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SCIENTIFIC INVESTIGATIONS

Objective sleep duration and response to combined pharmacotherapy and cognitive behavioral insomnia therapy among patients with comorbid depression and insomnia: a report from the TRIAD study

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Study Objectives: Several studies have shown that patients with short sleep duration show a poor response to cognitive behavioral therapy for insomnia (CBT-I), but such studies have not included patients with comorbid conditions. The current study was conducted to determine whether pretreatment sleep duration moderates the response of patients with major depression and insomnia disorders to a combined CBT-I and antidepressant medication treatment.

Methods: This study comprised a secondary analysis of a larger randomized trial that tested combined CBT-I/antidepressant medication treatment of patients with major depression and insomnia. Participants (n = 99; 70 women; M_{age} = 47.712.4 years) completed pretreatment polysomnography and then were randomly assigned to a 12-week treatment with antidepressant medication combined with CBT-I or a sham therapy. Short and longer sleepers were defined using total sleep time cutoffs of < 5, < 6, and < 7 hours for short sleep. Insomnia and depression remission ascertained respectively from the Insomnia Severity Index and Hamilton Rating Scale for Depression were used to compare treatment responses of short and longer sleepers defined by the cutoffs mentioned.

Results: Logistic regression analyses showed that statistically significant results were obtained only when the cutoff of < 5 hours of sleep was used to define "short sleep." Both the CBT-I recipients with < 5 hours of sleep (odds ratio = 0.053; 95% confidence interval = 0.006–0.499) and the sham-therapy group with ≥ 5 hours of sleep (odds ratio = 0.149; 95% confidence interval = 0.045–0.493) were significantly less likely to achieve insomnia remission than were CBT-I recipients with ≥ 5 hours of sleep. The shorter sleeping CBT-I group (odds ratio = 0.118; 95% confidence interval = 0.020–0.714) and longer sleeping sham-therapy group (odds ratio = 0.321; 95% confidence interval = 0.105–0.983) were also less likely to achieve insomnia and/or depression remission than was the longer sleeping CBT-I group with ≥ 5 hours of sleep.

Conclusions: Sleeping < 5 hours may dispose comorbid major depression/insomnia patients to a poor response to combined CBT-I/medication treatments for their insomnia and depression. Future studies to replicate these findings and explore mechanisms of treatment response seem warranted.

Clinical Trial Registration: Registry: ClinicalTrials.gov; Name: Treatment of Insomnia and Depression (TRIAD); URL: https://clinicaltrials.gov/ct2/show/results/NCT00767624; Identifier: NCT00767624.

Keywords: insomnia, major depression, short sleep, cognitive behavioral therapy for insomnia

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Several studies have shown that patients with insomnia with short objective sleep duration have a suboptimal response to cognitive behavioral therapy for insomnia (CBT-I), but it is not known if short sleep duration moderates the CBT-I response of those with insomnia and psychiatric comorbidities. The current study was conducted to determine if sleep duration moderates the CBT-I response of patients with insomnia and comorbid depression.

Study Impact: Results suggest that a pretreatment objective sleep duration of < 5 hours of sleep in patients with comorbid insomnia and depression predicts a relatively poor CBT-I response. Findings highlight the importance of pretreatment objective sleep duration as a moderator to CBT-I intervention and suggest those with short sleep may require an alternate or adjunctive insomnia therapy.

INTRODUCTION

Insomnia disorder (ID) is characterized by difficulties falling and/or staying asleep that persist for at least 3 months and occur at least 3 nights per week despite adequate opportunities and circumstances for sleep to occur.[1,2] Over 1/3 of all adults experience occasional insomnia symptoms, and 5–15% have a chronic ID.[3–8] Although its significance is often minimized,[9,10] ID has significant health consequences, including daytime fatigue, depression and increased suicide risk, substance abuse, impaired social/vocational functioning and reduced quality of life.[4,11–21] ID is commonly comorbid with, and exacerbates, other medical and psychiatric disorders.[4,22] Moreover, insomnia contributes to increased health care costs, totaling over $285M for prescription sleeping pills and $90B in total direct treatment-related costs annually in the United States.[23,24] ID has also been

identified as a novel risk factor for cardiometabolic morbidity and mortality, conferring a 3-fold to 5-fold increased odds of hypertension, diabetes, and all-cause mortality.[25,26] Thus, ID is a serious condition that poses significant health risks and warrants early and effective treatment.

