Cognitive Behavior Therapy and Pharmacotherapy for Insomnia

A Randomized Controlled Trial and Direct Comparison

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Background: Chronic sleep-onset insomnia is a prevalent health complaint in adults. Although behavioral and pharmacological therapies have been shown to be effective for insomnia, no placebo-controlled trials have evaluated their separate and combined effects for sleep-onset insomnia. The objective of this study was to evaluate the clinical efficacy of behavioral and pharmacological therapy, singly and in combination, for chronic sleep-onset insomnia.

Methods: This was a randomized, placebo-controlled clinical trial that involved 63 young and middle-aged adults with chronic sleep-onset insomnia. Interventions included cognitive behavior therapy (CBT), pharmacotherapy, or combination therapy compared with placebo. The main outcome measures were sleep-onset latency as measured by sleep diaries; secondary measures included sleep diary measures of sleep efficiency and total sleep time, objective measures of sleep variables (Nightcap sleep monitor recorder), and measures of daytime functioning.

Results: In most measures, CBT was the most sleep effective intervention; it produced the greatest changes in sleep-onset latency and sleep efficiency, yielded the largest number of normal sleepers after treatment, and maintained therapeutic gains at long-term follow-up. The combined treatment provided no advantage over CBT alone, whereas pharmacotherapy produced only moderate improvements during drug administration and returned measures toward baseline after drug use discontinuation.

Conclusions: These findings suggest that young and middle-age patients with sleep-onset insomnia can derive significantly greater benefit from CBT than pharmacotherapy and that CBT should be considered a first-line intervention for chronic insomnia. Increased recognition of the efficacy of CBT and more widespread recommendations for its use could improve the quality of life of a large numbers of patients with insomnia.

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INSOMNIA, DEFINED AS DIFFICULTY initiating or maintaining sleep with impaired daytime functioning attributed to poor sleep, is one of the most common complaints brought to a physician's office practice.[1,2] In the National Sleep Foundation's 2002 Sleep in America poll,[3] 35% of adults reported experiencing symptoms of insomnia every night and 58% reported insomnia at least a few nights per week.

Pharmacotherapy is the most frequently recommended intervention for insomnia.[4] However, long-term use of sedative-hypnotics is contraindicated due to moderate treatment efficacy and adverse effects that can outweigh benefits, including habituation, dependency, impairment of daytime psychomotor and cognitive performance, daytime drowsiness, iatrogenic sleep disturbance, rebound insomnia, and rapid eye movement (REM) sleep rebound.[4-8]

Although the short-term effects of pharmacotherapy are well documented and indicate that it produces moderate treatment between-group effect sizes (Cohen d=0.56 for sleep-onset latency), the intermediate to long-term benefits are unknown, since the duration of treatment studies averages 7 days with no long-term follow-up.[9] Furthermore, there is no evidence that treatment effects persist on termination of pharmacotherapy.[4] Before stronger recommendations can be made about the role of drug therapy in the treatment of chronic insomnia, longitudinal data from controlled clinical trials are needed to evaluate the effects of medication beyond the short-term treatment phase.

To our knowledge, only one well-designed randomized controlled trial[10,11] has directly compared pharmacotherapy to cognitive behavior therapy (CBT), and no studies have directly compared the ef-

ficacy of CBT and pharmacotherapy for sleep-onset insomnia, which is experienced as a primary or secondary sleep complaint by a significant percentage of patients with insomnia, particularly young and middle-aged adults. The purpose of the present study is to directly compare the separate and combined efficacy of CBT and pharmacotherapy in a placebo-controlled clinical trial that involved young and middle-aged adults with sleep-onset insomnia. Zolpidem tartrate was used for this study based on its documented efficacy, short half-life (2.4 hours) with no active metabolite, rapid onset of action of 30 minutes, and minimal residual effects.[12,13] Furthermore, zolpidem does not accumulate during repeated administration, causes minimal disruption of sleep architecture, has lowered potential for abuse due to more selective binding properties at GABA receptor subtypes, and is the most commonly prescribed sedative-hypnotic.[14,15] For these reasons, zolpidem is the best choice of a hypnotic for sleep-onset insomnia.

We tested 2 hypotheses: (1) that, during drug administration, a combined CBT and pharmacological treatment would be most effective for reducing sleep-onset latency, followed by pharmacotherapy alone and then CBT, with placebo being least effective and (2) that, after drug use discontinuation, the combined treatment would be most effective for reducing sleep-onset latency followed by CBT and that pharmacotherapy would return toward baseline and would fail to maintain an advantage over placebo. The primary outcome measure was sleep-onset latency as measured by sleep diaries, since the sleep diary is the standard outcome measure in both pharmacologic and behavioral insomnia treatment studies.

METHODS

PARTICIPANTS

Prospective participants were recruited primarily through newspaper advertisements. Inclusion and exclusion criteria are listed in **Table 1**. These criteria are consistent with those of the *International Classification of Sleep Disorders* and the *Diagnostic and Statistical Manual for Mental Disorders* for primary and chronic insomnia.[16,17]

Prospective participants underwent a 4-step screening assessment, which consisted of (1) a telephone screening by a licensed psychologist; (2) verification of sleep-onset insomnia as measured by sleep diaries; (3) a psychological assessment by a clinical psychologist using the *Structured Clinical Interview for DSM-IV* (*SCID-IV*),[18] a reliable and valid structured clinical interview to rule out psychoses, major depression, or alcohol or other drug abuse; and (4) a history and examination by a board-certified sleep physician to confirm a diagnosis of psychophysiologic insomnia, to exclude menopausal women with insomnia due to hot flashes and pregnant women, and to exclude patients suspected of having sleep apnea (snoring, daytime sleepiness, or obesity), restless legs, periodic limb movements, advanced or delayed phase disorder, or drug-dependent insomnia.

