TABLE 2. Influence of individual traits and environmental factors on wife's sleep timing

Wife's sleep onset time	β	p
Age	0.112	0.511
Chronotype	0.209	**0.002**
Depressive mood	0.117	0.063
Shiftwork schedule	0.028	0.680
Husband's shiftwork schedule	−0.176	**0.008**
Husband's sleep onset time	0.179	**0.023**
Husband's wake time	0.111	0.160
Sharing bedroom	−0.029	0.647
Years living together	−0.015	0.929
Meal times a week together	0.020	0.777
$R = 0.413$; $F(10,214) = 4.404$; $p < 0.001$		

Wife's wake time	β	p
Age	−0.074	0.650
Chronotype	0.372	**<0.001**
Depressive mood	0.015	0.805
Shiftwork schedule	−0.001	0.991
Husband's shiftwork schedule	0.080	0.201
Husband's sleep onset time	0.076	0.305
Husband's wake time	0.173	**0.022**
Sharing bedroom	−0.001	0.990
Years living together	−0.023	0.887
Meal times a week together	0.181	**0.008**
$R = 0.503$; $F(10,214) = 7.248$; $p < 0.001$		

Note: Boldface = significance.

mainly associated with her chronotype and with her husband's sleep timing.

DISCUSSION

We found that sleep onset time, wake time, and midsleep time did correlate significantly, but not strongly, between husbands and wives who shared daily routines and housing. Furthermore, years living together showed no significant correlation with the differences in sleep timing between husband and wife. Multiple regression analysis showed that an individual's sleep timing was mainly influenced by chronotype. No significant correlation was found between the husband and wife's chronotype in this study. This is in contrast to other studies reporting a significant correlation, although the correlation is thought to be based on initial assortative mating rather than interaction during marriage (Hur et al., 1998; Randler & Kretz, 2011). Taken together, the results suggest that a couple's sleep timings do not synchronize the longer they live together, and thus the saying "Like husband, like wife" may not simply apply in the specific case of sleep habits.

Environmental factors (work schedule, spouse's sleep timing, lifestyle, etc.) have been reported to interfere with individual sleep-wake cycles (Leonhard & Randler, 2009; Meadows et al., 2009; Wittmann et al., 2006; Yamazaki et al., 2005). The data presented here also indicate that spouse's sleep timing, spouse's shiftwork schedule, and number of meals/wk eaten together influence the sleep timing. Notably, wife's SOT was associated with spouse's shiftwork schedule and SOT, although husband's SOT was not. The wife tended to go to bed earlier if her husband was a nightshift worker, and go to bed later if her husband went to bed later. Living together with a spouse appears to be a strong factor influencing women's sleep timing. Most couples sleep with a steady partner, and they report being less satisfied when sleeping alone (Troxel et al., 2007, 2010). It is likely that a husband and wife go to bed together (same timing) if they have a good marital relationship. Troxel et al. showed a bidirectional link between sleep and closeness of the couple's relationship (Hasler & Troxel, 2010; Troxel, 2010); couples with matched sleep-wake timing report a better relationship than those with unmatched sleep-wake timing. These findings imply that the association between sleep and relationship quality might explain the influence of "spouse" on an individual's sleep timing.

There are some limitations in this study. The survey was performed using self-rating questionnaires in a cross-sectional and retrospective design. The present results would have been strengthened if additional data had been collected using other tools, such as sleep logs or actigraphs, and if the study had been conducted in a prospective and longitudinal manner. Also, Leonhard and Randler (2009) have reported that children are a

strong factor influencing their mother's sleep timing; our data did not include information about children (number, age, sex, etc.). In addition, a major model for sleep regulation is a two-process model, where the two components of circadian drive and homeostatic drive interact with each other to regulate the sleep-wake cycle (Daan et al., 1984). As individual differences in nocturnal sleep pressure have some influence on the preferred timing of the sleep-wake cycles (Mongrain et al., 2006), data on homeostatic drive (slow-wave activity in non–rapid eye movement sleep, etc.) would have provided a better understanding of an individual's sleep timing.

CONCLUSION

The present findings demonstrate that chronotype is the major factor influencing an individual's sleep timing, followed by spouse's sleep timing, spouse's work schedule, or number of meals/wk eaten together. This study suggests that an individual's sleep timing is strongly associated with individual traits and chronotype, although environmental factors do significantly influence sleep onset and wake times. Our findings imply that recognizing an individual's chronotype may help promote better physical, emotional, and mental well-being by improving quality of life issues surrounding sleep.

ACKNOWLEDGMENTS

We thank Dr. Shin Yamazaki for his comments on the manuscript. This study was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, and Technology of Japan and from the Ministry of Health, Labour, and Welfare of Japan. This study was partly supported by a Grant-in-Aid for the Strategic Research Program for Brain Sciences from the Ministry of Education, Culture, Sports, Science and Technology of Japan (Understanding of molecular and environmental bases for brain health). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Declaration of Interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

Adan A, Natale V. (2002). Gender differences in morningness-eveningness preference. *Chronobiol. Int.* 19:709–720.

Åkerstedt T, Nordin M, Alfredsson L, Westerholm P, Kecklund G. (2010). Sleep and sleepiness: impact of entering and leaving shiftwork—a prospective study. *Chronobiol. Int.* 27:987–996.

Baehr EK, Revelle W, Eastman CI. (2000). Individual differences in the phase and amplitude of the human circadian temperature rhythm: with an emphasis on morningness-eveningness. *J. Sleep Res.* 9:117–127.

Barclay NL, Eley TC, Buysse DJ, Archer SN, Gregory AM. (2010). Diurnal preference and sleep quality: same genes? A study of young adult twins. *Chronobiol. Int.* 27:297–317.

Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 28:193–213.

Carskadon MA, Wolfson AR, Acebo C, Tzischinsky O, Seifer R. (1998). Adolescent sleep patterns, circadian timing, and sleepiness at a transition to early school days. *Sleep* 21:871–881.

Daan S, Beersma DG, Borbely AA. (1984). Timing of human sleep: recovery process gated by a circadian pacemaker. *Am. J. Physiol.* 246:R161–R183.

Duffy JF, Dijk DJ, Hall EF, Czeisler CA. (1999). Relationship of endogenous circadian melatonin and temperature rhythms to self-reported preference for morning or evening activity in young and older people. *J. Invest. Med.* 47:141–150.

Foster RG, Roenneberg T. (2008). Human responses to the geophysical daily, annual and lunar cycles. *Curr. Biol.* 18:R784–R794.

Gachon F, Nagoshi E, Brown SA, Ripperger J, Schibler U. (2004). The mammalian circadian timing system: from gene expression to physiology. *Chromosoma* 113:103–112.

Hasler BP, Troxel WM. (2010). Couples' nighttime sleep efficiency and concordance: evidence for bidirectional associations with daytime relationship functioning. *Psychosom. Med.* 72:794–801.

Horne JA, Östberg O. (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int. J. Chronobiol.* 4:97–110.

Hur Y-M, Bouchard TJ, Lykken DT. (1998). Genetic and environmental influence on morningness-eveningness. *Pers. Individ. Diff.* 25:917–925.

Ishihara K, Saitoh T, Inoue Y, Miyata Y. (1984). Validity of the Japanese version of the Morningness-Eveningness Questionnaire. *Percept. Mot. Skills* 59:863–866.

Kerkhof GA. (1998). The 24-hour variation of mood differs between morning- and evening-type individuals. *Percept. Mot. Skills* 86:264–266.

Kitamura S, Hida A, Watanabe M, Enomoto M, Aritake-Okada S, Moriguchi Y, Kamei Y, Mishima K. (2010). Evening preference is related to the incidence of depressive states independent of sleep-wake conditions. *Chronobiol. Int.* 27:1797–1812.

