Efficacy of Cognitive-Behavioral Therapy for Insomnia Combined With Antidepressant Pharmacotherapy in Patients With Comorbid Depression and Insomnia: A Randomized Controlled Trial

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ABSTRACT

Objectives: The Treatment of Insomnia and Depression (TRIAD) study evaluated the efficacy of combining depression pharmacotherapy (using MED, an ecologically valid and generalizable antidepressant medication algorithm) with cognitive-behavioral therapy for insomnia (CBT-I) among individuals with comorbid insomnia and major depressive disorder (MDD) to determine if change in insomnia severity mediates antidepressant outcome.

Methods: This 16-week, 3-site, randomized controlled trial (RCT) randomly assigned 150 participants (recruited between March 2009 and August 2013), who met *DSM-IV-TR* criteria for insomnia and MDD and were not receiving treatment for either, to receive depression pharmacotherapy plus 7 sessions of either CBT-I or a credible control therapy for insomnia (CTRL). Depression pharmacotherapy followed a standardized 2-step algorithm, which included escitalopram, sertraline, and desvenlafaxine in a prescribed sequence. Primary measures were the Hamilton Depression Rating Scale and the depression module of the Structured Clinical Interview for *DSM-IV* Axis I Disorders, Research Version, Nonpatient Edition, administered by raters masked to treatment assignment, and the self-administered Insomnia Severity Index (ISI).

Results: CBT-I was superior to CTRL in reducing insomnia severity ($P = .028$). The overall difference in depression remission between the treatments was not statistically significant (44% in CBT-I and 36% in CTRL; number needed to treat = 15). However, planned secondary analysis revealed that improvements in insomnia at week 6 mediated eventual remission from depression, with early change in ISI predicting depression remission in the CBT-I ($P = .0002$) but not in the CTRL arm ($P = .26$).

Conclusions: CBT-I is an efficacious treatment for insomnia comorbid with MDD among patients treated with antidepressant medications. Improvement in insomnia may be related to the change in depression. Future studies should identify which patients are most likely to benefit from the addition of an insomnia-focused therapy to standard antidepressant treatments.

Trial Registration: ClinicalTrials.gov identifier NCT00767624

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Poor sleep is a common characteristic of depression. Many patients continue to have problems sleeping even after the depression is adequately treated.[1] Persistent poor sleep after depression treatment constitutes a significant risk for depression relapse.[2] Depressed patients with insomnia have more severe depressive illness, longer time to remission, lower rates of remission, and greater attrition and are more likely to have suicidal ideation than depressed patients without sleep disturbance.[1] The high prevalence of insomnia symptoms among depressed persons and their possible adverse impact on the course of depression suggest that insomnia should be a clinically relevant target for improving depression outcome and reducing suffering.

Research on matching patients to antidepressant pharmacotherapy is not sufficiently advanced to inform the practitioner about treating a depressed patient with insomnia. Common strategies include selecting a sedating antidepressant and coadministering of a hypnotic along with an antidepressant medication.[3–5] However, the efficacies of these strategies are unclear.[6] The aim of the current randomized controlled trial was to determine whether the coadministration of a nonpharmacologic treatment, cognitive-behavioral therapy for insomnia (CBT-I), along with an ecologically valid and generalizable antidepressant medication algorithm (MED), is an effective strategy among patients who have major depressive disorder (MDD) and insomnia. CBT-I is an effective skill-based brief psychotherapy.[7–9] It produces improvements in insomnia equivalent to those achieved during acute treatment with hypnotic medications and more durable outcome after study treatments are discontinued.[10] It has several advantages over hypnotic medications for addressing insomnia in the context of MDD, including favorable side-effect profile and better long-term outcomes.[10] The study of CBT-I is also important for resolving the uncertainty regarding the effects of insomnia therapy on depression outcome as hypnotic drugs may have direct therapeutic effects on anxiety or depression.

Clinical Points

- Poor sleep can hinder response to depression treatments, but empirically tested strategies for treating a depressed patient with insomnia are lacking.
- Adding cognitive-behavioral therapy for insomnia (CBT-I) to depression pharmacotherapy among people with depression comorbid with insomnia did not significantly improve depression. Early improvement in insomnia severity, however, predicted higher remission among those who received CBT-I.
- Cognitive-behavioral therapy for insomnia is effective for the treatment of insomnia that is comorbid with depression.

We hypothesized that patients in the MED + CBT-I arm would have a significantly greater likelihood of depression remission and, secondarily, a faster decrease in clinical ratings of insomnia and depression severities than those in MED + CTRL. We also hypothesized that improvement of insomnia would mediate antidepressant response.

METHODS

The Treatment of Insomnia And Depression (TRIAD) study (ClinicalTrials.gov identifier NCT00767624) was conducted at Duke University (Durham, North Carolina), Stanford University (Palo Alto, California), and the University of Pittsburgh (Pittsburgh, Pennsylvania). Sites followed identical study protocols, which were approved by each university's institutional review board. Randomization (1:1) was done centrally, within randomly generated blocks of 2 and 4, stratified by participating site.

Participants

Participants were recruited primarily through community advertisements between March 2009 and August 2013 and were screened after providing written consent. Participants had to meet the following criteria: age between 18 and 75 years; English fluency; *DSM-IV-TR* MDD criteria (based on the Structured Clinical Interview for *DSM-IV* Axis I Disorders, Research Version, Nonpatient Edition [SCID-I/NP][11]); 17-item Hamilton Depression Rating Scale (HDRS)[12] score ≥ 16; *DSM-IV-TR* criteria for insomnia (primary insomnia or insomnia due to another mental disorder, based on the Duke Structured Interview for Sleep Disorders[13,*]); and Insomnia Severity Index (ISI)[14] score ≥ 11. Participants were excluded if they had other conditions that would have necessitated medical care not included in the study or confounded the interpretation of study results (eg, concomitant insomnia or depression treatments) or had conditions incompatible with study treatment (eg, pregnancy). A full list of criteria is found in Supplementary eAppendix 1.

*Our criteria were consistent with those of *DSM-5*, in which both disorders are subsumed under the new category, insomnia disorder, with a chronic course.

