Assessment of objective sleepiness postadministration

Mean SL as determined by the MSLT on the day after administration of each drug is shown in Table 2 and Figure 2. Significant group differences in mean SL were observed for each drug for next-day SL as well as for next-morning SL and next-afternoon SL.

The mean next-day SL with ZPD was statistically equivalent to that for the placebo, whereas it tended to be reduced with DPH (test statistic = 1.760) and significantly reduced with KTF (test statistic = 3.357).

Similarly, the next-morning SL and next-afternoon SL with ZPD were statistically equivalent to those with the placebo. However, these values tended to be shorter with DPH compared with the placebo (test statistic = 2.066 and 2.159, respectively) and significantly shorter with KTF (test statistic = 4.202 and 3.474, respectively). For all drug sessions, next-morning SL was shorter than next-afternoon SL, and the difference was smallest with KTF.

Level of wakefulness based on AAC findings showed similar tendencies to that determined by the MSLT. For each session, significant differences in mean AAC were observed between the drug groups for next-day AAC and for next-morning AAC but not for next-afternoon AAC.

Mean next-day AAC with ZPD was statistically equivalent to that with the placebo. However, it was slightly lower with DPH and significantly lower with KTF (test statistic = 2.745). Similarly, compared with the placebo, next-morning AAC was somewhat higher with DPH (test statistic = 1.807) but was significantly lower with KTF (test statistic = 3.357).

Psychomotor performance scores postadministration

Results of the *n*-back test for each drug on the day after administration are shown in Table 2 and Figure 3. As the degree of difficulty increased from the one-back

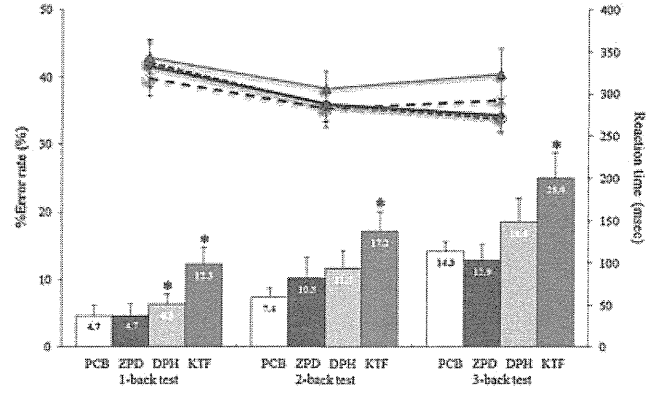

Figure 3. Psychomotor performance measured by the *n*-back test after administration of each drug. Percent error rate (left vertical axis, column) and reaction time (right vertical column, line) in the *n*-back test are shown by drug type. *Significant compared with placebo ($p < 0.05$; one-way analysis of variance followed by Dunnett's test). ZPD, zolpidem; DPH, diphenhydramine; KTF, ketotifen; PCB, placebo

