Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

Procedures

All study candidates completed an initial telephone screening, clinical interviews, daily sleep diaries, polysomnography, and several questionnaires. Patients meeting criteria were randomized to one of the first-stage therapies. After completing the initial 6-week treatment, remitters remained on maintenance therapy. Remitters from the zolpidem condition attend a monthly follow up visit with the physician, who provided medication supply for nightly use (if needed) until the next visit. Remitters from the BT condition received monthly phone calls during, but there were no further therapy visits. Non-remitters following first-stage treatment were encouraged to accept randomization to a second-stage 6-week treatment. Non-remitting participants treated with BT initially were randomized to either a second psychological treatment, i.e., cognitive therapy (CT), or switched to a medication therapy (Zol). Those treated with medication (ZOL) initially were tapered off their medication and randomized to either BT or to a different medication (trazodone, Traz). Subsequently, participants entered follow-ups and were contacted monthly for adverse event monitoring (i.e., in-person visits with the physician for participants receiving medication in second-stage therapy; phone calls by the research coordinator for participants in the BT and CT conditions). In-person visits were conducted at 3, 6, and 12 months after the end of second-stage treatment and participants were asked to complete additional electronic sleep diaries (2 weeks) and the different outcome questionnaires.

Selection criteria

Inclusion criteria (combination of criteria from the DSM, Insomnia Research Diagnostic Criteria, and ICSD)

- Males and females age ≥ 21 years
- Complaint of persistent (i.e., > 1 month) difficulties initiating or maintaining sleep despite adequate opportunity for sleep
- Sleep onset latency or wake time after sleep onset ≥ 30 minutes for 3 or more nights per week during two weeks of sleep diary monitoring
- Insomnia Severity Index (ISI) total score > 10 indicating at least "mild" insomnia
- Score ≥ 2 on either the interference or distress item of the screening ISI, indicating the insomnia causes significant distress or impairment in social, occupational, or other areas of functioning

Exclusion criteria

- Untreated psychiatric disorder (e.g., major depression)
- Lifetime diagnosis of any psychotic or bipolar disorder, *as sleep restriction and medications for insomnia may precipitate mania and hallucinations*
- Imminent risk for suicide
- Alcohol or drug abuse within the past year
- Progressive illness (e.g., cancer), or neurological degenerative disease (e.g., dementia)
- Current use of medications known to cause insomnia (e.g., steroids)
- Sleep apnea (apnea/hypopnea index > 15), restless legs syndrome, periodic limb movement during sleep (PLMS with arousal > 15 per hour), or a circadian rhythm sleep disorder (e.g., advanced sleep phase syndrome)
- Personal or familial (first-degree relatives) history of sleepwalking
- Women being pregnant or expecting to become pregnant during treatment

Individuals with a comorbid medical condition were excluded only if the medical condition was life-threatening or represented a contra-indication to using study medications. Individuals using sleep-promoting medications (prescribed or over-the-counter) were included if they were willing and able to discontinue medications at least two weeks before baseline assessment. Participants using alcohol as a sleep aid or alcohol after 7:00pm on a regular basis were required to discontinue this practice at least two weeks prior to baseline assessment. Individuals using psychotropic medications (e.g., anxiolytics, antidepressants) were not automatically excluded from the study. Those on stable dosages (for at least three months) of SSRI or SNRI medications and who showed at least partial remission from their mood or anxiety disorder were accepted in the study if they meet the selection criteria above. Patients using TCAs, MAOIs, or atypical antidepressants were excluded even if in remission as the effects of these medications on sleep could confound interpretation of the findings.

Measures

Screening Instruments. Structured clinical interviews were used to screen potential participants. The Insomnia Interview Schedule[1] is an interview assessing the nature, severity, and frequency of the current insomnia problem, as well as its history, course, and contributing factors. The Duke Structured Interview for Sleep Disorders[2] is used to assist in ascertaining sleep disorder diagnosis according to DSM-IV-TR[3] and International Classification of Sleep Disorders criteria.[4] This instrument has acceptable reliability and discriminant validity.[5] In addition, the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID)[6] is used to classify enrollees as having primary or comorbid insomnia and to identify study candidates with disorders leading to exclusion. All interviews were audio taped and reliability checks were conducted on 15% of them. The Folstein Mini-Mental State Exam (MMSE)[7] was administered to exclude participants with cognitive deficits (MMSE score < 27) that make them unable to give informed consent or participate in an interactive treatment.

