Cognitive Behavioral Therapy, Singly and Combined With Medication, for Persistent Insomnia

A Randomized Controlled Trial

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Context Cognitive behavioral therapy (CBT) and hypnotic medications are efficacious for short-term treatment of insomnia, but few patients achieve complete remission with any single treatment. It is unclear whether combined or maintenance therapies would enhance outcome.

Objectives To evaluate the added value of medication over CBT alone for acute treatment of insomnia and the effects of maintenance therapies on long-term outcome.

Design, Setting, and Patients Prospective, randomized controlled trial involving 2-stage therapy for 160 adults with persistent insomnia treated at a university hospital sleep center in Canada between January 2002 and April 2005.

Interventions Participants received CBT alone or CBT plus 10 mg/d (taken at bedtime) of zolpidem for an initial 6-week therapy, followed by extended 6-month therapy. Patients initially treated with CBT attended monthly maintenance CBT for 6 months or received no additional treatment and those initially treated with combined therapy (CBT plus 10 mg/d of zolpidem) continued with CBT plus intermittent use of zolpidem or CBT only.

Main Outcome Measures Sleep onset latency, time awake after sleep onset, total sleep time, and sleep efficiency derived from daily diaries (primary outcomes); treatment response and remission rates derived from the Insomnia Severity Index (secondary outcomes).

Results Cognitive behavioral therapy used singly or in combination with zolpidem produced significant improvements in sleep latency, time awake after sleep onset, and sleep efficiency during initial therapy (all $P<.001$); a larger increase of sleep time was obtained with the combined approach ($P=.04$). Both CBT alone and CBT plus zolpidem produced similar rates of treatment responders (60% [45/75] vs 61% [45/74], respectively; $P=.84$) and treatment remissions (39% [29/75] vs 44% [33/74], respectively; $P=.52$) with the 6-week acute treatment, but combined therapy produced a higher remission rate compared with CBT alone during the 6-month extended therapy phase and the 6-month follow-up period (56% [43/74 and 32/59] vs 43% [34/75 and 28/68]; $P=.05$). The best long-term outcome was obtained with patients treated with combined therapy initially, followed by CBT alone, as evidenced by higher remission rates at the 6-month follow-up compared with patients who continued to take zolpidem during extended therapy (68% [20/30] vs 42% [12/29]; $P=.04$).

Conclusion In patients with persistent insomnia, the addition of medication to CBT produced added benefits during acute therapy, but long-term outcome was optimized when medication is discontinued during maintenance CBT.

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INSOMNIA IS A PREVALENT PUBLIC health problem affecting large segments of the population on a situational, recurrent, or chronic basis.[1,2] Persistent insomnia is associated with significant impairments of daytime functioning, reduced quality of life, and when persistent insomnia is not treated, it heightens the risks for major depression and hypertension.[3-7] Despite its high prevalence, morbidity, and costs, insomnia often remains untreated; when treatment is initiated, it is often limited to self-help remedies (eg, alcohol, over-the-counter drugs) of questionable efficacy and safety.[8,9]

Cognitive behavioral therapy (CBT) and pharmacotherapy (benzodiazepine-receptor agonists) are the only 2 treatments with adequate evidence supporting their use in the clinical management of insomnia.[8] Numerous clinical trials have evaluated the efficacy of CBT and medication separately, but few have conducted head-to-head comparisons contrasting their separate and combined effects for insomnia.[10-17] Collectively, the limited evidence available indicates that both treatment modalities are effective in the short term; medication produces rapid symptomatic relief,[12,13] but these benefits typically are

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not maintained after treatment discontinuation. Conversely, CBT may take longer to implement but it produces more sustained benefits over time.[11,14,15,17] Combined CBT and medication appears to have a slight advantage over a single-treatment modality during the initial course of treatment, but their long-term effects are more variable across patients.[10,11,14,17] Thus, although combined approaches may be preferable to drug therapy alone, an important question that warrants further investigation is whether adding medication to CBT has an additive effect on short-term and long-term outcomes.

Insomnia therapies are typically implemented over brief intervals, averaging 10 days for medication[18] and 5 weeks for CBT.[19-21] Given the recurrent or persistent nature of insomnia,[22,23] such short-term treatment may be inadequate for long-term management. To optimize short-term and long-term outcomes, it is important to validate new treatment algorithms. The addition of an extended treatment phase incorporating maintenance CBT booster sessions could optimize long-term outcomes. Likewise, using hypnotic medications on an intermittent rather than nightly schedule may prevent tolerance and maintain efficacy.[24-26] Another model is to combine CBT with medication as an initial therapy and then discontinue medication after a few weeks while pursuing CBT so that patients can integrate their newly learned self-management skills.[16] Such maintenance strategies may enhance long-term outcomes compared with an acute intervention alone.

The objectives of this study were to evaluate the short-term and long-term effects of CBT, singly and combined with medication, for persistent insomnia and compare the efficacy of maintenance strategies to optimize long-term outcomes. The main research questions were: Is CBT combined with medication more effective than CBT alone for acute treatment of insomnia? When combining CBT with medication, is it preferable to discontinue medication after the initial treatment or continue the medication on an intermittent schedule to optimize the outcome?

METHODS

Patients were recruited from January 2002 to April 2005 through newspaper advertisements and referrals from health care practitioners in the Québec City area. Inclusion criteria were age of 30 years or older and diagnosis of chronic insomnia based on a combination of criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*)[27] and the *International Classification of Sleep Disorders*.[28] These criteria were further operationalized as (1) difficulties initiating and/or maintaining sleep, defined as a sleep onset latency and/or wake after sleep onset greater than 30 minutes, with a corresponding sleep time of less than 6.5 hours at least 3 nights per week (as measured by daily sleep diaries); (2) insomnia duration longer than 6 months; and (3) significant distress or impairment of daytime functioning (rating of ≥2 on item 5 of the Insomnia Severity Index [ISI]).

Exclusion criteria were (1) presence of a progressive medical illness (eg, cancer, dementia) directly related to the onset and course of insomnia; (2) use of medications known to alter sleep (eg, steroids); (3) lifetime diagnosis of any psychotic or bipolar disorder; (4) current diagnosis of major depression, unless treated and in remission; (5) more than 2 past episodes of major depression; (6) history of suicide attempt; (7) alcohol or drug abuse within the past year; (8) sleep apnea (apnea/hypopnea index >15), restless legs, or periodic limb movements during sleep (movement index with arousal >15 per hour); or (9) night-shift work or irregular sleep pattern. Patients with stable medical (eg, hypertension) or psychiatric disorders (eg, dysthymia, anxiety) were included in the study provided that these conditions were not the primary cause of insomnia. Patients using prescribed or over-the-counter sleep medications no more than twice weekly were enrolled after they withdrew from the medications. Individuals using alcohol as a sleep aid were required to discontinue this practice at least 2 weeks prior to baseline assessment.