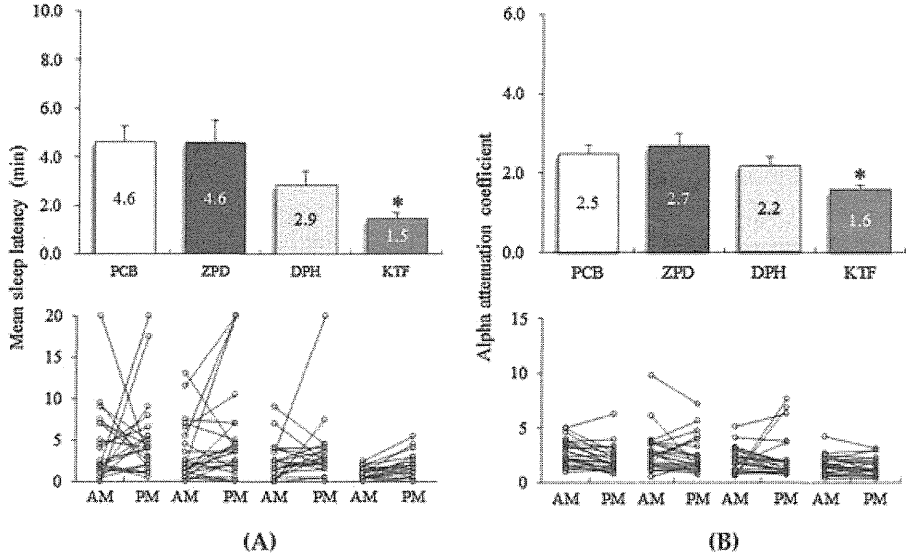

Figure 2. Objective sleepiness after administration of each drug measured by Multiple Sleep Latency Test (A) and alpha attenuation test (B). (A) Mean sleep latency (SL), by drug type, on the day after administration of each drug is shown in the upper panel. In the lower panel, SL of each participant during the morning and afternoon sessions is plotted. SL of 20 min indicates that the participants did not fall asleep during the sleep trial. (B) The upper panel shows the mean alpha attenuation coefficient, by drug type, on the day after administration of each drug. In the lower panel, the alpha attenuation coefficient of each participant during the morning and afternoon sessions are plotted. The smaller the value for SL and the alpha attenuation coefficient, the less wakeful the participant. *Significant compared with the placebo ($p < 0.05$; Steel's test). ZPD, zolpidem; DPH, diphenhydramine; KTF, ketotifen; PCB, placebo

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task to the three-back task, the percent error increased for all drug sessions. In terms of mean next-day percent error, the percent error with ZPD was similar to that with the placebo. However, it was significantly increased on the one-back task with DPH (test statistic = 2.441) and was increased on all back tests with KTF (one-back, two-back, and three-back tasks = 3.404, 2.981, and 2.370, respectively). In comparison with the placebo sessions, the next-morning percent error was significantly decreased on the one-back task with ZPD (test statistic = 3.521) and significantly increased on all back tasks with KTF (one-back, two-back, and three-back tasks = 4.953, 3.075, and 2.559, respectively). The next-afternoon percent error on the one-back and two-back tasks was significantly increased with KTF compared with the placebo (test statistic = 4.976 and 3.638, respectively). Although the next-morning percent error was higher than the next-afternoon one for all drug sessions, the largest difference was seen for the three-back task with KTF (10.4 ± 4.0, $p < 0.05$). In contrast, there were no significant differences in RT between the four sessions or between levels of difficulty ($n = 1$–3) (Table 2, Figure 3). However, next-morning RT on the two-back task was significantly longer than next-afternoon RT after KTF administration (Table 2).

On the three types of tasks for measuring RT in reaction to a stimulus, all drugs tended to show a prolonged time on the SRT, go/no go test, and CRT as task difficulty increased (Table 2). Mean next-day RT tended to be longer with DPH and KTF than with the placebo, but the differences were not significant. Next-morning RT was significantly longer for the SRT, go/no go test, and CRT following KTF administration compared with placebo administration (test statistics = 2.464, 2.927, and 2.441, respectively). In addition, next-morning RT was significantly longer than next-afternoon RT for the SRT and CRT after DPH administration and for the SRT, go/no go test, and CRT after KTF administration. No significant differences in the correct response rates for any of the tasks were observed between the four sessions or between different levels of difficulty (data not shown).

The number of correct responses on the DSST was in the order of placebo, ZPD, DPH, and KTF. However, no significant differences were seen between the drug groups for the mean number of correct responses for the next day, the next morning, or the next afternoon (Table 2). The number of responses tended to increase during the next-afternoon compared with the next-morning in all sessions. Whereas the differences in number of responses were insignificant following administration of the placebo, ZPD, and DPH, the number of responses the next morning after KTF administration was significantly lower than that the next afternoon.

DISCUSSION

To examine the carryover effects of DPH and KTF, which are first-generation and second-generation antihistamines with strong central sedative–hypnotic effects, we conducted a randomized, double-blind, placebo-controlled crossover study with the use of two controls, a placebo and the standard sleep aid ZPD. The sedative–hypnotic effects of these drugs were examined using various testing modalities such as subjective and objective sleepiness indicators, as well as suppression of psychomotor performance on multiple tasks (RT and accuracy). The results demonstrated that DPH and KTF are associated with a risk of significantly strong carryover effects, mainly hypnotic and sedative effects. Compared with the placebo, significantly strong subjective and objective sleepiness and suppression of psychomotor performance were observed the day after administration of KTF, followed by DPH. In general, first-generation antihistamines cross the BBB more effectively than second-generation antihistamines (Yanai and Tashiro, 2007), and the results of this study also suggest that first-generation antihistamines have a higher risk for sleepiness and poor psychomotor performance. However, DPH and KTF used in the present study are the first-generation and second-generation antihistamines, respectively, that readily cross the BBB, and therefore, it is necessary to keep in mind that, regardless of the generation, antihistamines with effective BBB-crossing properties develop strong carryover effects on the day after administration.