Insomnia Severity Index. The ISI is a 7-item self-report questionnaire that provides a global measure of perceived insomnia severity based on several indicators (e.g., difficulty falling or staying asleep, satisfaction with sleep, degree of impairment with daytime functioning). The total score ranges from 0-28: 0-7 (no clinical insomnia), 8-14 (sub threshold insomnia), 15-21 (insomnia of moderate severity), and 22-28 (severe insomnia). The ISI is validated and has proven sensitive to therapeutic changes [8,9]. Secondary outcomes included subjective sleep onset latency, time awake after sleep onset, and total sleep time derived from electronic sleep diaries kept daily by participants for two weeks at baseline and at each subsequent assessment period, as well as during first- and second-stage treatment.

Sleep Diary. Subjective estimates of sleep and wake times were obtained daily using a web-based sleep diary (Be Health Solutions). Participants were instructed to report the following information about their previous night's sleep: bedtime, sleep onset latency, number and length of nocturnal awakenings, time of final waking, rising time, and subjective rating of sleep quality. Additional questions query daytime napping, and caffeine, alcohol, and sleep medication use. Participants with missing data were contacted by phone to remind them to fill out the diary daily. Electronic sleep diaries were obtained for 2 weeks at baseline and at each subsequent assessment period, as well as for the entire treatment period (first- and second-stage).

Polysomnography. Participants underwent ambulatory nocturnal polysomnographic (PSG) monitoring at their home (Natus System) using their typical bedtimes and arising times for baseline/screening (two nights) and outcome assessment (two nights after each treatment phase). The first night was used to rule out other sleep disorders (e.g., apnea and PLMS). PSG monitoring was conducted according to standard procedures with regard to montage and sampling rate (256 Hz) and records were scored, blind to treatment assignment, in 30-second epochs using standard criteria[10] for sleep staging and sleep-associated events (e.g., apneas). Scoring was completed at the Duke University Insomnia and Sleep Research Program by

trained technologists under the supervision of an experienced polysomnographer, board-certified in sleep medicine (AK).

Sleep/wake variables derived from daily sleep diaries and PSG were : sleep onset latency (SOL), wake time after sleep onset (WASO), total sleep time (TST), sleep efficiency (SE).

Daytime Functioning Measures. Several outcomes were monitored to assess the impact of treatment on daytime functions and mood. Participants also completed the Pittsburgh Sleep Quality Index[11] and the Dysfunctional Beliefs and Attitudes about Sleep scale[1] at each assessment to examine changes in overall sleep quality and sleep-related cognitions. A clinical global improvement rating was completed by a blinded rater after each treatment. This rater also interviewed participants at the conclusion of their study involvement to determine whether they continued to meet diagnostic criteria for insomnia. To examine treatment-related changes in daytime functions and mood, participants completed the Multidimensional Fatigue Inventory (MFI),[12] the SF-36 Health Survey (SF-36),[13] the Work and Social Adjustment Scale (WSAS),[14] and the Beck Depression Inventory-II (BDI-II),[15] and the Trait part of the State-Trait Anxiety Inventory (STAI-Trait).[16]

Adverse events (AE) were monitored with the *Systematic Assessment for Treatment Emergent Events* (SAFTEE), a reliable and valid instrument for assessing AEs related to study treatments.[17] In addition to the standard treatment-emergent adverse events, two questions relevant to sleep and driving were added to this instrument about the impact of treatment on a) daytime sleepiness while driving or operating heavy machinery and b) cognitive impairments involving attention, concentration or memory while driving or operating heavy machinery). Administration of the SAFTEE was initiated upon recommendation from the Data and Safety Monitoring Baord about half way in the study. Thus, data on adverse events are available for approximately half the sample and only for the first treatment phase.

Treatment

Treatment implementation and monitoring. Treatments were administered in four 50-min consultation visits led by licensed clinical psychologists (BT, CT) or four 20-min visits with physicians/physicians' assistants (Zol, Traz) over a 6-week period. In addition to the main content pertaining to each treatment modality, both first-stage treatments (BT and Zol) included generic sleep hygiene education about the impact of stimulants, alcohol, caffeine, and exercise on sleep. Clinicians used treatment manuals and received ongoing supervision to standardize treatment administration. Participants' compliance with treatment (e.g., time spent in bed, use of medication) was monitored via sleep diaries and pill-count.