Of the 486 individuals who completed telephone screening for eligibility assessment, 242 completed second-stage screening consisting of (1) a clinical sleep/insomnia evaluation[29]; (2) the *Structured Clinical Interview for DSM-IV*[30] to rule out psychiatric disorders; (3) a medical history and physical examination; and (4) polysomnography. Eighty-two persons were excluded after this screening for various reasons (FIGURE 1).

Study Design

Participants were randomized to CBT alone (n=80) or combined therapy of CBT plus 10 mg of zolpidem nightly (n=80). After completing this 6-week initial treatment, they were randomized a second time to an extended treatment for the next 6 months. The patients who were treated with CBT alone for 6 weeks were randomized to either extended CBT for 6 months or no additional treatment. The patients who were treated with CBT plus zolpidem for 6 weeks were randomized to extended CBT alone with no additional zolpidem for 6 months or extended CBT plus zolpidem to be used on an as-needed basis rather than every night as in the initial 6-week treatment phase. Assignment to treatment groups for each period was determined by a computer-generated random allocation schedule. Assessments were conducted at baseline, at the end of the initial 6-week phase, at the end of the 6-month extended treatment phase, and at the 6-month follow-up. The protocol was approved by the Université Laval (Québec, Québec, Canada) ethics committee and all patients provided written informed consent.

Assessment Measures

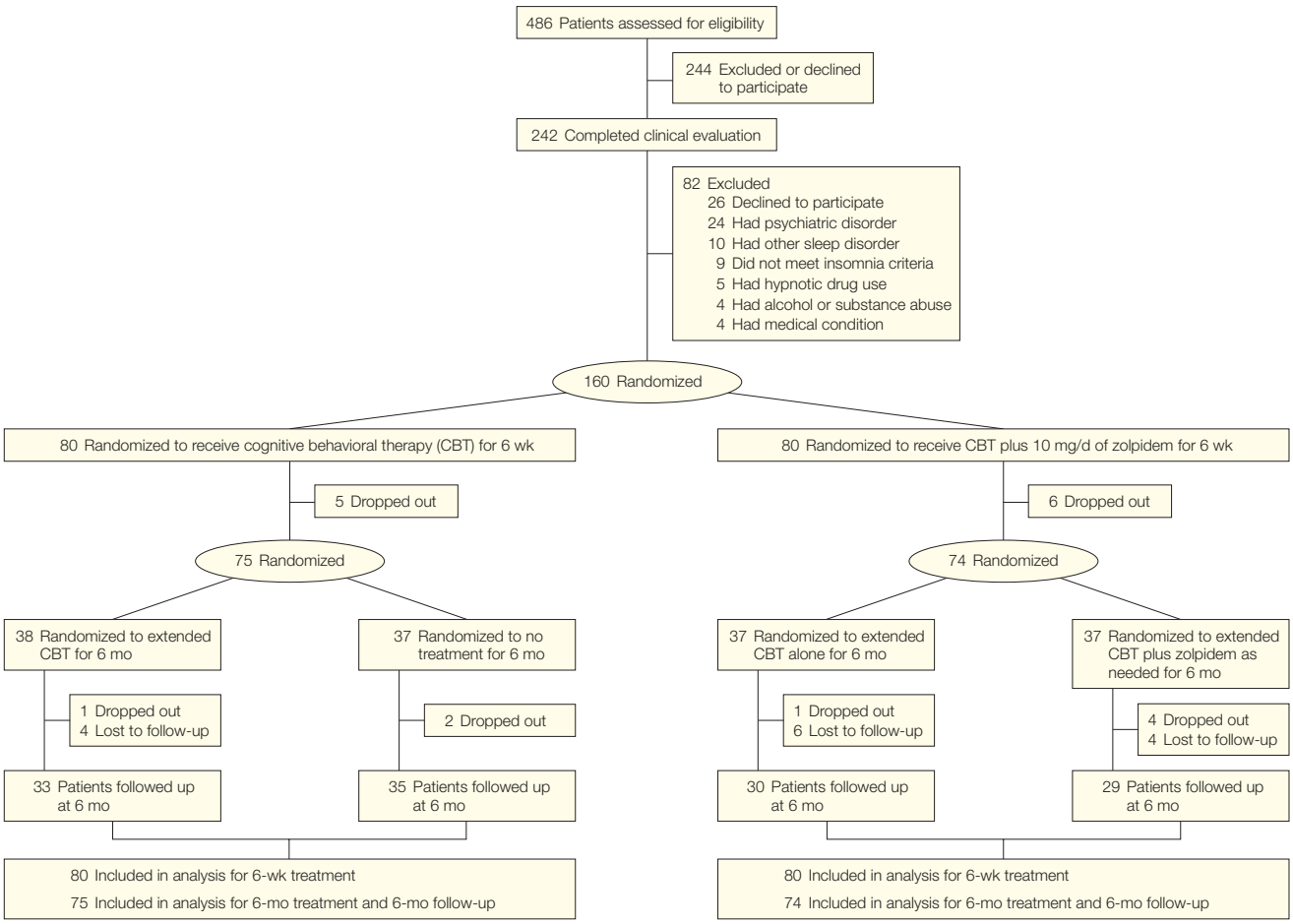
Participants kept daily sleep diaries during a 2-week baseline period, a 6-week acute treatment phase, for 1 week prior to each monthly therapy session during the extended 6-month treatment

phase, and for an additional 2 weeks during the 6-month follow-up phase. The primary dependent variables derived from the diaries were sleep onset latency, time awake after sleep onset (including the last awakening prior to rising for the day), total sleep time, and sleep efficiency (ratio of sleep time to the time spent in bed). The sleep diary is a standard assessment instrument in insomnia research,[31] which allows for prospectively monitoring sleep patterns over extended periods in the patient's home.