In contrast, ZPD, which is the standard medication for secondary insomnia, showed no carryover effects. In the psychomotor performance tests, sedative–hypnotic effects were more pronounced during more difficult tasks requiring working memory, as in the *n*-back task, than during relatively easy and simple tasks such as the SRT. Furthermore, decreases in accuracy, rather than in RT, were prominent after antihistamine administration.

No significant hypnotic and sedative carryover effects were observed after ZPD administration, the standard drug frequently used in clinical practice and used in this study as a control. ZPD is extremely fast acting, with short T_{max} at 1.7 h and $T_{1/2}$ at 2 h (Buysse, 2011), and hypnotic and sedative carryover effects are reported to be low (Rojas-Zamorano *et al.*, 2009). This held true for the participants in the present study as no significant differences were observed between ZPD and

the placebo for any items, including mean SL on the MSLT, AAC, and psychomotor performance tests. This was in clear contrast to the results obtained with the antihistamines.

We also compared sleep architecture from the night before administration as it is a confounding factor in the assessment of sleepiness and psychomotor performance suppression on the day after drug administration. No significant differences were observed between the placebo, ZPD, DPH, and KTF for the majority of sleep parameters, including TST, sleep efficiency, and rates of deep sleep. Interestingly, after DPH administration, a prolonged REM latency (mean = 39 min) and decreased %REM (mean 4.3%) were observed in comparison with the placebo. The present findings are consistent with previous reports on the prolongation of REM latency and a reduction in the percentage of REM sleep with first-generation antihistamines such as chlorpheniramine (Adam and Oswald, 1986; AASM, 2005; Boyle *et al.*, 2006; Rojas-Zamorano *et al.*, 2009; Church *et al.*, 2010; Buysse, 2011). The mechanism behind this modulatory effect on REM sleep by DPH and chlorpheniramine is not yet understood. However, in the present study, KTF did not modulate REM sleep. Thus, changes in REM sleep must have had very limited influence over the hypnotic and sedative carryover effects that we observed on the day after administration of the antihistamines that readily cross the BBB. Future study may be needed to examine instead the risks of emergence of rebound REM sleep-related symptoms (insomnia, nightmares, and REM sleep behavior disorder) when DPH is suddenly terminated after long-term use. Overall, at least among the healthy participants in this study, we did not observe any apparent changes in sleep architecture that can explain the differences in sleepiness and psychomotor performance between ZPD and the antihistamines the day after administration.

The present findings suggest a risk of carryover effects far surpassing pharmacokinetic predictions for antihistamines that readily cross the BBB. The strength of the carryover effects of DPH and KTF was significantly high the next morning (9–11 h postadministration) and tended to decrease the next afternoon (13–15 h postadministration). At first glance, this appears to be a change associated with the blood kinetics of antihistamines. However, T_{max} is 2.8 h and $T_{1/2}$ is 6.72 h for KTF (in healthy Japanese adults) (Novartis, 2002). The corresponding values for DPH are 2–4 h and 5–8 h (Glazko *et al.*, 1974). Therefore, the concentration of KTF and DPH administered before sleep would have dropped to half of the peak concentration at the time of the next-morning assessment. Although serum drug concentrations were not measured in the present study, it appears that the sedative–hypnotic effects of KTF and DPH continued significantly longer than the period during which such carryover effects were expected from their blood kinetics. In a positron emission tomography study using LigandTracer for histamine receptors in the brain, Yanai and colleagues (2007) demonstrated a large discrepancy between blood kinetics and receptor occupancy of antihistamine in the brain (Zhang *et al.*, 2010). Among the participants in their two studies, the receptor occupancy was 56% at 1.5 h after DPH administration (Tashiro *et al.*, 2008) but remained as high as 45% even after 12 h (Zhang *et al.*, 2010). Receptor occupancy at 2.7 h after KTF administration has also shown to be as high as 70% (Tashiro *et al.*, 2006; Yanai and Tashiro, 2007). Although there is no data on the successive changes in receptor occupancy over the 2.7-h period after KTF administration, it is speculated that high levels of occupancy are maintained over many hours, given its clinical characteristics as a strong sedative, despite being a second-generation antihistamine. These findings indicate that some antihistamines do have carryover effects that constitute lasting sedative–hypnotic side effects even after blood drug levels have lowered (Yanai and Tashiro, 2007; Zhang *et al.*, 2010).