Approximately 325 prospective participants were screened by telephone from January 1998 through February 2001. One hundred nineteen prospective participants underwent steps 2 through 4 of the assessment. Eight of these were excluded due to no evidence of insomnia, 11 were excluded due to failure to return the screening sleep diaries, 8 were excluded due to psychopathology, 9 were excluded due to suspected underlying sleep disorder, 12 were excluded due to lack of interest, and 8 were excluded due to inability to discontinue use of sleep medications. One in 5 participants (n=13) was randomly selected before randomization for a urine screen to determine whether they were using sleep medications, antianxiety agents, or antihistamines despite reporting otherwise. There were no positive random urine screen results for these substances.

Table 1. Inclusion and Exclusion Criteria

Inclusion criteria
Aged 25-64 years
A primary complaint of sleep-onset insomnia for at least 6 months defined as a sleep-onset latency of at least 1 hour 3 or more times per week as verified by screening sleep diaries
At least 1 negative daytime complaint (eg, fatigue, impaired mood, or performance) attributed to insomnia
Exclusion criteria
Current use of prescription or over-the-counter sleep medications or unwillingness or inability to discontinue use of these medications at least 4 weeks before beginning the study
Medical problems that would be a direct cause of insomnia
Current treatment for depression, alcohol or substance abuse, or psychosis
Previous diagnosis of sleep apnea or periodic limb movements or prior CBT for insomnia
Initiation of psychotherapy in the previous 6 months
Women of childbearing age who were pregnant, breastfeeding, or not practicing contraception
Shift work

Abbreviation: CBT, cognitive behavior therapy.

The remaining 63 participants were randomly assigned using computer-generated randomized blocks to either CBT (n=15), pharmacotherapy (n=15), combined CBT and pharmacotherapy (n=18), or placebo (n=15). Although pretreatment study power calculations, based on previous research and meta-analytic reviews,[19,20] deemed a sample size of 80 participants sufficient to accommodate a 20% attrition rate yet detect differences among active and placebo treatments, funding limitations precluded recruitment of an actual sample size of 80 participants. Nevertheless, the final sample of 63 participants was sufficient to detect differences among treatments.

Of the 63 participants, 52 (83%) were white, 2 (3%) were black, 2 (3%) were Hispanic, and 7 (11%) were Asian or Pacific Islanders. Forty-one (65%) reported only sleep-onset insomnia, and 22 (35%) reported sleep maintenance insomnia as a secondary complaint. **Table 2** presents the data for demographic and clinical variables by group. **Figure 1** illustrates participant flow in the study protocol.

All participants provided written consent before study initiation. The study was approved by the institutional review board of the Beth Israel Deaconess Medical Center in Boston, Mass, a major teaching hospital of Harvard Medical School, where all data were collected.

MEASURES

Sleep Diaries

Participants completed a daily sleep diary for 14 days before treatment, 14 days at midtreatment (weeks 3 and 4 of the 8-week treatment phase, whereas pharmacotherapy participants were still taking a full dose of zolpidem and CBT patients had not received a complete dose of CBT), and 14 days after treatment (the end of the 8-week treatment phase when pharmacotherapy participants had discontinued use of

Table 2. Demographic and Clinical Characteristics

Characteristic	CBT (n = 15)	Pharmacotherapy (n = 15)	Combination (n = 18)	Placebo (n = 15)
Age, mean (SD), y	47.1 (8.1)	45.4 (9.3)	49.1 (9.6)	46.6 (10.1)
Sex, M/F	5/10	4/11	6/12	4/11
Education, mean (SD), y	15.8 (3.2)	15.9 (2.8)	16.1 (2.9)	17.1 (3.3)
Occupation, No.				
Employed	10	11	14	12
Retired	3	2	1	1
Homemaker	2	2	3	2
Insomnia duration, mean (SD), y	10.2 (9.1)	9.8 (7.8)	9.6 (8.9)	8.9 (8.5)
Profile of Moods State depression scale score, mean (SD)				
Vigor	21 (10.1)	19.1 (11.2)	22.2 (9.7)	20.4 (8.7)
Fatigue	9.3 (6.9)	8.2 (6.4)	8.9 (5.8)	9.2 (6.1)
Beck Depression Inventory score, mean (SD)	4.4 (2.9)	5.1 (4.4)	4 (3.2)	4.8 (2.7)

Abbreviation: CBT, cognitive behavior therapy.