Leonhard C, Randler C. (2009). In sync with the family: children and partners influence the sleep-wake circadian rhythm and social habits of women. *Chronobiol. Int.* 26:510–525.

Martinez-Nicolas A, Ortiz-Tudela E, Madrid JA, Rol MA. (2011). Crosstalk between light and internal time in humans. *Chronobiol. Int.* 28:617–629.

Meadows R, Arber S, Venn S, Hislop J, Stanley N. (2009). Exploring the interdependence of couples' rest-wake cycles: an actigraphic study. *Chronobiol. Int.* 26:80–92.

Mongrain V, Carrier J, Dumont M. (2006). Circadian and homeostatic sleep regulation in morningness-eveningness. *J. Sleep Res.* 15:162–166.

Pittendrigh CS, Daan S. (1974). Circadian oscillations in rodents: a systematic increase of their frequency with age. *Science* 186:548–550.

Portaluppi F, Smolensky MH, Touitou Y. (2010). Ethics and methods for biological rhythm research on animals and human beings. *Chronobiol. Int.* 27:1911–1929.

Radloff LS. (1977). The CES-D scale: a self report depression scale for research in the general population. *Appl. Psychol. Meas.* 1:385–401.

Randler C. (2008). Morningness-eveningness comparison in adolescents from different countries around the world. *Chronobiol. Int.* 25:1017–1028.

Randler C, Kretz S. (2011). Assortative mating in morningness-eveningness. *Int. J. Psychol.* 46:91–96.

Roenneberg T. (2004). The decline in human seasonality. *J. Biol. Rhythms* 19:193–195; discussion 196–197.

Roenneberg T, Wirz-Justice A, Merrow M. (2003). Life between clocks: daily temporal patterns of human chronotypes. *J. Biol. Rhythms* 18:80–90.

Roenneberg T, Kuehnle T, Pramstaller PP, Ricken J, Havel M, Guth A, Merrow M. (2004). A marker for the end of adolescence. *Curr. Biol.* 14:R1038–R1039.

Roenneberg T, Kumar CJ, Merrow M. (2007). The human circadian clock entrains to sun time. *Curr. Biol.* 17:R44–R45.

Takahashi JS, Hong HK, Ko CH, McDearmon EL. (2008). The genetics of mammalian circadian order and disorder: implications for physiology and disease. *Nat. Rev. Genet.* 9:764–775.

Troxel WM. (2010). It's more than sex: exploring the dyadic nature of sleep and implications for health. *Psychosom. Med.* 72:578–586.

Troxel WM, Robles TF, Hall M, Buysse DJ. (2007). Marital quality and the marital bed: examining the covariation between relationship quality and sleep. *Sleep Med. Rev.* 11:389–404.

Troxel WM, Buysse DJ, Matthews KA, Kravitz HM, Bromberger JT, Sowers M, Hall MH. (2010). Marital/cohabitation status and history in relation to sleep in midlife women. *Sleep* 33:973–981.

Tzischinsky O, Shochat T. (2011). Eveningness, sleep patterns, daytime functioning, and quality of life in Israeli adolescents. *Chronobiol. Int.* 28:338–343.

Wittmann M, Dinich J, Merrow M, Roenneberg T. (2006). Social jetlag: misalignment of biological and social time. *Chronobiol. Int.* 23:497–509.

Yamazaki A, Lee KA, Kennedy HP, Weiss SA. (2005). Parent chronotypes and sleeping and crying/fussing in 4–5 week infants. *Sleep Biol. Rhythms* 3:158–161.

Brief Behavioral Therapy for Refractory Insomnia in Residual Depression: An Assessor-Blind, Randomized Controlled Trial

Norio Watanabe, MD, PhD; Toshi A. Furukawa, MD, PhD; Shinji Shimodera, MD, PhD; Ippei Morokuma, MD; Fujika Katsuki, RN, PhD; Hirokazu Fujita, MD, PhD; Megumi Sasaki, PhD; Chihiro Kawamura, BA; and Michael L. Perlis, PhD

Objective: Insomnia often persists despite pharmacotherapy in depression and represents an obstacle to its full remission. This study aimed to investigate the added value of brief behavioral therapy for insomnia over treatment as usual (TAU) for residual depression and refractory insomnia.

Method: Thirty-seven outpatients (mean age of 50.5 years) were randomly assigned to TAU alone or TAU plus brief behavioral therapy for insomnia, consisting of 4 weekly 1-hour individual sessions. The Insomnia Severity Index (ISI) scores (primary outcome), sleep parameters, and GRID-Hamilton Depression Rating Scale (GRID-HAMD) scores were assessed by blind raters and remission rates for both insomnia and depression were collected at 4- and 8-week follow-ups. The patients were recruited from February 18, 2008, to April 9, 2009.

Results: Brief behavioral therapy for insomnia plus TAU resulted in significantly lower ISI scores than TAU alone at 8 weeks ($P<.0005$). The sleep efficiency for the combination was also significantly better than that for TAU alone ($P=.015$). Significant differences were observed in favor of the combination group on both the total GRID-HAMD scores ($P=.013$) and the GRID-HAMD scores after removing the 3 sleep items ($P=.008$). The combination treatment produced higher rates of remission than TAU alone, both in terms of insomnia (50% vs 0%), with a number needed to treat (NNT) of 2 (95% CI, 1–4), and in terms of depression (50% vs 6%), with an NNT of 2 (95% CI, 1–5).

Conclusions: In patients with residual depression and treatment refractory insomnia, adding brief behavioral therapy for insomnia to usual clinical care produced statistically significant and clinically substantive added benefits.

Trial Registration: clinicaltrials.gov Identifier: NCT00610259

J Clin Psychiatry

Submitted: *March 21, 2010; accepted June 14, 2010.*
Online ahead of print: *March 8, 2011 (doi:10.4088/JCP.10m06130gry).*
Corresponding author: *Norio Watanabe, MD, PhD, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601 Japan (noriow@med.nagoya-cu.ac.jp).*

Insomnia occurs in 80%–90% of patients with untreated major depression.[1–3] Insomnia concurrent with depression not only is a major source of subjective distress but also most likely interacts with other depressive symptoms so as to confer greater illness severity.[4–6] Further, insomnia not only is the most likely symptom to persist following treatment[2,7] but also may constitute an obstacle for patients to achieve full remission and recovery,[8–10] and its persistence may serve as a risk factor for relapse.[11] Thus, insomnia is no longer considered a simple accompanying symptom of depression but is regarded as a comorbid disorder. Given this shift in perspective, it follows that it may be useful to provide targeted treatment for the insomnia that occurs in the context of depression.

To date, there have been two trials that evaluate how insomnia treatment can be combined with traditional antidepressant therapies: one with pharmacotherapy[12] and one with cognitive-behavioral therapy for insomnia.[13] A multicenter randomized controlled trial (RCT)[12] has found that adding a hypnotic to antidepressant treatment led to improvement in both sleep and depression. However, 50% and 58% of patients treated with the combination therapy were still nonremitters in terms of insomnia and depression, respectively, at the end of the trial. The cognitive-behavioral therapy for insomnia is based on a multicomponent approach that includes several modules,[14] including sleep hygiene education, sleep restriction, and stimulus control as first-line interventions and cognitive therapy, relaxation training, and sleep compression as adjunctive ones.[15] For primary insomnia, the efficacy of cognitive-behavioral therapy for insomnia has been well established.[16,17] For comorbid insomnia in depression, there has been only one trial[13] of cognitive-behavioral therapy for insomnia, which investigated the efficacy of adding 7-session individual cognitive-behavioral therapy for insomnia to antidepressant pharmacotherapy in acute phase treatment. The combination therapy achieved remission rates of 50% for insomnia and 62% for depression.

