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]
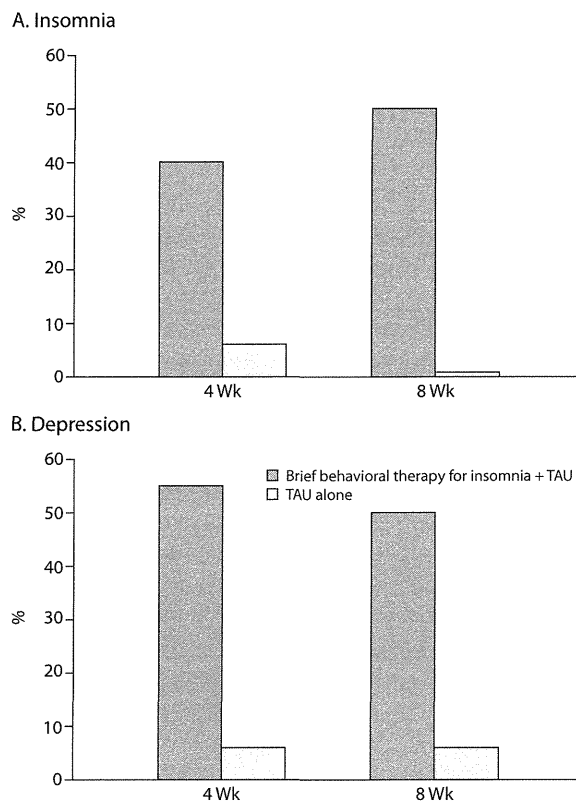
A. 17-Item GRID-Hamilton Depression Rating Scale

B. 14-Item GRID-Hamilton Depression Rating Scale
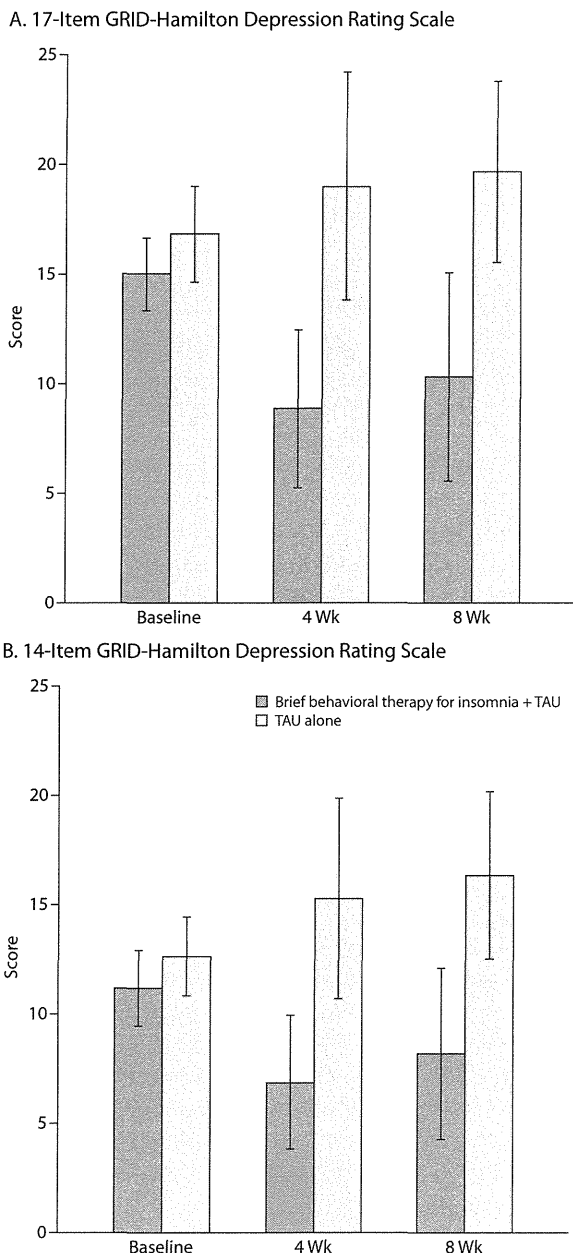
[a]Bar and error bar indicate mean and standard deviation, respectively.
Abbreviation: TAU = treatment as usual.

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

A. Insomnia

B. Depression

Abbreviation: TAU = treatment as usual.

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

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).

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.

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Assessment of Physical and Mental Health in Male University Students with Varying Sleep Habits

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Summary: Healthy sleep habits entail not only sleeping for a sufficient period (quantity) but also regularity of the sleep cycle and getting sound sleep (quality). University students often have erratic schedules that cause irregular sleep patterns even though sleep durations remain relatively constant. This study compared the physical and mental health of 90 male university students with different sleep habits. We created sleep habit scales using the Tokyo Metropolitan Institute for Neuroscience life habits inventory (TMIN-LHI; Miyashita, 1994) by performing a factor analysis and classifying sleeping habits based on regularity, quality, and quantity. Four types of sleep habits were identified by cluster analysis; good sleep was characterized by regular and high quality sleep but of relatively short sleep duration; long sleep was regular and relatively long but of low quality; short sleep was of high quality but short and irregular, while poor sleep was irregular, of low quality, and relatively long. The good sleep group had a significantly lower average waist circumference, and lower systolic and diastolic blood pressure. The long and poor sleep groups, which both had low quality sleep, scored lower than the national standard on the mental component summary (MCS) calculated from the Social Functioning-36 (SF-36) short-form health survey. Furthermore, the average MCS score of the poor sleep group was significantly lower than that of any other sleep habit group. Subjects with poor sleep also scored lowest on the Self-rating Depression Scale (SDS). In addition, the short and poor sleep groups were prone to glucose or lipid metabolism disorders. Maintaining good physical and mental health without sound sleep and a regular sleep cycle is difficult, even if sleeping hours are kept constant. Therefore, we included the assessment of regularity and quality in addition to hours of sleep in order to develop appropriate sleep guidelines for improved physical and mental health.

Key words university students, sleep habits, sleep hygiene, regularity of sleep, quality of sleep, sleep duration

INTRODUCTION

Metabolic syndrome and depression are now attracting considerable research attention. These disorders are closely related to various aspects of lifestyle, such as diet [1], exercise [2], and mental stress [3]. The Japanese population has a tendency to neglect sleep because of a national work ethic based on diligence [4]. In addition, working overtime is considered a virtue in Japan, and 24-h work operations are commonplace. Twenty-four hour stores are a regular feature and many young people work in late shifts. For them, work time and free time are more important than sleep duration [5].

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However, irregular and insufficient sleep can cause daytime drowsiness and a lack of concentration, reduced quality of life, and a decline in performance. For example, Belenky [6] has indicated that once chronic sleep insufficiency affects performance, complete recovery is difficult even if adequate sleep was secured for three consecutive nights. When chronic sleep insufficiency gradually accumulates in an individual, performance is drastically reduced even if sleepiness is not felt. Lack of sleep and insomnia also cause mental disorders. Kaneita's study [7] on 24,686 Japanese adults ascertained that sleep duration of less than six h and more than eight h was associated with symptoms of depression. Sleep deficiency can affect physical health as well. Gangwish [8] found that subjects who slept less than four hours were 73% more obese than those who slept more than seven h. Tochikubo [9] reported a high blood pressure throughout the day in subjects who had only 3-4 h of sleep the previous night. Knutsona [10] demonstrated that one week of sleep insufficiency caused impaired glucose tolerance because of a decline in insulin sensitivity levels. Therefore, adequate sleep is important not only for performing normal daytime activities efficiently, but also for good physical and mental health.