Treatments

Treatments lasted 16 weeks, with medication management visits every 2 weeks and seven 45-minute individual sessions (weeks 1, 2, 3, 4, 6, 8, and 12) of the same frequency and duration for both therapies. Study psychiatrists did not address insomnia issues and were masked to therapy assignment; sleep therapists did not discuss depression or other issues unrelated to sleep. See Supplementary eAppendix 1 and eTable 1 for additional details about therapy.

Cognitive-Behavioral Therapy for Insomnia

This therapy included sleep education (Session 1), sleep restriction[15] and stimulus control[16] (Session 2), strategies for reducing somatic and sleep-related cognitive arousal (Session 3), cognitive restructuring of sleep-related thoughts[17] (provided throughout), and relapse prevention (Session 7).

Control Therapy for Insomnia

This therapy consisted of systematic pairing of sleep-related distressing situations with emotionally neutral images and was previously used as a credible insomnia control therapy.[18,19] It included the same sleep education module as CBT-I but no other components of CBT-I.

Pharmacotherapy

To enhance feasibility and generalizability, the pharmacotherapy followed principles used in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study,[20] allowing structured flexibility in the choice of the first medication to be tried and 1 switch to another medication. The medications utilized included escitalopram, sertraline, and desvenlafaxine succinate. See eAppendix 1 for additional details about the pharmacotherapy.

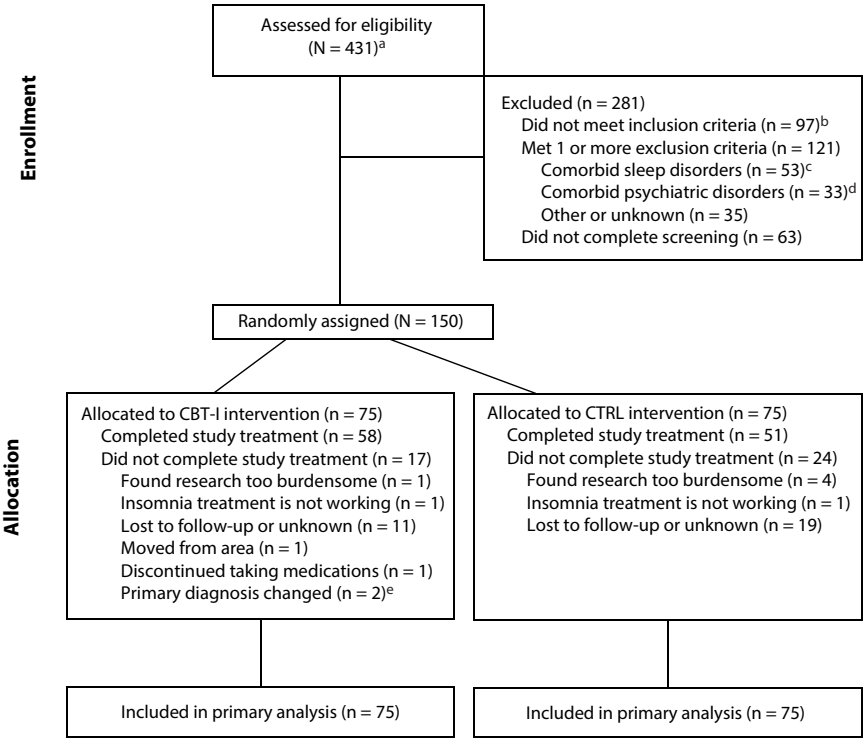
Measures

Depression and insomnia measures were collected at baseline and every 2 weeks thereafter. Depression measures included the HDRS[12] and SCID-I/NP depression module, administered by raters masked to treatment assignment. Analyses involving the relationship between insomnia and depression severity were conducted using the HDRS after removing the sleep items (HDRS-R). *Remission* was defined following American College of Neuropsychopharmacology (ACNP) recommendations[21] by presence of the following 2 criteria for at least 3 consecutive weeks: (1) absence of both depressed mood and anhedonia and (2) no more than 2 other *DSM-IV-TR* diagnostic criterion symptoms of depression. Insomnia severity was measured with the ISI.[22] Clinician Global Impressions (CGI)[23] and Frequency, Intensity, and Burden of Side Effects Ratings (FIBSER)[24] scales were administered during pharmacotherapy visits (every 2 weeks).

Analysis

Baseline and treatment (eg, number of visits) characteristics were compared using *t* tests and χ^2. Primary analyses were carried out on the intent-to-treat sample. Secondary analyses were conducted on a modified sample of 148 participants,

Figure 1. CONSORT Flowchart



[a]Reasons listed for ineligibility were, for the most part, based on the first ineligibility criterion met by a given person. That is, screening stopped as soon as it became clear that at least 1 exclusion criterion was met. Overall, 26.7% discontinued study participation. Those who dropped out were younger in age (mean ± SD 40.2 ± 11.7 vs 49.0 ± 12.1 years, $P < .0001$) and had a lower education level (mean ± SD 14.1 ± 2.67 vs 16.1 ± 3.3 years, $P < .001$) but did not differ on any other demographic or clinical variables or recruitment site. Treatment involved taking study medication and attending therapy sessions.
[b]Insomnia-related inclusion criteria were meeting *DSM-IV-TR* criteria for primary insomnia + scoring at least 11 on the ISI + having habitual bedtime 8 PM – 3 AM and habitual rise time 4 AM – 11 AM. Depression-related inclusion criteria were meeting *DSM-IV-TR* criteria for MDD and scoring at least 16 on the 17-item HDRS.
[c]The 2 most frequent comorbid sleep disorders were sleep apnea and restless legs syndrome.
[d]The 2 most frequent psychiatric comorbidities were bipolar disorder and posttraumatic stress disorder.
[e]One participant developed psychotic symptoms before starting the study treatments, and another developed bipolar disorder around week 4. These participants were included in the primary analysis.
Abbreviations: CBT-I = cognitive-behavioral therapy for insomnia, CONSORT = Consolidated Standards of Reporting Trials, CTRL = control therapy for insomnia, HDRS = 17-item Hamilton Depression Rating Scale, ISI = Insomnia Severity Index, MDD = major depressive disorder.

excluding 2 participants who were deemed ineligible after randomization (see Figure 1). The primary hypothesis, difference in time to depression remission, was tested using a Cox proportional hazards model, with treatment, site, and their interaction. Separate mixed-effects linear models with autoregressive error structure were used to examine the relative differences between treatments with respect to the rate of change in the ISI and with respect to change in the HDRS-R. These models included a random slope and fixed effects for treatment, site, and their interaction.

