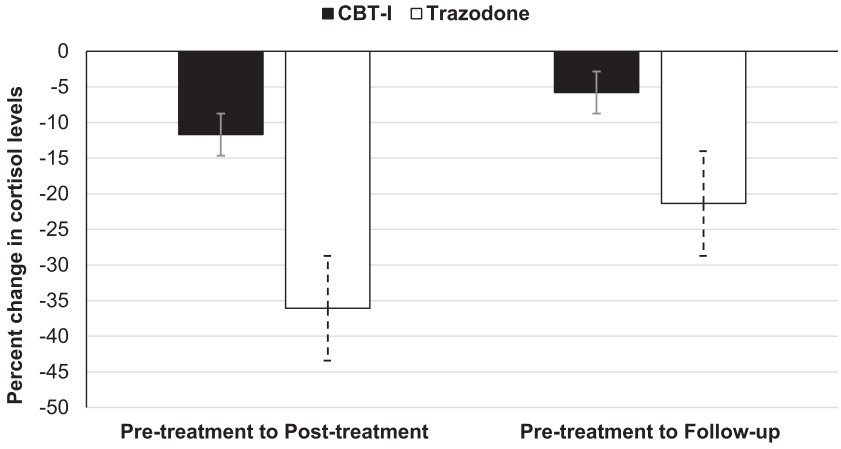
Data are means/estimated means (standard deviation).
[a]*P* values from repeated-measures ANOVA; data are means (standard deviation). [b]*P* values from ANCOVA; change data (Δ) are estimated marginal means (standard deviation) adjusted for pretreatment TST (measured with PSG). [c]Effect sizes are Cohen's *d* for independent samples. ***P* < .01. ANOVA = analysis of variance, ANCOVA = analysis of covariance, CBT-I = cognitive behavioral therapy for insomnia, ES = effect size, PSG = polysomnography, TIB = time in bed, TST = total sleep time.

Table 4—Postmeridian salivary cortisol levels.

	CBT-I (n = 8)	Trazodone (n = 7)	Treatment	*P* Values[a] Time	Interaction
Pretreatment	8.64 (4.17)	10.48 (8.18)	.855	.010**	.156
Posttreatment	7.63 (3.55)	6.70 (4.23)			
Follow-up	8.14 (2.23)	8.24 (1.19)			
			P Value[b]	ES[c]	
ΔPretreatment to posttreatment	–1.01 (1.46)	–3.77 (4.87)	.085	.793	
ΔPretreatment to follow-up	–0.503 (3.15)	–2.24 (8.31)	.967	.284	

Data are means/estimated means (standard deviation).
[a]*P* values from repeated-measures ANOVA; data are means (standard deviation) for average salivary cortisol levels across 12:00 PM, 3:00 PM, 6:00 PM, and 9:00 PM samples. [b]*P* values from ANCOVA; change data (Δ) are estimated marginal means (standard deviation) adjusted for pretreatment cortisol levels. [c]Effect sizes are Cohen's *d* for independent samples. ***P* < .01. ANOVA = analysis of variance, ANCOVA = analysis of covariance, CBT-I = cognitive behavioral therapy for insomnia, ES = effect size.

Figure 3—Percentage change in postmeridian salivary cortisol levels from pretreatment to posttreatment and to follow-up.



Data are mean and standard error values for percentage change in cortisol levels, where the solid lines represent the CBT-I group and the dotted lines represent the trazodone group. CBT-I = cognitive behavioral therapy for insomnia.

cortisol levels was higher for those in the trazodone group (–21.37%) from pretreatment to follow-up when compared with those in the CBT-I group (–5.79%). Furthermore, Pearson correlations showed a trend toward a significant relationship between the change in TST (measured with actigraphy) and the change in cortisol levels from pretreatment to posttreatment ($r = –0.472$; $P = .075$), whereas both the change in TST (measured with actigraphy) and the change in salivary cortisol levels from pretreatment to follow-up were not significant ($r = –0.260$; $P = .350$).

Effect on self-reported insomnia severity

A mixed between-within-subjects ANOVA was conducted to explore the impact of treatment (CBT-I, trazodone) on patients'

Table 5—ISI score.

