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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

Author(s): Rachel Manber, PhD; Daniel J. Buysse, MD; Jack Edinger, PhD; Andrew Krystal, MD; James F. Luther, MA; Stephen R. Wisniewski, PhD; Mickey Trockel, MD, PhD; Helena C. Kraemer, PhD; and Michael E. Thase, MD

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List of Supplementary Material for the article

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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

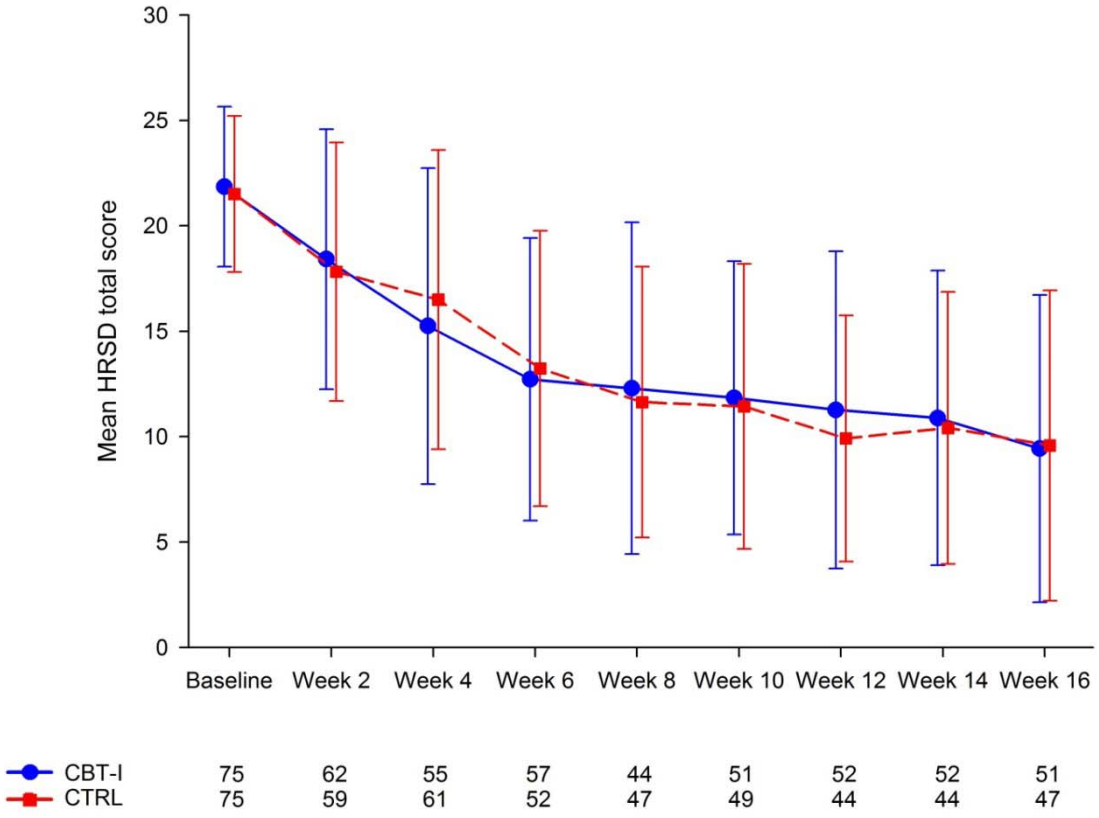
*After removing the two participants who were found ineligible after randomization the remission in CBTI increased to 39%. Remission from depression was defined as at least 3 weeks in which the core symptoms of MDD (depressed mood or anhedonia) were absent and no more than two of the other seven DSM-IV-TR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