University students often have erratic schedules that cause irregular sleep patterns. Kang [11] suggested that students with an irregular bedtime schedule might experience poor sleep quality. In addition, Buboltz [12] investigated that poor sleep habits might become a self-perpetuating cycle that students are unaware of and might be unable to alter. Chang [13] conducted a follow-up study on 1053 male university graduates for 34 years. Of these, 103 developed depression, and the risk of depression in those who had insomnia during their university days was twice as high as that in subjects who did not. Therefore, it has been suggested that poor sleep habits at a young age could have an effect on sleep habits in middle age in the same individual, and that sleep habits are not short-term but rather long-term factors.

When evaluating sleep, we tend to emphasize the number of hours (i.e., the quantity of sleep). However, maintaining a regular and sound sleep cycle are also important factors. Hayashi [14] stated that sleep habits could be measured in three dimensions (i.e., regularity, quality and quantity). In an earlier study, Takeuchi [15] identified these three factors of sleep from the Tokyo Metropolitan Institute for Neuroscience life habits inventory (TMIN-LHI) and classified sleep habits on the basis of these factors. Takeuchi's analysis takes into account not only the quantity of sleep but

also examines other perspectives, by which the issue can be more comprehensively understood. Minimizing hidden perspectives in this way provided a better understanding of the sleep habits of university students. However, no physical or mental data were investigated in that study, so the relationship between health condition and sleep habits was ambiguous. University students often have physical and mental problems besides sleep disorders [16]. In this study, we used Takeuchi's method to compare the physical and mental condition of university students in order to clarify the effects of certain factors that cause differences in sleep habits. In addition, because sleep habits differ between sexes [17], we restricted our study to males in order to obtain a more exact analysis. Therefore, we investigated sleep habits (sleep hygiene) in male university students for the purpose of demonstrating the association between sleep habits and physical and mental health.

MATERIALS AND METHODS
Study subjects and duration

The subjects of this study were male students of Kurume University (18-29 years; average age: mean ± standard deviation (SD), 19.4±1.8 years). None of the subjects had any physical or mental disease and none were on regular medication. In addition, obesity can cause secondary sleep disturbances because of sleep apnea syndrome. Therefore, a body mass index (BMI) of 18.5 to 24.9 was set as an inclusion factor for this study. In total, 90 students were included in this study, which was carried out in June 2010. There were no aggravating circumstances such as examinations or long breaks before or after the testing day.

Questionnaires

We used the TMIN-LHI, which is a detailed questionnaire comprising two sections. The first section includes 60 questions based on sleep habits and other lifestyle issues. The second section is a Morningness-Eveningness (ME) questionnaire created by Horne and Ostberg [18] and translated into Japanese by Ishihara [19]. It comprises 19 items. We calculated the ME score for our subjects on the basis of their grade slips.

Preparation of the sleep habits scale and classification of subjects
Selected Items

From TMIN-LHI, 26 of 60 items from section 1 were excluded. These were nominal items or the items targeting certain people who offered a specific answer, and had large ceiling or floor effects. We eventually

conducted a factor analysis with 35 items (i.e., the remaining 34 items from section 1 and the ME score from section 2).

Factor Analysis

We extracted factors by principal factor analysis and ran a promax rotation. Three factors were chosen on the basis of scree plot. The characteristic values were 6.120, 3.030 and 2.591 respectively, and the cumulative percentage was 33.5%.

Following analysis of the 35 items from the TMIN-LHI, which was done five times, 18 items were excluded. The remaining 17 items had factor loadings of $\geqq 0.35$. The explanatory power was 53.4% and the accumulated contribution rate was 46.0%. The confidence coefficients (α) of the three factors were 0.878, 0.683, and 0.670 for the first, second and third factor, respectively.

The three factors focused on in this study are described in Table 1 along with their factor loadings. The first factor comprised 8 items: regular bedtime, regular wake-up time, irregular bedtime, irregular wake-up time, ME score, irregular sleep duration, breakfast habits, and exercise habits. This regularity factor along with its items was named the related Sleep Regularity scale. The second factor comprised 5 items: difficulty of sleep latency, time to fall asleep, mood on waking

up in the morning, depth of sleep and experience of insomnia. This quality factor along with its items was named the related Sleep Quality scale. The third factor comprised 5 items: regular sleep duration, ideal sleep duration, regular wake-up time, value attached to sleep and time spent in commuting. This quantity factor along with its items was named the related Sleep Quantity scale.

Principal Component Analysis

Eight items from the first factor, five from the second factor and five from the third factor were subjected to principal component analysis, and each factor was given a standard score. We created a sleep habits scale by assuming the first score to be a scale score. The average score was initially fixed at 0. In the related Sleep Regularity scale, a positive score indicated mostly regular sleep habits and a negative score indicated mostly irregular sleep habits. In the related Sleep Quality scale, a positive score indicated a more sound sleep and a negative score indicated a very disturbed sleep. In the related Sleep Quantity scale, a positive score indicated longer sleep duration and more active procurement of sleep, and a negative score indicated shorter sleeping hours and more passive procurement of sleep.

Classifying Subjects

The Ward method of cluster analysis was selected

TABLE 1.
Extracted factors and factor loadings

	Items	Range	Factor Loadings
The First Factor $\alpha=0.878$	Q1: regular bedtime	early – late	0.868
	Q4: regular wake-up time	early – late	0.745
	Q2: irregular bedtime	small – large	0.713
	Q5: irregular wake-up time	small – large	0.689
	ME score	Eveningness – Morningness	–0.657
	Q8: irregular sleep duration	small – large	0.652
	Q37a: breakfast habits	always – never	0.616
	Q49: exercise habits	never – always	–0.596
The Second Factor $\alpha=0.683$	Q14: difficulty of sleep latency	easy – difficult	0.982
	Q13: time to fall asleep	short – long	0.529
	Q19: mood on waking up in the morning	pleasant – unpleasant	0.427
	Q20: depth of sleep	deep – light	0.417
	Q43: experience of insomnia	no – yes	0.408
The Third Factor $\alpha=0.670$	Q7: regular sleep duration	short – long	1.002
	Q11: ideal sleep duration	short – long	0.574
	Q4: regular wake-up time	early – late	0.397
	Q12: value attached to sleep	important – unimportant	–0.381
	Q45: time spent in commuting	short – long	–0.377

for classifying the subjects on the basis of principal component score for each factor. Four clusters were determined because they were the most balanced and the clearest following the dendrogram.

Physical factors

The subjects were instructed to measure their own height and weight. Waist circumference was measured at the umbilical region by members of the same study staff. The subjects also measured their own resting blood pressure and pulse with an automatic manometer (BP-203RV Type C, Nippon Colin, Tokyo, Japan) in a sitting position. If systolic blood pressure was ≥ 130 mmHg or diastolic blood pressure was ≥ 85 mmHg, subjects measured their blood pressure again. In the event that the second blood pressure measurement was unacceptable, the study staff measured it with a mercurial column manometer.

Mental health

We evaluated mental health using the Japanese version of the Social Functioning-36 (SF-36) [20-22] short-form health survey and Japanese version of the Self-rating Depression Scale (SDS) [23].

The Japanese version of the SF-36, which was developed by Fukuhara [20-22], is a general scale used to measure quality of life over a one-month period. All items are scaled, and the higher the scores, the better the quality of life. Physical component summary (PCS) and mental component summary (MCS) were derived from the SF-36: physical functioning, role physical, bodily pain, general health perceptions, vitality, social functioning, role emotional, and mental health. PCS score and MCS score can be compared to national standard values directly (50=national standard score). Furthermore, we can evaluate physical quality of life (QOL) from PCS and mental QOL from MCS in a comprehensive manner.