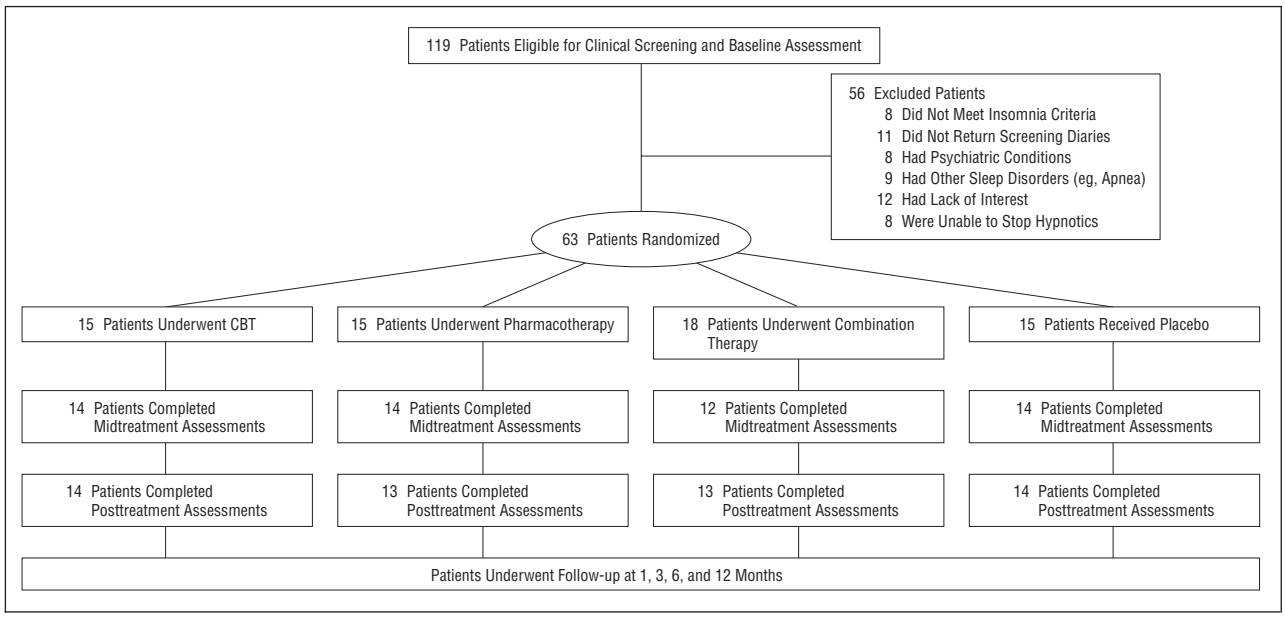

Figure 1. Participant flowchart. One patient did not complete midtreatment assessments; 8 patients withdrew. A total of 9 patients withdrew before completing posttreatment assessments. CBT indicates cognitive behavior therapy.

zolpidem and completed a 2-week washout period and CBT patients had received a full dose of CBT). Participants also completed 7 days of sleep diaries at each of the follow-up assessments (1, 3, 6, and 12 months after treatment). Several parameters were monitored in the diary, including bedtimes, sleep-onset latency, final awakening time, arising time, total sleep time, and sleep efficiency. The primary outcome variable was sleep-onset latency; secondary outcome variables included total sleep time and sleep efficiency (total sleep time divided by time allotted for sleep as measured from lights out to arising time). Participants were instructed to complete the diaries on arising.

Sleep diaries do not reflect absolute values obtained from electroencephalography, since patients with insomnia overestimate sleep-onset latency and underestimate total sleep time compared with electroencephalography-defined sleep.[21] However, sleep diaries show a valid, reliable, and acceptable correspondence to electroencephalography; provide a reliable index of changes in sleep; are the standard outcome measure used in behavioral and pharmacologic insomnia treatment studies and are cost-effective; sample insomnia over a much longer duration and in the natural environment; and measure the perception of sleep, which is a central factor in insomnia and the desire to seek clinical treatment.[4,16,22]

Nightcap Recordings

Participants underwent 3 nights of home-based Nightcap sleep monitor (Healthdyne Technologies, Marietta, Ga) recordings before and after treatment. The Nightcap sleep monitor is a 2-channel sleep monitor that measures sleep-onset latency and other measures of sleep (total sleep time, sleep efficiency) by using eyelid and head movement sensors attached to a Walkman-type, battery-operated recorder placed under a pillow. Compared with laboratory polysomnography, the Nightcap has reliably identified wake, REM, and non-REM sleep in 87% of 1-minute epochs, a level of agreement that approaches the 95% interrater reliability seen with polysomnographic analysis of sleep stages.[23] Because the Nightcap is not associated with a first night effect,[23] data were averaged for all 3 recording nights both before and after treatment. (In 6 patients, technical difficulties with the Nightcap, such as a dead battery or broken eye sensor, resulted in 2 nights of usable data, and 1 combination participant was unable to complete Nightcap recordings before and after treatment).

Daytime Functioning

Patients completed the Profile of Moods State scale (POMS) and the Beck Depression Inventory before and after treatment to assess mood-related changes in daytime functioning. Scores on the Beck Depression Inventory range from 0 to 63, with higher scores indicating greater depression.[24] The POMS is a 65-item adjective checklist that reflects measurements in terms of multiple mood states.[25] For this study, 2 mood dimensions measured by the POMS were used: vigor and fatigue. For the vigor scale, scores range from 0 to 32, with higher scores indicating greater vigor. For the fatigue scale, scores range from 0 to 28, with higher scores indicating greater fatigue.

Credibility Ratings

All participants completed a treatment credibility rating form after the initial treatment session that assessed both the level of confidence in the treatment and the logic of the treatment on a 7-point (Likert) rating scale.

DESIGN AND PROCEDURES

In this placebo-controlled, randomized trial, participants, after completing pretreatment assessments, were randomly assigned to 1 of 4 conditions: CBT (n=15), pharmacotherapy (n=15), combination therapy (n=18), and placebo (n=15). All treatments were administered based on a structured manual by a predoctoral and postdoctoral psychologist. There were 4 individual 30-minute treatment sessions and one 15-minute treatment session by telephone during the first 6 weeks of the 8-week treatment period; no treatment was offered during the final 2 weeks of the 8-week treatment period, allowing consolidation of CBT skills and/or a drug-free washout period (pharmacotherapy, combination). The first 3 individual sessions were weekly, whereas the last individual session and the telephone session were biweekly. Pharmacotherapy and placebo were administered in a standard double-blind fashion, whereas the combination condition received active medication. Due to the nonpharmacologic nature of CBT, neither participants nor therapists were blinded to it.