Currently the primary treatment options for ID include pharmacotherapy with various sleep-promoting medications (eg, benzodiazepine-receptor agonists, melatonin-receptor agonists, orexin antagonists, sedating antidepressants), and cognitive behavioral therapy for insomnia (CBT-I), which targets putative ID perpetuating mechanisms (eg, sleep-disruptive habits, prebed arousal, intrusive thinking while in bed, unhelpful beliefs about sleep).[27,28] Pharmacotherapy usually produces rapid symptomatic improvements, is widely available, and is generally well tolerated. However, there are concerns about potential adverse effects (eg, daytime sedation, falls among the elderly) and risks of tolerance and dependence with such treatment. Furthermore, there is minimal evidence documenting pharmacotherapy's sustained benefits with prolonged usage or after discontinuation. In contrast, CBT-I has minimal side effects, is preferred by many patients, and results in sustained sleep improvements after treatment is terminated. Whereas, CBT-I requires more health care provider time and has a slower therapeutic action than medications, evidence from meta-analyses, systematic reviews, and practice guidelines indicate that this therapy should be the initial treatment choice for all adults with ID.[29–33]

Of course, no one treatment benefits all patients with ID and such is the case for CBT-I. Studies have shown that about 60–65% of CBT-I recipients show clinically significant sleep improvements and 40–45% of those with ID achieve insomnia remission with this therapy.[34–36] Unfortunately, there are currently no standard guidelines for determining which patients with ID will and will not respond to CBT-I. However, Vgontzas et al[25,26,37–39] have suggested that patients with ID with objectively short sleep (ISS) durations of < 5 hours or < 6 hours of total sleep time (TST) per night are a severe insomnia phenotype subject to significant cardiometabolic and emotional disease (clinical depression, hypertension, diabetes) risk and poor response to nonmedicinal therapies. As tests of this latter contention, a total of 7 studies have compared the CBT-I responses of patients with ISS and patients with ID with longer, more normal sleep durations using a cutoff of < 6 hours (measured by polysomnography [PSG] or actigraphy) to define the ISS group.[40–43] Collectively results of all studies comparing the response of short and longer sleepers to CBT-I have shown the ISS group had a mere 29.8% (95% confidence interval [CI] = 13.5–46.2%) remission rate in response to CBT-I, whereas 53.5% (95% CI = 42.9–64.2%) of the longer sleeping insomnia with normal objective sleep duration group achieved insomnia remission.[44] More recently, Vgontzas and colleagues[45] showed that treatment with the medication trazodone, but not CBT-I, was effective for both increasing objectively measured TST and reducing salivary cortisol levels, suggestive of hypothalamic-pituitary-adrenal axis activation among a sample of patients with ISS who had < 7 hours of sleep per night as measured by actigraphy.

These findings are encouraging in terms of discriminating those who are likely CBT-I responders and nonresponders. However, the above cited studies, for the most part, included patients with ID without significant comorbidities so their results may not generalize to the larger ID population, which is mostly comprised of those with significant comorbid conditions.[4,22] Indeed, it remains to be determined if pretreatment objective sleep duration is a factor that moderates clinical outcomes among patients with ID with clinically significant comorbidities. If sleep duration is a factor in determining outcomes for such groups, it is possible that the cutoff for defining "short sleep" may vary across differing ID subgroups. Hence, research is needed to address such questions among comorbid ID samples.

One comorbid group that arguably merits attention are those who present with ID and major depression. Approximately two-thirds of patients with major depressive disorder (MDD) will experience insomnia,[46,47] and as many as 90% complain about poor sleep quality.[48] Individuals with insomnia are also 9.82 times more likely to have clinically significant depression compared to those without insomnia.[49] Insomnia has also been shown to be a risk factor for the onset of MDD,[49,50] whereas unresolved insomnia symptoms lead to MDD relapse.[51] Insomnia can negatively affect the trajectory of MDD by increasing its severity[52,53] and duration[54] and also hinder response to antidepressant treatment. Moreover, treatment of the insomnia presented by patients with depression cannot only resolve the sleep disturbance but also enhance chances for depression remission. Studies have shown that CBT-I leads to reduction of insomnia and depressive symptoms as well among a notable proportion of those with MDD.[55–58] Yet a subgroup of such patients fail to reach insomnia remission. Thus, efforts are needed to identify those patients with MDD who do and do not benefit from CBT-I and to determine whether their objective sleep duration discriminates these.

The current investigation was conducted to address these needs. We conducted this study to determine if one of the above-mentioned objective sleep duration cutoffs discriminates those patients with comorbid ID/MMD who do and do not benefit from CBT-I. Specifically, we tested the cutoffs of < 5 hours, < 6 hours, and < 7 hours of objective sleep duration measured by pretreatment PSG to discriminate patients who do and do not achieve insomnia and depression remission in response to intervention that includes CBT-I. The 3 cutoffs tested were chosen because those were used were used by Vgontzas and colleagues[25,26,45] to discriminate the ID subgroup with enhanced risks for morbidity/mortality and poor CBT-I treatment response. We hypothesized that (1) 1 more of these cutoffs would discriminate remitter and nonremitter groups and (2) the risk for nonremission in patients with ID and MDD would be greatest among those who have < 5 hours of objective sleep duration on their pretreatment polysomnograms.