Neither of these two trials, however, included patients with depression and insomnia refractory to adequate pharmacotherapy.[12,13] Thus, effective treatment is needed for insomnia in depression, especially one that persists after adequate pharmacotherapy. In the present study, we aimed to develop a brief behavioral therapy for insomnia by focusing on core components of cognitive-behavioral therapy for insomnia and to conduct an RCT to examine its effectiveness when added to treatment as usual (TAU), in comparison with TAU alone, for residual depression with refractory insomnia.

METHOD

Participants

Patients were recruited from February 18, 2008, to April 9, 2009, at 3 psychiatric outpatient departments in Japan.

We aimed to include patients with currently partially remitted, mild, or moderate depression, who presented with

significant insomnia, despite adequate pharmacologic treatment. Inclusion criteria were outpatients who (1) had *DSM-IV* major depressive disorder, as diagnosed by the Structured Clinical Interview for *DSM-IV* (SCID)[18]; (2) were aged between 20 and 70 years; (3) for the index episode, had already been on maximum doses of 2 types of antidepressants for at least 4 weeks each (depression is usually regarded resistant or refractory when at least 2 trials with antidepressants from different pharmacologic classes fail to produce a significant clinical improvement[19]); (4) had a score of 2 on at least 1 of the 3 sleep items of the GRID-Hamilton Depression Rating Scale (GRID-HAMD),[20] which has explicit anchor points for each assessment item and has excellent interrater validity among even untrained raters[21]; (5) had a score of 8 or more on the Insomnia Severity Index (ISI),[14,22,23] which is now considered a standard measure of the global severity of insomnia and is used in many studies[12,13,24] (the total score of 8–14 indicates subthreshold insomnia and 15–28, clinical insomnia); and (6) had a score between 8 and 23 on the 17-item GRID-HAMD, representing current subthreshold to moderate depression.[25]

Exclusion criteria were (1) mental or physical status requiring hospitalization; (2) serious suicidal risk; (3) having had or currently receiving any structured psychotherapy; (4) current diagnosis of primary anxiety or personality disorder, substance abuse or dependence, or psychosis; a history of schizophrenia or bipolar disorder; or significant medical problems; (5) duration of depression shorter than 2 months; (6) insomnia possibly being due to sleep apnea or periodic limb movements during sleep. Possible sleep apnea was assessed by using the Berlin Questionnaire[26]; (7) engaging in work involving night-shift; and (8) patients currently taking methylphenidate or modafinil. Any other psychotropic medications, including antidepressants and hypnotics, and prescriptions for medical conditions were allowed.

Study Design

Assessor-blind, individually randomized, parallel-group trial design was employed. An independent statistician generated the random allocation sequences by the computer, using variable blocks and stratified by the severity of depression (the total GRID-HAMD score of 14 or more, or less than 14) and by study sites. Allocation sequences were kept centrally, and the allocation was provided by facsimile to each site upon notification of a patient's enrollment.

Participants were randomized to brief behavioral therapy for insomnia plus TAU or TAU alone. Neither patients nor physicians of TAU were blind to allocation. However, all patients were requested not to reveal their allocated treatment to the assessors for the GRID-HAMD. After each assessment, an assessor guessed which group the patient had been assigned to, making it possible to examine if the blinding was successful.

Assessment Measures

Patients were assessed at baseline and at 4 and 8 weeks. Patients who dropped out of the intervention were asked to complete the assessments.

The primary outcome was the total ISI score at 8 weeks. The secondary outcomes were the total 17-item GRID-HAMD score and the 14-item GRID-HAMD score (excluding the 3 sleep items) at 4 and 8 weeks. The interrater reliability of the GRID-HAMD was calculated by audiotaping assessment sessions and having another rater assess the recordings independently. The secondary outcomes for sleep included the ISI score at 4 weeks and the Pittsburgh Sleep Quality Index (PSQI)[27,28] score, the sum of the 3 sleep items on the GRID-HAMD, and sleep parameters, such as sleep efficiency, total sleep time, sleep onset latency, time wake after sleep onset, collected through the PSQI, at 4 and 8 weeks. These sleep parameters are thought to enable quantification of the presenting sleep complaint.[14] Sleep diaries were employed only in the intervention arm as one of the active treatment components and thus not used to collect sleep parameters.

Dichotomous outcomes were also considered. Patients were considered as remitters for insomnia if their ISI score was less than 8[24] and as remitters for depression if their 17-item GRID-HAMD score was less than 8.[25] If any unfavorable event (ie, suicidal attempt, death, hospital admission) occurred during the study period, it was reported. All antidepressant and hypnotic dosages were converted into defined daily dose[29] and summed.

Sample Size

Sample size was based on a power analysis conducted for the ISI scores. Effect sizes were estimated from previous studies on insomnia in depression (a Cohen *d* of 0.95 on the ISI total scores at posttreatment between the combined escitalopram plus cognitive-behavioral therapy for insomnia arm and the escitalopram plus pseudodesensitization arm[30] and a Cohen *d* of 1.81 in sleep efficiency pre– to post–cognitive-behavioral therapy for insomnia[31]) and from brief behavioral therapy for insomnia pilot data from our group acquired prior to this study (the mean change in the ISI scores pretreatment to posttreatment was 6.75 in 4 patients). The mean ± SD change in the ISI scores pretreatment to posttreatment was estimated to be 6 ± 3 for the brief behavioral therapy for insomnia plus TAU group and 2 ± 3 for the TAU group. With 0.9 power to detect a significant difference at $P = .05$ (2-sided), it was calculated that 12 patients would be required for each arm. Thus, allowing for a 30% dropout rate, 18 participants would need to be recruited per group.