The MacArthur mediation model[25–27] was used to examine the possibility that change in ISI mediated change in remission from depression; that is, that part of the mechanism by which insomnia treatment affects depression lies in its ability to decrease insomnia severity. This analysis had 2 steps, progressing to the second step only if the model in the first step was statistically significant. In the first step, a regression analysis examined the relative differences between treatments on the rate of change in the ISI from baseline to week 6 (examining the effects of 4 therapy sessions). This time point was selected based on results from prior dose-response research in primary insomnia.[28] Change in the ISI from baseline to week 6 was estimated, based on all available data for each individual participant, as the slope of the regression line of the available ISI scores from baseline to week 6 relative to treatment week, whereby treatment week 0 was the baseline. In the second step, a mixed-effects linear model with autoregressive error structure was tested to determine if change in the ISI from baseline to week 6 mediated remission of depression. The model included treatment, change in the ISI from baseline to week 6 (individual slopes), and their interaction. Planned post hoc mixed-effects linear models with autoregressive error structure tested if change in the ISI from baseline to week

Table 1. Demographic and Baseline Clinical Characteristics

Measure	Total (N = 150)	Treatment		Analysis	
		CBT-I (n = 75)	CTRL (n = 75)	Test Statistic	*P*
Age, mean ± SD, y	46.6 ± 12.6	48.3 ± 12.7	45.0 ± 12.3	$t_{148} = 1.64$	.10
Sex, n (%)				$\chi^2_1 = 0.55$	.46
Male	40 (26.7)	22 (29.3)	18 (24.0)		
Female	110 (73.3)	53 (70.7)	57 (76.0)		
Race, n (%)[a]				$\chi^2_2 = 0.59$	.74
White	105 (70.9)	52 (70.3)	53 (71.6)		
Black	25 (16.9)	14 (18.9)	11 (14.9)		
Other	18 (12.2)	8 (10.8)	10 (13.5)		
Hispanic	15 (10.1)	4 (5.4)	11 (14.7)	$\chi^2_1 = 3.53$	.06
Education, mean ± SD, y	15.6 ± 3.3	15.9 ± 2.9	15.3 ± 3.6	$U_1 = 2.07$	.15
Employment status, n (%)[a]				$\chi^2_2 = 2.24$	.33
Employed	66 (44.3)	33 (44.0)	33 (44.6)		
Unemployed	57 (38.3)	32 (42.7)	25 (33.8)		
Other	26 (17.4)	10 (13.3)	16 (21.6)		
Marital status, n (%)[a]				$TP_0 < 0.01$	.25
Single	58 (38.9)	30 (40.0)	28 (37.8)		
Married/cohabiting	57 (38.3)	24 (32.0)	33 (44.6)		
Divorced/separated	29 (19.5)	17 (22.7)	12 (16.2)		
Widowed	5 (3.4)	4 (5.3)	1 (1.4)		
ISI, mean ± SD	18.9 ± 4.1	19.4 ± 4.3	18.3 ± 3.9	$t_{148} = 1.57$	.12
No. insomnia episodes	1.9 ± 2.5	2.0 ± 2.9	1.8 ± 2.2	$U_1 < 0.01$	.92
Age at first insomnia episode, y	31.6 ± 15.1	31.7 ± 16.2	31.6 ± 13.9	$t_{141} = 0.02$	.98
HDRS, mean ± SD	21.7 ± 3.7	21.9 ± 3.79	21.5 ± 3.7	$t_{148} = 0.57$	.58
No. prior depressive episodes	3.4 ± 5.1	4.1 ± 6.1	2.8 ± 3.8	$U_1 = 0.33$	.57
Age at first depressive episode, y	26.6 ± 14.5	26.6 ± 14.7	26.5 ± 14.5	$U_1 < 0.01$	1.00

[a]Percent values are relative to nonmissing values.
Abbreviations: CBT-I = cognitive-behavioral therapy for insomnia, CTRL = control therapy for insomnia, HDRS = 17-item Hamilton Depression Rating Scale, ISI = Insomnia Severity Index, TP = Fisher exact table probability.

6 mediated remission of depression within each treatment arm. We similarly used the MacArthur mediation model to examine the possibility that change in HDRS-R mediated change in remission from insomnia (defined as ISI < 8), using individual slopes of HDRS-R values during the first 6 weeks of treatment. Our power computation was based on the primary hypothesis of differential time to remission. Our original target recruitment was 255 participants (ie, 85 participants per site), with an estimated 80% power to detect hazard ratios of 1.61, 1.69, 1.79, 1.89, and 2.04 for varying levels of the cumulative survival estimates of 0.1, 0.2, 0.3, 0.4, and 0.5, assuming a 5% 2-tailed significance level of .05.

RESULTS

Of the 431 who gave their consent and were assessed for eligibility, a total of 40 male and 110 female eligible participants were randomly assigned to treatment (Figure 1). All but 1 participant started antidepressant medications. Demographic and clinical characteristics of the participants are presented in Table 1. There were no significant differences in demographic and clinical characteristics between treatment groups. The mean ± SD number of therapy visits attended was 4.8 ± 2.7, with no significant difference between treatment arms ($P = .38$). The mean ± SD number of medication management visits was 6.8 ± 2.8, with no difference between the treatment arms (6.9 ± 2.8 for CBT-I vs 6.4 ± 2.8 for CTRL; $P = .07$). The starting antidepressant medication was escitalopram for 78% of patients (75% for MED + CBT-I and 80% for MED + CTRL), sertraline for 14% (18% and 11%, respectively), and desvenlafaxine for 8% (7% and 9%, respectively), with no group differences (*P* values > .23). The mean ± SD maximum dose taken was 16.8 ± 4.9 mg for escitalopram, 109.0 ± 60.4 mg for sertraline, and 75.0 ± 28.4 mg for desvenlafaxine, with no significant treatment group differences (*P* values > .48). CBT-I participants reported greater frequency of medication side effects ($\chi^2 = 9.1$, $P = .03$) and higher maximum side effect burden ($\chi^2 = 9.6$, $P = .02$) than CTRL participants. However, no participant discontinued the study due to antidepressant side effects.