METHODS

Design

The current study entailed a secondary analysis of data collected from the parent, multisite TRIAD (treatment of Insomnia and Depression) Study[59] conducted to determine the efficacy of combined CBT-I and antidepressant medication for the

treatment of those with comorbid major depressive and insomnia disorders. The parent study was a clinical trial in which participants were randomly assigned to a combined CBT-I + antidepressant medication (selected via medication algorithm) or a quasi-desensitization sham insomnia therapy + antidepressant medication at 3 collaborating study sites (Stanford University, University of Pittsburgh, Duke University). Study protocols were identical at each of the 3 sites, and data (not including protected health information) were collected centrally by the Data Coordinating Center at the University of Pittsburgh. The parent study protocol was reviewed and approved by the institutional review boards at each study site, and data and safety monitoring was conducted on a yearly basis by an external Data and Safety Monitoring Board whose membership was approved by the funding agency, the National Institute of Mental Health. Data for the current report were taken from a subset of the total study sample as described below.

Participants

Those enrolled in the larger parent study were English-speaking individuals between 18 and 75 years of age who (1) met *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (DSM-IV-TR) criteria for MDD (assessed by a trained Structured Clinical Interview for Psychiatric Disorders [SCID] interviewer); (2) scored at least 16 on the 17-item Hamilton Rating Scale for Depression (HRSD-17)[46] and at least 11 on the Insomnia Severity Index[60]; (3) had habitual bedtimes between 8 PM and 3 AM and habitual rise times between 4 AM and 11 AM; and (4) met DSM-IV-TR[11] criteria for primary insomnia assessed by the Duke Structured Interview for Sleep Disorders,[61,62] except for the criterion that excludes insomnia occurring exclusively during the course of another mental disorder. As this later exclusion is no longer included in the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5)[1] criteria for an ID diagnosis, it can be surmised that study enrollees would have met current DSM-5 criteria for ID. Exclusion criteria for the parent study eliminated those with other sleep disorders, unstable or terminal medical conditions, concurrent psychiatric conditions requiring treatment not provided by the parent study (eg, psychosis, bipolar disorder), persons engaged in other treatments for depression or insomnia, imminent suicide potential, and pregnant women. In addition, those with a current (past 6 months) SCID/DSM-IV-TR psychoactive substance use disorder diagnosis (except nicotine dependence) as well as those who consumed more than 3 cups of caffeinated beverages per day, used any illicit drugs, or consumed more than 14 alcoholic drinks per week (or > 4 per occasion) were also excluded. More detail about the inclusion and exclusion criteria for the parent study can be found in our previous report.[59]

To be included in the current study, participants had to have enrolled in an ancillary study conducted in conjunction with the parent study, completed the ancillary study's pretreatment laboratory PSG, and then began treatment. A total of 99 (69.6%) of the 148 participants enrolled in the parent study met these criteria and were considered for inclusion in the current investigation. The sample consisted of 70 women and 29 men who collectively had a mean age of 47.7 ± 12.4 years and had completed an average of 15.6 ± 3.0 years of formal education. Of the total sample, 72 (72.7%) were Caucasians.

Measures

Hamilton Rating Scale for Depression

The 17-item version of the HRSD-17[46] was administered prior to, during, and immediately after treatment to assess changes/improvements in depression symptoms. The HRSD-17 is a semistructured interview that was administered by independent raters masked to treatment assignment. Study raters were all certified by having their ratings of 2 taped interviews fall within 2 points of the score assigned to the interviews by an expert rater. For the purposes of the current study, this instrument was used to determine depression remission by the end of the acute treatment phase of the study. A HRSD-17 score < 8 was used to define depression remission at the end of the treatment phase of the study. Remission status of patients who withdrew from the study before completing treatment was determined using the last HRSD-17 score they obtained before study withdrawal.

Insomnia Severity Index

The Insomnia Severity Index (ISI)[60,63] is a 7-item self-report instrument that was used at the same study time points as was the HRSD-17 to assess changes/improvements in insomnia symptoms and insomnia remission. The ISI provides a global measure of perceived insomnia severity based on several indicators (eg, difficulty falling or staying asleep, satisfaction with sleep, degree of daytime impairment). The total score ranges from 0 to 28, with each 7-point score range indicating increasing insomnia severity: 0–7 (no clinical insomnia), 8–14 (subthreshold insomnia), 15–21 (insomnia of moderate severity), and 22–28 (severe insomnia). An ISI score < 8 was used to define insomnia remission at the end of the treatment phase of the study. As was the case with the HRSD-17, insomnia remission status of patients who withdrew from the study before completing treatment was determined using the last ISI score they obtained before study withdrawal.