TREATMENT CONDITIONS

Pharmacotherapy

Participants assigned to the active medication condition were prescribed zolpidem (Ambien) to be taken 30 minutes before bedtime and were provided with basic sleep education information by a study therapist. The initial zolpidem dose was 10 mg nightly for 28 days, then 5 mg nightly for 7 days, then 5 mg every other night for 7 days. Pharmacotherapy participants were instructed not to exceed the prescribed dose. Participants met with a study physician for an initial 30-minute consultation on medication management. During this session, precautions and possible adverse effects were reviewed. All women of childbearing age also completed a pregnancy test (none of the results were positive). Aside from the discussion of medication, no other behavioral or cognitive recommendations were allowed in this treatment session. Patients then spoke by telephone with the physician twice during the next 4 weeks regarding questions concerning medication or adverse effects and to review the medication tapering guidelines for weeks 5 and 6 of the treatment phase. Because the physician follow-up sessions were conducted by telephone, a formal pill count could not be conducted. Therefore, patients completed a weekly compliance checklist that indicated whether they took their medication "never," "some nights," "most nights," or "all nights." Of the 27 placebo and pharmacotherapy completers, 25 reported that they took the medication on all nights and 2 reported that they took the medication on most nights. Of the 13 combination treatment completers, 12 reported that they took the medication on all nights and 1 reported most nights.

Pharmacotherapy participants completed 3 individual treatment sessions and 1 telephone appointment with a study therapist during the last 7 weeks of the 8-week treatment phase (2 weekly sessions and 2 biweekly sessions) to review basic sleep education information.

Cognitive Behavior Therapy

Participants receiving CBT attended 4 individual 30-minute treatment sessions and completed 1 telephone treatment session during a 6-week period. The first 3 treatment sessions were weekly and were followed by the final treatment session 2 weeks later; the telephone session was 2 weeks after the final treatment session. Treatment consisted of a sleep-focused, structured, multifactorial intervention that involved cognitive, behavioral, relaxation, and educational components that targeted sleep-onset insomnia.

The cognitive component was designed to assist participants in recognizing, challenging, and changing stressful, distorted sleep cognitions that exacerbate insomnia by elevating psychophysiologic arousal. The behavioral components of CBT included modified sleep restriction therapy, modified stimulus control, and relaxation training that have been previously evaluated and described.[20,26] Modified sleep restriction therapy consists of curtailing time in bed to more closely approximate actual sleep time. Participants were also instructed to maintain a consistent arising time, even after a poor night's sleep, to synchronize the endogenous circadian rhythm that regulates sleep and wakefulness. Modified stimulus control techniques were designed to teach participants to associate the bed and bedtime with sleep as opposed to frustrating wakefulness and "trying" to sleep. Participants were instructed to (1) use the bedroom primarily for sleep and sex; (2) go to bed only when drowsy; (3) if unable to fall asleep within 20 to 30 minutes, get out of bed and go to another room to engage in a quiet, relaxing activity until drowsy; and (4) repeat this step as often as necessary and use for middle-of-the-night awakenings. Relaxation techniques involved muscle relaxation, breathing, and mental focusing techniques that were practiced during the day and at bedtime.

Combined CBT and Pharmacotherapy

Participants in the combination group received both zolpidem and CBT.

Placebo

Participants in the placebo group were treated according to a protocol identical to those receiving the active medication. The placebo medication was provided in identical gelatin capsules and dosages. Participants in this condition were offered an active treatment after the 1-month follow-up assessment.

FOLLOW-UP

Placebo codes were broken after the 1-month follow-up, and all placebo patients and any patients who reported unsuccessful treatment were offered the option of receiving another treatment of their choice at that time. Six (43%) of 14 placebo completers opted for crossover treatment: 5 chose CBT and 1 chose active medication. Five (38%) of the 13 pharmacotherapy completers reported unsuccessful treatment and opted for cross-

over to CBT. These 11 crossover participants did not complete additional follow-up diaries, and their crossover data were not included in the data analysis. At each follow-up, participants were sent 1 week of sleep diaries and were asked to complete the diaries and return them by mail.

DATA ANALYSIS PLAN

Multiple outcome measures were collected as part of this study, but the present report focuses on the outcome measures (sleep diaries, Nightcaps, and daytime mood measures) and selected sleep variables (sleep-onset latency, total sleep time, sleep efficiency) that are the most relevant to sleep-onset insomnia. The primary comparisons sought to determine whether active treatments were more effective than placebo, whether the combined treatment was more sleep effective than CBT or pharmacotherapy alone, and whether there were differential improvement rates at midtreatment (during drug administration for pharmacotherapy participants and when CBT patients had not received a full dose of CBT), after treatment (after pharmacotherapy participants discontinued drug administration and completed a 2-week washout period and CBT patients had received a full dose of CBT), and at follow-up.

RESULTS

Of the 63 participants enrolled in the study, 54 completed the treatment protocol; 8 dropped out before the second week of the 8-week treatment phase (1 in the CBT group, 1 in the placebo group, 1 in the pharmacotherapy group, and 5 in the combination group) and 1 (pharmacotherapy) dropped out after the third week of treatment. (One participant in the combination group did not complete midtreatment diaries due to a brief hospitalization but did complete posttreatment assessments.) Of the 9 dropouts, all discontinued treatment because of lack of interest. There were no significant differences in the number of dropouts in each condition and in demographic and clinical variables between dropouts and completers.

We used both a conservative intent-to-treat analysis (with the last observation carried forward) and an analysis of study completers. Conceptually, the intent-to-treat analysis provides a perspective on the average outcome of patients referred (randomized) to treatment, whereas the completer analysis provides a perspective on the average outcome achieved by patients who received a full duration of (completed) treatment.