	CBT-I (n = 8)	Trazodone (n = 7)	Treatment	*P* Values[a] Time	Interaction
Pretreatment	15.38 (1.84)	17.57 (3.30)	.624	<.001***	.189
Posttreatment	4.63 (2.72)	5.29 (4.15)			
Follow-up	5.00 (2.50)	4.29 (4.60)			
			P Value[b]	ES[c]	
ΔPretreatment to posttreatment	–10.75 (2.86)	–12.29 (4.34)	.901	.424	
ΔPretreatment to follow-up	–10.38 (3.02)	–13.29 (3.77)	.298	.859	

Data are means/estimated means (standard deviation).
[a]*P* values from repeated-measures ANOVA; data are means (standard deviation). [b]*P* values from ANCOVA; change data (Δ) are estimated marginal means (standard deviation) adjusted for pretreatment ISI. [c]Effect sizes are Cohen's *d* for independent samples. ***$P < .001$. ANOVA = analysis of variance, ANCOVA = analysis of covariance, CBT-I = cognitive behavioral therapy for insomnia, ES = effect size, ISI = Insomnia Severity Index.

ISI scores assessed at pretreatment, posttreatment, and follow-up (see **Table 5**). There was not a significant interaction between treatment and time (Wilks lambda = 0.758; F [2, 13] = 1.918; $P = .189$). However, the main effect for time was significant (Wilks lambda = 0.066; F [2, 13] = 84.830; $P = .000$) and the main effect for group was not significant (F [1, 13] = 0.252; $P = .624$). Furthermore, an ANCOVA was conducted to examine the difference between groups on the change in ISI scores from pretreatment to posttreatment and from pretreatment to follow-up while controlling for pretreatment ISI scores. Although there was not a significant difference in the change in ISI scores from pretreatment to posttreatment between groups, the magnitude of the difference in the means was moderate ($P = .901$; Cohen's $d = 0.424$). In addition, there was not a significant difference in the change in ISI scores from pretreatment to follow-up between groups, but the magnitude of the difference in the means was large ($P = .298$; Cohen's $d = 0.859$).

Effect on self-reported sleep

There were no significant differences in TIB at pretreatment for patients treated using CBT-I ($M = 453.75$; SD = 43.73) and patients treated using trazodone ($M = 437.14$; SD = 130.88; t (13) = –0.339; $P = .740$; 2-tailed), at posttreatment for the CBT-I group ($M = 438.75$; SD = 27.48) and the trazodone group ($M = 462.85$; SD = 82.80; t (13) = 0.779; $P = .450$; 2-tailed), or at follow-up for the CBT-I group ($M = 437.50$; SD = 23.29) and the trazodone group ($M = 439.28$; SD = 43.05; t (13) = 0.102; $P = .920$; 2-tailed). Furthermore, the posttreatment sleep prescription for patients receiving CBT-I as per their sleep restriction protocol ($M = 367.50$; SD = 21.21) was significantly different than their pretreatment TIB ($M = 453.75$; SD = 43.73; $P = .002$).

There were no significant differences in sleep efficiency (as per the sleep diary data) at pretreatment for patients treated using CBT-I ($M = 76.56$; SD = 12.31) and patients treated using trazodone ($M = 73.43$; SD = 18.91; t (11) = –0.359; $P = .726$; 2-tailed), at posttreatment for the CBT-I group ($M = 86.97$; SD = 4.28) and the trazodone group ($M = 93.95$; $SD = 6.67$; t (8) = 1.97; $P = .085$; 2-tailed), or at follow-up for the CBT-I group ($M = 84.65$; SD = 9.69) and the trazodone group ($M = 90.55$; SD = 6.77; t (9) = 1.18; $P = .265$; 2-tailed).

DISCUSSION

This is the first preliminary, open-label, randomized study comparing trazodone, the second most widely prescribed sleeping aid in the United States, with CBT-I, the first-line treatment for insomnia, in patients with the ISS phenotype. The primary finding of this study is that trazodone, but not CBT-I, significantly and markedly lengthened objective ad libitum sleep duration but not in-lab PSG sleep duration, both at posttreatment and at long-term follow-up. Another important finding is that trazodone, but not CBT-I, reduced cortisol levels in a clinically meaningful manner. Finally, trazodone and CBT-I had a similar effect on self-reported insomnia severity.