Polysomnography

Two pretreatment ambulatory PSG studies were conducted on all participants included in this study using Compumedics Siesta ambulatory digital PSG systems. On study nights, participants were allowed to follow their normal sleep schedules without fixing the amount of time they spent in bed. Participants at the Stanford and Pittsburgh sites underwent the PSG monitoring in their homes, whereas those at the Duke site underwent PSG monitoring in sleep lab bedrooms, but these studies were unattended by any lab technologists. The initial PSG assessed sleep apnea and periodic movements of sleep and served as an adaptation night. This PSG included 5 electroencephalogram leads (C3/A2, C4/A1, Fz/A1+A2, O1/A2, O2/A1), 2 electrooculogram leads, a submentalis (surface) electromyogram, one echocardiogram lead, bilateral anterior tibialis electromyogram, oral/nasal airflow (thermocouple), nasal pressure (nasal cannula linked to pressure transducer), respiratory effort

(inductance plethysmography), finger pulse oximeter, snoring (microphone), and a position sensor. A second, baseline PSG was conducted within a week of the first PSG, but prior to treatment and included only electroencephalogram, electrooculogram, and electromyogram leads for the purpose of sleep staging. Participants were instructed to adhere to their habitual sleep schedule, intake of caffeine and alcohol, and nap behavior on days of PSG. All PSGs were scored at the Duke study site blind to treatment condition via a secure password protected web-based system under the direction of ADK, an experienced board-certified sleep medicine specialist, using standard scoring criteria.[64] Two experienced scorers scored each PSG record. Acceptable agreement between the two scorers was set at 90% of all the epochs. A third scorer was used to adjudicate records for which agreement was below criterion. For the current study, values of TST derived from the second, baseline PSG were used to classify our groups of short and longer sleepers.

Procedures

Selection and prescreening

All participants underwent a selection and prescreening process as part of the protocol for the TRIAD parent study. Specifically, individuals completed (1) an initial telephone screening to determine general study eligibility; (2) a sleep diary; (3) the Structured Clinical Interview for the DSM-IV-TR (SCID)[65] to diagnose a current Major Depressive Episode and rule out other Axis I disorders; (4) an SCID-II Patient Questionnaire and, if necessary based on this information, a SCID-II clinical interview[66]; (5) an abbreviated version of the Duke Structured Interview for Sleep Disorders[61] to assign an insomnia diagnosis and rule out other sleep disorders; (6) laboratory tests (thyroid stimulating hormone, liver panel, and pregnancy test for women of childbearing age), a medical history, and a review of systems; (7) the Epworth Sleepiness Scale[67] to exclude anyone with an Epworth Sleepiness Scare score above 10 in the group of study candidates who had a respiratory disturbance index of 10–15 events/h on the initial PSG night; and (8) the Mini-Mental Status Exam[68] to exclude individuals with cognitive impairment defined by a score < 25. Participants who met the selection criteria moved on to complete pretreatment measures, including the HRSD-17 and ISI. In addition, those included in this investigation also completed their PSG prior to beginning their respective treatments.

Treatment

Participants were randomized to 1 of the study's 2 treatment conditions: (1) pharmacotherapy for depression with CBT-I or (2) pharmacotherapy for depression with a sham psychological treatment for insomnia used as a control condition (CTRL). The participants completed outcome measures, including the HRSD-17 and ISI, biweekly during the treatment phase and after treatment completion. A more thorough description of the treatment conditions can be found in the main TRIAD paper.[59]

Over the course of 16 weeks, participants met with a psychiatrist every other week to receive their pharmacotherapy for depression, which followed the STAR*D study protocol.[69] While providing pharmacotherapy, the psychiatrist remained blind to the insomnia therapy each participant was assigned. Specific medications utilized for this study's pharmacotherapy included escitalopram (ESC), sertraline (SERT), and desvenlafaxine succinate (DSV). The pharmacotherapy consisted of 2 phases, each lasting 8 weeks. Phase 1 involved an initial medication selection. Specifically, the first medication utilized was ESC, unless the participant had a history of ESC failure, in which case SERT was the first medication prescribed. However, if the participant had a history of SERT failure, but no history of venlafaxine or DSV failure, the first medication used was DSV. Phase 2, beginning at week 8, involved assessing antidepressant response, using the Clinician Global Impressions scale,[70] to indicate any needed dosage or medication changes. If a nonresponse was indicated (Clinician Global Impressions scale score of 3 or more for the last 2 consecutive visits), the medication was changed (ESC to SERT or SERT to DSV) or altered (if already on DSV, the dose was increased). Of note, participants were able to switch medications (ESC to SERT or SERT to DSV) at any time during the treatment phase if they reported intolerability. Details regarding the timing and dosing of medication is provided in the online supplemental materials. Concurrent to their pharmacotherapy, participants completed 7 individual sessions (at weeks 1–4, 6, 8, and 12) of psychotherapy, either CBT-I or CTRL (sham therapy), with a psychotherapist. Both psychotherapies focused exclusively on sleep/insomnia-related issues. If a non-sleep issue was introduced by the participant, they were redirected to the focus of the session, except if the issue required immediate intervention (ie, suicidality). The CBT-I treatment followed the standardized protocol, including education (session 1), sleep restriction and stimulus control (session 2), cognitive restructuring and relaxation specific to sleep and somatic arousal (session 3), and continued modifications and relapse prevention (sessions 4–7). The CTRL treatment included a quasi-desensitization procedure that has been used successfully as a control in other insomnia outcome studies[34,58,71] and involved participants creating a 12-item hierarchy of sleep-related distressing situations and pairing each situation with emotionally neutral images. Psychotherapists were randomly assigned to learn and deliver either CBT-I or CTRL and received competency evaluations and regular supervision by study experts. All psychotherapists remained blind to the study hypotheses, as well as to the fact that 1 type of therapy was a sham.