The completer analysis was based on 54 participants (14 CBT participants, 14 placebo participants, 14 pharmacotherapy participants, and 12 combination participants for the midtreatment comparisons and 14 CBT participants, 14 placebo participants, 13 pharmacotherapy participants, and 13 combination participants for the posttreatment comparisons), whereas the intent-to-treat analysis was based on 63 participants (15 CBT participants, 15 placebo participants, 15 pharmacotherapy participants, and 18 combination participants). Because the intent-to-treat and completer analysis produced similar outcomes, results are reported for the completer analysis. There were no significant baseline differences across conditions for demographic, sleep, or mood variables; credibility ratings; or number of sleep diaries completed. Means and standard deviations are presented in **Table 3**.

SLEEP DATA

The primary dependent measure was sleep-onset latency as measured by sleep diaries at pretreatment, midtreatment, and posttreatment. Secondary measures of sleep included sleep efficiency and total sleep time from the sleep diary measured at pretreatment, midtreatment, and posttreatment and objective measures of sleep-onset latency, sleep efficiency, and total sleep time from the Nightcap measured at pretreatment and posttreatment. Because sleep-onset latency is typically reported as a percent change variable in insomnia treatment studies,[20] we analyzed sleep-onset latency as a percent change score. Because sleep efficiency and total sleep time are typically reported as absolute change variables in insomnia treatment studies,[16,27] we analyzed these 2 variables as absolute change scores.

For the sleep diaries, we used 1-way analyses of variance both for the pretreatment-to-midtreatment comparison (hypothesis 1 that the efficacy of combination > pharmacotherapy > CBT > placebo during drug administration) and the pretreatment-to-posttreatment comparison (hypothesis 2 that the efficacy of combination > CBT > pharmacotherapy = placebo after drug use discontinuation). Significant group effects, indicating a differential treatment effect across groups, were followed by pairwise comparisons using the conservative Newman-Keuls test.

Using data analytic strategies similar to those used in several recent randomized clinical trials for insomnia,[16,27] we also examined group differences in rates of clinically significant improvement as assessed by the percentage of participants achieving a normal sleep status (sleep-onset latency ≤30 minutes or sleep efficiency ≥85%) at midtreatment and posttreatment on sleep diary and Nightcap measures using the Fisher exact tests to examine differences between pairs of treatment groups.

SLEEP DIARIES

Sleep-Onset Latency

There was a near-significant difference ($P = .051$) among groups on percent change in sleep-onset latency from pretreatment to midtreatment; the CBT and combination groups both showed a 44% change in sleep-onset latency followed by 29% for the pharmacotherapy group and 10% for the placebo group. Post hoc comparisons indicated that the combination group showed greater ($P = .05$) reductions in sleep-onset latency than the placebo group at midtreatment. These percent changes in sleep-onset latency at midtreatment represented an effect size (d = mean of treatment group − mean of control group/pooled standard deviation) of 1.17 for the CBT group, 1.08 for the combination group, and 0.51 for the pharmacotherapy group. There was a significant difference among groups on percent change in sleep-onset latency from pretreatment to posttreatment ($F_{3,53} = 5.27$, $P = .003$); both the CBT and combination groups showed a 52% re-

Table 3. Sleep Latency, Sleep Efficiency, and Total Sleep Time*

Assessment Modes	CBT	Pharmacotherapy	Combination Therapy	Placebo
Sleep latency, min				
Sleep diary				
Before treatment	67.9 (30.5) (n = 15)	71.5 (38.4) (n = 15)	72.6 (40.8) (n = 18)	71.7 (26.9) (n = 15)
Midtreatment	36.8 (25.5) (n = 14)	45.0 (32.5) (n = 14)	38.4 (28.2) (n = 12)	66.8 (37.7) (n = 14)
After treatment	34.1 (25.6) (n = 14)	58.7 (44.5) (n = 13)	38.7 (36.8) (n = 13)	63.9 (47.6) (n = 14)
1-mo follow-up	37.7 (29.4) (n = 13)	58.9 (53.1) (n = 11)	50.0 (41.1) (n = 12)	48.3 (37.1) (n = 13)
3-mo follow-up	39.5 (31.6) (n = 12)	NA	41.9 (31.8) (n = 11)	NA
6-mo follow-up	37.6 (26.4) (n = 11)	NA	42.3 (35.3) (n = 11)	NA
12-mo follow-up	34.7 (31.5) (n = 9)	NA	40.8 (43.8) (n = 9)	NA
Nightcap				
Before treatment	38.7 (50.6) (n = 14)	48.3 (30.9) (n = 15)	53.5 (35.5) (n = 17)	39.0 (28.4) (n = 15)
After treatment	23.2 (15.2) (n = 13)	42.2 (40.1) (n = 12)	42.2 (40.1) (n = 12)	58.4 (46.8) (n = 14)
Sleep efficiency, %				
Sleep diary				
Before treatment	66.2 (15.7) (n = 15)	67.1 (14.0) (n = 15)	69.7 (11.4) (n = 18)	64.9 (18.1) (n = 15)
Midtreatment	80.1 (7.5) (n = 14)	76.1 (16.7) (n = 14)	78.7 (12.8) (n = 12)	66.8 (21.4) (n = 14)
After treatment	83.5 (6.7) (n = 14)	67.2 (20.4) (n = 11)	80.4 (15.3) (n = 13)	71.3 (15.6) (n = 14)
1-mo follow-up	76.1 (9.8) (n = 13)	70.7 (18.8) (n = 11)	76.5 (19.0) (n = 12)	77.5 (16.1) (n = 13)
3-mo follow-up	76.0 (11.4) (n = 12)	NA	77.2 (20.1) (n = 11)	NA
6-mo follow-up	79.6 (13.5) (n = 11)	NA	80.9 (12.8) (n = 11)	NA
12-mo follow-up	79.9 (11.3) (n = 8)	NA	84.5 (9.1) (n = 9)	NA
Nightcap				
Before treatment	83.4 (13.1) (n = 15)	80.8 (11.2) (n = 15)	79.9 (9.7) (n = 17)	84.6 (10.3) (n = 15)
After treatment	88.9 (6.9) (n = 13)	82.9 (10.8) (n = 12)	85.5 (15.1) (n = 12)	76.8 (14.3) (n = 14)
Total sleep time, min				
Sleep diary				
Before treatment	306.6 (70.2) (n = 15)	303.7 (60.9) (n = 15)	341.6 (68.5) (n = 18)	291.7 (89.5) (n = 15)
Midtreatment	347.4 (46.8) (n = 14)	343.4 (76.8) (n = 14)	351.3 (69.4) (n = 12)	296.8 (99.6) (n = 14)
After treatment	355.2 (44.4) (n = 14)	372.9 (83.7) (n = 13)	366.9 (80.5) (n = 13)	321.2 (76.7) (n = 14)
Nightcap				
Before treatment	367.7 (78.4) (n = 15)	367.1 (77.4) (n = 15)	356.1 (87.2) (n = 17)	345.0 (86.1) (n = 15)
After treatment	365.1 (60.7) (n = 13)	315.5 (96.9) (n = 12)	406.9 (67.1) (n = 12)	303.3 (89.0) (n = 14)