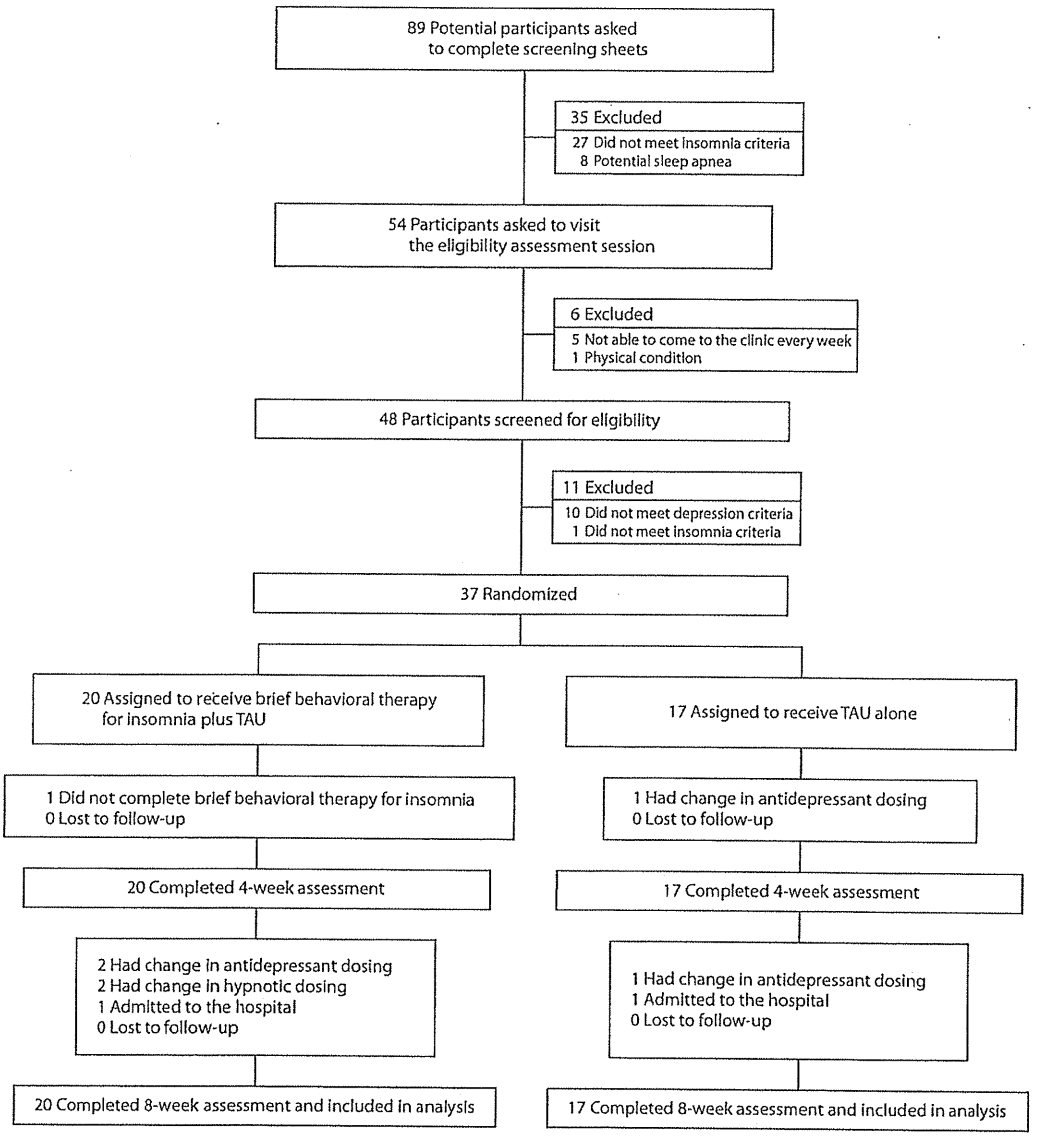
Trial Interventions

The treatment regimen for the present study was developed and highly structured based on a published treatment manual for cognitive-behavioral therapy for insomnia[15] and was provided to therapists as a written manual. The program consisted of 4 weekly individual sessions, each lasting approximately 50 minutes (Table 1). The number of the sessions, while fewer than traditional cognitive-behavioral therapy for insomnia[15] and those in the previous studies,[13,24] is nevertheless in keeping with (1) the finding that 4 sessions may constitute the optimal dose for cognitive-behavioral therapy for insomnia[32] and (2) recent studies showing the

Table 1. Overview of Principles in Treatment Sessions in the Brief Behavioral Therapy for Insomnia Condition

Session	Module	Description
1	Sleep diary	The aim is to increase patients' awareness of their own maladaptive sleep habits, thus paving the way for the correction of these habits. In addition, the sleep diary allows both the patient and the clinician to gather the data needed to measure and guide treatment
	Sleep hygiene education	The patient learns about the impact of lifestyle habits, such as exercise; diet and alcohol use; and the influence of environmental factors, such as light, noise, and temperature in the bedroom
2	Introduction of the behavioral model of insomnia	Discussion of predisposing, precipitating, and perpetuating factors of patient's insomnia. Presenting the perspective to the patient so that he or she understands why the interventions may benefit, which is thus likely to enhance adherence
	Sleep restriction	Involves a strict schedule of bed times and rising times, restricting patients' allowed time in bed to the actual sleeping time according to the patients' sleep diary; the aim is to increase homeostatic sleep drive through partial sleep deprivation
	Stimulus control	The aim is to break associations between the sleep environment and wakefulness by teaching the participant not to engage in bedroom activities incompatible with sleep and to stay in bed only when asleep or sleepy
3	Sleep titration	The objective is to assess treatment gains and compliance and to make adjustments to the patient's sleep schedule according to a weekly average sleep efficiency
4	Sleep titration	Same as above
	Relapse prevention	Involves a review of how insomnia started and how it maintained over time. Afterward, discussion about the approach to maintaining clinical gains in the long run and what to do when insomnia recurs

Figure 1. Participant Flow Diagram



Abbreviation: TAU = treatment as usual.

Table 2. Sociodemographic and Clinical Characteristics of Participants

Characteristic	Brief Behavioral Therapy for Insomnia+TAU (n=20)	TAU Alone (n=17)	All Participants (N=37)
Age, mean (SD), y	52.9 (11.6)	47.8 (10.1)	50.5 (11.1)
Sex, n (%)			
Female	15 (75.0)	8 (47.1)	23 (62.2)
Male	5 (25.0)	9 (52.9)	14 (37.8)
Education, n (%)			
<High school	3 (15.0)	0 (0.0)	3 (8.1)
High school diploma	12 (60.0)	9 (52.9)	21 (56.8)
Some college or university	5 (25.0)	7 (41.2)	12 (32.4)
Postgraduate degree	0 (0.0)	1 (5.9)	1 (2.7)
Occupation, n (%)			
Employed, full time	3 (15.0)	6 (35.3)	9 (24.3)
Employed, part time	3 (15.0)	3 (17.6)	6 (16.2)
Homemaker	11 (55.0)	5 (29.4)	16 (43.2)
Unemployed	3 (15.0)	3 (17.6)	6 (16.2)
Marital status, n (%)			
Married	15 (75.0)	8 (47.1)	23 (62.2)
Divorced or widowed	3 (15.0)	5 (29.4)	8 (21.6)
Single	2 (10.0)	4 (23.5)	6 (16.2)
Duration of index episode, mean (SD), mo	21.3 (16.9)	30.4 (45.7)	25.5 (33.2)
Duration of treatment for index episode, mean (SD), mo	18.1 (11.1)	27.8 (46.5)	22.5 (32.4)
No. of depressive episodes, mean (SD)	2.0 (1.0)	1.5 (0.7)	1.8 (0.9)
Habitual alcohol intake, n (%)	1 (5.0)	2 (11.8)	3 (8.1)
Total antidepressant usage, mean (SD), DDD	1.7 (0.9)	1.5 (0.9)	1.6 (0.9)
TCA usage, mean (SD), DDD	0.1 (0.4)	0.1 (0.2)	0.1 (0.3)
SSRI usage, mean (SD), DDD	1.0 (0.8)	0.9 (1.1)	0.9 (0.9)
SNRI usage, mean (SD), DDD	0.3 (0.8)	0.1 (0.1)	0.2 (0.6)
Other usage, mean (SD), DDD	0.2 (0.1)	0.4 (0.5)	0.3 (0.4)
Hypnotic usage, mean (SD), DDD	0.7 (0.9)	1.1 (0.7)	0.9 (0.8)
Insomnia Severity Index score, mean (SD)	15.3 (4.7)	17.4 (3.3)	16.3 (4.2)
Pittsburgh Sleep Questionnaire Index score, mean (SD)	12.5 (2.8)	13.8 (3.0)	13.1 (2.9)
Subjective sleep parameters, mean (SD)			
Sleep efficiency, mean (SD), %	66.4 (14.3)	67.7 (14.0)	67.0 (14.0)
Total sleep time, min	312.0 (111.1)	283.5 (66.5)	298.9 (93.2)
Sleep onset latency, min	55.8 (50.8)	58.3 (54.4)	56.9 (51.7)
Wake after sleep onset, min	104.0 (85.8)	88.2 (79.3)	96.7 (82.1)
Hamilton Depression Rating Scale score, mean (SD)			
Total (17 items)	15.0 (3.6)	16.8 (4.2)	15.8 (3.9)
3 Sleep items	3.8 (1.4)	4.2 (1.4)	4.0 (1.4)
Without sleep items (14 items)	11.2 (3.7)	12.3 (3.5)	11.9 (3.6)

Abbreviations: DDD = defined daily dose, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TAU = treatment as usual, TCA = tricyclic antidepressant.

effectiveness of brief behavioral therapy for primary insomnia.[33,34] Patients allocated to brief behavioral therapy for insomnia were asked to self-administer these skills after the termination of the intervention sessions at 4 weeks until the final assessment at 8 weeks.