Statistical analyses

All statistical analyses conducted were performed using version 9.3 of the Statistical Analysis System software. Our primary study analyses consisted of 3 sets of logistic regression analyses to respectively test participants' pretreatment PSG sleep objective sleep duration as a moderator for insomnia remission, depression remission, and remission of either or both of these conditions achieved by the end of the 16-week treatment phase of the study. In the first set of analyses, short sleep duration was defined as a PSG TST < 5 hours. The second set of analyses used a TST < 6 hours, whereas the third set of analyses used a TST < 7 hours to define short sleep duration. In each of the logistic regression analyses we tested the main effects of type

of insomnia treatment received (CBT-I vs CTRL) and sleep duration subgroup (short vs longer TST) as well as the interaction of these 2 effects. In conducting these analyses, we tested several covariates including age, sex, educational level, proportion of treatment completed, initial antidepressant prescribed (ESC vs other medication), and whether the initial antidepressant was switched (yes vs no) during treatment. Only the proportion of treatment completed was a significant predictor, so this covariate was included in our final logistic regression models retained. In addition, we conducted analyses (analyses variance, Fisher's exact tests) to determine whether the 4 insomnia treatment × sleep duration subgroups considered in the final logistic regression analyses differed in their ethnic and female/male compositions, mean ages, educational levels, baseline ISI and HAMD scores, or the first and last antidepressant received in the study. We also conducted an analysis to compare the mean pretreatment TSTs of the 4 subgroups to document that the short and long sleepers did indeed differ in regard to their sleep times.

RESULTS

Logistic regression results

Of the 3 sets of logistic regression analyses conducted, only the set of analyses in which short sleepers were defined by a sleep duration of < 5 hours per night produced significant results. In these analyses, we found significant insomnia treatment × sleep duration group interactions in analyses that considered insomnia remission in isolation (Wald $\chi^2(1) = 6.5814$, $P = .0103$) and remission of either or both insomnia and depression (Wald $\chi^2(1) = 6.8882$, $P = .0087$). The analysis of depression remission considered in isolation did not show any significant results. **Table 1** showed the numbers and proportions of each treatment × sleep duration subgroup that achieved insomnia remission, depression remission, and remission of both insomnia and depression. As suggested by data shown, those CBT-I-treated patients with < 5 hours of sleep showed a significantly lower chance (odds ratio [OR] = 0.053; 95% CI = 0.006–0.499) of insomnia remission than did those in the CBT-I group with ≥ 5 hours of sleep. Moreover, those longer sleepers in the CTRL group showed a lower chance (OR = 0.149; 95% CI = 0.045 – 0.493) of insomnia remission than did the longer sleeping CBT-I group. Our analyses also showed that CBT-I recipients who slept < 5 hours (OR = 0.118; 95% CI = 0.020–0.714) and CTRL assignees who slept ≥ 5 hours (OR = 0.321; 95% CI = 0.105–0.983) were significantly less likely to achieve remission in 1 or both conditions than were the longer sleepers who received CBT-I. Among the short sleepers, those assigned to the CTRL group showed a significantly greater chance of remission in 1 or both conditions than those assigned CBT-I (OR = 6.890; 95% CI = 1.015–46.720). The overall pattern of remission outcomes was not significantly different for the remainder of the paired subgroup comparisons. **Figure 1** shows the proportions of each subgroup that remained unremitted, showed only insomnia remission or depression remission, or achieved both insomnia and depression remission by the end of the study's 16-week treatment phase. A Fisher's exact test showed the groups differed significantly ($P = .009$) in their remission statuses with those CBT-I-treated patients with ≥ 5 hours of sleep on PSG showing the greatest tendency to achieve remission status, whereas the CBT-I-treated patients with short sleep duration were least likely to achieve insomnia or depression remission.

Since we used the last observed values of the ISI and HRSD-17 for determining the remission statuses of those who dropped out prior to completing treatment, we recognized such data do not necessarily represent the possible final remission statuses of such participants had they completed the entire treatment phase. Given this consideration, we conducted a sensitivity analysis with only the 70 participants who completed all treatment and provided ISI and HRSD-17 at the end of treatment. The proportions of participants in each subgroup achieving remission of insomnia, depression, and both insomnia and depression remission are provided in **Table S1** in the supplemental material. A Fisher's exact test conducted with this reduced sample was again significant ($P = .0237$), implying significantly different remission rates across subgroups. Again, the proportion of overall combined insomnia and depression remission was lowest in the CBT-I group (14.3%) with < 5 hours of sleep and highest in the CBT-I group (56.7%) with ≥ 5 hours of sleep.