Abbreviations: CBT, cognitive behavior therapy; NA, not applicable.
*Data are presented as mean (SD).

duction in sleep-onset latency followed by 17% for the placebo group and 14% for the pharmacotherapy group. Post hoc comparisons indicated that both the combination and CBT groups showed greater reductions on sleep-onset latency at posttreatment than the pharmacotherapy group ($P=.02$ for the combination group, $P=.03$ for the CBT group) and the placebo group ($P=.001$ for the combination group, $P=.02$ for the CBT group). These percent changes in sleep-onset latency after treatment represented a treatment effect size of 1.22 for the CBT group, 1.12 for the combination group, and –0.1 for the pharmacotherapy group (**Figure 2**).

The proportions of participants who met a normal sleep criterion of sleep-onset latency of 30 minutes or less at midtreatment were 3 (21%) of 14 for the placebo group, 5 (36%) of 14 for the pharmacotherapy group, 6 (50%) of 12 for the combination group, and 7 (50%) of 14 for the CBT group. There were no significant differences among groups on this criterion at midtreatment. The proportions of participants who met a normal sleep criterion of sleep-onset latency of 30 minutes or less after treatment were 2 (14%) of 14 for the placebo group, 2 (15%) of 13 for the pharmacotherapy group, 6 (46%) of 13 for the combination group, and 8 (57%) of 14 for the CBT group. There were significantly more ($P=.05$, 2-tailed Fisher exact test) participants in CBT who met this criterion than placebo participants. There were also significantly more ($P=.05$, 2-tailed) CBT participants who met this criterion than pharmacotherapy participants.

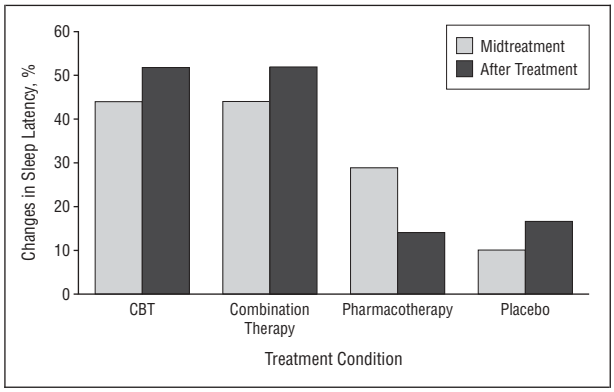

Figure 2. Changes in sleep-onset latency as measured by sleep diaries. CBT indicates cognitive behavior therapy.

Sleep Efficiency

There was a significant difference among groups on absolute change in sleep efficiency from pretreatment to midtreatment ($F_{3,53}=3.1$, $P=.04$); CBT participants showed a 14% increase in sleep efficiency followed by 10% for

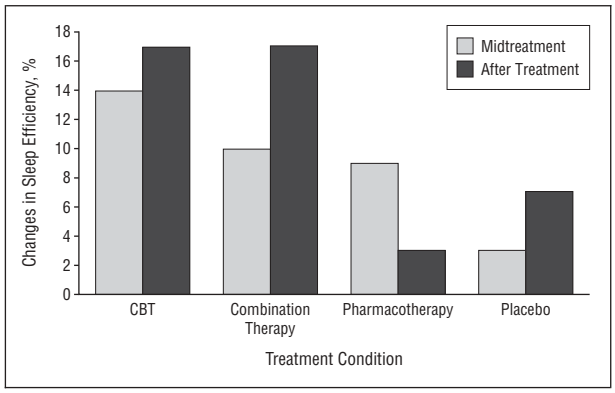

Figure 3. Changes in sleep efficiency as measured by sleep diaries. CBT indicates cognitive behavior therapy.

combination participants, 9% for pharmacotherapy participants, and 3% for placebo participants. Post hoc comparisons indicated that CBT participants showed significantly greater increases in sleep efficiency at midtreatment than placebo participants ($P=.03$). There was also a significant difference among groups on absolute change in sleep efficiency from pretreatment to posttreatment ($F_{3,51}=4.07$, $P=.01$); CBT participants showed a 17% increase in sleep efficiency followed by 11% for combination participants, 7% for placebo participants, and 3% for pharmacotherapy participants. Post hoc comparisons indicated that CBT participants showed greater increases in sleep efficiency after treatment than pharmacotherapy participants ($P=.007$) (**Figure 3**). (Because 2 pharmacotherapy participants did not provide sufficient information on the posttreatment sleep diaries to calculate sleep efficiency, the pretreatment to posttreatment completer analysis was based on a sample size of 11 pharmacotherapy participants.)