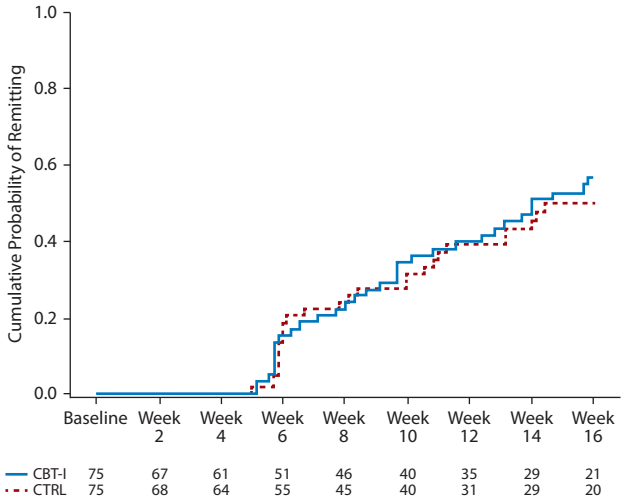
Depression Remission

Overall, 39.3% of participants attained remission: 43.8% in CBT-I and 36.0% in CTRL (number needed to treat [NNT] = 15). Cox proportional hazards model revealed no statistically significant difference in time to remission between the treatments ($P = .33$, relative hazard ratio = 1.152) and no significant site or site-by-treatment interaction effects (*P* values = .06 and .42, respectively; Figure 2). Remission rates by site are presented in Supplementary eTable 2. Depression remission was not significantly related to baseline depression severity (Supplementary eTable 3). Secondary analysis using the modified sample of 148 participants yielded similar results.

Depression and Insomnia Severity

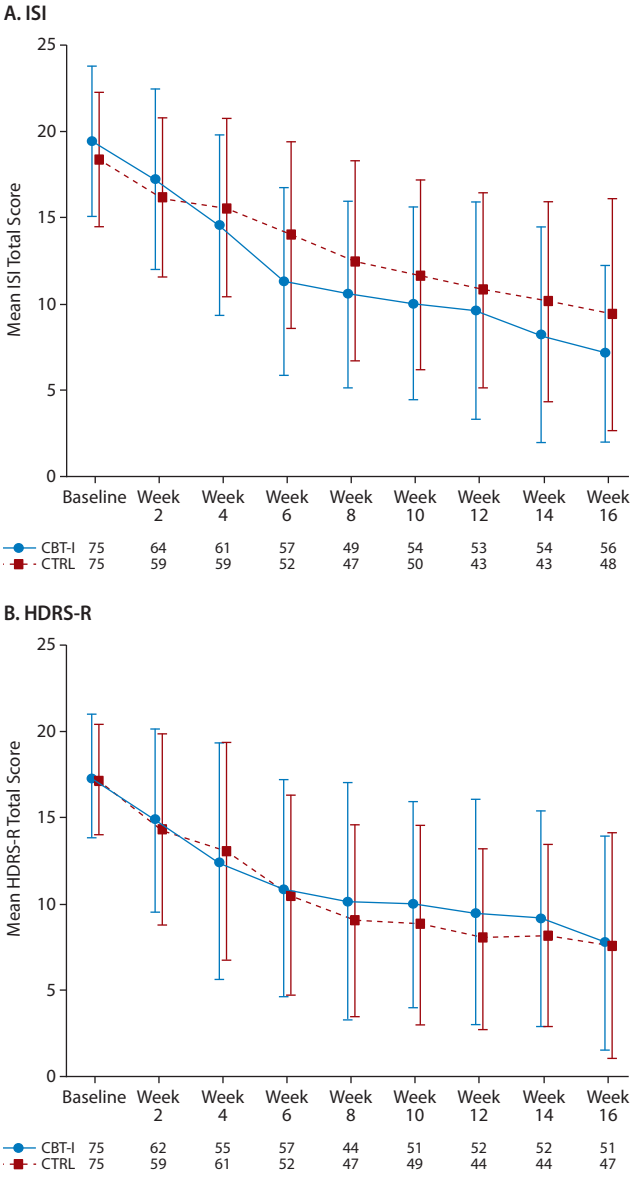
Figure 3 (and Supplementary eFigure 1) depicts the results of mixed effects models. HDRS-R (and HDRS) decreased over time ($P < .0001$), but there were no significant

Figure 2. Time to Depression Remission[a]



[a]*Depression remission* was defined as at least 3 weeks in which the core symptoms of MDD (depressed mood or anhedonia) were absent and no more than 2 of the other 7 *DSM-IV-TR* diagnostic symptoms of depression were present.
Abbreviations: CBT-I = cognitive-behavioral therapy for insomnia, CTRL = control therapy for insomnia, MDD = major depressive disorder.