Table 1—Proportions of each treatment × sleep duration subgroup that achieved insomnia remission, depression remission, and insomnia and/or depression remission.

	Insomnia Therapy			
	CBT-I		CTRL	
	Sleep Duration (n)		Sleep Duration (n)	
Remission Status*	≥ 5 hours (41)	< 5 hours (10)	≥ 5 hours (29)	< 5 hours (19)
Insomnia remission, n (%) [A]	24 (58.4)[a]	1 (10.0)[b]	7 (20.7)[b]	7 (36.8)[a,b]
Depression remission, n (%) [B]	16 (39.0)	2 (20.0)	8 (27.6)	9 (47.4)
A and B remission, n (%)	16 (39.0)[a]	1 (10.0)[b]	4 (13.8)[a,b]	5 (26.3)[a,b]

Insomnia remission determined by an Insomnia Severity Index score < 8 at the end of treatment. Depression remission determined by a Hamilton Rating Scale for Depression score < 8 at the end of treatment. *Values that have different superscript letters are significantly different from each other as determined by logistic regression. CBT-I = cognitive behavioral therapy for insomnia, CTRL = quasi-desensitization sham control.

Figure 1—Proportions of each subgroup achieving insomnia remission, depression remission, or both insomnia and depression remission.

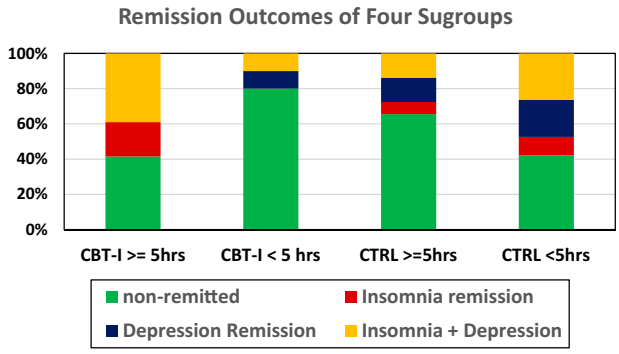

Figure shows the proportions of each subgroup that (1) did not achieve either insomnia or depression remission (green portion of each bar); (2) achieved insomnia remission only (red portion of each bar); (3) achieved depression remission only (blue portion of each bar); and (4) achieved both insomnia and depression remission (yellow portion of each bar). CBT-I = cognitive behavioral therapy for insomnia, CTRL = quasi-desensitization sham control.

In addition to these analyses, we conducted separate analyses to determine the proportions of each subgroup showing clinically significant responses (ie, responder rates) in regard to their insomnia and depression. These analyses that are described in the supplemental materials did not show significant subgroup differences.

Pretreatment characteristics of subgroups

To determine whether there were any pretreatment characteristics among the subgroups that could have explained the above-described findings, we conducted a series of analyses to compare these groups in terms of their mean ages, years of education, female/male compositions, racial compositions, pretreatment scores on the ISI and HAMD, and pretreatment values of PSG-measured TST. Treatment (CBT-I) × sleep duration group (< 5 hours vs ≥ 5 hours) analyses of variance were conducted to test continuous variables, whereas Fisher's exact tests were used to test for differences in female/male and racial compositions of the groups. Results of these analyses are shown in **Table 2**. The information shown there indicates the subgroups did not differ significantly regarding their mean ages, average years of education, mean pretreatment ISI and HRSD-17 scores, female/male and racial compositions. Only in the case of pretreatment TST was there a significant finding obtained documenting the preordained subgroup differences in this measure. Thus, it does not appear that the subgroups differed in characteristics other than TST that might have explained their different degrees of treatment responses.

First and second antidepressant medication prescribed

To determine whether differences in the antidepressant medications our subgroups received might explain the differences in treatment responses shown by them, we compared the proportions of each subgroup who received ECS, SERT, and DSV as their first medication and as a second medication. **Table 3** shows the proportion of individuals in each subgroup who received each of these medications as a first and as a last medication during treatment. A total of 76 patients were prescribed ECS, 17 were prescribed SERT, and 6 patients received DSV as their first medication. There were no significant differences among the distribution of these first prescribed medications across the 4 subgroups (Fisher's exact $P = .94$). Medications were switched for several the study participants during treatment, so that 56 of them were taking ECS, 23 were taking SERT, and the remaining 20 were taking DSV as their second/last medication prescribed during treatment. Again, there was no significant difference in the distribution of these second/last medications prescribed across subgroups (Fisher's exact $P = .48$). Also, the proportion of patients switched from 1 antidepressant medication to another during treatment did not differ across subgroups (Fisher's exact $P = .76$). Hence, it appears that differences in the antidepressants prescribed for the subgroups likely did not account for the differences in the treatment responses they displayed.