The proportions of participants who met a normal sleep criterion of 85% or more on sleep efficiency at midtreatment were 2 (14%) of 14 for the placebo group, 4 (29%) of 14 for the CBT group, 4 (33%) of 12 for the combination group, and 5 (36%) of 14 for the pharmacotherapy group. There were no significant differences among groups on this criterion at midtreatment. The proportions of participants who met a normal sleep criterion of 85% or more on sleep efficiency after treatment were 3 (21%) of 14 for the placebo group, 3 (27%) of 11 for the pharmacotherapy group, 7 (54%) of 13 for the combination group, and 8 (57%) of 14 for the CBT group. There were no significant differences among groups on this criterion after treatment, although there was a near-significant ($P=.06$) trend for more participants in CBT meeting this criterion than placebo participants.

Total Sleep Time

There were no significant differences among groups on changes in total sleep time from pretreatment to midtreatment; all groups exhibited increased sleep time (7, 19, 41, and 44 minutes per night for the placebo, combination, CBT, and pharmacotherapy groups, respectively). Similarly, there were no significant differences in total sleep time from pretreatment to posttreatment; all groups exhibited increased total sleep time (32, 25, 49, and 78 minutes per night for the placebo, combination, CBT, and pharmacotherapy groups, respectively).

Follow-up

Because there were no differences among groups on total sleep time after treatment, we limited out follow-up analyses (1, 3, 6, and 12 months) to sleep-onset latency and sleep efficiency compared with after treatment. Also, because almost half of the pharmacotherapy and placebo participants chose to receive another treatment after the 1-month follow-up period (when placebo codes were broken), an insufficient number of pharmacotherapy and placebo participants were available for meaningful follow-up comparisons after the 1-month follow-up. Therefore, the 3-, 6-, and 12-month follow-up analysis only included CBT and combination participants. These follow-up tests examined whether there was within-group deterioration on sleep-onset latency or sleep efficiency at follow-up compared with after treatment using *t* tests.

Neither pharmacotherapy nor placebo participants showed a significant change on sleep-onset latency or sleep efficiency from posttreatment to 1-month follow-up. Likewise, the CBT participants did not show a significant change on sleep-onset latency at 1-, 3-, 6-, or 12-month follow-up compared with posttreatment. The CBT participants showed a significant decrease in sleep efficiency at 1-month ($P=.008$) and 3-month follow-up ($P=.003$) compared with posttreatment. However, CBT showed no change in sleep efficiency at 6-month and 12-month follow-up compared with posttreatment. The combination participants showed a significant ($P=.01$) increase in sleep-onset latency at 1-month follow-up but not at 3-, 6-, or 12-month follow-up. The combination patients showed a near-significant ($P=.06$) trend for a decrease on sleep efficiency at 1-month follow-up but not at 3-, 6, or 12-month follow-up.

Nightcap Recordings

One participant each in the CBT, pharmacotherapy, and combination groups who completed posttreatment sleep diaries did not complete the posttreatment Nightcap assessment. Therefore, the completer analysis was based on sample sizes of 12 for the pharmacotherapy group, 12 for the combination group, 13 for the CBT group, and 14 for the placebo group. There were no significant differences among groups on changes in Nightcap sleep-onset latency from before treatment to after treatment. However, consistent with previous studies,[22] pretreatment disturbance in objective (Nightcap) sleep-onset latency was more modest compared with sleep diary sleep-onset latency. This resulted in more moderate change scores across groups and may have contributed to a floor sleep effect. Additionally, with the exception of an unexplained increase in sleep-onset latency after treatment for the placebo group (who showed a decrease in posttreatment sleep-onset latency as measured by sleep diaries), the patterns of results for Nightcap sleep-onset latency paralleled the sleep diary sleep-onset latency re-

sults. For example, on the completer analysis, the greatest percent change in Nightcap sleep-onset latency was exhibited by CBT participants (40%), followed by combination participants (29%) and then pharmacotherapy participants (13%).

The proportions of participants who met a normal sleep criterion of 30 minutes or less on Nightcap sleep-onset latency at posttreatment were 4 (29%) of 14 for the placebo group, 6 (50%) of 12 for the pharmacotherapy group, 8 (67%) of 12 for the combination group, and 10 (77%) of 13 for the CBT group. There were significantly more participants in the CBT group who met this criterion than in the placebo group ($P=.02$, 2-tailed Fisher exact test). Only CBT participants exhibited a normative posttreatment Nightcap sleep-onset latency mean of 30 minutes or less, and most of the CBT and combination participants achieved this normal sleep-onset latency criterion after treatment.

For Nightcap sleep efficiency, there was a significant difference among groups after treatment ($F_{3,47}=2.9$, $P=.04$). Post hoc comparisons indicated that both CBT and combination participants exhibited greater increases in sleep efficiency than placebo participants after treatment ($P=.02$ for CBT participants, $P=.01$ for combination participants). The proportions of participants who met a normal sleep criterion of Nightcap sleep efficiency of 85% or more after treatment were 3 (21%) of 14 for the placebo group, 7 (58%) of 12 for the pharmacotherapy group, 7 (58%) of 12 for the combination group, and 9 (69%) of 13 for the CBT group. There were significantly more CBT participants who met this criterion than placebo participants ($P=.02$, 2-tailed Fisher exact test). Only CBT and combination participants achieved a normative Nightcap sleep efficiency mean of 85% or more after treatment. For Nightcap total sleep time, there were no significant differences among groups on changes in total sleep time before and after treatment.