Treatment monitoring and treatment compliance. All therapy sessions were audiotaped for review by supervisors and study coordinators and for guiding therapists' supervision during the course of treatment. In addition, patients' compliance with treatment was monitored by pill counts performed by the treating physician at each consultation visit and by the medication intake reported on the daily sleep dairy (medication conditions) and by a percentage of compliance with behavioral homework assignments as rated by the therapists (BT and CT) and a computation of compliance with the sleep window derived from the sleep diary data (BT).

Data analytical plan. To identify the most effective treatment sequence while taking into account the nature of the SMART design (i.e., two distinct randomizations, where the second is conditional on the response to the first), the analytic strategy was based on Nahum-Shani and colleagues recommendations (2012).[18] Percentages of response/remission according to four treatment sequences and five times (post1 to FU12) were analyzed using a weighted generalized estimating equations model (WGEE).[19] Inverse probability weights were included in the WGEE and computed as the product of two sets of normalized weights: (1) those estimated from the *missing* model, to correct for attrition conditional on strata variables and first-stage

therapy, and (2) weights from the *randomization* model, to take into account that some patients were randomized twice (initial non-responders) while others only once (initial responders). Based on recommendations for clinical trials,[20] strata variables (site, age, gender, comorbidity status) and baseline ISI were included as covariates. A priori contrasts were used to test significance for means comparisons between and within sequences.

Sample size and detectable effect size. All sensitivity power analyses were computed following procedures outlined by Stroup[21] for mixed models and Dahmen et al.[22] for weighted GEE models and were based on a two-tailed 5 % alpha and 80 % power. Based on studies conducted by our group[9,23] and on recent reviews,[24] attrition rates of 10 % were used as attrition estimates in the computation of detectable differences.

Power computations for the hypotheses related to the primary outcome (remission rate) are reported here using the GEESIZE program.[22] For hypothesis 1a, our expected sample size of 224 (n = 200 at post-1 after attrition) will give a standard 80 % power to detect a difference of 17.7 % in sustained remission rates between BT and zolpidem after stage-1 therapies. For hypothesis 2a, the initial sample size of 224 (effective sample at Post 2 = 178 after taking into account attrition) will give a standard power to detect a increment of 9.9 % in remission rates between Post I and Post II assessments (all conditions confounded), assuming a working correlation of 0.70. For hypothesis 2b, the same sample after attrition, excluding patients who are already remitted (effective sample size = 90) will give a standard level of power to detect a difference of 18.3 % in remission rates at Post II between patients who switched treatments and those who did not. If remitted patients are included to increase power, sensitivity would also be increased, allowing the detection of a difference of 13.3 % or larger in remission rates between patients who switched treatments and those who did not.

Study Hypotheses.

Hypothesis 1a. The proportion of patients achieving remission with the first-stage therapy and sustain remission through follow-up will be higher among those receiving BT than among those receiving zolpidem.

Hypothesis 1b. A lower proportion of patients with insomnia and comorbid psychiatric disorders will achieve remission with first-stage therapies than will those without comorbid psychiatric disorders.

Hypothesis 1c. Secondary outcomes (sleep, fatigue, and mood) will show greater improvements through treatment and follow-up for those receiving BT than for those receiving zolpidem.

Hypothesis 2a. The insomnia remission rate after the second-stage treatment for all conditions combined will be 20 % higher than with first-stage treatment (that is, increment from 40 % to 60 %).

Hypothesis 2b. Of all patients who enter second-stage treatment, a greater proportion who switches modalities (from psychological to medication treatment, or vice versa) will achieve remission and sustain it through follow-up than will those staying within a treatment modality.

Hypothesis 2c. CMI patients who enter second-stage treatment will show a higher remission rate with treatments that target sleep and mood symptoms (CT and trazodone) than with treatments targeting primarily sleep (BT and zolpidem). This added therapeutic effect will be higher in patients with comorbid psychiatric disorders relative to those without.