Zung [24,25] developed SDS as simple test to assess depression, and Fukuda translated it into Japanese [23]. It comprises 20 items, all graded according to four ranks of 1-4 points each. We used an integrated scoring system as follows: ≤ 39 points indicated normal mental health, 40-49 points indicated slight depression, and ≥ 50 points indicated moderate depression.

Blood tests

Blood samples were taken and fasting blood sugar (FBS), immunoreactive insulin levels, high-density cholesterol (HDL-C), low-density cholesterol (LDL-C), leptin, des-acyl ghrelin, and high molecular weight adiponectin (HMW-adiponectin) were measured. In addition, the homeostasis model of assessment-insulin resistance (HOMA-IR) was calculated from FBS and immunoreactive insulin values; HOMA-IR= (immunoreactive insulin×FBS)/405 [26].

Statistical analysis and software

The mean and SD values of each item were expressed as mean $\pm$ SD. Shapiro-Wilk test was used as the normality test. If the item showed a normal distribution, one-way analysis of variance (ANOVA) and Tukey's honestly significant difference (HSD) tests were used as parametric tests. In the event that the item did not have a normal distribution, the Kruskal-Wallis H test and Scheffe test were used as nonparametric tests. We used SPSS15.0J Base System SC Kit-software and set the significance level at p<0.05.

Ethical concerns

Prior to enrollment, subjects were informed about the purpose and method of this study, following which they asked to sign written informed consent forms. If the subjects were minors, we obtained their parents' approval. We ensured that no one of the subjects would be pressured or harmed because of nonparticipation. Personal data were strictly monitored to maintain confidentiality and to protect the privacy of subjects. This study was approved by the Kurume University Mii Campus Ethical Review Board.

RESULTS

Characteristics of each type of sleep habits

Figure 1 illustrates the four categories of sleep habits with the mean and SD of each scale score. The first type was the most regular and sound sleep, but there was a slight tendency towards shorter sleep duration. It was termed the "good sleep" type. The second type was somewhat regular and characterized by insomnia and longer sleeping period. It was called "long sleep" type. The third type was somewhat irregular but sound sleep and was characterized by the shortest sleep duration among all subjects. It was called "short sleep" type. The fourth type was the most irregular and was characterized by extreme insomnia and long sleep duration. It was referred to as the "poor sleep" type.

The upper section of Table 2 lists the averages for regular sleep duration, ideal sleep duration, regular bedtime, regular wake-up time, irregular sleep duration, irregular bedtime, irregular wake-up time and time to fall asleep for the four sleep habits groups. Regular sleep duration averaged 6.7±1.2 h. There were sig-

Good sleep

Regularity
1.5

Quantity —————— Quality

n = 25
related Sleep Regularity: 0.959 ± 0.603
related Sleep Quality: 0.673 ± 0.807
related Sleep Quantity: −0.266 ± 0.542
Total score: 1.367 ± 1.057

Long sleep

Regularity
1.5

Quantity —————— Quality

n = 31
related Sleep Regularity: 0.094 ± 0.589
related Sleep Quality: −0.145 ± 1.059
related Sleep Quantity: 0.514 ± 0.607
Total score: 0.463 ± 1.142

Short sleep

Regularity
1.5

Quantity —————— Quality

n = 20
related Sleep Regularity: −0.287 ± 0.567
related Sleep Quality: 0.117 ± 0.472
related Sleep Quantity: −1.086 ± 0.702
Total score: −1.256 ± 0.663

Poor sleep

Regularity
1.5

Quantity —————— Quality

n = 14
related Sleep Regularity: −1.511 ± 0.727
related Sleep Quality: −1.048 ± 0.779
related Sleep Quantity: 0.887 ± 1.143
Total score: −1.671 ± 1.321

Fig. 1. Four types of sleep habits and corresponding scale scores (means ± SD).
Good sleep was the most regular and sound sleep, but there was a slight tendency towards shorter sleep duration. Long sleep was somewhat regular and characterized by insomnia and longer sleeping period. Short sleep was somewhat irregular but sound sleep and was characterized by the shortest sleep duration. Poor sleep was the most irregular and was characterized by extreme insomnia and long sleep duration.

nificant differences in regular sleep duration (multiple comparison; short sleep vs. good sleep, long sleep and poor sleep: p<0.001), ideal sleep duration (short sleep vs. long sleep: p<0.05 and poor sleep: p<0.01), regular bedtime (good sleep vs. long sleep: p<0.01, short sleep and poor sleep: p<0.001, long sleep vs. poor sleep: p<0.001, short sleep vs. poor sleep: p<0.05), regular wake-up time (good sleep vs. long sleep and poor sleep: p<0.001, long sleep vs. short sleep: p<0.05 and poor sleep: p<0.001, short sleep vs. poor sleep: p<0001), irregular sleep duration (good sleep vs. short sleep: p<0.05 and poor sleep: p<0.001, long sleep vs.

poor sleep: p<0.001, short sleep vs. poor sleep: p<0.001), irregular bedtime (good sleep vs. short sleep: p<0.01 and poor sleep: p<0.001, long sleep vs. poor sleep: p<0.001, short sleep vs. poor sleep: p<0.05), irregular wake-up time (good sleep vs. short sleep: p<0.05 and poor sleep: p<0.001, long sleep vs. poor sleep: p<0.001, short sleep vs. poor sleep: p<0.001), and time to fall asleep (good sleep vs. poor sleep: p<.001, short sleep vs. poor sleep: p<0.01).

Physical characteristics of subjects

The middle section of Table 2 describes the physi-

TABLE 2.

Characteristics of each type of sleep habits (mean ± SD)

		Total	Good sleep	Long sleep	Short sleep	Poor sleep	p value
	n	90	25	31	20	14	
Sleep data	regular sleep duration (h)	6.7±1.2	6.7±0.8	7.3±0.7	5.3±0.9	7.1±1.5	<0.001*
	ideal sleep duration (h)	7.4±1.2	7.3±0.9	7.7±1.1	6.8±0.7	8.1±1.7	0.003*
	regular bedtime (o' clock)	24.7±1.3	23.6±1.1	24.6±0.9	25.2±1.0	26.1±1.1	<0.001*
	regular wake-up time (o' clock)	7.8±1.4	6.7±0.9	8.2±0.9	7.4±0.9	9.6±1.3	<0.001*
	irregular sleep duration (min)	71.0±62.9	32.4±35.6	60.0±49.6	79.5±53.6	152.1±67.1	<0.001*
	irregular bedtime (min)	94.0±73.6	50.0±25.8	78.7±42.3	117.0±79.6	173.6±102.7	<0.001*
	irregular wake-up time (min)	81.6±74.1	41.2±31.0	62.3±37.9	90.0±66.0	184.3±103.2	<0.001*
	time to fall asleep (min)	25.3±16.4	17.8±9.3	28.1±17.9	21.0±11.1	38.6±20.3	<0.001*
Physical data	Age (years)	19.4±1.8	19.0±0.9	19.6±2.1	19.2±2.4	19.9±1.3	n.s.
	BMI (kg/m²)	21.0±1.7	20.2±1.6	21.2±1.8	21.3±1.5	21.3±1.8	n.s.
	waist circumference (cm)	72.1±5.1	69.9±4.7	72.1±5.6	73.9±3.9	73.4±5.2	0.040*
	systolic blood pressure (mmHg)	116.2±10.1	110.1±9.6	117.2±10.6	118.0±9.1	120.9±7.7	0.011*
	diastolic blood pressure (mmHg)	66.3±9.6	62.4±6.6	68.1±10.3	65.0±9.4	70.9±10.3	0.026*
	pulse (/min)	69.7±10.3	64.8±10.5	70.8±10.3	71.9±10.2	72.7±7.6	0.038*
Blood test data	FBS (mg/dl)	86.8±7.2	85.9±5.0	86.1±5.2	85.7±4.5	91.7±13.6	0.049*
	immunoreactive insulin (μIU/ml)	6.9±7.0	5.7±2.2	6.3±3.4	6.5±3.0	11.1±16.2	n.s.
	HOMA-IR	1.6±2.3	1.2±0.5	1.4±0.7	1.4±0.7	3.0±5.5	n.s.
	HDL-C (mg/dl)	61.2±10.0	63.5±9.5	57.7±8.4	65.0±11.8	59.3±9.3	0.035*
	LDL-C (mg/dl)	90.2±19.3	93.7±20.0	87.1±18.4	85.9±15.3	97.2±23.4	n.s.
	leptin (ng/ml)	2.4±1.1	2.0±0.8	2.5±1.3	2.7±1.0	2.4±1.0	0.024†
	desacyl-ghrelin (fmol/ml)	203.7±99.6	240.6±129.5	182.5±75.3	181.4±88.6	216.4±88.5	n.s.
	HMW-adiponectin (μg/ml)	5.2±2.7	5.9±2.7	5.1±2.8	4.9±2.7	4.6±2.5	n.s.