Participants underwent 7 nights of sleep laboratory evaluation, including 3 nights at baseline, 2 after the 6-week acute treatment phase, and 2 at the end of the 6-month extended treatment phase. Bedtime and arising times on those nights were based on usual sleep schedule at home, as determined by the participants' sleep diaries. Standard polysomnography montage was used.[32] Respiration (air flow, tidal volume, and oxygen saturation) and anterior tibialis electromyogram were monitored during the first night to screen for sleep apnea and periodic limb movements during sleep. Sleep stages were scored visually by experienced technicians, who were blinded to participants' treatment groups, and according to standardized criteria.[32] Primary dependent variables were sleep latency (lights out to first 5 minutes of consecutive sleep), time awake after sleep onset, total sleep time, and sleep efficiency (ratio of sleep time to the actual time spent in bed). These variables were averaged over 2 nights (using polysomnography) for each assessment phase.

The ISI[33,34] is a 7-item patient-reported outcome assessing the severity of initial, middle, and late insomnia; sleep satisfaction; interference of insomnia with daytime functioning; noticeability of sleep problems by others; and distress about sleep difficulties. A 5-point scale is used to rate each item, yielding a total score ranging from 0 to 28. A higher score indicates more severe insomnia within the following 4 severity categories of absence of insomnia (score of 0-7); subthreshold insomnia (score of 8-14); moderate insomnia (score of 15-21); and severe insomnia (score of 22-28). The ISI has adequate psychometric properties and is sensitive to measure treatment response.[33] It was completed at each assessment phase. Patients were considered treatment responders if their ISI

Figure 1. Flow of Patients in Trial



change score compared with baseline was greater than 7 and as treatment remitters if their absolute ISI score was less than 8. An independent assessor, blinded to the participant's treatment group, rated the degree of change at each assessment phase on a scale of 0 (unchanged or worse) to 3 (marked improvement).

Treatment Groups

Cognitive behavioral therapy is a multicomponent intervention that features behavioral, cognitive, and educational components.[29,34] The behavioral intervention included recommendations to restrict time in bed to the actual time slept and gradually increasing it back to an optimal sleep time.[35] Each patient was prescribed an individualized sleep window, which was adjusted weekly. In addition, patients were instructed to (1) go to bed only when sleepy at night; (2) use the bed and bedroom only for sleep and sex (ie, no reading, TV watching, or worrying); (3) get out of bed and go in another room whenever unable to fall asleep or return to sleep within 20 minutes and return to bed only when sleepy again; and (4) arise at the same time every morning.[36] A short daytime nap before 3 PM was optional during the early phase of the acute 6-week treatment. Cognitive behavioral therapy aimed to alter faulty beliefs and misconceptions about sleep.[34] Examples of faulty beliefs that were targeted included unrealistic sleep expectations (eg, the absolute need to sleep 8 hours every night) and amplification of the consequences of insomnia (eg, all daytime impairments are due to poor sleep). Sleep hygiene education was provided about the effects of caffeine, alcohol, and exercise on sleep, and the effects of noise, light, and excessive temperature. Cognitive behavioral therapy was administered by master's level clinical psychologists using a treatment manual.[34]

During the acute treatment phase, patients attended 6 weekly 90-minute group therapy sessions. Patients assigned to extended CBT attended 6 additional monthly, individually tailored CBT sessions. The focus of these maintenance sessions was on consolidating treatment strategies learned during initial therapy and developing methods for coping with residual insomnia. Their content was based on a case-by-case functional analysis and identification of remaining factors exacerbating sleep disturbances; techniques of relaxation, worry management, and problem solving were used as needed. Patients assigned to the treatment group that received no additional CBT during the extended 6-month phase did not have any follow-up CBT visits after the acute 6-week treatment phase.

Patients assigned to the CBT plus zolpidem group received CBT (as described above) and 10 mg/d of zolpidem. A non–benzodiazepine-receptor agonist, zolpidem has a rapid onset of action and a short half-life (mean of 2.5 hours); it is absorbed from the gastrointestinal tract and there is no accumulation during repeated administration; its therapeutic benefits are similar to benzodiazepine hypnotic drugs, but there are fewer residual effects on daytime functioning and minimal rebound insomnia upon discontinuation; in addition, zolpidem produces little alteration of sleep architecture.[37,38] The medication was provided in the context of brief (15- to 20-minute), weekly, consultation sessions with a primary care physician. These sessions focused on reviewing sleep diaries and changes in insomnia symptoms during the previous week, and monitoring of potential adverse effects. Patients were encouraged to comply with the medication regimen but no CBT intervention was allowed during these sessions. The physician used a structured treatment manual with specific guidelines to deliver treatment according to the study protocol. A pill count was conducted at each consultation visit.

During the 6-week acute treatment phase, patients were instructed to take the medication (10 mg of zolpidem) nightly, 30 minutes before bedtime. During the extended 6-month treatment phase, patients initially treated with CBT plus zolpidem attended 6 additional, monthly, and individualized CBT sessions as described above. In addition, those assigned to extended CBT plus zolpidem as needed met with the physician monthly and received 10 zolpidem pills per month with the instruction to take a pill only when it was needed (as opposed to nightly during the acute treatment phase). Unused zolpidem pills were returned at each visit. At the end of the 6-month extended CBT phase, zolpidem was tapered as described below. Patients assigned to CBT alone during the 6-month treatment phase received their last supply of zolpidem with a written withdrawal schedule. They were instructed to decrease the dose from 10 mg to 5 mg during the first week and then to take 5 mg every other night until they ran out of zolpidem. Patients were informed of possible rebound insomnia during withdrawal and these concerns were addressed during extended CBT.

