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Speed and trajectory of changes of insomnia symptoms during acute treatment with cognitive–behavioral therapy, singly and combined with medication

Charles M. Morin^{a,b,*}, Simon Beaulieu-Bonneau^{a,b}, Hans Ivers^{a,b,c}, Annie Vallières^{a,b,c}, Bernard Guay^b, Josée Savard^{a,c}, and Chantal Mérette^{b,d}

^aÉcole de psychologie, Université Laval, Québec, QC, Canada

^bCentre de recherche de l'Institut universitaire en santé mentale de Québec, Québec, QC, Canada

^cCentre de recherche du CHU de Québec, Québec, QC, Canada

^dFaculté de médecine, Université Laval, Québec, QC, Canada

Abstract

Objectives—To examine the speed and trajectory of changes in sleep/wake parameters during short-term treatment of insomnia with cognitive–behavioral therapy (CBT) alone versus CBT combined with medication; and to explore the relationship between early treatment response and post-treatment recovery status.

Methods—Participants were 160 adults with insomnia (mean age, 50.3 years; 97 women, 63 men) who underwent a six-week course of CBT, singly or combined with 10 mg zolpidem nightly. The main dependent variables were sleep onset latency, wake after sleep onset, total sleep time, sleep efficiency, and sleep quality, derived from sleep diaries completed daily by patients throughout the course of treatment.

Results—Participants treated with CBT plus medication exhibited faster sleep improvements as evidenced during the first week of treatment compared to those receiving CBT alone. Optimal sleep improvement was reached on average after only one week for the combined treatment compared to two to three weeks for CBT alone. Early treatment response did not reliably predict post-treatment recovery status.

Conclusions—Adding medication to CBT produces faster sleep improvement than CBT alone. However, the magnitude of early treatment response is not predictive of final response after the

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*Corresponding author. Address: École de Psychologie, Université Laval, Pavillon Félix-Antoine Savard, 2325, rue des Bibliothèques, Québec, QC, Canada G1V 0A6. Tel.: +1 418-656-3275; fax: +1 418-656-5152. cmorin@psy.ulaval.ca (C.M. Morin).

Conflicts of interest

None declared.

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six-week therapy. Additional research is needed to examine mechanisms involved in this early treatment augmentation effect and its impact on long-term outcome.

Keywords

Insomnia; Sleep; Cognitive-behavioral therapy; Medication; Combined therapy; Treatment response

1. Introduction

Insomnia is the most prevalent of all sleep disorders, with 25% of the adult population reporting sleep difficulties and 6–10% fulfilling diagnostic criteria for a chronic insomnia disorder [1–3]. Chronic insomnia can have detrimental consequences in a variety of domains, including mental and cardiovascular health, cognitive functioning, work productivity, and quality of life [4]. Of the different insomnia therapies available, only benzodiazepine-receptor agonists and cognitive-behavioral therapy (CBT) are recognized as having adequate evidence in terms of efficacy and safety [5–8].

Whereas each individual treatment option has its own benefits and limitations, investigators have also combined CBT and medication in order to take advantage of their respective strengths and presumably optimize treatment response [9–12]. Medication is often thought to bring about rapid relief of sleep disturbances, whereas CBT provides more sustained improvements over time. For example, in a study comparing a behavioral intervention against medication and reporting weekly changes [13], medication was effective during the first week of therapy but sleep improvements were not sustained at short-term follow-up, whereas sleep improvements were slightly delayed with behavioral therapy but also better sustained over time. Such findings have led investigators to believe that combined therapy would provide the best outcomes by capitalizing on the rapid improvements with medication and sustained benefits of CBT.

Most CBT studies of insomnia focus on sleep changes occurring from baseline to post-treatment (typically 4–8 weeks), whereas drug trials often examine the impact of medications on sleep during the first few nights of use and then for a few more nights upon drug discontinuation. However, there are limited data regarding the trajectory of sleep over the course of acute treatment (i.e. first few weeks of therapy). Information on the speed of recovery and trajectory of sleep changes during initial treatment could be informative in studies comparing different combinations or sequences of medication and CBT. Indeed, if hypnotic medications are associated with faster sleep improvements and CBT with more sustained changes over time, it is plausible that adding medication to CBT would result in faster sleep changes without compromising their long-term maintenance. In order to test this assumption, a classic pre-post examination of data is inadequate; rather, sleep has to be monitored on an ongoing basis during the course of treatment.