Figure 3. Change in ISI and HDRS-R[a] Scores Over the Course of Treatment by Treatment Group[b]



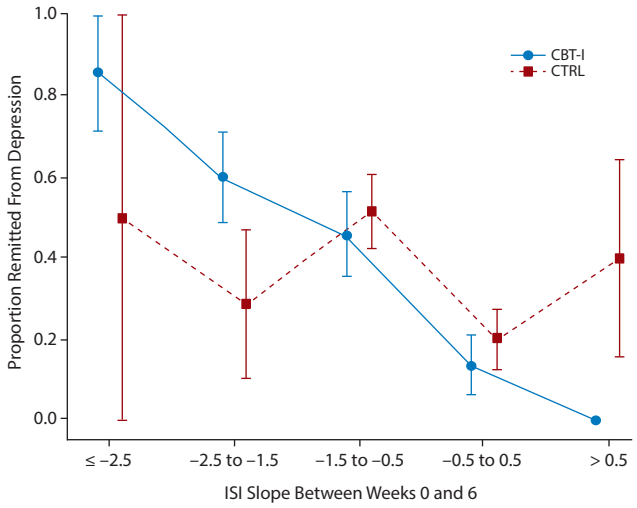
[a]HDRS-R is the score on the Hamilton Depression Rating Scale after removing the 3 sleep items. (Change in the HDRS full scale can be found in Supplementary eFigure 1.)
[b]Vertical lines represent standard deviations.
Abbreviations: CBT-I = cognitive-behavioral therapy for insomnia, CTRL = control therapy for insomnia, HDRS = 17-item Hamilton Depression Rating Scale, HDRS-R = score on the HDRS after removing the 3 sleep items, ISI = Insomnia Severity Index.

differences between treatments ($P = .48$ for HDRS). There were no significant site or site by treatment interaction effects (P values $> .18$). The change in insomnia severity over time differed by treatment group ($P = .028$), with greater reduction among those receiving CBT-I than CTRL. There were no significant site or site by treatment interaction effects (P values = .14 and .46, respectively). *Remission from insomnia*, defined as ISI < 8,[14] was significantly higher among those receiving CBT-I than CTRL (54% vs 29%, $P < .01$, NNT = 4) and was not significantly related to baseline depression severity (Supplementary eTable3). Secondary analysis using the modified sample of 148 participants yielded similar results.

Relationship Between Improvements in Insomnia and Depression

The first step of the mediation analysis, with change in ISI by week 6 as dependent variable (ΔISI6), revealed a differential treatment effect, with significantly greater reduction in estimated individual slopes of ISI by week 6 in CBT-I ($P = .001$). The second step of the mediation analysis, with depression remission as the outcome variable, revealed a nonsignificant trend for the interaction between ΔISI6 and treatment arm ($P = .064$). Planned post hoc analyses within each treatment arm, with depression remission as the outcome variable, revealed a significant effect of ΔISI6 in the CBT-I arm ($P = .0004$) but not in the CTRL arm ($P = .26$). Secondary mediation analysis using the modified sample of 148 participants revealed a significant mediation effect. The first step revealed a significantly greater reduction in ISI slope by week 6 (ΔISI6) in CBT-I ($P = .001$). The second step revealed that the interaction between ΔISI6 and treatment arm on posttreatment depression remission was also significant ($P = .038$). Planned post hoc analyses within each treatment arm revealed a significant effect of ΔISI6 on depression remission in CBT-I ($P = .0002$) but not in CTRL ($P = .26$). Figure 4 provides a graphical depiction of the secondary mediation analysis. There was no significant differential effect of treatments on the slope of HDRS-R during the first 6 weeks ($P = .82$). Therefore, early (week 6) change in depression did not mediate improvement in insomnia over the course of treatment.

Figure 4. Relationship Between Change in Insomnia Severity by Week 6 and Remission From Depression[a]



[a]Change in insomnia severity by week 6 was defined as the slope of ISI scores over the first 6 weeks (ΔISI6). *Depression remission* was defined as at least 3 weeks in which the core symptoms of MDD (depressed mood or anhedonia) were absent and no more than 2 of the other 7 *DSM-IV-TR* diagnostic symptoms of depression were present. The error bars represent the standard error around the proportion meeting remission criteria.

Abbreviations: CBT-I = cognitive-behavioral therapy for insomnia, CTRL = control therapy for insomnia, ISI = Insomnia Severity Index, MDD = major depressive disorder.

DISCUSSION

In this 16-week randomized controlled trial, CBT-I led to greater improvement in insomnia than did CTRL among individuals with comorbid depression/insomnia who concomitantly received antidepressant medication. Differential effects of treatments on insomnia severity were observed by week 6. The depression remission rate in CBT-I (44%) was somewhat larger than in CTRL (36%), but—contrary to our hypothesis—this difference was not statistically significant. In interpreting the findings, one should note that CBT-I was an add-on treatment to an intervention that has well-established efficacy for depression. In most cases, effect sizes of add-on treatments for a condition tend to be small and, thus, require much larger sample sizes for demonstration of significant differences. Importantly, and of clinical relevance, is our secondary finding that improvement in insomnia during the first 6 weeks mediated overall depression remission, an effect present in CBT-I but not in CTRL. The reverse is not true. The observed improvement in insomnia over the course of treatment was not mediated by early (week 6) change in depression symptom severity.

The finding of significant efficacy of CBT-I for insomnia comorbid with MDD is consistent with other research demonstrating the efficacy of CBT-I for people who experience insomnia in the context of depression.[19,29,30] CBT-I is particularly attractive for the treatment of insomnia comorbid with MDD because it minimizes drug-drug interactions with antidepressant medications and can be easily integrated into psychotherapy for depression. However, we found that CBT-I recipients reported a greater frequency and burden of side effects of antidepressant medications than did CTRL recipients, despite equivalent dosing of starting medications. One possible explanation is that the sleep restriction and stimulus control components of CBT-I might have led to a transient mild sleep deprivation that could have increased sensitivity to side effects. For example, sleep restriction therapy alone can lead to daytime sleepiness.[11,31] In the current protocol, we used a liberal version of the traditional sleep restriction protocol,[15] whereby the initial time in bed was 30 minutes longer,[32,33] that should have reduced the likelihood of sleep deprivation side effects relative to the standard protocol. Other modifications of CBT-I that could reduce the risk of sleep deprivation include (1) replacing sleep restriction with sleep compression,[34,35] a procedure by which time in bed is reduced gradually rather than abruptly, and (2) postponing the introduction of sleep restriction and limiting its use to patients who do not respond to the other CBT-I strategies.[36] The observed difference in antidepressant side effects was not expected and underscores the importance of testing the use of CBT-I for specific comorbidities, even though CBT-I has strong empirical support for the treatment of insomnia in noncomorbid samples. Our findings also highlight the importance of systematically evaluating side effects in behavioral treatments.