Data Management and Analysis

Sample size was based on a power analysis conducted for sleep efficiency and ISI scores. Effect sizes were estimated from previous studies.[14,18,39] Comparisons between patients receiving CBT alone and CBT plus zolpidem yielded an effect size of 0.55 for sleep efficiency (difference of 5 points) and 0.82 for the ISI score (difference of 4 points). With a sample size of 80 individuals per treatment group during the 6-week acute treatment phase and an α level of .05 (2-tailed), power was estimated at 94% and 98% to detect effect sizes of that magnitude.[40]

Descriptive and inferential statistics were computed using SAS statistical software version 9.1.3 (SAS Institute Inc, Cary, North Carolina).[41] Because individuals were randomized twice, 2 sets of analyses were performed. The first set was based on a 2 (treatment groups) $\times$ 2 (baseline and 6-week phase) split-plot randomized design and the second set was based on a 4 (treatment groups) $\times$ 4 (baseline, 6-week phase, 6-month phase, and 6-month follow-up) split-plot random-

ized design. All analyses were based on the intent-to-treat model. To avoid imputation of missing data, linear mixed models[42] were used to test group, time, and interaction effects for continuous dependent variables and generalized linear mixed models[43] were used to test the binary dependent variables. A priori contrasts were used to investigate specific hypotheses, such as differences before and after treatment and maintenance of treatment gains at follow-up. To control for multiple comparisons, a per family error rate was adopted in which all comparisons for each dependent variable were performed within the nominal error rate. The simultaneous test procedure for factorial design[44] was used to compute the appropriate corrected α level of .05 for main effects and interactions, .05 for temporal changes during acute treatment, and .02 for temporal changes after extended treatment and follow-up. Confidence intervals (CIs) were computed at 95% for all tests and temporal changes that failed to reach significance after correction were labeled accordingly.

Table 1. Sociodemographic and Clinical Characteristics of Participants[a]

Characteristic	CBT Alone for 6 wk (n = 80)	CBT + Zolpidem for 6 wk (n = 80)	All Participants (N = 160)
Age, mean (SD), y	51.7 (10.8)	48.8 (9.7)	50.3 (10.1)
Education duration, mean (SD), y	14.7 (3.6)	14.7 (3.5)	14.7 (3.5)
Sex, No. (%)			
Female	50 (62.5)	47 (58.8)	97 (60.6)
Male	30 (37.5)	33 (41.2)	63 (39.4)
Occupation, No. (%)			
Employed	53 (66.3)	62 (77.5)	115 (71.9)
Retired	22 (27.5)	16 (20.0)	38 (23.8)
Homemaker	2 (2.5)	0	2 (1.3)
Unemployed	0	2 (2.5)	2 (1.3)
Marital status, No. (%)			
Single	4 (5.0)	11 (13.8)	15 (9.4)
Married or common law	57 (71.2)	52 (65.0)	109 (68.1)
Divorced or separated	15 (18.8)	12 (15.0)	27 (16.9)
Widowed	4 (5.0)	5 (6.2)	9 (5.6)
Insomnia duration, mean (SD), y	17.5 (15.2)	15.3 (11.9)	16.4 (13.6)
Type of insomnia, No. (%)			
Initial	3 (3.8)	1 (1.2)	4 (2.5)
Middle	17 (21.2)	19 (23.8)	36 (22.5)
Late	1 (1.2)	1 (1.2)	2 (1.2)
Mixed	59 (73.8)	59 (73.8)	118 (73.8)
Comorbidity, No. (%)			
Medical	48 (60.0)	44 (55.0)	92 (57.5)
Psychiatric	11 (13.8)	13 (16.3)	24 (15.0)
Prior hypnotic drug usage	34 (42.5)	29 (36.3)	63 (39.4)

Abbreviation: CBT, cognitive behavioral therapy.
[a]Data may not equal 100% due to missing data.

RESULTS

The sample included 160 adults (97 women and 63 men) with a mean (SD) age of 50.3 (10.1) years (range, 30-72 years) and a mean (SD) education duration of 14.7 (3.5) years. All patients were white, predominantly married or in a common-law relationship (68.1%), and employed (73.3%). The majority (73.8%) reported mixed sleep-onset and maintenance insomnia. The mean (SD) insomnia duration was 16.4 (13.6) years. Although all patients were free of sleep medication prior to entering the study, 63 patients (39.4%) had previously used a sleep medication. In terms of comorbidity, 24 patients (15.4% of the sample) presented a comorbid psychiatric disorder (most commonly an anxiety disorder) and 92 patients (57.5%) presented at least 1 comorbid medical disorder (most commonly a cardiovascular condition). Descriptive data of demographic and clinical variables are summarized in TABLE 1.

Treatment Attrition and Integrity

The overall attrition rate was 6.9% after acute (6-week phase) treatment (n=11), 11.9% after extended (6-month phase) treatment (n=19), and 20.6% at 6-month follow-up (n=33). Attrition was not significantly different between treatment groups and, except for more men than women dropping out of acute treatment, there was no significant difference between treatment completers and those who dropped out based on demographic, clinical, or sleep/insomnia variables.

During the 6-week treatment phase, the mean (SD) number of therapy sessions attended was 5.6 (0.6) for the CBT group and 5.8 (0.4) for the CBT plus zolpidem group. During the 6-month treatment phase, the mean (SD) number of therapy sessions attended was 5.5 (0.7) for the extended CBT alone group, 5.4 (1.1) for the extended CBT alone with no additional zolpidem group, and 5.5 (0.9) for the CBT plus zolpidem as needed group. Records from pill counts revealed that compliance decreased over time during the 6-week treatment phase as 90.9% of pills were taken during the first week and 79.1% were taken during the sixth week ($F_{5,361}=6.28$; $P<.001$). During the 6-month treatment phase, patients in the CBT plus zolpidem as needed group took an average of 52.8% of available zolpidem pills each month, with a nonsignificant decrease from 58.6% in the first month to 43.9% in the sixth month.

Sleep Diary Data

Means, change scores, and Cohen *d* values for sleep diary variables are displayed in TABLE 2. After the 6-week acute treatment phase, simple effects analyses revealed significant reductions from baseline to the 6-week treatment phase in sleep onset latency for the CBT group (–19.9 minutes; 95% CI, –26.1 to –3.6 minutes) and the CBT plus zolpidem group (–11.9 minutes;

95% CI, –18.2 to –5.6 minutes). For time awake after sleep onset, significant and larger reductions also were observed for the CBT group (–68.7 minutes; 95% CI, –79.7 to –57.8 minutes) and the CBT plus zolpidem group (–82.9 minutes; 95% CI, –94.0 to –71.9 minutes). A small and nonsignificant decrease of total sleep time of 5.6 minutes was observed for the CBT group while an increase of 10.3 minutes was observed for the CBT plus zolpidem group. For sleep efficiency, large and significant increases were observed for the CBT group (14.4%; 95% CI, 11.8% to 16.9%) and the CBT plus zolpidem group (15.8%; 95% CI, 13.3% to 18.4%). Finally, tests for interactions showed that the CBT plus zolpidem group produced a significantly greater increase of total sleep time compared with patients treated with CBT alone during the 6-week acute treatment phase (difference of 15.9 minutes; 95% CI, 1.0 to 30.8 minutes).