The first objective of this study was to examine the course of sleep changes over acute treatment for insomnia and investigate whether adding medication to CBT influences the speed of sleep changes. CBT delivered alone was compared to CBT combined with zolpidem on sleep changes reported by patients on daily sleep diaries kept over a six-week

treatment period. A second objective was to determine the number of weeks required to reach an optimal sleep improvement. Third, the study aimed to explore the relationship between the initial sleep change and post-treatment sleep status.

2. Methods

This article reports secondary analyses of a larger randomized clinical trial examining the impact of different treatment sequences using CBT, singly and combined with zolpidem, throughout six- and 12-month periods. The present report focuses specifically on weekly changes during the first six-week treatment phase. Study participants, procedures, and results pertaining to the main research questions have been described in more details elsewhere [14]. The Institutional Research Board of Ethics from the Institut Universitaire en Santé Mentale de Québec approved the study protocol.

2.1. Participants and study design

Participants were recruited through newspaper advertisements and referrals from health care practitioners in the Québec City area. Inclusion criteria were: aged ≥ 30 years and diagnosis of chronic insomnia based on a combination of criteria from the Diagnostic and statistical manual of mental disorders (DSM-IV-TR) [15] and the International Classification of Sleep Disorders [16]. 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 >30 min, with a corresponding sleep time of <6.5 h at least three nights per week (as measured by daily sleep diaries); (2) insomnia duration longer than six months; and (3) significant distress or impairment of daytime functioning (rating of ≥ 2 on item 5 of the Insomnia Severity Index).

Exclusion criteria were (1) presence of a progressive medical illness (e.g. cancer, dementia) directly related to the onset and course of insomnia; (2) use of medications known to alter sleep (e.g. steroids); (3) lifetime diagnosis of any psychotic or bipolar disorder; (4) current diagnosis of major depression, unless treated and in remission; (5) more than two 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 $>15/h$); or (9) night-shift work or irregular bedtime and arising times. Patients with stable medical (e.g. hypertension) or psychiatric disorders (e.g. dysthymia, anxiety) were included in the study provided that these conditions were not the primary cause of insomnia. Patients using sleep medications no more than twice weekly were enrolled after they withdrew from the medications for at least two weeks. Individuals using alcohol as a sleep aid were also required to discontinue this practice at least two weeks prior to baseline assessment.

Of the 486 individuals who completed telephone screening for eligibility assessment, 242 completed second-stage screening, and 160 of those were included in the study. Participants were randomized to CBT alone ($n = 80$) or combined CBT plus zolpidem ($n = 80$). After completing this six-week initial treatment, they were randomized a second time to an extended treatment for the next six months. The current report focuses solely on the first treatment phase.

2.2. Measures

2.2.1. Sleep diary—Participants kept daily sleep diaries during a two-week baseline period and the six-week acute treatment phase (weeks 1–6). The primary dependent variables derived from the diaries were sleep onset latency (SOL), wake time after sleep onset (WASO; excluding the last awakening prior to rising for the day), total sleep time (TST), sleep efficiency (SE; ratio of sleep time to the time spent in bed), and sleep quality (SQ). The sleep diary is a standard assessment instrument in insomnia research [17], which allows for prospectively monitoring sleep patterns over extended periods in the patient's home.

2.2.2. Insomnia Severity Index (ISI)—The ISI [18,19] is a seven-item instrument assessing the nature, severity and impact of sleep disturbances in the past month. Total score ranges from 0 to 28 (0–7: absence of insomnia; 8–14: subthreshold insomnia symptoms; 15–21: moderate insomnia; 22–28: severe insomnia).

2.3. Treatment conditions

Participants in both conditions (CBT alone and CBT plus zolpidem) received six weekly consultation sessions of CBT, a multicomponent intervention that features behavioral, cognitive, and educational components [18,20]. CBT sessions were facilitated by master's level clinical psychologists using a treatment manual [20]. The following procedures were introduced sequentially during treatment (see Box 1).