The antidepressant therapy used in this study aimed to simulate standard antidepressant treatment. To minimize variability, the medications allowed were limited to 3 specific agents, 2 selective serotonin reuptake inhibitors (SSRIs) and 1 serotonin-norepinephrine reuptake inhibitor (SNRI). Although this arguably might somewhat limit generalizability of the results, we note that the current practice guidelines for the treatment of depression suggest the use of an SSRI, such as escitalopram and sertraline, an SNRI, mirtazapine, or bupropion for most patients with mild to moderate depression.[37(pS15)] The effects of CBT-I in combination with a more sedating antidepressant medication, such as mirtazapine, or a less sedating medication, such as bupropion, might be less or more robust in terms of insomnia and depression. Another limitation of the study design is that, by allowing medication switch, our results do not inform clinical guidelines for any single antidepressant medication. Our results also have no direct bearing on another, related, clinical treatment strategy of combining CBT-I with an empirically supported depression-focused psychotherapy.

The fact that the majority of participants (70%) were white and the exclusion of some comorbid sleep and psychiatric disorders limit generalizability to other racial/ethnic groups and comorbid presentations. Another potential limitation to generalizability is the demanding screening process, resulting in randomization of only 40% of consenting participants. Also, this study employed therapists who had no prior experience in administering CBT-I. Perhaps more favorable depression remission would have been obtained with more

experienced therapists. Lastly, it is commonly observed that some sleep-related improvements resulting from CBT-I are gradual and often continue long after therapist contact ceases.[38] Hence, it is possible that patients receiving CBT-I with antidepressant medication may experience better depression outcomes than CTRL patients over a longer time frame than scrutinized herein.

The absence of a statistically significant difference between CBT-I and CTRL on depression remission is not consistent with past findings that CBT-I reduced depressive symptom severity and suicidal ideation among treatment-seeking patients with insomnia, many with depression and other comorbidities.[29,30] Also, the difference in depression remission in the present study was much smaller than in our randomized pilot study of 30 participants (64% vs 33%), in which the same CTRL was used.[19] One explanation of the discrepancy in findings is that the current sample included participants with more severe depression, greater number of lifetime depressive episodes, and earlier age at first depression onset, as well as lower insomnia severity. The latter may have reduced the effect size of CBT-I with respect to change in insomnia severity and the associated statistical power to detect a treatment arm difference in depression remission rates (44% vs 36%), particularly given that the final sample was smaller than the target sample that was based on our original power analysis. The use of 3 different antidepressant medications may have contributed to high variability in depression and insomnia outcomes and, thus, to reduced statistical power to detect a treatment arm difference in depression. A prior larger study evaluating fluoxetine and eszopiclone coadministration found significantly greater remission from depression in the eszopiclone group (42%) than the placebo augmentation group (33%).[39]

We did find that reduction in insomnia severity during the first 6 weeks of treatment was associated with better antidepressant outcome in the CBT-I group, suggesting that insomnia is an important factor to consider and address in the management of MDD. Studies with CBT-I among patients with comorbid depression and insomnia are important for resolving the uncertainty regarding the effects of insomnia therapy on depression outcome as hypnotic medications and sedating antidepressants may have direct therapeutic effects on anxiety or depression. Clinical care would also be enhanced by the development of treatment algorithms to guide practitioners in the management of depression comorbid with insomnia.

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Drug names: bupropion (Wellbutrin and others), desvenlafaxine (Pristiq, Khedezla, and others), escitalopram (Lexapro and others), eszopiclone (Lunesta), fluoxetine (Prozac and others), mirtazapine (Remeron and others), sertraline (Zoloft and others).

Author contributions: James F. Luther, MA, and Stephen R. Wisniewski, PhD, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Potential conflicts of interest: **Dr Manber** has received an unrestricted gift from Phillips Respironics and is on the advisory board General Sleep. **Dr Buysse** has served as a paid consultant (less than $5,000 for any 12-month period) for Merck, Eisai, Otsuka, and Emmi Solutions and has also served as faculty on continuing medical education (CME) programs produced by CME Outfitters and Medscape. **Dr Krystal** receives grant support from National Institutes of Health, Teva, Sunovion, Astellas, Abbott, Neosync, Brainsway, Janssen, Advanced Neuromodulation Systems St. Jude, and Novartis; and is a consultant to Abbott, AstraZeneca, Attentiv, Teva, Eisai, Jazz, Janssen, Merck, Neurocrine, Otsuka, Lundbeck, Roche, Somnus, Sunovion, Somaxon, Takeda, and Transcept. **Dr Thase** reports no conflicts of interest specifically pertaining to this project; however, during the past 3 years, he has been an advisor/consultant to Alkermes, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Lundbeck, MedAvante, Merck, Mylan, Neuronetics, Otsuka, Pamlab/Nestle, Pfizer, Roche, Shire, Sunovion, Takeda, and Teva, as well as the US Food and Drug Administration and the National Institute of Mental Health; during the same time frame, he has received honoraria for international continuing education talks that were supported by AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck, and Pfizer; and has received research grants from Alkermes, AstraZeneca, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Otsuka, and Roche, as well as from the National Institute of Mental Health and the Agency for Healthcare Research and Quality. **Dr Edinger** has received grant support from Philips Respironics and Merck. **Dr Wisniewski** and **Mr Luther** have a research grant with Janseen Research and Development. **Drs Trockel** and **Kraemer** report no conflicts.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Efficacy of Cognitive-Behavioral Therapy for Insomnia Combined With Antidepressant Pharmacotherapy in Patients With Comorbid Depression and Insomnia: A Randomized Controlled Trial

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List of Supplementary Material for the article