Hypothesis 2d. Secondary outcomes will show response patterns consistent with Hypotheses 2a through 2c.

eResults

This paper reports about the primary endpoints defined by the ISI scores and secondary endpoints derived from the Sleep Diary data. Additional secondary endpoints about PSG measures of sleep and measures of daytime functioning, mood, fatigue and quality of life are reported in a separate paper.

Of the 337 potential study patients who underwent in-person screening across the two study sites (170 at Laval University and 167 at NJH), 211 (121 at Laval University and 90 at NJH) were randomized to one of the two first-stage treatment conditions: 107 were assigned to Zolpidem and 104 were assigned to behavioral therapy (BT). Insomnia remission was achieved by 24 participants who completed first-stage treatment with Zolpidem and 34 participants who completed first-stage BT. Forty-three patients (20.4%) did not complete first-stage therapy, with more patients (but not statistically significant) in the medication (18.7%) relative to BT condition (11.5%). The main reasons for discontinuing therapy were: (a) treatment (medication) not effective (n = 4), (b) medication side effects (n = 11), (c) time constraints too great (n = 4), (d) onset of new or worsening of pre-existing medical/psychological condition (n = 8), (e) initiating alternate treatment for insomnia (n = 1), or loss of interest/refusal of treatment (n = 15). Of the unremitted participants after stage-one therapy, 108 participants (54 of the 107 initially assigned to Zolpidem and 54 of 104 initially assigned to BT) accepted randomization to a second stage treatment, with 27 participants per condition. Of those, 30 (27.8%) did not complete second-stage treatment: BT+Zol = 10; BT+CT = 2; Zol+BT = 6; Zol+Tra=12). The main reasons for discontinuation during second-stage therapy were: (a) refusal of treatment (mostly medication) (n = 14), (b) onset of a new medical condition (n = 2), (c) initiated another treatment for insomnia (n = 2), and (d) lost to follow up (n = 5). AEs reported in association with zolpidem were all expected according to the product monograph (e.g., morning grogginess, daytime sleepiness, anxiety, dizziness, nausea, headache, fatigue, and heart palpitations).

The study aims were to evaluate the remission and responder rates of study participants to our first stage and second stage treatments and to examine the effect of psychiatric comorbidity on treatment outcome. As noted above, insomnia remission was determined by a participant achieving a score < 8 on the Insomnia Severity Index at each evaluation. An insomnia treatment response was defined by an ISI score decline $\geq$ 8 points relative to baseline ISI scores.

Treatment Compliance. Patients reported using Zolpidem on average three nights (2.98) per week when assigned to this condition during the first-stage therapy and 4.27 nights per week when this treatment was introduced as second stage therapy following BT. Trazodone was used on average 4.27 nights per week when patients were assigned to that treatment during the second stage therapy. Compliance with BT as rated by therapists was generally high during first (86.5%) or second stage therapy (84.6%), while compliance with CT was slightly lower (78.5%), although those ratings are not directly comparable given that somewhat different anchor points are used to rate adherence to BT and CT. Compliance with the recommended "sleep window" (+ or – 30 min.) during BT was very good to excellent during both first (5.3 nights/week) or second stage therapy (5.1 nights per week).

Adverse Events. Data derived from the SAFTEE measure during the first treatment phase revealed that a higher percentage of patients treated with BT reported daytime sleepiness relative to those treated with zolpidem (13% vs 4%). Conversely, a higher percentage of patients treated with zolpidem relative to those treated with BT reported cognitive problems involving attention, concentration or memory (16% vs 7.4%).