Representativeness of study sample

We also considered whether the subset of study participants included in the current study may have been different from those participants who were enrolled in the larger parent study but were excluded from this study's sample. Differences between participants in the larger study who were and were not included in the current study sample could call into question whether the findings reported would likely generalize to the larger sample. A series of statistical comparisons showed those included in the current sample did not differ from those excluded in regard to their mean ages ($F = 2.10$; $P = .15$), mean years of education ($F = 2.09$, $P = .15$), mean baseline HRSD-17 scores ($F = 0.01$, $P = .92$), mean baseline ISI scores ($F = 1.29$, $P = .26$), female/male compositions (Fisher's exact $P = .55$), white/non-white compositions (Fisher's exact $P = .43$), proportions of individuals receiving each of the 3 antidepressants as a first (Fisher's exact $P = .10$) or last (Fisher's exact $P = .52$) medication, proportions of individuals receiving CBT-I and CTRL (Fisher's exact $P = .39$), or proportions of individuals achieving insomnia (Fisher's exact $P = 1.00$) or depression (Fisher's exact $P = .86$) remission. Hence, the findings reported would likely generalize to the larger parent study sample.

DISCUSSION

The current study was conducted to determine whether short sleep duration, as measured objectively, attenuates the treatment responses of patients with insomnia and comorbid major depressive disorder. We also attempted to determine whether any of the previously tested cutoffs of < 5 hours, < 6 hours, or < 7 hours to define short sleep separated those patients more and less likely to respond to the interventions provided in this study. Whereas previous studies have shown that defining

Table 2—Demographic characteristics and pretreatment TST and ISI and HAMD scores of the four insomnia treatment × sleep duration subgroups.

	Insomnia Therapy [A]				Analysis of Variance Results $F(df = 3, 95)$ & P for Variables with Continuous Distributions		
	CBT-I		CTRL				
	Sleep Duration [B]		Sleep Duration [B]				
Variable	≥ 5 hours	< 5 hours	≥ 5 hours	< 5 hours	A	B	A × B
Age in years, mean (SD)	47.9 (13.2)	48.4 (15.1)	45.8 (11.5)	49.9 (11.0)	$F = 0.01$ $P = .92$	$F = 0.62$ $P = .43$	$F = 0.39$ $P = 53$
Years of education, mean (SD)	16.0 (3.4)	15.1 (2.2)	15.3 (2.7)	15.4 (2.9)	$F = 0.07$ $P = .79$	$F = 0.32$ $P = .57$	$F = 0.53$ $P = .47$
Baseline ISI score, mean (SD)	20.4 (3.7)	21.9 (3.5)	19.5 (3.9)	21.3 (3.6)	$F = 0.77$ $P = .38$	$F = 3.58$ $P = .06$	$F = 0.02$ $P = .89$
Baseline HAMD score, mean (SD)	22.0 (3.3)	21.4 (3.4)	22.9 (3.1)	22.8 (3.6)	$F = 2.19$ $P = .14$	$F = 0.19$ $P = .66$	$F = 0.17$ $P = .68$
Baseline TST, mean (SD)	397.1 (56.2)[a,*]	241.3 (49.4)[b]	409.7 (74.3)[a]	242.2 (51.2)[b]	$F = 0.23$ $P = .63$	$F = 134.10$ $P = .0001$**	$F = 0.18$ $P = .68$
					Analysis of Dichotomous Variables – Fisher's Exact Test P		
Number of females/males	30/13	7/3	24/7	13/6	$P = .92$		
Race, White/non-White	32/11	7/3	24/7	11/8	$P = .40$		

*Values of TST that have different superscript letters are significantly different from each other as determined by an analysis of variance and a posteriori comparisons. **Statistically significant result. HAMD = Hamilton Rating Scale for Depression, ISI = Insomnia Severity Index, TST = total sleep time as measured by polysomnography prior to treatment initiation.

"short sleepers" as those with fewer than 6 or 7 hours of sleep separates patients who do and do n0ot respond to CBT-I, we did not find that to be the case in our comorbid sample. Only when we used < 5 hours of TST as a cutoff for defining short sleep did we observe statistically significant different treatment responses of the so defined short and longer sleepers. We did hypothesize that the risk for nonremission in patients with ID and MDD would be greatest among those who have < 5 hours of objective sleep duration. Yet it is notable that when short sleep was defined as < 6 or 7 hours of TST, we did not find any differences in insomnia and depression remission rates between those falling above and below these cutoffs. Thus, our findings did not replicate the findings of prior CBT-I treatment studies.[40–43] Consequently, our results suggest that what constitutes treatment confounding short sleep may differ in patients with ID with and without MDD as a comorbid condition.

In comparing our results with those of prior studies that examined the CBT-I responses of short sleepers, it is important to note that treatment in the current study included antidepressant medication combined with CBT-I. Prior tests of short sleepers not only excluded those with MDD and other psychiatric comorbidities but also tested CBT-I used in isolation. From the data we obtained it is not clear how our combined CBT-I/antidepressant medication treatment served to lower the TST threshold below which CBT-I's effectiveness markedly diminished. However, it may be useful to consider the putative

Table 3—First and last antidepressant medications prescribed.