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This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

eAppendix 1: Methods

Exclusion Criteria: Participants were excluded if they had any of the following: current active suicidal potential; psychotic features; seasonal pattern of depression; onset of current MDD episode within 2 months of childbirth; or ECT or vagal nerve stimulation treatment during the last year. Participants were also excluded if they had other conditions that would have necessitated medical care not included in the study, as well as conditions that could have confounded the interpretation of study results. These included: 1) Concomitant insomnia or depression treatment, including hypnotic medications within 3 days and antidepressants within 7 days (28 days for fluoxetine); recently initiated psychotherapy for depression (patients who were in therapy for more than 4 months were not excluded if they met depression severity criteria); over the counter remedies with claimed psychotropic properties (e.g., melatonin, Kava, valerian root, Sam-e, St. John's Wort.) 2) Failure or intolerance for past adequate trials of all study medications. This was operationally defined as at least 6 weeks of therapy at established or usual antidepressant doses (sertraline 100 mg/day; escitalopram 20 mg/day; desvenlafaxine 100 mg/day). 3) History of treatment with CBT-I. 4) Uncontrolled or unstable medical conditions, determined by medical personnel at each site on the basis of medical history and other available clinical data. (Common minor and well-controlled conditions, such as hypertension, diabetes, asthma, and hypothyroidism were not excluded.) 5) Conditions incompatible with study pharmacotherapy, including pregnancy or breast-feeding, not using a reliable birth control method, uncontrolled seizure disorder, and diseases or conditions that result in altered drug metabolism or hemodynamic responses (e.g., hepatic or renal dysfunction). 6) Presence of any of the following sleep disorders according to criteria of the International Classification of Sleep Disorders, 2nd Edition (ICSD-2)[1], based on DSISD and, as applicable, by polysomnography and review of CPAP adherence data: a) Sleep-disordered breathing with apnea-hypopnea index (AHI) >15 events per hour on a screening PSG, or an AHI between 10 and 15 if associated with excessive daytime sleepiness (Epworth Sleepiness Scale score > 10), and that was not adequately treated (nightly use of CPAP for at least 4 hours and absence of CPAP related disturbance in sleep for the past 4 weeks); b) Restless Legs Syndrome symptoms experienced more than once a week; c) hypersomnolence disorders; d) Periodic Limb Movement Disorder with movement arousal index > 15 on a screening PSG; e) Any parasomnia occurring more than once a week; f) Any circadian rhythm disorder if habitual sleep schedule fell outside the following range: bedtime 8PM-3AM and rise time 4AM-11AM. We also excluded participants with a fixed night shift work between midnight and 5 a.m. and those with rotating work schedules that require night shifts. 7) Current diagnosis of the following (SCID/DSM-IV-TR) disorders: Schizophrenia or other psychotic disorders, bipolar disorder (including history of manic or hypomanic response to an antidepressant medication), dementia disorders or related cognitive disorders (determined by Mini-Mental Status Exam score below 26), post-traumatic stress disorder, anorexia or bulimia nervosa, or obsessive compulsive disorder, axis II diagnosis of antisocial, schizotypal or severe borderline personality disorder. 8) Current (within past 6 months) psychoactive substance use disorder diagnosis (SCID/DSM-IV-TR), with the exception of nicotine dependence. 9) Consumption of more than 3 cups of caffeinated beverages per day, illicit drugs, or more than 14 alcoholic drinks per week (or more than 4 per occasion).

Rater certification: Certification on the HRSD was required before and periodically during the study and consisted of rating taped interviews and scoring them within two points of interviews was an expert rater.

Medication Algorithm: The pharmacotherapy algorithm consisted of two phases, each lasting 8 weeks. The first medication used was selected based on the following rules: If there was no history of ESC failure, the first medication was ESC. Otherwise, if there was no history of SERT failure, the first medication was SERT; and if there was history of SERT failure in the past but no history of venlafaxine or DVS failure, then the first medication was DVS. At week 8, the patient was **evaluated for a potential** switch to another medication. If the patient had CGI score 3 or more for the last two consecutive visits, indicating non-response, a switch from ESC to SERT or from SERT to DVS was recommended. If the patient is already on DVS, the dose could be increased. To minimize study attrition, the patient was moved to the next level of the algorithm if at any time intolerance to the current medication was noted, regardless of treatment week (ESC to SERT or SERT to DVS). Medication management visits occurred at baseline and biweekly thereafter.

The initial recommended doses were: ESC (10 mg/day), SERT (50 mg/day), or DVS (50 mg/day). Medications were preferentially taken in the morning, with food, though evening dosing could be implemented if there were complaints of excessive sedation or if the patient had a strong preference for evening dosing. Dose escalation was allowed from week 4 onward. If the patient had not achieved an adequate response based on CGI Improvement Score (>1), and was tolerating the medication, the dosage of current medication could be increased. The maximum doses were 20 mg/day for ESC, 200 mg/day for SERT and 100 mg/day for DVS. Once patients achieve a CGI response, assuming acceptable tolerability, the recommendation was to continue the current dosage.

Psychotherapy: Table S1 summarizes the timing of medication management and psychotherapy visits. A “Welcome to the Study” letter informed participants that the study psychotherapist would address only sleep-related issues and would not provide general psychotherapy or discuss issues related to study medication. Unless clinical presentation necessitated an immediate intervention, if a participant spontaneously raised non-sleep issues, the therapist gently redirected patients to the prescribed content of the session. To further minimize provision of depression psychotherapy, hierarchy items in the CTRL therapy included only sleep related items and cognitive therapy in CBT-I was focused only on sleep-related beliefs and thoughts.

Psychotherapists were naïve to study therapies. They were randomized and trained to deliver the therapy to which they were assigned and were not informed about the fact that one of the insomnia therapies was actually a sham control intervention. Training consisted of a workshop, self-guided reading, and role plays. Competency of therapists was determined based on audio recording of work samples conducted by two of the authors (JE for CTRL and RM for CBT-I), who ascertained that core prescribed treatment components were implemented and that proscribed recommendations were not provided.

Additional details about the implementation of CBT-I in depression

Stimulus control and sleep restriction: One challenge to the implementation of the stimulus control and sleep restriction is the tendency of people with depression to go to and stay in bed not because they feel sleepy or need more sleep but because they want to escape from emotional suffering or because not much else feels good to do. To address this challenge, a common variant of the protocol was used, whereby the specific sleep restriction recommendation for an initial time in bed was equal to the average total sleep time plus 30 minutes[2,3]. In addition, therapists were advised to be watchful for these obstacles to adherence with the recommendations to go to bed at the prescribed time and only when sleepy and to get

up the same that and to support adherence by exploring the issue and explicitly discuss what else the patient can do, other than be in bed.