* significant difference (by ANOVA test), † significant difference (by Kruskal-Wallis H test), n.s = not significant.

cal characteristics of subjects associated with the four types of sleep habits. There were significant differences in waist circumference (multiple comparison; good sleep vs. short sleep: p<0.05), systolic blood pressure (good sleep vs. poor sleep: p<0.05), diastolic blood pressure (good sleep vs. poor sleep: p<0.05), and pulse (no difference in multiple comparison). However, no significant differences were observed in age or BMI among the subjects.

Mental health of subjects

Figure 2 shows data for the four types of sleep habits based on responses to PCS and MCS of SF-36. While PCS scores of all groups were higher than the national standard value (≧50), MCS scores of two groups (i.e., long sleep and poor sleep) were lower than the national average. There was a significant difference in MCS but no significant difference in PCS

among the subjects. Scores for poor sleep were significantly lower than for the other types of sleep with regard to MCS (vs. good sleep: p<0.001, vs. long sleep: p<0.05, vs. short sleep: p<0.01). Figure 3 shows data for the four types of sleep habits based on responses to SDS. Scores for poor sleep were significantly higher than those for the other types of sleep (vs. good sleep: p<0.001, vs. long sleep: p<0.05, vs. short sleep: p<0.05).

Blood test results

The bottom section of Table 2 lists the results of blood tests for each group. There were significant differences in FBS (no difference in multiple comparison), HDL-C (long sleep vs. short sleep: p<0.05), and leptin (good sleep vs. short sleep: p<0.05), but no significant differences in immunoreactive insulin levels, HOMA-IR, LDL-C, des-acyl ghrelin, and HMW-
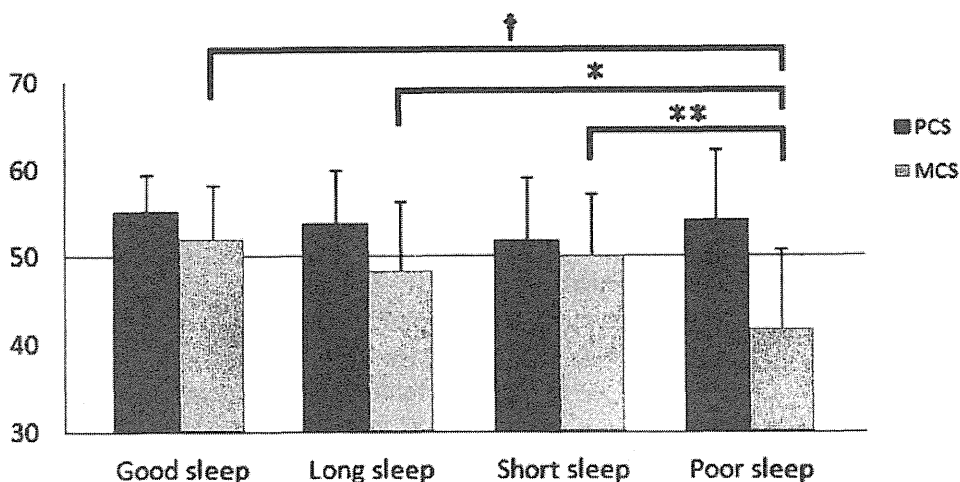
Fig. 2. PCS and MCS as measured by SF-36 (national standard value = 50, *p<0.05, ** p<0.01, †p<0.001 by Tukey's HSD test).
While PCS scores of all groups were higher than national standard value (≧50), MCS scores of long sleep and poor sleep were lower than it. Scores for poor sleep were significantly lower than for the other types of sleep with regard to MCS.
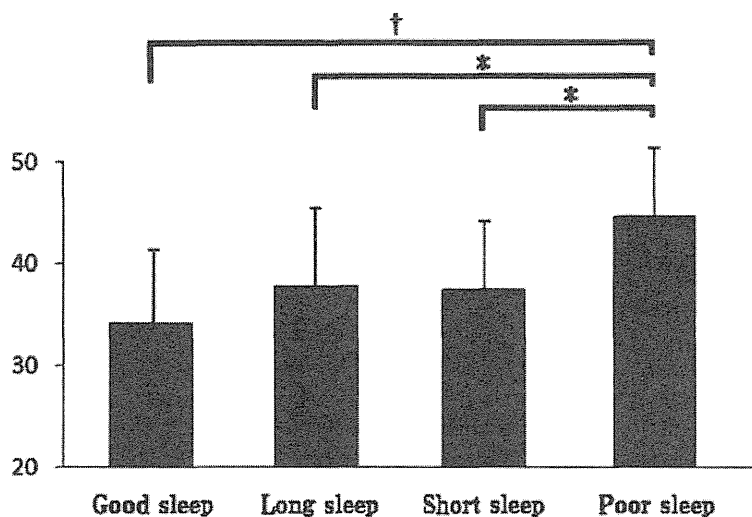
Fig. 2. SDS of four sleep habits (*p<0.05, †p<0.001 by Tukey's HSD test).
Poor sleep had significantly higher score when compared to the scores for the other types.

adiponectin among the subjects.

DISCUSSION

Methodology

The purpose of this study was to measure the impact of different sleep habits (sleep hygiene) on physical and mental health in a cohort of 90 male university students by classifying sleep habits. We developed comprehensive scales that described sleep regularity, quality, and quantity by factor analysis and principal component analysis. Cluster analysis was then employed to classify the sleep habits these students into four groups. Measures of sleep habits must consider not only the number of hours slept (quantity), but must also account for regularity and quality of sleep to

clearly identify those facets of sleep patterns that most influence mental and physical health. Takeuchi [15] classified sleep habits on the basis of all three factors, and this method proved to be more precise than methods that only evaluated single factors such as sleep duration. We investigated the physical and mental health of the present subjects after classifying sleep habits by means of Takeuchi's comprehensive scoring method. Our analysis underscores the importance of measuring all three dimensions to establish a consistent relation between sleep habits and physical and mental health.