MOOD DATA

There were no significant differences among groups on changes in daytime mood before and after treatment. All groups showed minimal levels of depressed mood and only moderate pathological levels of fatigue and vigor before treatment, which may have contributed to a floor effect.

COMMENT

The present findings indicate that CBT, alone or in combination with pharmacotherapy, is more effective than pharmacotherapy alone or a placebo for the treatment of sleep-onset insomnia. Furthermore, CBT alone was equal or superior to a combination of CBT and pharmacotherapy on most outcome measures. Of the 3 active treatments, CBT yielded the greatest number of normal sleepers after treatment as measured by a subjective and objective sleep-onset latency of 30 minutes or less and a sleep efficiency of 85% or more, moved participants to a near normative value of 34 minutes after treatment on sleep diary measures of sleep-onset latency, and resulted in a posttreatment mean of less than 30 minutes on Nightcap-measured sleep-onset latency.

These results did not confirm hypothesis 1 that, during drug administration, the combined treatment would be most effective in reducing sleep-onset latency, followed by zolpidem and then CBT compared with placebo. On most measures at midtreatment, the combined treatment yielded no advantage over CBT alone. In addition, CBT showed a consistent advantage over zolpidem at midtreatment (despite the fact that participants had not received a full dose of CBT), and zolpidem produced only a moderate treatment effect size (0.51) during drug administration as evidenced by a 29% decrease in sleep-onset latency

The results only partially confirmed hypothesis 2 that, after drug use discontinuation, the combined treatment would be most efficacious followed by CBT and that zolpidem would show a significant deterioration back toward baseline. As predicted, CBT was more effective than zolpidem on drug use discontinuation and zolpidem returned measures toward baseline on therapy discontinuation and was no more sleep effective than a placebo. (Additionally, almost as many pharmacotherapy participants [38%] as placebo participants [43%] reported unsuccessful treatment and opted for crossover to CBT after the 1-month follow-up.) However, the combined treatment was not more effective than CBT alone; it also showed deterioration on sleep-onset latency at follow-up, perhaps because participants were less invested in CBT and therefore more vulnerable to relapse.

Although the Nightcap results did not reach statistical significance (in part because the magnitude of clinical improvements was smaller compared with sleep diaries), they paralleled the pattern of results observed with the sleep diaries. These more normative, objective, pretreatment values also underscore the subjective nature of insomnia. The reason for the increase in the posttreatment Nightcap sleep-onset latency in the placebo group is unclear, particularly since the placebo group showed a reduction in posttreatment sleep-onset latency as measured by sleep diaries. One possibility is that by the time the posttreatment Nightcap recordings were conducted, placebo patients were aware that they were taking a placebo, which has been demonstrated in previous studies[28] on sedative-hypnotics. If this were indeed the case, placebo participants may have experienced heightened performance anxiety associated with their sleep being measured objectively a second time without the aid of an active treatment.

The mood measures also showed no significant changes, perhaps due to a floor effect. It is also possible that, despite improvements in sleep parameters, insomnia therapies do not improve daytime functioning. Future research needs to address this issue.

Although this is the largest controlled trial, to our knowledge, comparing CBT and pharmacotherapy in the treatment of sleep-onset insomnia, the sample size was relatively small, which may have reduced power to detect more differences among the treatments. Although the trial would also have benefited from objective polysomnographic screening for underlying sleep disorders, sleep-onset insomnia is rarely caused by sleep apnea,[5,6]

and the usual screening given by internists and family practitioners before prescribing sleeping pills does not involve polysomnography. Furthermore, our results suggest that patients who present with sleep-onset insomnia can derive significant benefit from CBT without the significant expense of screening polysomnography.

Because this sample consisted mainly of individuals who responded to newspaper advertisements, the results may not be generalizable fully to patients with clinical insomnia or patients who are more refractory to treatment, such as drug-dependent patients with insomnia or those with major depression. However, a meta-analytic review[22] of behavioral therapies for insomnia concluded that, in fact, patients with clinical insomnia respond better to treatment than solicited volunteers, perhaps because of better compliance and treatment by more qualified therapists. Also, the long-term follow-up data must be interpreted with caution because of increased attrition over time.

Despite these limitations, the results of this study have important implications for the clinical treatment of insomnia. Our findings replicate and extend the findings by Morin et al[16] on the treatment of sleep-maintenance insomnia in older adults by demonstrating that young and middle-age patients with sleep-onset insomnia can derive significantly greater benefit from CBT than pharmacotherapy and that CBT is the treatment of choice for chronic insomnia. The present results were observed with just more than 2 hours of treatment time by predoctoral and postdoctoral psychologists, making CBT very cost-effective relative to pharmacotherapy.

Despite repeated calls for the integration of CBT with more traditional biomedical interventions, CBT is not well known by health care practitioners and remains underused in clinical practice. As a consequence, insomnia is undertreated and drugs are overused and often prescribed for long-term use on a regular basis, despite many adverse effects and repeated recommendations for their short-term, intermittent use. Many sleep centers now offer CBT administered by sleep psychologists, and CBT is also widely available to patients in a self-help format.[29] Increased recognition of the efficacy of CBT and more widespread recommendations for its use could improve the quality of life of a large numbers of patients with insomnia.

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