After the extended 6-month treatment phase, simple effects analyses revealed no significant change in sleep onset latency for all 4 treatment groups from the end of the acute 6-week phase to the end of the extended 6-month phase. For time awake after sleep onset, 3 treatment groups exhibited small increases but it was only significant after applying α corrections for the CBT plus zolpidem as needed group (15.9 minutes; 95% CI, 2.8-28.9 minutes). The change for the extended CBT alone group with no additional zolpidem was 6.3 minutes for this same period, which was not significant. For total sleep time for the 6-month phase, significant increases were observed for the extended CBT group (26.3 minutes;

Table 2. Means and Standard Errors for Sleep Parameters as Measured by Daily Sleep Diaries

	Initial Treatment				Extended Treatment				Follow-up		
	Mean (SE)		Change From Baseline to 6 wk, Mean (95% CI)	*d*	Treatment Group	6-mo Maintenance Phase, Mean (SE)	Change From 6 wk to 6 mo, Mean (95% CI)	*d*	6-mo Follow-up, Mean (SE)	Change From 6 mo to Follow-up, Mean (95% CI)	*d*
	Baseline	6-wk Acute Phase									
Sleep Onset Latency, min											
CBT	37.18 (2.69)	17.32 (2.77)	–19.9 (–26.1 to –3.6)	–0.83	CBT	18.91 (2.53)	3.6 (–3.4 to 10.5)	0.17	16.43 (2.08)	–1.8 (–9.1 to 5.5)	–0.09
					No treatment	22.41 (2.63)	3.6 (–3.7 to 10.8)	0.17	18.30 (2.04)	–4.1 (–11.5 to 3.3)	–0.20
CBT + zolpidem	29.73 (2.69)	17.80 (2.80)	–11.9 (–18.2 to –5.6)	–0.50	CBT only, no zolpidem	18.27 (2.58)	0.2 (–7.0 to 7.3)	0.01	14.07 (2.12)	–3.9 (–11.4 to 3.7)	–0.19
					CBT + zolpidem as needed	15.23 (2.66)	–2.4 (–9.8 to 5.0)	–0.12	16.19 (2.18)	1.1 (–6.8 to 8.9)	0.05
Time Awake After Sleep Onset, min											
CBT	116.50 (4.93)	47.79 (5.07)	–68.7 (–79.7 to –57.8)	–1.56	CBT	61.63 (5.43)	12.7 (0.4 to 25.0)[a]	0.32	56.05 (5.53)	–5.4 (–18.3 to 7.5)	–0.13
					No treatment	58.99 (5.61)	13.6 (0.7 to 26.5)[a]	0.34	62.68 (5.45)	3.3 (–9.8 to 16.3)	0.08
CBT + zolpidem	128.55 (4.93)	45.62 (5.13)	–82.9 (–94.0 to –71.9)	–1.88	CBT only, no zolpidem	48.16 (5.52)	6.3 (–6.4 to 18.9)	0.16	47.21 (5.64)	–1.4 (–14.7 to 12.0)	–0.03
					CBT + zolpidem as needed	65.82 (5.68)	15.9 (2.8 to 28.9)	0.39	63.90 (5.77)	–2.1 (–16.0 to 11.9)	–0.05
Total Sleep Time, min											
CBT	343.97 (7.06)	338.38 (7.17)	–5.6 (–16.1 to 4.9)	–0.09	CBT	363.41 (8.40)	26.3 (11.2 to 41.4)	0.43	382.70 (10.25)	21.0 (5.2 to 36.7)	0.34
					No treatment	385.34 (8.61)	41.5 (25.7 to 57.2)	0.68	388.77 (10.14)	5.0 (–11.0 to 21.0)	0.08
CBT + zolpidem	348.87 (7.06)	359.14 (7.22)	10.3 (–0.3 to 20.9)	0.16	CBT only, no zolpidem	390.82 (8.50)	27.3 (11.9 to 42.8)	0.45	399.26 (10.41)	9.5 (–6.9 to 25.9)	0.16
					CBT + zolpidem as needed	372.54 (8.69)	18.1 (2.1 to 34.1)[a]	0.30	390.81 (10.59)	17.8 (0.8 to 34.8)[a]	0.29
Sleep Efficiency, %											
CBT	68.99 (1.32)	83.36 (1.35)	14.4 (11.8 to 16.9)	1.22	CBT	81.43 (1.48)	–2.0 (–5.0 to 1.1)	–0.18	83.81 (1.48)	2.3 (–1.0 to 5.5)	0.21
					No treatment	82.38 (1.53)	–1.6 (–4.8 to 1.6)	–0.15	82.50 (1.46)	0.2 (–3.0 to 3.5)	0.02
CBT + zolpidem	68.64 (1.32)	84.46 (1.37)	15.8 (13.3 to 18.4)	1.34	CBT only, no zolpidem	85.49 (1.51)	0.1 (–3.1 to 3.2)	0.01	86.68 (1.50)	1.2 (–2.1 to 4.6)	0.11
					CBT + zolpidem as needed	82.04 (1.55)	–1.4 (–4.7 to 1.8)	–0.13	82.68 (1.54)	0.6 (–2.8 to 4.1)	0.06

Abbreviations: CBT, cognitive behavioral therapy; CI, confidence interval.
[a] These comparisons were no longer significant after applying α corrections (*P* values between .02 and .05).

95% CI, 11.2-41.4 minutes), no additional treatment group (41.5 minutes; 95% CI, 25.7-57.2 minutes), and the extended CBT alone with no additional zolpidem (27.3 minutes; 95% CI, 11.9-42.8 minutes). For sleep efficiency, no significant change was observed. Tests for interactions revealed no significant group differences in the magnitude of changes occurring on any of these variables during the extended 6-month treatment phase.

Comparisons of 6-month follow-up data with the 6-month treatment data showed no further changes for any variable except for total sleep time, which was further increased in the extended CBT alone group (21.0 minutes; 95% CI, 5.2-36.7 minutes). Thus, sleep improvements achieved with treatment were well maintained over time.