Cognitive therapy: The focus of the cognitive therapy techniques used was exclusively on sleep-relate cognitions. When intrusive and ruminative thoughts were present, scheduled worry[4]/ constructive worry [5] was recommended.

Relapse prevention: Relapse prevention is commonly used in clinical practice but seldom explicitly described in published CBT-I protocols. In this study relapse prevention focused on prevention of insomnia. It included identifying what treatment elements were helpful and encouragement to use them should sleep difficulties emerge in the future in order to prevent a few nights of poor sleep from developing into another episode of insomnia disorder.

See Manber and Carney (2015)[6] for additional details on implementing CBT-I when treating insomnia comorbid with depression, as well as with other psychiatric conditions.

Supplementary eTable 1: Schedule of Medication Management Visits and Insomnia Therapy Sessions

	Treatment Week															
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Medication Management Visits	x		x		x		x		x		x		x		x		x
Insomnia Therapy Sessions		x	x	x	x		x		x				x				

Supplementary eTable 2: Remission from Depression by Site

	CBT-I	**CTRL**	**p-value**
Duke University (N=17)	50.0%	55.6%	.82
University of Pittsburgh (N=60)	37%*	37%	1.0
Stanford University (N=73)	46.0%	30.6%	.18

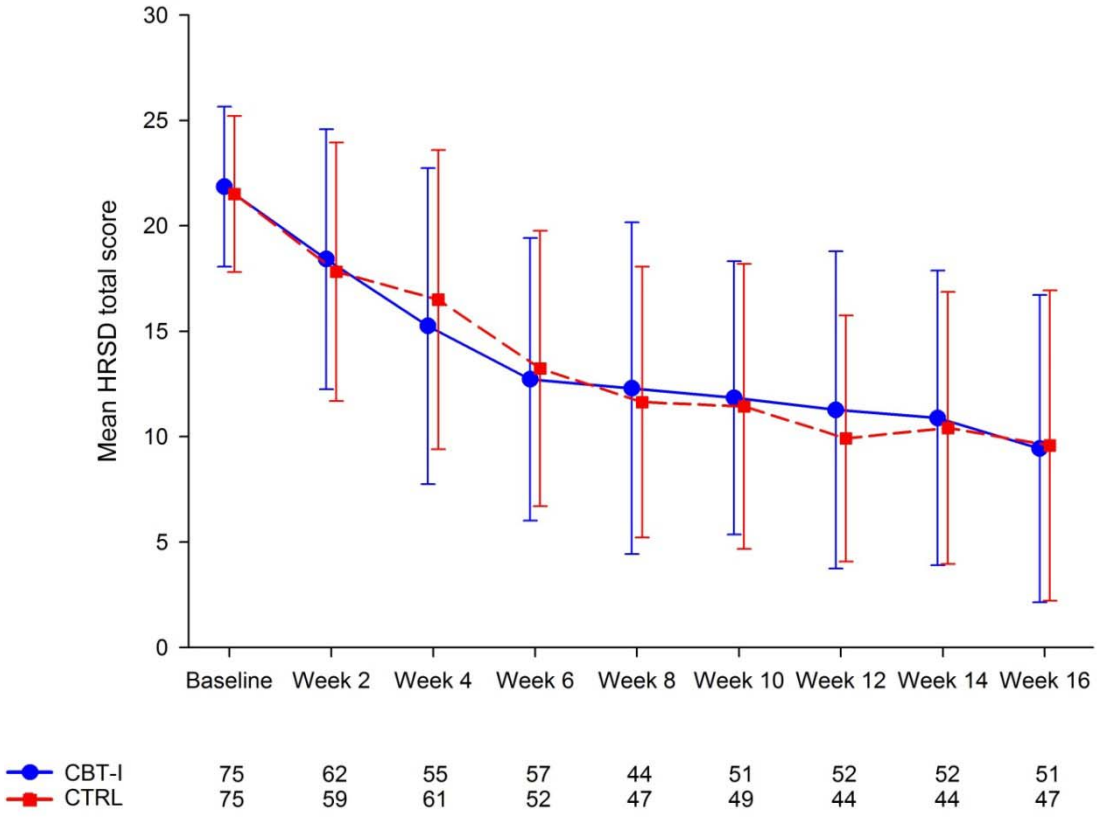
*After removing the two participants who were found ineligible after randomization the remission in CBTI increased to 39%. Remission from depression was defined as at least 3 weeks in which the core symptoms of MDD (depressed mood or anhedonia) were absent and no more than two of the other seven DSM-IV-TR diagnostic symptoms of depression were present. CBT-I is Cognitive behavioral therapy for insomnia; CTRL is the control therapy for insomnia.

Supplementary eTable 3: Remission of Depression and Insomnia by Baseline Depression Severity.

	Depression Remission		Insomnia Remission	
Baseline HRSD	CBTI	CTRL	CBTI	CTRL
<19 (N=37)	42.1	33.3	36.8	22.2
19-22 (N=56)	50.0	48.4	56.0	32.3
>22 (N=57)	35.5	23.1	48.4	23.1

CBT-I is Cognitive behavioral therapy for insomnia; CTRL is the control therapy for insomnia. HRSD is the 17-item Hamilton Rating Scale for Depression. Depression remission was defined as at least 3 weeks in which the core symptoms of MDD (depressed mood or anhedonia) were absent and no more than two of the other seven DSM-IV-TR diagnostic symptoms of depression were present. Insomnia remission was defined as an ISI score < 8 on the last available observation.

Supplementary eFigure 1: Change in the full scale HRSD over the Course of Treatment by Treatment Group.



HRSD is the 17-item Hamilton Rating Scale for Depression (including the three sleep items). CBT-I is Cognitive behavioral therapy for insomnia; CTRL is the control therapy for insomnia. Vertical lines represent standard deviations.

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