Interpretation of each type of sleep habits

Good sleep is defined by consistent and normal sleep duration. Those subjects in the good sleep group kept very early hours and scored higher in Morningness. Daily changes of sleep duration, bedtime, and wake-up time were quite small. They also fell asleep easily. Good sleep is the exemplary sleeping pattern. In long sleep subjects, regular bedtimes were normal and regular, but regular wake-up time was later. In addition, both usual and ideal sleep durations were longer than the average. In other words, this group preferred to rise later. They fell asleep with difficulty and had lower quality sleep; that may cause them to oversleep. In the short sleep group, regular bedtimes were later and regular wake-up times were earlier. While this group fell asleep easily, they had irregular sleep habits. They preferred to stay up late and were less concerned about sleep because their ideal sleep duration was shorter than that of any of the other groups. These factors could be expected to result in short sleeping times. Subjects in the poor sleep group seemingly got plenty of sleep according to regular sleep duration, but sleep regularity was poor, and these subjects found it difficult to fall asleep. In addition, their ideal sleep duration was longer than that of any of the other groups. This group may lack sufficient sleep due to chronic insomnia.

In Takeuchi's study [15], several extracted sleep habits were similar to sleep disorders defined by the American Sleep Disorders Association (ASDA), including sleep deficit syndrome, circadian rhythm disorder, and delayed sleep phase syndrome. In the current study, both short and poor sleep subjects had lower than average total scale scores, indicating problematic sleep habits. Short sleep was similar to sleep deficit syndrome as defined by the ASDA in that there was a large gap between actual and ideal sleep durations. In contrast, poor sleep resembled exogenous circadian rhythm disorders such as jet lag. A change in time zone of over three hours causes jet lag with disturbance of sleep induction [27]. The sleep habits of subjects with poor sleep appeared similar to those of daily travelers suffering from jet lag. If the subjects in the poor sleep group graduate from university with the same sleep habits, they might not be able to conform to regular office hours. Thus, they should receive therapy to correct irregular lifestyle habits and to manage insomnia.

Physical characteristics of subjects

Lack of sleep may be linked to obesity due to increased food consumption [8]. There was a significant difference in average waist circumference between the short and the good sleep groups. However, the good sleep group had the second shortest average sleep duration; thus, shorter sleep duration alone does not lead to weight gain. If individuals continue to sleep for irregular hours and have an inconsistent circadian rhythm, the clock gene begins to express abnormalities, which may lead to easy accumulation of visceral fat [28,29]. Therefore, it is suggested that people with irregular as well as short sleep habits, like the short sleep group in this study, may be prone to visceral fat obesity even if their age and BMI are similar to individuals with good sleep habits.

There were significant differences in blood pressure and pulse between the poor and good sleep groups. Ishii [30] demonstrated that irregular sleep habits could disrupt autonomic nervous system function leading to hypertension and rapid pulse. In addition, Javaheri [31] reported that sleep disturbance could cause hypertension even in young healthy men without arteriosclerosis such as the poor sleep subjects in this study. Extremely irregular sleep habits with insomnia, as exhibited by the poor sleep group, may increase blood pressure and pulse due to an autonomic disorder.

Mental health of subjects

Apropos of the relationship between sleep and mental disease, insomnia and depression are often associated with poor sleep habits. Predictably, poor sleep, the type for which the related Sleep Quality scores were extremely low, indicated the worst mental condition. With respect to MCS measured on the basis of SF-36 and SDS scores, subjects in the poor sleep group had very bad scores that were significantly poorer than the scores of subjects of any other sleep type. SDS scores in this group were ≥ 40, which is considered to reflect a state of neurosis. People who have sleep habits like those in the poor sleep group are therefore prone to depression. The mental condition of subjects in the long sleep group, whose related Sleep Quality scores were second-lowest after those in the poor sleep

group, was also lower than national standard value in MCS in spite of surpassing that of subjects in the short sleep group whose total sleep habits scale score was far worse.

The timing of onset of depression and insomnia has not been sufficiently investigated. However, according to Ohayan [32], insomnia often precedes depression. Furthermore, for people who suffer from insomnia for more than one year, the risk of depression can be 40 times greater than that in those without insomnia [33]. It is important, therefore, that the symptoms observed in the poor sleep group of this study should be immediately resolved, and people whose sleep habits fall into the long sleep category should also be concerned about the relation between their sleep habits and mental condition.

Blood test results

Of the saccharometabolism items (FBS, immunoreactive insulin, and HOMA-IR), only FBS showed a significant difference among subjects with the four types of sleep habits. However, for all three items, the good sleep group had the lowest values and the poor sleep group showed the highest values. As mentioned above, an inconsistent circadian rhythm because of irregular sleep habits leads to abnormalities in the clock gene, which in turn may lead to visceral fat accumulation [28,29]. Eventually, insulin resistance and impaired glucose tolerance can also result.

Of the lipometabolism items (HDL-C and LDL-C), only HDL-C showed a significant difference between long sleep and short sleep. While subjects in the good sleep and short sleep groups had high levels of HDL-C, those in the long sleep and poor sleep groups had low levels of HDL-C. It has been suggested that deterioration in sleep quality and hypersomnia play a role in decreasing HDL-C. Contrary to our result, however, Bjorvatn [34] reported that sleep of short duration decreased HDL-C. This point, therefore, needs further study and consideration.

In the blood tests for leptin, des-acyl ghrelin, and HMW-adiponectin, only leptin showed a significant difference among subjects with the four types of sleep habits. Leptin and des-acyl ghrelin are appestat factors that are influenced by sleep. Sleep of short duration decreases leptin and increases des-acyl ghrelin, which in turn can bring about obesity due to enhanced appetite [35]. We predicted that leptin would decrease and des-acyl ghrelin would increase in the short sleep and poor sleep groups. However, there was no difference in des-acyl ghrelin, and leptin increased in subjects in the short sleep group. There was a significant difference in

circulating leptin between the short and good sleep groups. Leptin levels often increase with obesity because increased visceral fat leads to leptin resistance [36]. Visceral fat accumulation resulting from a chronic lack of sleep and irregular sleep habits might cause leptin resistance. Most previous studies were short-term (i.e., they analyzed acute sleep insufficiency). The effects of long-term sleep habits have not been adequately considered. Other studies analyzed only sleep duration and not regularity and quality. Therefore, it has been suggested that irregular as well as short sleep habits over the long-term, like short sleep in this study, cause leptin resistance and a compensatory increase in leptin.

In this study, there was no significant difference in HMW-adiponectin between groups. However, HMW-adiponectin levels were highest in the good sleep group and lowest in the poor sleep group. Few studies have reported the relationship between adiponectin and sleep. There is a possibility that the small number of subjects in our study prevented us from finding a significant difference for this parameter. Therefore, the relationship between adiponectin and sleep requires further analysis with a larger study sample.

The limitations of this study include the inclusion of males only and the relatively small sample population. Triglyceride, which is one of the diagnostic criteria of metabolic syndrome, was not measured, so we were unable to estimate the relation between sleep habits and metabolic syndrome. We also did not ask about club activities and part-time jobs, factors which could impact regularity of sleep. In addition, TMIN-LHI is a not scale for scoring but a simply questionnaire, and is not subject to validation. Finally, the analyses in this study have a variability related to the subjects. University students have unique lifestyles and sleep habits compared to the general population, and their sleep characteristics may differ from those in heterogeneous subjects like general members of society or the aged.