Therapists for brief behavioral therapy for insomnia were 5 psychiatrists and a psychiatric nurse. All therapists had 3 or more years of clinical experience in psychiatry; however, all but one psychiatrist had not received formal cognitive-behavioral therapy training. They participated in a 2-day intensive training course on brief behavioral therapy for insomnia before the study commencement and received ongoing supervision monthly thereafter.

Treatment as usual involved having patients meet with their physician (psychiatrist) biweekly during which time they discussed their depression symptoms and obtained medication. Each session typically lasted 10 minutes. Physicians empathetically listened to patients' distress during the sessions, but changing types and doses of medication was not allowed in the first 4 weeks of the study unless rapid exacerbation of depression occurred. Physicians were allowed to discuss sleep hygiene as defined in the handout prepared for the study, but they were not permitted to discuss sleep restriction and stimulus control for insomnia.

For the assessment of integrity of both brief behavioral therapy for insomnia and TAU sessions, all sessions were audiotaped and 20% of each condition were randomly selected and evaluated by 2 independent researchers for adherence to the treatment manual or to the TAU materials.

Data Management and Analysis

Descriptive and inferential statistics were computed using SPSS for Windows 16.0.[35] All analyses were based on the intent-to-treat model. When there were no missing data, analysis of covariance was used to test group effects while controlling for the baseline scores. When missing data were observed, linear mixed models[36] were used for continuous variables, and dropouts were assumed nonremitters for dichotomous variables. A P value $< .05$ was set to test the null hypothesis. For dichotomous variables, risk ratios and their 95% confidence intervals (CIs) were calculated. A number needed to treat (NNT) was calculated when a 95% CI of risk ratio did not include 1.0.

No statistical tests were planned to detect a difference at baseline between the 2 arms because we aimed to avoid multiple tests, and the decision to adjust for baseline data in RCTs should not be determined by whether baseline differences are statistically significant.[37] However, when clinically important differences at baseline were noted from a clinician's point of view, a sensitivity analysis was performed by adjusting for all such possible confounds.

The protocol was approved by the ethics committees of all the recruiting centers. Written informed consent was obtained from all participants. The study is registered at clinicaltrials.gov (identifier: NCT00610259).

RESULTS

Enrollment and Baseline Characteristics of the Participants

Eighty-nine patients were screened and 37 patients satisfied the eligibility criteria, with 20 participants randomly assigned to receive the brief behavioral therapy for insomnia plus TAU therapy and 17 to the TAU therapy alone (Figure 1). Table 2 summarizes the sociodemographic and clinical

Table 3. Adjusted Results[a] for Sleep, Depression, and Medication Usage at 4 and 8 Weeks

Measure	4 Weeks				8 Weeks			
	Brief Behavioral Therapy for Insomnia + TAU	TAU Alone	$F_{1,34}$	*P* Value	Brief Behavioral Therapy for Insomnia + TAU	TAU Alone	$F_{1,34}$	*P* Value
Questionnaire, mean (SE)								
Insomnia Severity Index score	10.6 (1.1)	15.9 (1.2)	7.19	.01	9.2 (1.1)	15.9 (1.2)	15.38	<.0005
Pittsburgh Sleep Questionnaire Index score	8.6 (0.9)	12.9 (1.0)	9.78	.004	8.4 (0.8)	12.5 (0.9)	10.36	.003
HDRS sleep items score	2.0 (0.5)	3.6 (0.5)	5.66	.023	2.1 (0.4)	3.3 (0.5)	3.31	.078
Subjective sleep parameter								
Sleep efficiency, mean (SE), %	83.1 (3.3)	67.5 (3.6)	10.43	.003	84.5 (4.0)	69.3 (4.4)	6.60	.015
Total sleep time, mean (SE), min	357.7 (16.6)	300.7 (18.0)	5.36	.027	362.8 (21.3)	309.9 (23.1)	2.81	.103
Sleep onset latency, mean (SE), min	26.9 (8.2)	59.3 (8.9)	7.16	.011	48.9 (23.1)	75.9 (25.0)	0.63	.432
Wake after sleep onset, mean (SE), min	38.3 (14.4)	89.3 (15.6)	5.74	.022	43.6 (12.9)	59.7 (14.0)	0.71	.404
GRID-HAMD score, mean (SE)								
Total score (17 items)	9.9 (1.7)	17.8 (1.9)	9.35	.004	11.3 (1.8)	18.4 (2.0)	6.81	.013
Without sleep items (14 items)	7.6 (1.5)	14.5 (1.7)	8.96	.005	9.0 (1.5)	15.4 (1.7)	7.83	.008
Medication, mean (SE), DDD								
Antidepressants	1.6 (0.0)	1.6 (0.0)	1.14	.293	1.6 (0.1)	1.6 (0.1)	0.46	.503
Hypnotics	0.9 (0.0)	0.9 (0.0)	NA	NA	0.9 (0.1)	0.9 (0.1)	0.00	.979

[a]Each analysis is adjusted for its baseline score.
Abbreviations: DDD = defined daily dose, GRID-HAMD = GRID-Hamilton Depression Rating Scale, NA = not applicable, TAU = treatment as usual.

parameters at baseline. All patients were Japanese adults and took antidepressant medications at baseline, with a defined daily dose range between 0.5 and 4.17. Possible clinically significant differences were found in sex, education, occupation, marital status, duration of index episode, duration of treatment for index episode, and hypnotic usage at baseline.

Attrition and Study Integrity

Attrition. Two participants did not complete the brief behavioral therapy for insomnia plus TAU condition, and 1 subject did not complete the TAU condition. In the brief behavioral therapy for insomnia plus TAU group, 1 patient discontinued brief behavioral therapy for insomnia after reporting that it was too difficult to comply with the prescribed sleep schedule. Beyond this reason, 1 subject in the brief behavioral therapy for insomnia plus TAU condition and 1 subject in the TAU group were admitted to hospital due to exacerbation of depression. All 3 participants nevertheless completed all the study assessments (Figure 1).

Medication. Antidepressant dosage was changed for 2 participants each in the 2 groups. Hypnotic dosage was changed for 2 participants in the combination group and for none of the participants in the TAU alone group. No between-group differences in defined daily doses of either drug were found for either class of medications (Table 3).

Treatment integrity. Sixteen randomly selected brief behavioral therapy for insomnia sessions were checked for adherence. Overall, 78.4% of the quality checkpoints had been fulfilled by the therapists. With regard to TAU, the researchers checking for adherence suspected that 2 of 30 sessions (6.7%) went beyond the sleep hygiene handout and used some techniques included in brief behavioral therapy for insomnia.

Assessment integrity. Nine assessors were employed for administering the GRID-HAMD. Twenty randomly selected recorded assessments were used to examine interrater reliability. Single-measure intraclass correlation coefficients between the 2 raters were 0.92 (95% CI, 0.81–0.97).

Integrity of the blind assessors. κ Values for agreement between the actual allocation and the allocation guessed by a blind assessor at each assessment were 0.41 (95% CI, 0.13–0.69) at 8 weeks and 0.15 (95% CI, 0.00–0.45) at 4 weeks. This indicated that the blinding of the assessors was satisfactory.