Therapy	PSG Sleep Duration	First Medication n (%)			Last Medication n (%)		
		ECT	SERT	DSV	ECT	SERT	DSV
CBT-I	≥ 5 hours	29 (70.7)	9 (22.0)	3 (7.32)	20 (48.8)	11 (26.8)	10 (24.4)
	< 5 hours	9 (90.0)	1 (10)	0 (0.0)	7 (70.0)	3 (30.0)	0 (0.0)
CTRL	≥ 5 hours	22 (75.9)	5 (17.2)	2 (6.9)	16 (55.2)	7 (24.1)	6 (20.7)
	< 5 hours	16 (84.2)	2 (10.5)	1 (5.3)	13 (68.4)	2 (10.5)	4 (21.1)
Total sample*		76 (76.8)	17 (17.2)	6 (6.1)	56 (56.6)	23 (23.2)	20 (20.2)

*Percentages are rounded to the nearest decimal point and, thus, collectively may exceed 100%. CBT-I = cognitive behavioral therapy for insomnia, CTRL = quasi-desensitization sham control therapy, DSV = desvenlafaxine, ECT = escitalopram, SERT = sertraline.

significance of short sleep in regard to its pathophysiology among patients affected by it. Vgontzas et al[39] have proposed that objectively short sleep duration among individuals with ID connotes a chronic state of physiological hyperarousal that results in heightened morbidity outcomes and poor response to CBT-I. Vgontzas et al have supported this contention by showing individuals with short sleep and no significant comorbidities have elevated 24-hour cortisol levels that are suggestive of heightened activation of the hypothalamic-pituitary-adrenal axis. Moreover, in their recent pilot study, Vgontzas et al[45] showed that TST sleep time increases markedly and cortisol levels decrease from pre- to posttreatment time points when short sleepers are treated with the antidepressant trazodone, an agent known to reduce (hypothalamic-pituitary-adrenal) activation. Given this observation, it seems reasonable to speculate that the antidepressants used in the current study curtailed hypothalamic-pituitary-adrenal activation sufficiently to allow CBT-I to be effective in those with ≥ 5 hours of sleep. In contrast, the antidepressant medications used herein may have had insufficient effect on the hyperarousal of those with < 5 hours of nocturnal sleep time thus rendering CBT-I ineffective with this group. Perhaps the sleep restriction component of CBT-I may not be beneficial and is contraindicated for those patients with depression with short sleep. It seems possible that the short sleeping ID/MDD phenotype has sleep disturbance largely due to the ongoing depressive illness, so antidepressant medication may represent the best treatment for this group. The finding that short sleepers in the CTRL group who received antidepressant medication as their only active treatment had relatively better insomnia and depression treatment responses than did similar patients receiving CBTI seems consistent with these speculations. Yet more research that incorporates measures of physiological hyperarousal and examines the effects of CBT treatment components is needed to determine if our speculations are supported.

In considering our findings, it is important to consider the limitations of this study. The findings reported were derived from a secondary analysis of existing data obtained from a randomized trial. The current study did not randomize equal numbers of short and longer sleepers to the 2 insomnia treatment arms of the study, and as a result only 29 (29.3%) of the 99 participants included in the current investigation fell into the short sleeper group. Given this, the cell sizes for some of the statistical comparisons conducted were small, likely rendering such comparisons to be underpowered. Furthermore, identifying sleep duration phenotypes based on one PSG night may have limited reliability. It is also important to note that we lacked guidance from prior research as to what might constitute an optimal cutoff for treatment confounding short sleep in samples with comorbid ID and MDD. As such, our investigation was, admittedly, largely exploratory. In addition, our sample included mostly Caucasians and was predominantly comprised of women. Hence, future studies of this nature would benefit by the inclusion of a more ethnically diverse sample comprised of relatively equal proportions of males and females. It also should be noted that we did not track antidepressant medication adherence of the study patients, so it is possible that differences in adherence rates across treatment groups could have affected observed outcomes. Finally, we examined only 2 categorical outcome measures, insomnia and depression remission, so future studies would benefit by a much more extensive number of outcomes that assess sleep and diurnal functioning of the samples scrutinized. Nonetheless, the findings reported seem meritorious of consideration, and future studies that examine the impact of short sleep on patients with MDD and other comorbid subgroups seem warranted.

ABBREVIATIONS

CBT-I, cognitive behavioral therapy for insomnia
CI, confidence interval
CTRL, quasi-desensitization therapy for insomnia control condition
DSM, *Diagnostic and Statistical Manual of Mental Disorders*
DSV, desvenlafaxine
ESC, escitalopram
HRSD-17, Hamilton Rating Scale for Depression-17 item version
ID, insomnia disorder
ISI, Insomnia Severity Index
ISS, insomnia with short objective sleep duration
MDD, major depression
OR, odds ratio
PSG, polysomnography
SCID, Structured Clinical Interview for Psychiatric Disorders
SERT, sertraline
TST, total sleep time

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