CONCLUSION

We found significant differences in certain physical characteristics, mental health, and blood test results among four different sleep habit groups in male university students. Although all subjects in this study were young men with normal BMI, irregular sleep habits caused increases in waist circumference, blood pressure, and pulse, and impaired saccharometabolism and lipometabolism even if sleep duration was kept constant. In addition, the mental condition of subjects with poor quality sleep was not as good as that of sub-

jects with good quality sleep. It is important to gain a comprehensive understanding of sleep habits in order to maintain good physical and mental health among male university students. Further studies to validate these scales may be required in the fields of sleep medicine and preventive medicine.

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Carryover effect on next-day sleepiness and psychomotor performance of nighttime administered antihistaminic drugs: a randomized controlled trial

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Background   Antihistamines with strong sedative–hypnotic properties are frequently prescribed for insomnia secondary to allergy, but the potential risks of such administration have not been fully elucidated.
Subjects and methods   This randomized, double-blind, placebo-controlled crossover study was conducted to evaluate next-day sleepiness and psychomotor performance following the administration of antihistamines. Twenty-two healthy male participants participated in four drug administration sessions with more than a 1-week interval between the sessions. Either zolpidem 10 mg, or diphenhydramine 50 mg, or ketotifen 1 mg, or a placebo was administered before sleep, and polysomnography was conducted to evaluate sleep. In the morning and afternoon of the day after administration, the participants were evaluated for subjective sleepiness, objective sleepiness, and psychomotor performance.
Results   The antihistamines with high blood–brain barrier-crossing efficiency were significantly associated with sleepiness and psychomotor performance decline the next day. Ketotifen showed the strongest carryover effect, followed by diphenhydramine. Compared with the placebo, no significant carryover effect was observed with zolpidem.
Conclusion   The results suggest that the risk–benefit balance should be considered in the ready use of antihistamines that easily cross the blood–brain barrier for alleviating secondary insomnia associated with allergies. Copyright © 2012 John Wiley & Sons, Ltd.

KEY WORDS—antihistaminic drugs; carryover effect; diphenhydramine; ketotifen; zolpidem

INTRODUCTION

The effectiveness of benzodiazepine and non-benzodiazepine hypnotics in treating insomnia secondary to physical and mental illness (comorbid insomnia) has been demonstrated by several randomized control trials (Asnis *et al.*, 1999; Fava *et al.*, 2006; Stewart *et al.*, 2006), and these drugs are now used as standard therapeutic drugs in clinical practice. However, many drugs with sedative–hypnotic properties are also used off-label to treat secondary insomnia, and a typical example of this is antihistamines commonly used to treat patients with atopic dermatitis and asthma. Antihistamines with strong sedative–hypnotic properties are often intentionally administered before sleep to ameliorate insomnia symptoms in addition to allergy symptoms.

The strength of antihistamine sedative–hypnotic effects is determined by differences in the drug's ability to cross the blood–brain barrier (BBB) (Yanai and Tashiro, 2007). In general, first-generation antihistamines are highly effective in crossing the BBB but have low specificity toward histamine receptors. In contrast, second-generation antihistamines have a low tendency to cross the BBB and high specificity toward histamine receptors (Simons, 1994; Yanai and Tashiro, 2007). In fact, positron emission tomography showed that the first-generation antihistamine diphenhydramine (DPH) produced as high as 56% occupancy of histamine H1 receptors in the brain at 90 min postadministration (Zhang *et al.*, 2010). Because of the strong clinical sedative–hypnotic effects, DPH has been widely marketed as an over-the-counter hypnotic. Some of the second-generation antihistamines also have strong sedative–hypnotic properties. For example, the brain histamine H1 receptor occupancy of ketotifen (KTF) reaches 72% at 160 min postadministration (T_{max})

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(Tashiro et al., 2006). A functional brain imaging study using near-infrared spectroscopy showed impaired psychomotor performance and significant decrease in cerebral blood flow response in the lateral prefrontal cortex 3 h after KTF administration, compared with the placebo group (Tsujii et al., 2009). Several other studies have also shown that psychomotor performance is acutely and transiently suppressed after administration of an antihistamine with strong sedative–hypnotic effects (Weiler et al., 2000; Tashiro et al., 2005; Boyle et al., 2006).

In this randomised, double-blind, placebo-controlled crossover study, we examined the risk–benefit balance of two types of antihistamines with effective BBB-crossing properties as a treatment for secondary insomnia, with the primary endpoints set as next-day objective and subjective sleepiness and psychomotor performance following administration before sleep.

MATERIALS AND METHODS

Participants

Healthy Japanese men were recruited for the study through newspaper advertisements and other media outlets. Before the study, the participants were interviewed by physicians, administered questionnaires including the Pittsburgh Sleep Quality Index and Epworth Sleepiness Scale, and underwent polysomnography (PSG) to screen out the presence of serious physical diseases, sleep disorders, and psychiatric diseases that might affect the study evaluation. Those taking hypnotics, tranquilizers, antihistamines, or other drugs with sedative–hypnotic properties were excluded. This yielded 22 healthy adult male participants (mean age, 22.2 ± 0.8 years; mean height, 171.5 ± 1.1 cm; mean body weight, 64.7 ± 2.3 kg; mean body mass index, 22.0 ± 0.8 kg/m^2). All the participants underwent and completed all the study sessions. Prior to screening, the participants received oral and written explanations of the purpose and methods of the study as well as expected drawbacks and possible occurrences. Written informed consent was obtained from all the participants. This study protocol was approved by the Ethics Committee of the National Center of Neurology and Psychiatry.

Study protocol and drug assignment

This random, double-blind, placebo-controlled crossover study involved four drug administration sessions (3 days, 2 nights per session) conducted with more than a 1-week interval between the sessions. Each session consisted of a night to adjust to the new sleep environment, a night to administer the drug and measure nocturnal PSG, and the day after to evaluate sleepiness and psychomotor performance (Figure 1). The sleep of the participants at home was continuously monitored for 1 week with an actigraph (AMI Inc.,

Figure 1. Experimental protocol. Order and time of tests for subjective and objective sleepiness and psychomotor performance conducted on the day after drug administration. PSG, polysomnography; VAS, Visual Analog Scale; AAT, Alpha Attenuation Test; DSST, Digit Symbol Substitution Test; SRT, simple reaction time; CRT, choice reaction time; MSLT, Multiple Sleep Latency Test

Ardsley, NY, USA). The mean sleep onset time was set relative for each participant at midnight (00:00). Intake of caffeinated drinks, alcoholic drinks, and nicotine products was prohibited 24 h prior to each session. The participants arrived at the testing center at 19:00 on the evening of the adjustment night (Day 1), PSG sensors were attached, and lights were turned out at 00:00. Lights were turned on, and the participants were instructed to get out of bed at 08:00. At 23:45 on the night that the drug was administered (Day 2), the participants were orally administered either DPH 50 mg, or KTF 1 mg, or zolpidem (ZPD) 10 mg as the control standard drug, or placebo (antiflatulent with *Bifidobacterium* species) inserted into opaque capsules. Lights were turned off, and PSG measurements began. On the day after administration (Day 3), lights were turned on, and the participants were instructed to arise at 08:00. That morning, the participants consumed a breakfast of 500 kcal and were then evaluated for objective and subjective sleepiness (see the following text) and psychomotor performance during the morning (9–11 h after drug administration) and afternoon (13–15 h after drug administration). $T_{1/2}$ (T_{max}) for KTF, DPH, and ZPD in healthy Japanese adults are 6.72 h (2.8 h) (Novartis, 2002), 5–8 h (2–4 h) (Glazko *et al.*, 1974), and 2 h (1.7 h) (Buysse, 2011), respectively.

The study drugs were randomly assigned to the four administration sessions. The order of administration, which was based on a Latin square design, was determined by a controller unrelated to the study.