Polysomnography Data

Means, change scores, and Cohen *d* values for polysomnographic sleep variables are displayed in TABLE 3. With 6-week treatment, there was a significant, albeit modest, reduction of sleep onset latency for the CBT group (–6.4 minutes; 95% CI, –9.1 to –3.8 minutes) and the CBT plus zolpidem group (–2.8 minutes; 95% CI, –5.5 to –0.2 minutes). Significant and larger reductions of time awake after sleep onset were observed for the CBT group (–27.2 minutes; 95% CI, –34.9 to –19.5 minutes) and the CBT plus zolpidem group (–27.1 minutes; 95% CI, –34.8 to –19.3 minutes). For total sleep time, significant decreases were observed for the CBT group (–25.9 minutes; 95% CI, –34.9 to –16.8 minutes) and the CBT plus zolpidem group (–18.5 minutes; 95% CI, –27.6 to –9.4 minutes). For sleep efficiency, sig-

Table 3. Means and Standard Errors for Sleep Parameters as Measured by Polysomnography

	Initial Treatment				Extended Treatment			
	Mean (SE)		Change From Baseline to 6 wk, Mean (95% CI)	*d*	Treatment Group	6-mo Maintenance Phase, Mean (SE)	Change From 6 wk to 6 mo, Mean (95% CI)	*d*
	Baseline	6-wk Acute Phase						
Sleep Onset Latency, min								
CBT	17.22 (1.11)	10.80 (1.15)	–6.4 (–9.1 to –3.8)	–0.64	CBT	10.91 (1.57)	–0.4 (–4.1 to 3.3)	–0.04
					No treatment	15.56 (1.62)	5.2 (1.4 to 9.0)	0.56
CBT + zolpidem	14.03 (1.12)	11.21 (1.16)	–2.8 (–5.5 to –0.2)	–0.28	CBT only, no zolpidem	9.31 (1.57)	–1.8 (–5.5 to 1.9)	–0.19
					CBT + zolpidem as needed	12.80 (1.69)	1.4 (–2.5 to 5.3)	0.15
Time Awake After Sleep Onset, min								
CBT	64.51 (3.57)	37.34 (3.68)	–27.2 (–34.9 to –19.5)	–0.85	CBT	48.93 (4.80)	10.6 (0 to 21.3)[a]	0.34
					No treatment	43.42 (4.91)	7.1 (–3.9 to 18.1)	0.23
CBT + zolpidem	61.21 (3.59)	34.15 (3.71)	–27.1 (–34.8 to –19.3)	–0.85	CBT only, no zolpidem	47.79 (4.81)	15.4 (4.8 to 26.1)	0.50
					CBT + zolpidem as needed	53.11 (5.10)	16.9 (5.6 to 28.2)	0.54
Total Sleep Time, min								
CBT	371.42 (4.77)	345.58 (4.90)	–25.9 (–34.9 to –16.8)	–0.61	CBT	348.40 (7.40)	8.7 (–5.8 to 23.1)	0.20
					No treatment	361.84 (7.57)	10.4 (–4.6 to 25.3)	0.24
CBT + zolpidem	377.62 (4.80)	359.10 (4.93)	–18.5 (–27.6 to –9.4)	–0.43	CBT only, no zolpidem	362.78 (7.41)	2.3 (–12.2 to 16.8)	0.05
					CBT + zolpidem as needed	343.64 (7.86)	–14.2 (–29.6 to 1.1)	–0.33
Sleep Efficiency, %								
CBT	82.30 (0.86)	87.76 (0.88)	5.5 (3.8 to 7.2)	0.71	CBT	85.12 (1.16)	–2.1 (–4.6 to 0.4)	–0.28
					No treatment	86.22 (1.19)	–2.1 (–4.6 to 0.4)	–0.28
CBT + zolpidem	83.72 (0.86)	88.71 (0.89)	5.0 (3.3 to 6.7)	0.65	CBT only, no zolpidem	86.41 (1.17)	–2.7 (–5.2 to –0.2)[a]	–0.36
					CBT + zolpidem as needed	84.12 (1.24)	–4.2 (–6.8 to –1.5)	–0.56

Abbreviations: CBT, cognitive behavioral therapy; CI, confidence interval.
[a] These comparisons were no longer significant after applying α corrections (*P* values between .02 and .05).

nificant increases were observed in the CBT group (5.5%; 95% CI, 3.8% to 7.2%) and the CBT plus zolpidem group (5.0%; 95% CI, 3.3% to 6.7%). Tests for interactions revealed no differential treatment effects during the 6-week treatment phase.

After the 6-month extended treatment phase, simple effects analyses revealed a significant increase of sleep onset latency for the group that received CBT for 6 weeks and then no additional treatment (5.2 minutes; 95% CI, 1.4 to 9.0 minutes). For time awake after sleep onset, there was no further significant change for CBT with or without additional treatment. However, the combined groups receiving CBT during the 6-month phase reported similar significant increases of time awake after sleep onset (CBT alone with no additional zolpidem, 15.4 minutes [95% CI, 4.8 to 26.1 minutes]; CBT plus zolpidem as needed, 16.9 minutes [95% CI, 5.6 to 28.2 minutes]). For total sleep time, no significant changes were observed for any of the groups. For sleep efficiency, only the CBT plus zolpidem as needed group showed a significant worsening over time (–4.2%; 95% CI, –6.8% to –1.5%). Tests for interactions revealed a greater increase of sleep onset latency in the CBT with no additional treatment group compared with the extended CBT group (difference of 5.6%; 95% CI, 0.3% to 10.9%).

Treatment Response and Remission Rates

Insomnia Severity Index descriptive statistics and Cohen *d* values are displayed in TABLE 4. During the 6-week treatment phase, significant decreases in insomnia severity were observed in the CBT alone group (–8.3 units; 95% CI, –9.4 to –7.2 units) and the CBT plus zolpidem group (–8.8 units; 95% CI, –9.9 to –7.7 units). No additional change was observed during the extended 6-month treatment phase or during the 6-month follow-up period. The mean ISI scores were in the moderate severity range at baseline (17.3 and 17.6), and decreased to below the clinical threshold after the 6-week acute

Table 4. Insomnia Severity Index Means and Standard Errors and Percentages of Treatment Responders and Remitters