Box 1

Session-by-session cognitive-behavioral therapy outline

Session 1

- Treatment overview
- Psycho-education on sleep and insomnia
- Restriction of time in bed: prescription of first sleep window

Session 2

- Stimulus control: introduction of strategies
- Adjustment of sleep window
- Psycho-education on insomnia

Session 3

- Cognitive therapy
- Follow-up on sleep window and stimulus control

Session 4

- Cognitive therapy
- Follow-up on sleep window and stimulus control

Session 5

- Sleep hygiene education

- Follow-up on restriction of time in bed and stimulus control

Session 6

- Maintenance of treatment gains
- Relapse prevention
- Follow-up on sleep window and stimulus control

2.3.2. Restriction of time in bed—This was introduced at session 1 and consisted of limiting time spent in bed to the actual sleep time and gradually increasing it back to an optimal sleep time [21]. Each participant was prescribed an individualized sleep window, which was adjusted weekly. It was increased by 15–20 min when sleep efficiency was >90%, decreased by the same amount when sleep efficiency was <80%, and kept stable when sleep efficiency was 80–90%. The recommended sleep window was always 5 h per night in CBT and always 5.5 h in the combined condition.

2.3.3. Stimulus control—This was introduced at session 2 and included the following instructions: (1) go to bed only when sleepy at night; (2) use the bed and bedroom only for sleep and sex (i.e. no reading, TV watching, or worrying); (3) get out of bed and go into another room whenever unable to fall asleep or return to sleep within 20 min and return to bed only when sleepy again; (4) arise at the same time every morning; and (5) avoid daytime napping [22].

2.3.4. Cognitive therapy—Cognitive therapy (sessions 3–4) aimed to alter faulty beliefs and misconceptions about sleep [20]. Examples of faulty beliefs that were targeted included unrealistic sleep expectations (e.g. the absolute need to sleep 8 h every night) and amplification of the consequences of insomnia (e.g. all daytime impairments are due to poor sleep).

2.3.5. Sleep hygiene education—This was introduced at session 5 and concerned the effects on sleep of caffeine, alcohol, exercise, light, noise, and temperature. Treatment consolidation and relapse prevention strategies were covered in the sixth and last therapy session. Whereas these different components were introduced sequentially during the course of therapy, each of them was revisited with the therapist at subsequent sessions in order to address compliance issues.

Patients assigned to the combined CBT plus medication condition also received 10 mg of zolpidem (oral formulation); they were instructed to take it nightly, 30 min before bedtime. Zolpidem is a non-benzodiazepine agonist at the subtypes of benzodiazepine receptors; it has a rapid onset of action and a short half-life (mean, 2.5 h). It is absorbed from the gastrointestinal tract and there is no accumulation during repeated administration. Its therapeutic benefits are similar to benzodiazepines, but there are fewer residual effects on daytime functioning, minimal rebound insomnia upon discontinuation, and little alteration of sleep architecture [23–25]. The medication was provided in the context of brief (15–20 min),

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. Participants were encouraged to comply with the medication regimen but no CBT intervention was allowed during these sessions. The physician used a structured treatment manual. Patients were instructed to return unused medications and a pill count was conducted at each consultation visit.

2.4. Data management and analysis

Descriptive and inferential statistics were computed using SPSS Statistics for Windows [26]. Regarding the first study objective, five sleep diary variables (i.e. SOL, WASO, TST, SE, SQ) were analyzed with mixed models' repeated measures analysis of variance (ANOVA) using group (CBT, CBT plus zolpidem) $\times$ time (two baseline weeks, six treatment weeks) factorial design. Only group $\times$ time interaction effects were examined, with an alpha level of 0.05. To control for inter-individual differences in sleep parameters and insomnia severity, baseline data (two-week average) were included in the model as a covariate. The values for denominator's degrees of freedom were obtained by a Satterthwaite approximation [27]. For each significant interaction effect, 12 post-hoc comparisons were performed: group effect for each of the six treatment weeks, and treatment–contrast interactions comparing groups on the change score from baseline (two-week average) to treatment week 1, weeks 1–2, 2–3, 3–4, 4–5, and 5–6. A Holm–Bonferroni correction was applied to control for multiple comparisons. According to this procedure, for each set of contrasts *P*-values were ranked in ascending order and each contrast was interpreted against a specific alpha level according to the following formula: $0.15 \div (13 - \text{contrast's rank})$, yielding alpha levels for contrasts 1–12 of 0.0125, 0.0136, 0.015, 0.0167, 0.0188, 0.0214, 0.025, 0.03, 0.0375, 0.05, 0.075, and 0.15, respectively.