Insomnia Severity

Relative to TAU alone, treatment with combined brief behavioral therapy for insomnia and TAU therapy resulted in significantly lower ISI total scores at 8 weeks ($P<.0005$), with a mean (SE) score of 9.2 (1.1) in the combination and 15.9 (1.2) in the TAU alone, after adjusting for the baseline scores (Table 3). In a sensitivity analysis adjusting for other possibly clinical confounds at baseline, the ISI score at 8 weeks was still significantly in favor of the combination therapy ($P=.036$, data available upon request).

Significant superiority in favor of the combination group was also observed in the adjusted ISI score at 4 weeks ($P=.01$). Total PSQI scores and the sleep efficiency for the combined brief behavioral therapy for insomnia plus TAU group were significantly better than those for the TAU alone at both 8 and 4 weeks (Table 3).

Depression Severity

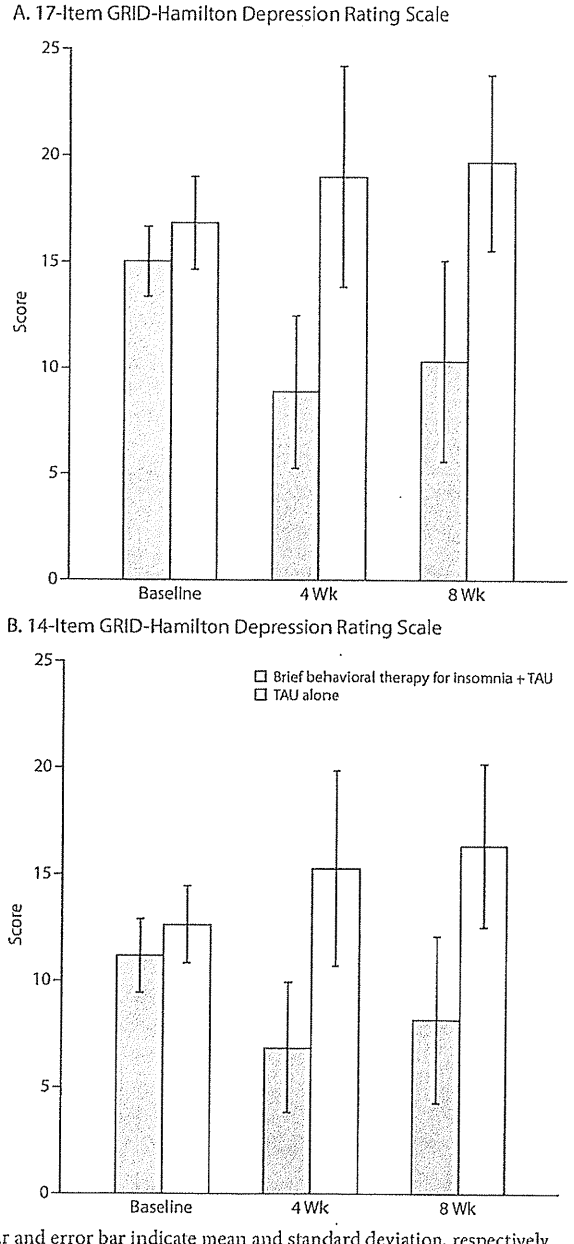
For the total 17-item GRID-HAMD scores, significant differences were observed in favor of the combined brief behavioral therapy for insomnia plus TAU group both at 8 weeks ($P=.013$) and at 4 weeks ($P=.004$) (Table 3, Figure 2).

After removing the 3 sleep items, significant differences were observed in favor of the combination therapy group both at 8 weeks ($P=.008$) and at 4 weeks ($P=.005$) (Table 3).

Remission of Insomnia and Depression

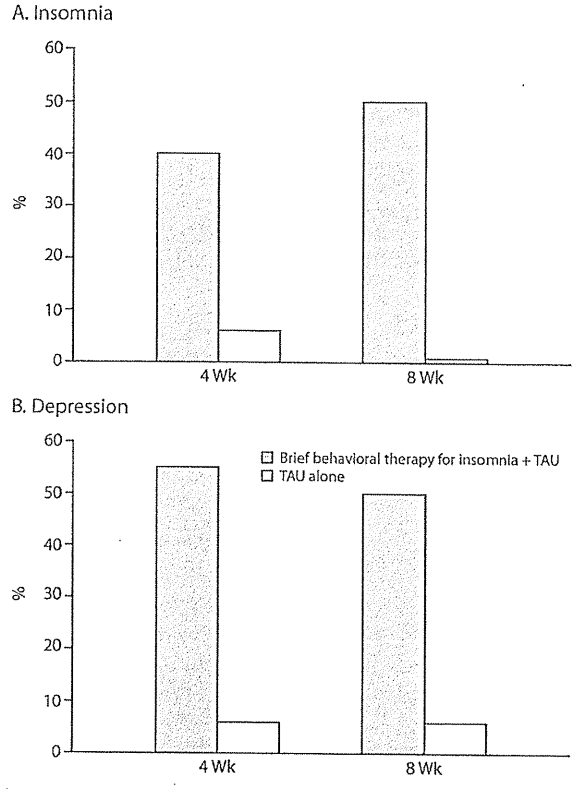
At 8 weeks, 10 participants (50.0%) in the combination group and 0 (0.0%) in the TAU alone group achieved remission in terms of insomnia, resulting in an NNT of 2 (95%

Figure 2. 17-Item and 14-Item (removing 3 sleep items) GRID-Hamilton Depression Rating Scale Scores at Baseline and at 4- and 8-Week Follow-Ups[a]



[a]Bar and error bar indicate mean and standard deviation, respectively.
Abbreviation: TAU = treatment as usual.

Figure 3. Proportions of Treatment Remitters in Terms of Insomnia and Depression at 4- and 8-Week Follow-Ups



Abbreviation: TAU = treatment as usual.

CI, 1–4) (Figure 3). Ten (50.0%) in the combination group and 1 (5.9%) in the TAU alone group achieved remission in terms of depression, resulting in a risk ratio of 8.50 (95% CI, 1.21–59.8), and an NNT of 2 (95% CI, 1–5).

At 4 weeks, 8 participants (40.0%) in the combination group and 1 participant (5.9%) in the TAU alone group achieved remission in terms of insomnia, resulting in a risk ratio of 6.80 (95% CI, 0.94–49.0). Eleven participants (55.0%) in the combination group and 1 participant (5.9%) in the TAU alone group achieved remission in terms of depression, resulting in a risk ratio of 9.35 (95% CI, 1.34–65.22) and an NNT of 2 (95% CI, 1–4).

DISCUSSION

This study represents the first randomized trial examining the use of psychotherapy for insomnia in conjunction with usual care in the treatment of residual depression and refractory insomnia despite adequate pharmacotherapy. For the primary outcome of insomnia, adding brief behavioral therapy for insomnia to TAU produced significantly greater reduction in insomnia than TAU alone. Remission in insomnia was achieved by 50% of patients treated with the combined therapy, while none of those treated with TAU alone did so (NNT = 2). Moreover, in terms of depression, greater improvement in the severity of depression was observed for patients treated with the combined therapy in comparison with TAU alone, even after removing the 3 sleep items. At 8 weeks, remission from refractory major depression was achieved among 50% of those treated with added behavior therapy, while it was achieved in only 6% of those treated with TAU alone (NNT = 2).