Measured parameters

Polysomnography. Polysomnography (Grass Technologies™, West Warwick, RI, USA) was conducted to measure sleep architecture on the evening that each drug was administered as well as sleepiness the next day. The sleep stages were recorded continuously throughout the night and determined using the Rechtschaffen and Kales criteria (Rechtschaffen and Kales, 1968), brain waves, eye movement, electromyogram of the mentalis muscle, and electrocardiogram. During the screening, thoracic–abdominal breathing, air flow determined with a thermistor, electromyography of a lower limb muscle (tibialis anterior), and arterial oxygen saturation were also measured to rule out disorders such as sleep respiratory disorders and periodic limb movement disorder.

Data analysis was conducted and double checked by a technician unfamiliar with the study and the participants. Sleep parameters were calculated as follows: total sleep time (TST), defined as the total period of sleep time while in bed from lights out to arising time, excluding any wakeful period; sleep efficiency, the ratio of TST during the total time in bed; sleep latency (SL), the period between going to bed and falling asleep; and rapid eye movement (REM) latency, the time from falling asleep to the first REM cycle. For each sleep stage (Stage 1, Stage 2, slow wave sleep, and REM), the emergence ratio to TST was computed. Regarding awakening while in bed, total awake time was composed of all wakeful periods during the total time in bed, whereas awake time after sleep onset excluded SL from the total awake time. Arousal was calculated by dividing the number of awakenings by TST shown by brain waves appearing over 3-s epochs during sleep.

Evaluation of sleepiness. A Visual Analog Scale (VAS) was used to evaluate subjective sleepiness on Day 3 (McCormack *et al.*, 1988). The participants were asked to mark their degree of sleepiness on a 0–100 mm straight line, where the left end represented the strongest state of sleepiness and the right end represented a state with no sleepiness. The distance from the left end was taken as the VAS score.

The Multiple Sleep Latency Test (MSLT) (Carskadon *et al.*, 1986) and Alpha Attenuation Test (Alloway *et al.*, 1997) were used to assess objective sleepiness. The MSLT measures SL during a 20-min session in which the participant has the chance to sleep, where SL is the time from lights out until the participant enters sleep. These sessions were conducted in the morning and afternoon of Day 3. The time the participant took to reach the state where he or she was in a sleep stage for over 50% of a 30-s epoch after lights off (SL) was measured every 30 s on the basis of the brainwave criteria of Rechtschaffen and Kales (1968). The mean SL for the morning + afternoon sessions was calculated. When participants did not enter sleep during the MSLT, SL was set at 20 min.

In the Alpha Attenuation Test, eyes were opened and closed alternatively three times over a 1-min period. The alpha attenuation coefficient (AAC) was obtained by dividing the 8–13 Hz α power value derived from electrodes 02-A1 at eyes closed by α power at eyes open (Alloway *et al.*, 1997). The closer AAC was to 0, the lower the level of wakefulness.

Tests of psychomotor performance. Psychomotor performance on Day 3 was assessed with the (i) *n*-back test, (ii) three different tasks to measure reaction time (RT) to a stimulus, and (iii) the Digit Symbol Substitution Test (DSST).

(i) The *n*-back test is a working memory task that evaluates RT and error in recalling a stimulus *n* times back in a series of different stimuli (Kirchner, 1958). The participants are shown four consecutive circles at 1.8-s intervals on a computer monitor. The circles are arranged randomly, with one circle displayed red and the other three circles displayed blue. The participants are asked to push the numbered button that corresponds to the place where the red circle was *n* times before the currently displayed configuration. One-back tasks ask the placement directly before the current configuration. One-back, two-back, and three-back tasks were conducted in the present study. Each *n*-back task was conducted 60 times per session, and the mean RT and percent error were calculated. RTs less than 100 ms were considered too short to make a fair judgment and were thus excluded from the analysis.

(ii) Three different tasks were conducted as tests of RT: the simple reaction time (SRT) test, the go/no go test, and the choice reaction time (CRT) test. The SRT test measures the time required before detection of a given stimulus (Tiplady, 1988); the participants were asked to press a designated button as quickly as possible when a '+' symbol appeared on the computer monitor, and RT was measured. This was conducted 56 times over one session, and mean RT was calculated. The go/no go test involves participants immediately pressing a button when a go signal is displayed but remaining stationary when a no go signal is displayed. The go and no go signals are displayed in random order (Newman *et al.*, 1985). In this study, 'O' was set as the go signal and '×' as the no go signal. Signals were displayed 50 times in one session, and the mean RT for the go signal was calculated. The CRT with multiple stimuli requires participants to respond to

each stimulus appropriately (Sherwood and Kerr, 1993). In this study, nine squares (■) were shown in a 3 × 3 configuration, and one square (■) was randomly replaced with a triangle (▲). The participants were instructed to press the number key that corresponded to the placement of the different shape. The task was completed 60 times for one session. RTs less than 100 ms were considered too short to make a fair judgment and were excluded from the analysis.

(iii) The DSST assigns nine different shapes to the numbers one through nine. The participants were asked to enter the shape that corresponds to an indicated number (Wechsler, 1955). One session lasted 90 s, and the number of responses was determined by the number of correctly recorded shapes.

Statistical analysis

Because the Kolmogorov–Smirnov test showed normal distribution of PSG parameters in all drug sessions, Dunnett's test was conducted to compare the drug sessions. Morning and afternoon VAS normality, mean SL determined by the MSLT, AAC, and psychomotor test mean scores could not be substantiated. Therefore, Steel's test was conducted for between-drug session comparisons. SPSS for Windows 11.5.1 (SPSS Inc., Chicago, IL, USA) was used for Dunnett's test and Wilcoxon's signed rank sum test, with significance set at $p < 0.05$. The critical value of each session for the Steel test was set at 2.349. All data are shown as means standard error.

RESULTS

Influence of each drug on sleep architecture

The PSG parameters of each drug are shown in Table 1. Compared with the placebo, DPH had significantly

Table 1. Sleep parameters after administration of each drug

Sleep parameter	PCB	ZPD	DPH	KTF	p-value
Total sleep time (min)	441.9 ± 5.0	446.7 ± 5.3	444.1 ± 5.5	444.5 ± 3.5	n.s.
Sleep efficiency (%)	91.5 ± 1.2	92.4 ± 1.0	92.2 ± 1.2	92.0 ± 0.8	n.s.
Sleep latency (min)	13.2 ± 3.3	17.3 ± 4.5	17.6 ± 4.9	16.8 ± 3.5	n.s.
REM latency (min)	99.9 ± 10.8	96.0 ± 10.0	138.5 ± 13.5[a]	91.8 ± 10.2	<0.05
Time spent in sleep stage/total sleep time (%)					
Stage1	10.4 ± 1.0	8.2 ± 1.0	8.7 ± 0.8	8.7 ± 0.8	n.s.
Stage2	51.9 ± 1.2	51.6 ± 1.4	54.7 ± 1.1	55.1 ± 1.1	n.s.
Slow wave sleep	17.2 ± 1.4	20.8 ± 1.8	20.5 ± 1.6	17.3 ± 1.3	n.s.
REM sleep	20.5 ± 1.6	19.4 ± 0.9	16.2 ± 0.9[a]	18.9 ± 0.8	<0.05
Total awaking time (min)	41.2 ± 5.8	36.7 ± 5.0	37.8 ± 5.7	38.8 ± 4.0	n.s.
Wake after sleep onset (min)	28.3 ± 4.1	19.5 ± 2.0	21.1 ± 2.6	22.4 ± 2.7	n.s.
Arousal (no./h of sleep)	12.3 ± 0.9	10.4 ± 0.8	11.4 ± 0.9	11.7 ± 0.9	n.s.