In order to investigate the second study objective (i.e. time to optimal sleep improvements), change scores from baseline to week 6 were computed for SOL, WASO, SE, and SQ, separately for each treatment group. Cumulative percentages were then computed for change scores from one week to the following week against the overall change score (baseline to week 6). These descriptive analyses were not performed for TST, as the overall baseline to post-treatment change for this variable was too small. To assess the third objective of the study (whether initial treatment response predicted post-treatment status), change scores from baseline to week 1 (initial sleep change) were ranked from worst to best changes for each dependent variable (SOL, WASO, TST, SE, SQ). For each variable the total sample (both treatment groups combined) was divided into three groups of equal size: group 1: worst change, corresponding to the lower third of the sample on initial sleep change; group 2: average change, corresponding to the middle third; group 3: best change, corresponding to the higher third. A series of five two-way ANOVAs was performed with treatment condition and initial change subgroup (worst, average, best change for SOL, WASO, TST, SE, or SQ, respectively) as fixed factors. The main effect of treatment condition was not examined as it was previously reported elsewhere [14].

3. Results

3.1. Sample description

The sample included 160 adults (97 women and 63 men) with a mean age of 50.3 years (SD, 10.1; range, 30–72) and a mean education of 14.7 years (SD, 3.5). The majority of participants (73.8%) reported mixed sleep-onset and maintenance insomnia. The mean (SD) insomnia duration was 16.4 (13.6) years. All patients were free of sleep medication prior to entering the study. The overall attrition rate was 6.9% ($n = 11$) during treatment and was not significantly different between the two groups.

3.2. Speed of sleep changes during acute treatment period

Figure 1 presents weekly sleep diary data (adjusted means and standard errors) over the baseline (two-week average) and treatment periods (weeks 1–6) for the five selected sleep parameters, as well as for time spent in bed (TIB), separately for the CBT and CBT plus medication conditions. There were no significant group differences for TIB, either for the two-week baseline or any individual treatment week; no further analyses were performed on this variable. Mixed model ANOVAs revealed a significant group $\times$ time interaction effect for sleep onset latency ($F(7, 329) = 3.28, P = 0.02$), wake time after sleep onset ($F(7, 262) = 6.29, P < 0.001$), total sleep time ($F(7, 230) = 6.11, P < 0.001$), sleep efficiency ($F(7, 212) = 7.81, P < 0.001$), and sleep quality ($F(7, 263) = 13.35, P < 0.001$). Post-hoc comparisons revealed that groups significantly differed on all five sleep parameters at treatment week 1. For all comparisons, the CBT plus medication group exhibited lower SOL ($M = 18.3$ vs 30.9 min), lower WASO ($M = 19.0$ vs 34.7 min), higher TST ($M = 324.1$ vs 288.6 min), higher SE ($M = 83.8$ vs 74.1%), and SQ ($M = 3.2$ vs 2.8 on a scale of 1–5) than the CBT alone group. The groups did not differ for the remainder of the treatment period (weeks 2–6) for SOL, but the combined CBT plus medication condition maintained its advantage over the CBT condition for weeks 2–5 for WASO (differences between conditions ranging from –9.0 to –15.7), TST (differences ranging from 19.4 to 29.9), SE (differences ranging from 3.0 to 6.9), and SQ (differences ranging from 0.35 to 0.41), except at week 4 for SE (difference = 2.2, *NS*). For the last treatment week (week 6), groups did not differ on any of the five parameters.