	Initial Treatment				Extended Treatment				Follow-up		
	Mean (SE)										
	Baseline	6-wk Acute Phase	Change From Baseline to 6 wk, Mean (95% CI)	*d*	Treatment Group	6-mo Maintenance Phase, Mean (SE)	Change From 6 wk to 6 mo, Mean (95% CI)	*d*	6-mo Follow-up, Mean (SE)	Change From 6 mo to Follow-up, Mean (95% CI)	*d*
Insomnia Severity Index Patient Raw Score, units											
CBT	17.26 (0.47)	8.94 (0.48)	–8.3 (–9.4 to –7.2)	–2.00	CBT	8.68 (0.73)	–1.0 (–2.5 to 0.6)	–0.23	8.94 (0.71)	0.3 (–1.3 to 1.9)	0.06
					No treatment	8.11 (0.75)	–0.2 (–1.8 to 1.4)	–0.04	8.85 (0.69)	0.7 (–0.8 to 2.3)	0.18
CBT + zolpidem	17.55 (0.47)	8.76 (0.49)	–8.8 (–9.9 to –7.7)	–2.11	CBT only, no zolpidem	6.95 (0.74)	–0.4 (–2.0 to 1.2)	–0.09	5.82 (0.74)	–1.1 (–2.8 to 0.6)	–0.26
					CBT + zolpidem as needed	8.71 (0.76)	–1.4 (–3.0 to 0.2)	–0.32	8.77 (0.75)	0 (–1.7 to 1.7)	0.01
Treatment Responders[a]											
		No./Total (%)[b]				No./Total (%)[b]	OR (95% CI)		No./Total (%)[b]	OR (95% CI)	
CBT		45/75 (59.46)			CBT	24/38 (62.87)	1.23 (0.62 to 2.45)		21/33 (62.80)	1.00 (0.45 to 2.20)	
					No treatment	20/37 (55.01)	0.76 (0.35 to 1.67)		20/35 (57.15)	1.09 (0.54 to 2.22)	
CBT + zolpidem		45/74 (61.11)			CBT only, no zolpidem	27/37 (73.88)	1.26 (0.44 to 3.49)		24/30 (80.86)	1.49 (0.62 to 3.61)	
					CBT + zolpidem as needed	26/37 (69.56)	1.94 (0.78 to 4.85)		19/29 (64.87)	0.81 (0.31 to 1.91)	
Treatment Remitters[c]											
CBT	0	29/75 (39.19)			CBT	17/38 (43.87)	1.92 (0.78 to 4.74)		14/33 (43.89)	1.00 (0.51 to 1.97)	
					No treatment	17/37 (45.29)	0.85 (0.34 to 2.14)		14/35 (40.28)	0.81 (0.37 to 1.79)	
CBT + zolpidem	0	33/74 (44.44)			CBT only, no zolpidem	21/37 (56.89)	0.85 (0.43 to 1.66)		20/30 (67.78)	1.59 (0.78 to 3.27)	
					CBT + zolpidem as needed	22/37 (59.76)	3.50 (1.53 to 8.04)		12/29 (41.73)	0.48 (0.25 to 0.93)	

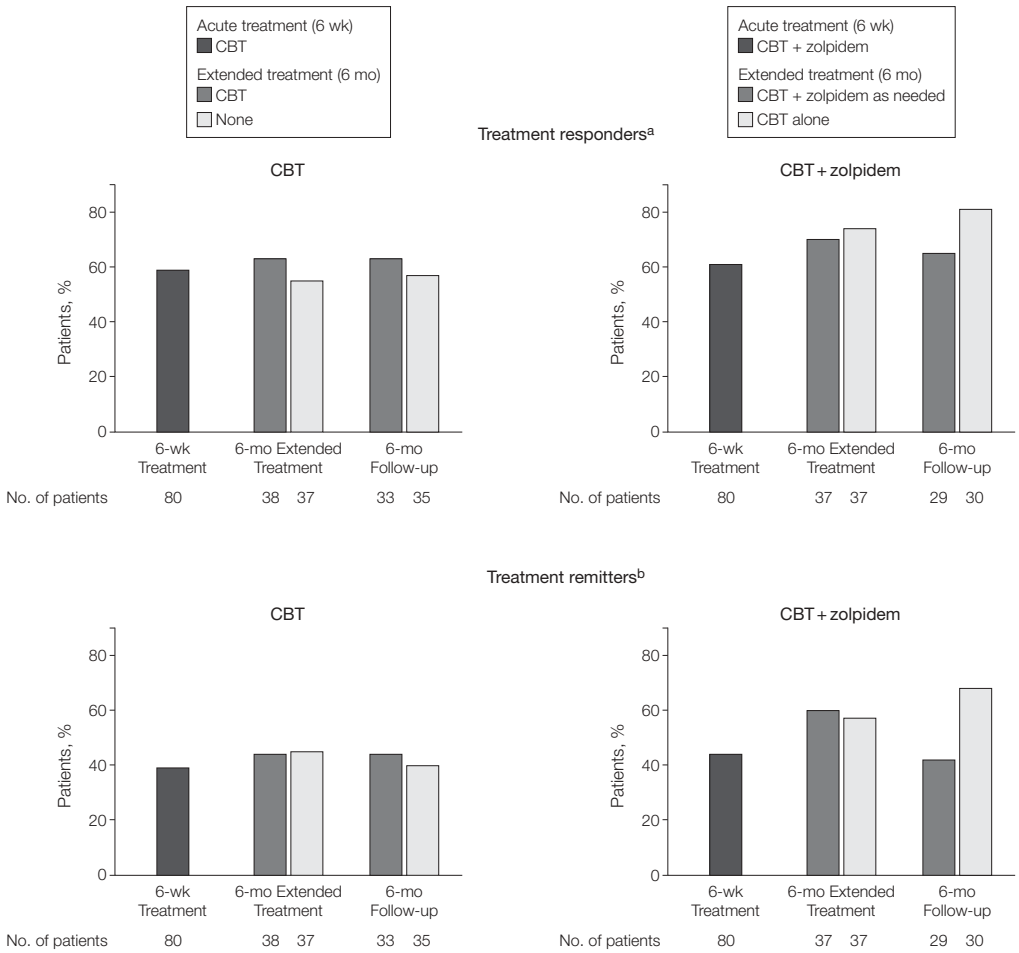
Abbreviations: CBT, cognitive behavioral therapy; CI, confidence interval; OR, odds ratio.
[a] Insomnia Severity Index score reductions of 8 units or greater compared with baseline Insomnia Severity Index score.
[b] Indicates estimated percentage (derived from generalized linear mixed models), which was adjusted for missing data and may not correspond exactly to the actual frequency.
[c] Insomnia Severity Index score less than 8 units.

treatment phase (8.9 and 8.8), and either remained within that range after extended treatment or declined further within the no insomnia category (ISI score <8) for the group receiving extended CBT alone with no additional zolpidem.