Manber and colleagues'[13] recent trial of adding cognitive-behavioral therapy for insomnia to escitalopram in the acute phase treatment of major depression may suggest that cognitive-behavioral therapy for insomnia can be employed as part of the first-line treatment. However, availability of cognitive-behavioral therapy is universally limited for many reasons, including shortage of trained clinicians and associated costs.[38] In practice, combined hypnotic and

antidepressant therapy might be broadly selected as the first-line treatment rather than combined psychotherapy plus antidepressant treatment.[12]

On the other hand, our findings suggest that residual depression comorbid with insomnia may be effectively targeted by adding psychotherapy for insomnia that is less intensive than the standard cognitive-behavioral therapy for insomnia, that can be administered by less experienced clinicians, and that may therefore be feasible in routine clinical settings. The observed effect size (Cohen *d*) for the 17-item GRID-HAMD score was 1.01 (95% CI, 0.30–1.67) at 8 weeks. This figure is appreciably greater than that of 0.32 (95% CI, 0.11–0.53), recently reported in the meta-analysis of combining full package cognitive-behavioral therapy for depression with pharmacotherapy over pharmacotherapy alone.[39] Reserving brief behavioral therapy for insomnia for the patient population that exhibits greater morbidity, instead of administering full-package cognitive-behavioral therapy for depression or cognitive-behavioral therapy for insomnia as a part of the first-line treatment, may have the apparent practical advantage of matching the limited supply of knowledgeable practitioners to those most in need.

Although the present findings are very promising, the study is not without some methodological limitations. First, no polysomnographic data were collected in the present study. We decided not to use polysomnography for the following reasons: (1) the patients had been visiting our outpatient clinics regularly, and a validated screening questionnaire for sleep apnea[26] was administered to all the patients, thus sleep apnea and periodic limb movement syndromes had already been screened out through consultations; and (2) in most general outpatient settings, especially for primary care clinics, routine use of polysomnography is not feasible. Considering the subjective nature of insomnia, our decision not to use polysomnography does not undermine the importance of our findings. In addition, sleep parameters were collected through the PSQI, which has not been validated for this purpose. Although sleep diary was not used to collect these data because it was employed only in the intervention arm as an active treatment component, this issue should be listed among the limitations. Second, the sample sizes were relatively small and concerns about the generalizability of the results may be raised, although the sizes were derived from our power calculation. In addition, the present study evaluated the patients up to 8 weeks only, and the long-term consequences of the combination treatment were unclear. Further replication study with a larger sample and long-term follow-ups is needed to evaluate these outcomes with more confidence. Third, we could not answer whether brief behavioral therapy for insomnia itself or careful watching for patients resulted in improvement in insomnia and in depression. Although an attention-placebo arm, such as relaxation or a quasi desensitization, was employed in previous studies on psychotherapy for insomnia,[13,40] we aimed to conduct the study to examine the effectiveness of adding psychotherapy to usual clinical care, but not to examine the efficacy of brief behavioral therapy for insomnia itself. Fourth, because the present study was conducted in Japan, several differences possibly influencing the results may exist between our settings and those in other countries in terms of characteristics of the enrolled patients and in health care systems. Several previous studies have reported that there may be certain differences between Western culture and others that need to be considered in the application of cognitive-behavioral therapy, such as patient's knowledge and beliefs about health and therapy[41] and insight into symptoms.[42] Replication studies might be needed before application of our results to patients in countries with different health care systems.

However, strengths of our study include our enthusiastic follow-ups of the patients. Even after patients were admitted to the hospital, blind assessors were sent. We, therefore, have no missing data and our results are robust. Another major strength of our study is its focus on the "effectiveness" design, as evidenced by the broad eligibility criteria for enrollment, use of less skilled therapists, preparation of a detailed manual, and shortening the treatment procedure to 4 sessions. All of these factors should contribute to the greater applicability and feasibility of our findings.

In conclusion, the results of our study suggest that adding brief behavioral therapy for insomnia to TAU is a promising treatment option for many patients with residual depression and refractory insomnia. Clinicians seeing depressed patients with persistent insomnia may consider adding brief behavioral therapy for insomnia to their usual clinical care as the second-line treatment for those who do not respond to adequate pharmacotherapy. Replication studies with a larger sample and long-term follow-ups in a different cultural setting may be needed to confirm the findings of the study with more confidence.

Author affiliations: Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences (Drs Watanabe and Furukawa); Department of Psychiatric and Mental Health Nursing, Nagoya City University School of Nursing (Dr Katsuki), Nagoya; Department of Neuropsychiatry, Kochi Medical School (Drs Shimodera, Morokuma, and Fujita, and Ms Kawamura), Kochi; Center for Education and Research on the Science of Preventive Education, Naruto University of Education, Tokushima (Dr Sasaki), Japan; and Behavioral Sleep Medicine Program, Department of Psychiatry, University of Pennsylvania, Philadelphia (Dr Perlis).
Potential conflicts of interest: **Dr Watanabe** has received research funds from the Japanese Ministry of Education, Science, and Technology; and has received speaking fees and research funds from Asahi Kasei, Dai-Nippon Sumitomo, GlaxoSmithKline, Pfizer, and Schering-Plough. **Dr Furukawa** has received research funds and speaking fees from Astellas, Dai-Nippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Meiji, Otsuka, Pfizer, Schering-Plough, Yoshitomi, and the Japanese Ministry of Education, Science, and Technology; has served on research advisory boards for Meiji and Mochida; and is currently serving on a research advisory board for Sekisui Chemicals and Takeda Science Foundation. **Dr Shimodera** has received speaking fees from Asahi Kasei, Dai-Nippon Sumitomo, GlaxoSmithKline, Astellas, Eli Lilly, Janssen, Meiji, Otsuka, Pfizer, and Schering-Plough. **Dr Katsuki** has received research funds from the Japanese Ministry of Education, Culture, Sports, Science and Technology. **Dr Sasaki** has been a part-time research staff for Sekisui Chemicals. **Dr Perlis** is an employee of the University of Pennsylvania and has received research funds, speaking fees and consulting fees from Cephalon, Sanofi-Aventis, Vanda, and Internet Didactic Services. **Drs Morokuma** and **Fujita** and **Ms Kawamura** report no conflicts of interest.
Funding/support: This study was funded by a Grant-in-Aid for Scientific Research (No. 19230201) from the Ministry of Health, Labour and Welfare, Japan.

Role of sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the article.
Disclaimer: The contents of this article are solely the responsibility of the authors.
Previous presentation: A preliminary analysis of this work was presented in symposium at the 9th Annual Meeting of the Japanese Association of Cognitive Therapy; October 11–13, 2009; Chiba, Japan; and in New Research Poster Session at the 163rd Annual Meeting of the American Psychiatric Association; May 22–26, 2010; New Orleans, Louisiana.
Acknowledgments: The authors thank all the assessors and the therapists (Nao Shiraishi, MD; Yoshie Murata, MSc; Jun Mayumi, MD; Mako Morikawa, MD; Yumi Nakano, MD, PhD, at Nagoya City University Graduate School of Medical Sciences, and Ryosuke Fujito, MD, at Kochi Medical School) and the administrative staff (Kozue Maki at Nagoya City University Graduate School of Medical Sciences) for their contribution to this study. The authors also thank Mitsuhiko Yamada, MD, PhD; Naohiro Yonemoto, MSc; and Masatoshi Inagaki, MD, PhD, at National Center of Neurology and Psychiatry, Japan, for their advice regarding the design and statistical issues, and Izuru Miyoshi, MD, PhD, at National Center of Neurology and Psychiatry, for providing the central allocation. None of the acknowledged individuals report any financial or other conflicts of interest relative to the subject of the article.