The treatment–contrast interactions compared the two groups on change scores for sleep parameters from baseline (two-week average) to week 1, and from each treatment week to the following week (weeks 1–6). Groups differed significantly on the treatment–contrast effect from baseline to week 1 for all variables except SOL. Participants in the CBT plus medication condition achieved better sleep improvement from baseline to week 1 compared to participants in the CBT alone condition for WASO (averaged reduction of 47.7 vs 25.1 min), SE (averaged increase of 15.1 vs 5.1%), and SQ (averaged increase of 0.4 vs –0.1); the reduction of sleep time during the first week of treatment was smaller in the combined condition relative to CBT alone condition (averaged reduction of 23.5 vs 57.6 min). Three more treatment–contrast interactions were significant: groups differed on the change scores for SOL from week 1 to week 2, for WASO from week 5 to week 6, and for SE from week 2 to week 3. In all three cases, the magnitude of sleep improvement or, in some cases, lack of

deterioration was higher in the CBT alone condition relative to the CBT plus medication condition.

3.3. Number of weeks required to reach optimal sleep improvement

In the CBT alone condition, maximal sleep improvement (>100% of the overall change observed from baseline to end of treatment) was reached after two weeks of treatment for SOL, and after three weeks for WASO and SE. Thereafter, sleep remained stable until the end of treatment. For SQ, maximal improvement was obtained only at the final week of treatment (week 6); 80% of the maximal improvement was reached after treatment week 3. In the combined CBT plus medication condition, sleep improvement reached 100% of the maximal change after only one or two weeks of treatment for SOL, WASO, and SE, and after three weeks for SQ. In other words, there was no or little further improvement beyond the first two weeks of therapy (or third week for SQ). For TST, the mean overall change throughout treatment was quite small, with a decrease of 2 min for the CBT alone condition and an increase of 7 min for the CBT plus medication condition. In the CBT alone condition, TST decreased by 16.6% (58 min) after the first week of treatment relative to the baseline value, and then it gradually increased on a weekly basis until the end of treatment (week 6). In the CBT plus medication condition, the initial decrease was only 6.8% (24 minutes) of baseline TST, followed by weekly increases until the next-to-last week of therapy (week 5), and finally a slight decrease from week 5 to week 6.

3.4. Relationship between initial treatment response and post-treatment outcome

Table 1 presents the results of five (i.e. one per sleep diary variable) two-way ANOVAs for the initial change subgroup main effect and the treatment condition $\times$ initial change subgroup interaction on the post-treatment Insomnia Severity Index (dependent variable). None of the effects examined was significant, suggesting that the initial sleep change (i.e. worst, average, or best change subgroup for SOL, WASO, TST, SE, or SQ, respectively) was not predictive of post-treatment sleep status.

3.5. Treatment process variables

Because treatment process variables such as treatment acceptability, expected efficacy, and compliance might influence outcome, we examined group differences on these variables. At baseline, treatment acceptability was not significantly different between conditions ($M = 7.50$ on a scale of 0–10 for CBT and $M = 7.92$ for combined group; $t(157) = 1.90$, $P = 0.06$). There was no significant group difference in expected efficacy of each treatment ($M = 6.45$ vs 6.66 , $P = 0.45$, for short-term expected efficacy, and $M = 7.66$ vs 7.96 , $P = 0.16$ for long-term). The mean (SD) number of therapy sessions attended was 5.6 (SD = 0.6) for the CBT group and 5.8 (SD = 0.4) for the combined group ($t(146) = 1.87$, $P = 0.06$). In all, 67.6% of patients in the CBT condition attended all six scheduled therapy sessions, whereas 78.7% did so in the combined condition ($\chi^2(1) = 2.39$, $P = 0.12$). Records from pill counts in the combined condition revealed that compliance decreased over the six-week treatment, as 90.9% of pills were taken during the first week and 79.1% were taken during the sixth week ($F(5, 361) = 6.28$; $P < 0.001$). We had previously examined compliance with behavioral procedures in the two groups [28]. These data showed no significant differences on

compliance between patients treated with CBT alone and those treated with CBT plus medication, except for compliance with sleep restriction at week 5 (i.e. higher compliance for the CBT alone condition). Thus, adding medication to CBT neither impeded nor enhanced compliance with behavioral treatment procedures for insomnia.