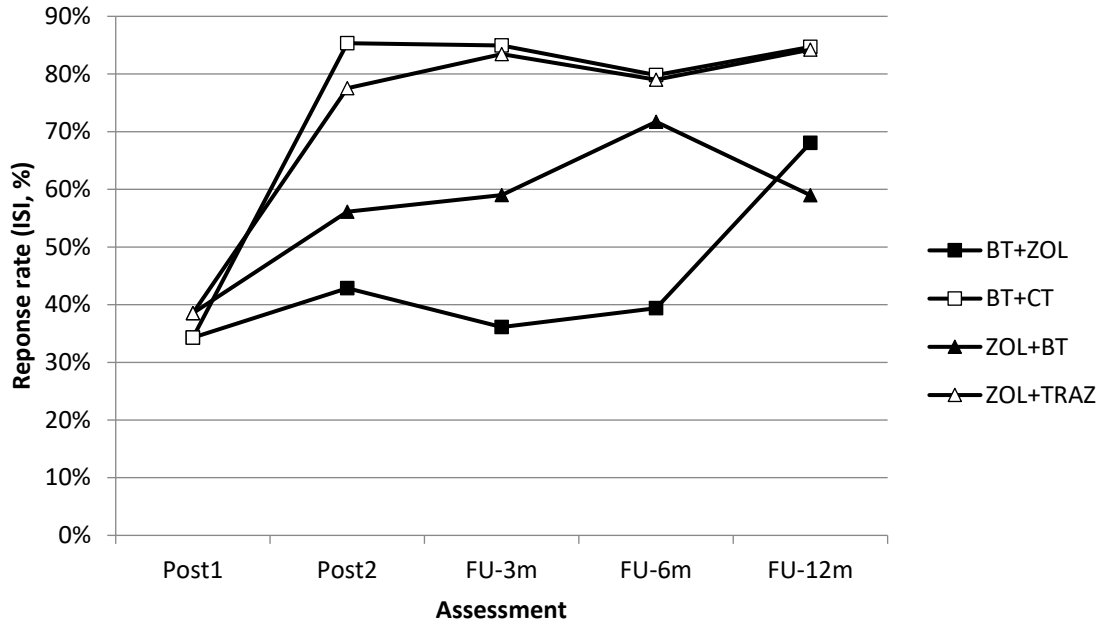eFigure. Response and remission rates among patients with comorbid psychiatric disorders

Figure 4a. *Response rates for patients **with** psychiatric comorbidity according to condition and assessment (standard errors ranged from 0.10 to 0.18).*
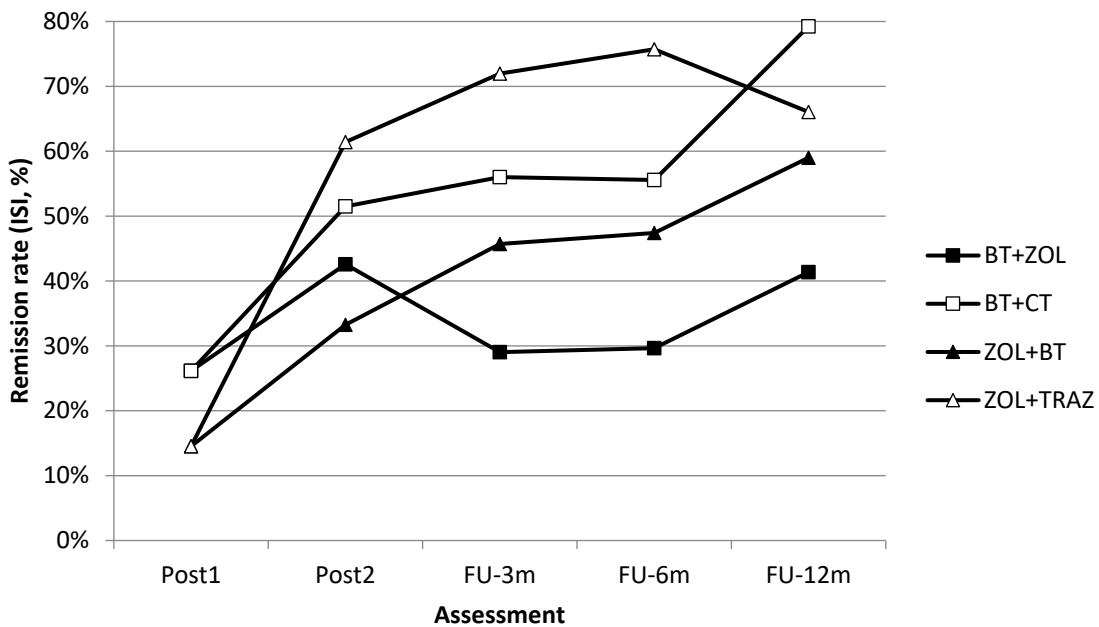

Figure 4b. *Remission rates for patients **with** psychiatric comorbidity according to condition and assessment (standard errors are 0.08 at post1 and ranged from 0.11 to 0.18 for later assessments).*

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