It has been proposed that the ISS phenotype is associated with physiological hyperarousal (ie, activation of the stress system) and significant medical sequelae. Researchers have also hypothesized that this insomnia phenotype would respond better to biologic treatments than to psychological treatments (ie, CBT-I). The current study supports this hypothesis: Trazodone increased objective sleep duration, per data from 2-week actigraphy, by about 50 minutes at both posttreatment and follow-up, whereas CBT-I reduced objective sleep duration by about 10 minutes. It has been argued that CBT-I does not allow for an increase in TST because of the sleep restriction protocol, which is a typical component of CBT-I and was also applied in our study. However, TIB at all 3 time points was not different between the 2 treatments. These data indicate that the significant and marked difference in TST between the 2 groups was not a result of the sleep restriction protocol present in CBT-I.

The observed effect of CBT-I on objective sleep duration is consistent with recent studies reporting that CBT-I does not affect objective sleep duration among patients with the ISS phenotype.[10,37,38] Furthermore, in a review study, 11 out of 37 studies utilized objective sleep data to examine the effects of CBT-I, and those results could not prove that CBT-I is effective in improving objective sleep duration.[3] Moreover, regardless of measurement method, CBT-I has not been found to extend objective sleep duration, as measured with either PSG or actigraphy.[36] Furthermore, most studies examining the effect of CBT-I have comprised samples of patients with chronic insomnia with a rather "normal" (≥ 6 hours) objective sleep duration.[3] In the current study, the increase in TST after the use

of trazodone but not CBT-I was observed when utilizing 2-week actigraphy but not when using PSG, where both treatments were associated with lengthening TST. A possible explanation for this discrepancy is that the PSG recording was fixed to 8 hours and the actigraphy was ad libitum. It seems that patients treated using CBT-I during the 8-hour PSG recording slept longer because of allowing more TIB than was typical of their sleep restriction protocol. In support of this hypothesis, actigraphy data obtained concomitantly during the 8-hour fixed-protocol PSG indicated similar trends to the PSG findings and opposite of the actigraphy measures obtained ad libitum. In this study, we used the cutoff of < 7 hours via actigraphy, which was the closest meaningful cutoff to the median of 6.8 hours. This cutoff is higher than the cutoff of 6 hours, which was the median PSG sleep duration in earlier physiological studies and in large random general population samples.[8,12,17] The median value of TST will likely differ based on the method used (ie, actigraphy tends to overestimate TST when compared to PSG), population studied (ie, general random population sample vs clinical or volunteer sample), and age of the population sample. We have emphasized that the previously suggested cutoff of 6 hours for the ISS phenotype has been used as an internally valid marker of the severity of insomnia and not as a recommended optimal sleep duration for the general population.[12]

The second important finding from this study was the clinically meaningful reduction of cortisol levels after the use of trazodone but not CBT-I. It has been previously shown that the ISS phenotype is associated with activation of the HPA axis, which can be the underlying mechanism leading to medical sequelae. Furthermore, at posttreatment there was a marginally significant association between lengthening of TST and reduction of cortisol levels, supporting the previously observed association between short sleep duration and elevated cortisol levels in the ISS phenotype.[8] Although causality cannot be inferred from the current study—ie, the reduction of cortisol leads to increased TST or vice versa—it has been shown that increased nighttime cortisol levels induced by intravenous injection of the corticotrophin-releasing hormone is associated with increased wake after sleep onset and decreased TST in midlife individuals.[42] Future studies with larger clinical samples should examine the direction of the association between pharmacologically induced changes in sleep duration and cortisol levels using mediation analyses. Our finding that trazodone reduces cortisol is consistent with previous studies that have shown that doxepin, which is similar to trazodone as a sedative antidepressant, also reduces cortisol levels.[7] At long-term follow-up, the drop of cortisol levels with the use of trazodone (21%) was somewhat lower compared to the drop at posttreatment (36%). This difference may be attributed to the inherent variability of salivary cortisol because of (1) measuring cortisol in saliva vs plasma samples, (2) obtaining the saliva samples in less-controlled environments such as home/work vs laboratory collection, and (3) less frequent time-sampling that is better suited for cortisol, which has a pulsatile secretory pattern. However, we cannot rule out the possibility of the development of tolerance of the HPA axis after the 9-month use of trazodone. From a clinical standpoint, a change of cortisol levels of more than 15% is considered physiologically meaningful and associated with a significant impact on physical and mental health.[43]