REM, rapid eye movement; PCB, placebo; ZPD, zolpidem; DPH, diphenhydramine; KTF, ketotifen; n.s., not significant.
[a]Significant difference from placebo ($p < 0.05$) determined by Dunnett's test. Data are expressed as mean ± standard error of mean.

longer REM latency (99.9 ± 10.8 vs. 138.5 ± 13.5 s) and reduced %REM (20.5 ± 1.6 vs. $16.2 \pm 0.9\%$). No significant differences in other sleep parameters were observed between ZPD, antihistamines (DPH and KTF), and the placebo.

Assessment of subjective sleepiness postadministration

Table 2 shows subjective and objective sleepiness the day after administration of each drug and the results of the different psychomotor performance tasks. Among the different drug groups, significant differences were observed in mean next-day and next-morning sleepiness but not next-afternoon sleepiness.

Mean next-day sleepiness caused by ZPD was comparable with that caused by the placebo. It was significantly strong with KTF (test statistic = 2.723) and tended to be strong with DPH (test statistic = 2.019). Likewise, next-morning sleepiness caused by KTF was significantly strong (test statistic = 3.192) and that caused by DPH tended to be strong (test statistic = 2.223) compared with the placebo. Next-morning sleepiness was significantly stronger than next-afternoon sleepiness for all drug sessions. This difference was smallest with ZPD (VAS score 9.7 ± 5.3) and large for DPH and KTF (18.5 ± 5.9 and 21.4 ± 4.0, respectively).

Table 2. Subjective sleepiness, objective sleepiness, and psychomotor performance on the day after administration of each drug

Test	Time	Treatment session			
		PCB	ZPD	DPH	KTF
VAS	AM	59.5 ± 4.9^a	57.6 ± 4.6^a	74.0 ± 3.8^a	80.2 ± 3.9^{ab}
	PM	46.5 ± 5.6	47.9 ± 4.9	55.5 ± 4.7	58.9 ± 4.2
	Mean	53.0 ± 4.5	52.8 ± 4.0	64.8 ± 3.1	69.5 ± 3.5^b
MSLT (min)	AM	4.2 ± 1.0	3.5 ± 0.8	2.3 ± 0.5	1.1 ± 0.1^{ab}
	PM	5.0 ± 1.1	5.7 ± 1.3	3.4 ± 0.9	1.9 ± 0.3^b
	Mean	4.6 ± 0.6	4.6 ± 0.9	2.9 ± 0.5	1.5 ± 0.2^b
AAC	AM	2.8 ± 0.3^a	2.8 ± 0.4	2.1 ± 0.2	1.6 ± 0.2^b
	PM	2.1 ± 0.3	2.6 ± 0.4	2.3 ± 0.4	1.5 ± 0.2
	Mean	2.5 ± 0.2	2.7 ± 0.3	2.2 ± 0.2^b	1.6 ± 0.1^b
DSST	AM	77.8 ± 3.3	77.3 ± 1.6	73.5 ± 2.7	70.8 ± 2.5^a
	PM	80.6 ± 3.1	79.6 ± 1.9	78.2 ± 3.8	77.8 ± 2.8
	Mean	79.2 ± 2.9	78.5 ± 1.6	75.9 ± 2.9	74.3 ± 2.3
SRT (ms)	AM	340.4 ± 32.6	328.1 ± 19.2	368.7 ± 30.0^a	403.8 ± 30.8^{ab}
	PM	320.6 ± 19.3	314.9 ± 14.0	336.5 ± 23.3	345.6 ± 20.4
	Mean	330.5 ± 24.1	321.5 ± 15.6	352.6 ± 22.8	374.7 ± 22.0
Go/no go (ms)	AM	507.3 ± 27.5	524.3 ± 32.9	677.3 ± 73.0	688.5 ± 51.5^{ab}
	PM	502.1 ± 34.2	508.3 ± 36.7	583.5 ± 60.9	557.7 ± 38.6
	Mean	504.7 ± 21.7	516.5 ± 24.3	630.4 ± 47.5	623.1 ± 33.4
CRT (ms)	AM	685.0 ± 63.2	674.1 ± 44.3	747.8 ± 58.0^a	867.5 ± 61.4^{ab}
	PM	619.3 ± 40.0	597.9 ± 26.9	640.3 ± 39.6	722.8 ± 50.4
	Mean	652.2 ± 37.3	636.0 ± 26.3	694.1 ± 35.6	795.2 ± 40.8
One-back test %Error (%)	AM	6.7 ± 3.4	3.6 ± 1.3^b	7.3 ± 2.4^b	16.3 ± 4.5^b
	PM	2.7 ± 1.1	5.7 ± 2.4^b	5.4 ± 1.6^b	8.3 ± 2.4^b
	Mean	4.7 ± 1.7	4.7 ± 1.8	6.3 ± 1.5^b	12.3 ± 2.6^b
Two-back test %Error (%)	AM	9.1 ± 2.7	11.4 ± 3.5	15.1 ± 4.7	20.5 ± 3.6^b
	PM	5.6 ± 1.9	9.2 ± 3.4	8.3 ± 2.6	13.9 ± 3.2^b
	Mean	7.3 ± 1.6	10.3 ± 3.1	11.7 ± 2.7	17.2 ± 2.9^b
Three-back test %Error (%)	AM	16.1 ± 3.5	15.4 ± 3.2	23.3 ± 4.6	30.2 ± 4.6^{ab}
	PM	12.5 ± 2.7	10.4 ± 2.8	13.9 ± 3.6	19.8 ± 3.9
	Mean	14.3 ± 2.7	12.9 ± 2.4	18.6 ± 3.5	25.0 ± 3.8^b
One-back test RT (ms)	AM	348.4 ± 29.4	338.9 ± 25.9	323.3 ± 26.3	359.0 ± 21.4
	PM	324.7 ± 30.8	327.7 ± 27.1	313.3 ± 19.2	328.0 ± 20.4
	Mean	336.6 ± 27.8	333.3 ± 25.8	318.3 ± 21.7	343.5 ± 19.5
Two-back test RT (ms)	AM	313.5 ± 26.0	299.0 ± 23.8	296.4 ± 29.0	338.5 ± 28.8^a
	PM	276.5 ± 18.5	293.3 ± 23.2	266.2 ± 20.9	272.4 ± 18.4
	Mean	295.0 ± 20.2	296.2 ± 21.4	274.6 ± 23.2	305.5 ± 20.1
Three-back test RT (ms)	AM	287.3 ± 23.2	284.0 ± 22.1	317.4 ± 34.0	339.0 ± 27.6
	PM	254.3 ± 17.7	265.0 ± 17.6	267.3 ± 19.2	308.4 ± 35.8
	Mean	270.8 ± 17.9	274.5 ± 18.8	292.4 ± 24.4	323.7 ± 30.0

VAS, Visual Analog Scale; MSLT, Multiple Sleep Latency Test; AAC, alpha attenuation coefficient; DSST, Digit Symbol Substitution Test; SRT, simple reaction time; CRT, choice reaction time; RT, reaction time. PCB, placebo; ZPD, zolpidem; DPH, diphenhydramine; KTF, ketotifen.
[a]Significant difference from PM determined by Wilcoxon signed rank test ($p < 0.05$).
[b]Significant difference from placebo determined by Steel's test ($p < 0.05$). Data are expressed as mean $\pm$ standard error of mean.