REFERENCES

1. Hamilton M. Frequency of symptoms in melancholia (depressive illness). *Br J Psychiatry.* 1989;154(2):201–206.
2. Carney CE, Segal ZV, Edinger JD, et al. A comparison of rates of residual insomnia symptoms following pharmacotherapy or cognitive-behavioral therapy for major depressive disorder. *J Clin Psychiatry.* 2007;68(2): 254–260.
3. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention? *JAMA.* 1989;262(11): 1479–1484.
4. McCall WV, Reboussin BA, Cohen W. Subjective measurement of insomnia and quality of life in depressed inpatients. *J Sleep Res.* 2000;9(1):43–48.
5. Turek FW. Insomnia and depression: if it looks and walks like a duck.... *Sleep.* 2005;28(11):1362–1363.
6. Perlis M, Smith M, Orff H. Major depressive disorder (MDD) is associated with a primary defect within the serotonergic system. *Sleep Med Rev.* 2002;6(5):353–357, discussion 359.
7. Nierenberg AA, Keefe BR, Leslie VC, et al. Residual symptoms in depressed patients who respond acutely to fluoxetine. *J Clin Psychiatry.* 1999;60(4):221–225.
8. Dew MA, Reynolds CF 3rd, Houck PR, et al. Temporal profiles of the course of depression during treatment: predictors of pathways toward recovery in the elderly. *Arch Gen Psychiatry.* 1997;54(11):1016–1024.
9. Ohayon MM, Roth T. Place of chronic insomnia in the course of depressive and anxiety disorders. *J Psychiatr Res.* 2003;37(1):9–15.
10. Pigeon WR, Hegel M, Unützer J, et al. Is insomnia a perpetuating factor for late-life depression in the IMPACT cohort? *Sleep.* 2008;31(4):481–488.
11. Reynolds CF 3rd, Frank E, Houck PR, et al. Which elderly patients with remitted depression remain well with continued interpersonal psychotherapy after discontinuation of antidepressant medication? *Am J Psychiatry.* 1997;154(7):958–962.
12. Fava M, McCall WV, Krystal A, et al. Eszopiclone co-administered with fluoxetine in patients with insomnia coexisting with major depressive disorder. *Biol Psychiatry.* 2006;59(11):1052–1060.
13. Manber R, Edinger JD, Gress JL, et al. Cognitive behavioral therapy for insomnia enhances depression outcome in patients with comorbid major depressive disorder and insomnia. *Sleep.* 2008;31(4):489–495.
14. Morin CM, Espie CA. *Insomnia: A Clinical Guide to Assessment and Treatment.* New York, NY: Guilford Press; 2004.
15. Perlis ML, Jungquist C, Smith MS, et al. *Cognitive Behavioral Treatment of Insomnia: A Session-by-Session Guide.* New York, NY: Springer Science; 2005.
16. Montgomery P, Dennis J. Cognitive behavioural interventions for sleep problems in adults aged 60+. *Cochrane Database Syst Rev.* 2003; (1):CD003161.
17. Morin CM, Bootzin RR, Buysse DJ, et al. Psychological and behavioral treatment of insomnia: update of the recent evidence (1998–2004). *Sleep.* 2006;29(11):1398–1414.
18. Kitamura T, Tomita T, Okano S, et al. *Structured Clinical Interview for DSM-IV Axis I Disorders.* Tokyo, Japan: Nippon-Hyoron-sha Co, Ltd; 2003.
19. Berlim MT, Turecki G. Definition, assessment, and staging of treatment-resistant refractory major depression: a review of current concepts and methods. *Can J Psychiatry.* 2007;52(1):46–54.
20. Furukawa T, Akechi T, Ozaki N, et al. *GRID-HDRS-17.* Tokyo, Japan: The Japanese Society of Clinical Neuropsychopharmacology; 2003.
21. Tabuse H, Kalali A, Azuma H, et al. The new GRID Hamilton Rating Scale for Depression demonstrates excellent inter-rater reliability for inexperienced and experienced raters before and after training. *Psychiatry Res.* 2007;153(1):61–67.
22. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med.* 2001; 2(4):297–307.
23. Munezawa T, Morin CM, Inoue Y, et al. Development of the Japanese version of the Insomnia Severity Index (ISI-J). *Jap J Psychiatr Treat.* 2009; 24(2):219–225.
24. Morin CM, Vallières A, Guay B, et al. Cognitive behavioral therapy, singly and combined with medication, for persistent insomnia: a randomized controlled trial. *JAMA.* 2009;301(19):2005–2015.
25. Furukawa TA, Akechi T, Azuma H, et al. Evidence-based guidelines for interpretation of the Hamilton Rating Scale for Depression. *J Clin Psychopharmacol.* 2007;27(5):531–534.
26. Netzer NC, Stoohs RA, Netzer CM, et al. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med.* 1999;131(7):485–491.
27. Buysse DJ, Reynolds CF 3rd, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989;28(2):193–213.
28. Doi Y, Minowa M, Uchiyama M, et al. Psychometric assessment of subjective sleep quality using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI-J) in psychiatric disordered and control subjects. *Psychiatry Res.* 2000;97(2–3):165–172.
29. The WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD (Defined Daily Dose) Index 2009. http://www.whocc.no/atcddd/. Accessed November 12, 2010.
30. Manber R, Edinger J, San Pedro M, et al. Combining escitalopram oxalate (EsCIT) and individual cognitive behavioral therapy for insomnia (CBTI) to improve depression outcome. Presented at the 21st Annual Meeting of the Associated Professional Sleep Societies;. June 9–14, 2007; Minneapolis, Minnesota.
31. Taylor DJ, Lichstein KL, Weinstock J, et al. A pilot study of cognitive-behavioral therapy of insomnia in people with mild depression. *Behav Ther.* 2007;38(1):49–57.
32. Edinger JD, Wohlgemuth WK, Radtke RA, et al. Dose-response effects of cognitive-behavioral insomnia therapy: a randomized clinical trial. *Sleep.* 2007;30(2):203–212.
33. McCrae CS, McGovern R, Lukefahr R, et al. Research Evaluating Brief Behavioral Sleep Treatments for Rural Elderly (RESTORE): a preliminary examination of effectiveness. *Am J Geriatr Psychiatry.* 2007;15(11): 979–982.
34. Germain A, Moul DE, Franzen PL, et al. Effects of a brief behavioral treatment for late-life insomnia: preliminary findings. *J Clin Sleep Med.* 2006;2(4):403–406.
35. SPSS Inc. SPSS for Windows. 16.0J ed. Tokyo, Japan: SPSS Japan Inc; 2007.
36. Brown H, Prescott R. *Applied Mixed Models in Medicine.* New York, NY: Wiley & Sons; 1999.
37. Altman DG, Schulz KF, Moher D, et al; CONSORT GROUP (Consolidated Standards of Reporting Trials). The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med.* 2001;134(8):663–694.
38. Edinger JD, Means MK. Cognitive-behavioral therapy for primary insomnia. *Clin Psychol Rev.* 2005;25(5):539–558.
39. Cuijpers P, Dekker J, Hollon SD, et al. Adding psychotherapy to pharmacotherapy in the treatment of depressive disorders in adults: a meta-analysis. *J Clin Psychiatry.* 2009;70(9):1219–1229.
40. Morin CM, Colecchi C, Stone J, et al. Behavioral and pharmacological therapies for late-life insomnia: a randomized controlled trial. *JAMA.* 1999;281(11):991–999.
41. Naeem F, Gobbi M, Ayub M, et al. Psychologists experience of cognitive behaviour therapy in a developing country: a qualitative study from Pakistan. *Int J Ment Health Syst.* 2010;4(1):2.
42. Rathod S, Kingdon D, Smith P, et al. Insight into schizophrenia: the effects of cognitive behavioural therapy on the components of insight and association with sociodemographics—data on a previously published randomised controlled trial. *Schizophr Res.* 2005;74(2–3):211–219.