4. Discussion

The main objective of this study was to examine the speed and magnitude of changes on sleep/wake parameters during acute treatment of insomnia with CBT delivered alone or combined with a hypnotic medication. Results showed that the addition of medication to CBT produced faster sleep improvements relative to CBT alone. Optimal sleep improvement was obtained after only one week of treatment with combined therapy, compared with two to three weeks with CBT alone. Initial treatment response was not predictive of post-treatment sleep status. These findings suggest that medication may provide an early augmentation therapeutic effect when added to CBT, which is consistent with some previous studies [29], but this initial advantage is not necessarily maintained towards the end of treatment or predictive of recovery at the end of a six-week treatment course.

Tracking the different trajectory of changes during the course of insomnia treatment with daily sleep monitoring is of significant interest to gain a better understanding of the mechanisms of treatment response. Unlike our previous report [14] which focused on pre- to post-therapy comparisons and indicated no differential treatment effects, the current reanalysis of weekly data showed a different course of sleep progress over the initial six-week treatment period, with combined CBT plus medication producing quicker improvements relative to CBT alone on four of the five selected sleep/wake parameters (WASO, TST, SE, and SQ). Likewise, combined therapy also produced better sleep improvements than CBT alone on these four variables at each of the first five weeks of treatment. However, treatment conditions no longer differed on any of the sleep parameters during the last treatment week. It therefore appears that even if medication provided an added value to CBT early on in treatment, both CBT alone and combined treatment reached a plateau towards the sixth week of therapy. The question then becomes: is there a real added value to this initial augmentation effect? Our findings suggest that despite the initial advantage of combined therapy, early treatment response was not predictive of post-treatment recovery status. If initial treatment response is not related to short-term outcome, the next question is whether initial treatment response has any long-term impact, i.e. weeks or months after completing treatment. Our previously published data showed that, at the six-month follow-up, the best response and remission rates were for individuals who were treated initially with combined therapy but then switched to CBT alone during the extended treatment phase [14].

There are several potential explanations for the added value of medication. The first one is that medication may potentiate the impact of CBT during the early course of treatment by fostering better compliance with some behavioral and sleep-scheduling recommendations. For instance, if patients sleep longer or more efficiently early in treatment (perhaps due to the more rapid relief produced by medication), they may be more inclined to comply with

behavioral recommendations (e.g. restriction of time in bed) than if their sleep remains disrupted for several weeks before improvements become noticeable. This explanation is not supported, however, by the finding of no differential compliance with CBT between the two groups (except at week 5, when CBT showed better compliance with sleep restriction). A second explanation is that medication may contribute to stabilize sleep patterns by reducing its night-to-night variability, an important feature of chronic insomnia in some patients [30]. Another potential explanation is that medication may attenuate some of the adverse effects on daytime functioning (e.g. sleepiness) that are associated with sleep restriction therapy, particularly during the first week of treatment [31]. By improving sleep, medication might have a protective effect against these adverse effects, at least during the initial introduction of CBT. On the other hand, one could also argue that combining a hypnotic medication with sleep restriction therapy may exacerbate residual daytime sedation. This may be a plausible concern given the evidence that sleep restriction produces significant residual daytime sleepiness [31,32].

There are limitations to the scope and interpretation of the current findings. For instance, the lack of a group that just received zolpidem or a placebo precludes any direct comparison about the speed and magnitude of changes in patients treated with medication alone. It could also be argued that administration of medication alone is simpler and, in some instances, produces substantial increase of sleep duration (e.g. [33]), thus questioning the need to add a more demanding behavioral intervention. Whereas such questions are legitimate, other issues such as treatment acceptability, compliance, side-effects, and discontinuation, must be considered when selecting among several treatment options. It is also important to consider both short- and long-term outcomes, i.e. whether early treatment response is related to long-term outcome, and previous studies directly contrasting CBT and medication have shown that medication may have a slight advantage in the short run but that CBT produces better-sustained benefits over time.

Despite potential benefits of combined therapy for insomnia, some caution is indicated particularly when sleep restriction is used in conjunction with medication. For instance, given the evidence that sleep restriction produces daytime sleepiness [31,32], such residual effects may be potentiated when sleep restriction is combined with a hypnotic medication – even one with a short half-life (2.5 h for zolpidem). A related issue is that we used 10 mg zolpidem with all participants, whereas the US Food and Drug Administration recently recommended using a reduced 5 mg dose with women (and the recommendation for the elderly was always 5 mg) in order to reduce the risk of residual daytime sedation. Thus, for these reasons, clinicians should be cautious when combining zolpidem with CBT, particularly when CBT involves restriction of time in bed.