A treatment responders' analysis was conducted on response and remission rates, which were compared across treatment groups and time using generalized linear mixed models. Patients were considered treatment responders if their ISI change score compared with baseline was greater than 7 (equivalent to 1 category on the ISI) and were considered treatment remitters if their absolute ISI score was less than 8 units (ie, no insomnia category). The proportions of treatment responders (59.5% for the CBT alone group and 61.1% for the CBT plus zolpidem group; $P=.84$) and treatment remitters (39.2% for the CBT alone group and 44.4% for the CBT plus zolpidem group; $P=.52$) were equivalent in the 2 groups after the 6-week acute treatment phase (FIGURE 2). After the 6-month extended treatment phase, no significant time effect was found but a significant group × time interaction was obtained for remission ($F_{6,253}=2.16$; $P=.05$). Overall, combined therapy groups produced a higher remission rate compared with the CBT alone groups during the 6-month extended therapy phase and the 6-month follow-up period (56% [43/74 and 32/59] vs 43% [34/75 and 28/68]; $P=.05$).

Simple effects analysis revealed that remission rates for the group receiving extended CBT alone with no additional zolpidem increased steadily over time from 44.4% after the 6-week treatment phase to 56.9% after the 6-month extended treatment phase, to 67.8% at 6-month follow-up, while the remission rates observed for the group receiving extended CBT plus zolpidem as needed increased from 44.4% during the 6-week phase to 59.8% during the

Figure 2. Proportions of Treatment Responders and Remitters According to Treatment Condition and Assessment Phase



CBT indicates cognitive behavioral therapy. These data are from the end of each of the listed periods.
[a] Defined as a change in score on the Insomnia Severity Index of 8 units or higher from baseline.
[b] Defined as an Insomnia Severity Index score of less than 8 units.

6-month phase but decreased at 6-month follow-up to 41.7%. This resulted in a different trajectory of change at 6-month follow-up between both groups initially treated with CBT plus zolpidem ($F_{1,253}$=4.19; P=.04); no other contrasts between treatment groups were significant (P value range, .15-.91).

After the 6-week acute treatment phase, 66 of the 74 patients (89.2%) in the CBT alone group were rated as moderately or markedly improved by an independent assessor compared with 60 of the 72 patients (83.3%) in the CBT plus zolpidem group; this group difference was not significant. After the extended 6-month treatment phase, 29 of 34 patients (85%) in the CBT group were rated as moderately or markedly improved compared with 29 of 33 patients (87.9%) in the no additional treatment group, 28 of 32 patients (87.5%) in the extended CBT with no additional zolpidem group, and 19 of 26 patients (73.1%) in the CBT plus zolpidem as needed group; no significant group differences were found among the 4 groups.

COMMENT

The findings indicate that CBT, used singly or in combination with zolpidem, was effective for treating persistent insomnia. The addition of medication produced some added benefits, albeit modest, to outcomes during the acute 6-week treatment phase, mostly in terms of increased sleep time. Overall, 60% of patients achieved a treatment response and 42% were in remission after the 6-week treatment phase and these rates increased to 65% and 51% after 6 months of extended treatment. Patients treated with a combined approach of CBT plus zolpidem during the initial 6-week treatment phase achieved better long-term outcomes when zolpidem was discontinued after the initial 6-week trial. In general, sleep improvements were well sustained over time. Generalization of the present findings should be cautious because all patients were white and less than 10% were older than 65 years. However, sex, education, insomnia severity, and presence of medical or psychiatric comorbidity did not moderate treatment response.

Previous studies combining CBT with medication[11,14,17] have reported either no added value or only a slight advantage over single therapy alone. The present findings suggest that combining medication with CBT may provide an added benefit during the initial course of therapy, but the clinical significance of such added benefit is unclear. Although a gain of 15 minutes in sleep time is marginal, it may nonetheless be important given that CBT typically involves restricting time spent in bed and produces an initial reduction in sleep time. When combined with medication as in the present study, CBT did not reduce sleep time but may have enhanced compliance with the CBT regimen. When outcome was measured in terms of treatment response and remission rates, there was no added value in combining medication with CBT, at least during the initial 6-week treatment phase.

Examination of different maintenance treatment regimens showed that extended, individualized CBT did not add significant benefits to the initial group therapy–based CBT. Although this finding was unexpected, it is plausible that some patients had already reached a ceiling effect with the initial CBT and there was probably no need for additional therapy. Conversely, for patients who still presented residual insomnia, a more intense treatment regimen (ie, bimonthly CBT visits), or a switch to a different therapy or medication could have enhanced outcome. For the CBT plus medication group, patients who discontinued taking the medication after the initial 6-week course of therapy did better than those who continued taking the medication on an intermittent schedule. This result is not consistent with some evidence,[24,25] suggesting that intermittent medication use fosters long-term maintenance of therapeutic benefits. On the other hand, after patients have received CBT plus medication therapy, it makes good clinical practice to discontinue medication while patients are still receiving CBT. Such practice would minimize drug exposure and risk for dependence with long-term medication and would provide patients with more time to integrate newly learned psychological and behavioral skills to overcome insomnia.[16] Thus, this sequential regimen would seem preferable to a combined approach in which both therapies are initiated and discontinued at the same time, which was a common practice in most of the previous studies.[14,15,17]

The present study evaluated only 3 maintenance strategies and it is plausible that other treatment sequences might prove more effective. For instance, patients who fail to achieve an adequate response (or remission) during initial therapy could receive a second-level therapy that might involve either adding or switching to a different treatment modality. A patient treated with CBT initially would be switched to medication, whereas someone treated with medication initially would be switched to CBT or to another class of hypnotic medication. When selecting initial treatment in clinical practice, it also may be necessary to take into account practical (availability and acceptability of different treatment options) and clinical considerations (acute vs chronic insomnia, prior treatment exposure, comorbidity), as well as evidence of efficacy.[45-47]

Although the present findings are promising, there is currently no treatment that works for every patient with insomnia and additional studies are needed to develop treatment algorithms to guide practitioners in the clinical management of insomnia.[48] Questions of clinical and scientific interest for further investigations include whether CBT or medication should be the first-line therapy for persistent insomnia and how best to proceed with second-line treatment for those who do not respond to initial treatment. Additional studies also are needed to examine how best to integrate CBT and medication as a function of insomnia severity, prior treatment exposure, psychological and

medical comorbidity, and patient preference.

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