In terms of self-reported insomnia severity, both treatments reduced it in a clinically meaningful manner. Trazodone seemed to have a moderately larger effect on self-reported insomnia severity when compared with CBT-I. Although a reduction of insomnia symptom severity of ≥ 8 is clinically meaningful at the individual level, future studies with larger clinical samples are needed to replicate this finding. Bathgate and colleagues[10] have shown that CBT-I is more effective in the INS phenotype than in the ISS phenotype, in regard to self-reported outcomes. However, recent studies that analyzed their data retrospectively did not report a differential effect of CBT-I between the ISS and INS phenotypes on self-reported measures.[44,45] Future prospective studies with larger and placebo-controlled samples are needed to resolve these inconsistent findings. Furthermore, although CBTI may have also improved self-reported sleep difficulties, it was within the trazodone group that the other marker of the ISS phenotype was actually improved (ie, objective TST). This finding is important given that objective short sleep without insomnia is not the same as objective short sleep with insomnia complaints in remission and the reported higher persistence rate, and potential for relapse, of the ISS phenotype.[17]

Given that the current study is small, preliminary, open-label, and randomized, definite clinical implications cannot be derived. However, there are several noteworthy signals of clinical importance. First, trazodone but not CBT-I significantly affected, in a clinically meaningful manner, objective sleep duration and cortisol levels in the ISS phenotype. These findings suggest that this medication is potentially better suited for half of the chronic insomnia population and can offer protection from the adverse medical sequelae associated with the ISS phenotype. Interestingly, in our small study, none of the patients dropped out because of adverse effects of trazodone. There has been a question of whether the wide use of trazodone by physicians is because of its efficacy or because its safety profile is more favorable compared with that of other hypnotic drugs. Our study suggests that trazodone seems to be effective for patients with the ISS phenotype. Because of our small sample size, extreme values may be more common, but given the large TST gain in the trazodone group, this medication may be best suited for the ISS phenotype. The large TST gain may be partially explained by the lowering effect of trazodone on cortisol levels, which are higher in the ISS phenotype.[8] Given the paucity of data in regard to the efficacy and safety of this drug and because it is not approved by the U.S. Food and Drug Administration for sleep, larger randomized placebo-controlled studies are needed to examine the efficacy and safety of this drug and its advantage over other established treatments such as CBT-I.

The results of the current study should be interpreted in light of some limitations. The preliminary nature, small sample size (small samples are more likely to show more extreme differences by chance alone), and open-label design prevent definitive conclusions about the effects of trazodone compared with CBT-I on clinically relevant outcomes. Future prospective studies with larger samples and that are placebo-controlled are

needed to examine the differential effect of pharmacological vs cognitive behavioral therapy for the ISS phenotype, among various clinical samples. As previously stated, the effect of trazodone and CBT-I on cortisol levels may have been affected because of the inherent variability secondary to the pulsatile secretory pattern of the hormone and its measurement. Therefore, future studies utilizing cortisol as an outcome should obtain more frequent cortisol samples at the time that the difference is maximized (ie, evening presleep period) and in well-controlled environments (ie, a sleep laboratory). Another limitation of the study is the fixed 8-hour recording of PSG that was used vs an ad libitum TIB during PSG recordings. Traditionally, clinical trials that have assessed the efficacy of hypnotic medications have used a fixed recording time (8 hours) for more valid comparisons within and between study groups.[46] However, this design was not ideal in the current study given that one of the essential components of CBT-I is sleep restriction. Furthermore, the cutoff point to define the objective short sleep duration phenotype seems to vary based on age, clinical population, and method of assessment (ie, PSG vs actigraphy). These factors should be considered when defining the ISS phenotype in clinical and general population samples.

CONCLUSION

The current study was the first preliminary, open-label, randomized study to examine whether the ISS phenotype responds better to pharmacological treatment than to CBT-I. This randomized trial suggests that trazodone, but not CBT-I, significantly improves objective sleep duration and reduces HPA axis activation, which has been shown to be a mediator of morbidity and mortality associated with this insomnia phenotype.

ABBREVIATIONS

ANCOVA, univariate analysis of covariance
ANOVA, analysis of variance
CBT-I, cognitive behavioral therapy for insomnia
HPA, hypothalamic-pituitary-adrenal
INS, insomnia with normal sleep duration
ISI, Insomnia Severity Index
ISS, insomnia with short sleep duration
PSG, polysomnography
TIB, total time in bed
TST, total sleep time

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