Another issue of potential concern for clinical practice is that despite improvements in sleep continuity and sleep quality during the initial six-week therapy, the average reported sleep duration never exceeded 6 h during that period, an outcome that is not optimal for most people with insomnia. With the increasing evidence of an association between objective short sleep duration (i.e. less than 5 or 6 h per night) and negative health outcomes [34], this lack of improvement in total sleep duration post therapy raises some questions about the significance of some of these findings and their implications for clinical practice. Additional

research is warranted to examine further the long-term association between sleep duration and health outcomes in insomnia and whether this morbidity is reversible when sleep duration is increased with treatment.

The present findings have potential implications for both clinical treatment and future research. At the clinical practice level, the findings suggest that it may be helpful to add medication, at least on a short-term basis, when initiating treatment for chronic insomnia. Whether this practice should be implemented with all or only certain patients remains unclear. As previously noted, however, when medication is combined with CBT initially, it is critical to discontinue medication after a few weeks and ensure that patients remain in CBT and receive additional guidance to foster integration of their newly learned psychological and behavioral strategies to manage insomnia. This is particularly important when using medication in order to prevent an individual from attributing sleep improvements to medication alone. At the research level, a closer examination of treatment mechanisms would be informative in order to understand better the trajectory of changes and the types of factors that contribute to the initial advantage of adding medication, an advantage that is gradually lost during the course of therapy. Another important implication for future research will be to examine further the long-term impact of this initial booster effect from adding medication to a CBT regimen.

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Fig. 1. Weekly sleep diary data (adjusted means and standard errors) over two-week baseline and six-week acute treatment periods for sleep onset latency, wake time after sleep onset, total sleep time, sleep efficiency, and sleep quality for cognitive-behavioral therapy (CBT) alone and CBT plus zolpidem conditions. Contrasts (i.e. group effect for treatment weeks 1–6, and for change score from baseline to week 1, and from each treatment week to the following week) are flagged for statistical significance.

Table 1

Effects of cognitive-behavioral treatment on the Insomnia Severity Index (ISI).

Variable used for creation of subgroups	Post-treatment ISI for initial change subgroups				Two-way ANOVA		
	Worst initial change		Average initial change		Best initial change		Treatment condition × initial change subgroup interaction
	EMM (95% CI) <i>n</i>		EMM (95% CI) <i>n</i>		EMM (95% CI) <i>n</i>		
SOL	8.11 (6.84–9.37) 49		9.60 (8.30–10.91) 47		8.92 (7.65–10.18) 50	$F(2, 140) = 1.33, P = 0.27$	$F(2, 140) = 1.94, P = 0.15$
WASO	8.45 (7.10–9.81) 48		8.18 (6.92–9.43) 50		9.97 (8.59–11.35) 48	$F(2, 140) = 2.01, P = 0.14$	$F(2, 140) = 0.39, P = 0.68$
TST	8.48 (7.05–9.91) 47		8.62 (7.37–9.86) 52		9.45 (8.05–10.86) 47	$F(2, 140) = 0.56, P = 0.57$	$F(2, 140) = 0.34, P = 0.71$
SE%	8.03 (6.65–9.41) 48		8.74 (7.47–10.01) 49		9.96 (8.56–11.36) 49	$F(2, 140) = 1.93, P = 0.15$	$F(2, 140) = 0.57, P = 0.57$
SQ	8.92 (7.42–10.41) 49		8.45 (7.13–9.77) 48		9.06 (7.40–10.72) 49	$F(2, 140) = 0.19, P = 0.83$	$F(2, 140) = 0.08, P = 0.93$

ANOVA, analysis of variance; EMM, estimated marginal mean; CI, confidence interval; SOL, sleep onset latency; WASO, wake time after sleep onset; TST, total sleep time; SE%, sleep efficiency; SQ, sleep quality.

Initial change subgroup sizes are not identical and do not add up to 160 due missing data on the post-treatment ISI (treatment dropouts).