The following limitations of the present study should be considered in interpreting its clinical meaningfulness. Because this study tested healthy individuals, the usefulness of antihistamines that readily cross the BBB in the treatment of patients with allergies or insomnia cannot be determined from the results of this study. However, it is unlikely that the carryover effects of antihistamines would not occur in patients with physical illness or poor sleep. It is therefore necessary to clarify whether the benefits outweigh the risks of using such antihistamines to treat insomnia secondary to allergies and, more specifically, to confirm that antihistamines alleviate insomnia and that quality of life improvement cancels out any carryover effects these drugs bring about. At present, there have been no clinical trials to verify the risk–benefit balance of antihistamines that readily cross the BBB to treat insomnia secondary to allergies. We believe that prescriptions should be adjusted for each target symptom, with second-generation antihistamines with a lower BBB-crossing tendency being used to treat allergies and concomitant use of hypnotics to treat secondary insomnia. Important drug options would include the standard drugs such as ZPD, used as a control in this study whose treatment effect for secondary insomnia has been demonstrated (Asnis *et al.*, 1999), and hypnotics with low risks of sedative–hypnotic carryover effects and high ω1 receptor specificity (Depoortere *et al.*, 1986; Perrault *et al.*, 1990; Benavides *et al.*, 1992; Sanger *et al.*, 1994).

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CONCLUSION

This randomized, double-blind, placebo-controlled crossover study examined the carryover effects the day after administering antihistamines that readily cross the BBB before sleep. The results showed that antihistamines taken before sleep significantly increased subjective and objective sleepiness and significantly reduced psychomotor performance the next day, generating clinically identifiable sedative–hypnotic carryover effects. The carryover effects suggest the danger of their presence even following the lowering of blood drug levels. These carryover effects of antihistamines are adverse events that can greatly interfere with the quality of life of patients. Therefore, the present findings indicate that thorough consideration must be given to the risks of readily using antihistamines that easily cross the BBB for the treatment of insomnia secondary to allergies.

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CONFLICT OF INTEREST

No conflict of interest declared.

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EVENING PREFERENCE IS RELATED TO THE INCIDENCE OF DEPRESSIVE STATES INDEPENDENT OF SLEEP-WAKE CONDITIONS

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Although evening preference has recently been identified as a risk factor for depression, it has not been substantiated whether evening preference is a direct risk factor for depressive states, or if it is associated secondarily through other factors, such as delayed sleep timing and shortened sleep duration. The objective of this study is to investigate associations in Japanese adult subjects between evening preference and incidence of depressive states, adjusting for various sleep parameters related to depressive states. The Morningness-Eveningness Questionnaire (MEQ), the Pittsburgh Sleep Quality Index (PSQI), and the Center for Epidemiologic Studies Depression Scale (CES-D) were administered to 1170 individuals (493 males/677 females; mean and range 38.5 and 20–59 yrs) to assess their diurnal preferences, sleeping states, and presence of depression symptoms. Subjects were classified into five chronotypes based on MEQ scores. Evening preference was associated with delayed sleep timing, shortened sleep duration, deteriorated subjective sleep quality, and worsened daytime sleepiness. Logistic regression analysis demonstrated that the extreme evening type (odds ratio [OR] = 1.926, $p = .018$) was associated with increased incidence of depressive states and that the extreme morning type (OR = 0.342, $p = .038$) was associated with the decreased incidence of depressive states, independent of sleep parameters, such as nocturnal awakening (OR = 1.844, $p < .001$), subjective sleep quality (OR = 2.471, $p < .001$), and daytime sleepiness (OR = 1.895, $p = .001$). However, no significant associations were observed between the incidence of depressive states and sleep duration, sleep timing, and sleep debt (levels of insufficient sleep). Although the findings of this study do not demonstrate a causative relationship between evening preference and depression, they do suggest the presence of functional associations between mood adjustment and biological clock systems that regulate diurnal preference. They also suggest that evening preference might increase susceptibility to the induction of mood disorders. (Author correspondence: mishima@ncnp.go.jp)

Keywords Chronotype; Circadian rhythms; Depression; Eveningness; Neuropsychopharmacology; Sleep

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INTRODUCTION

Depression is one of the most common mental illnesses. Its prevalence is very high, with the 12-month prevalence being 3 ~ 5% (Kawakami et al., 2005; Narrow et al., 2002) and lifetime prevalence being 3 ~ 20% (Kessler et al., 2007). Causing tremendous clinical and socioeconomic impact on afflicted individuals, depression is undoubtedly a serious illness. The 2001 World Health Organization (WHO) Global Burden of Disease analysis, using disability-adjusted life years (DALYs), reports that depression is a primary risk factor for years of life lived with a disability (Lopez et al., 2006).

Although the pathogenic mechanisms of depression are not fully understood, existing studies report possible associations with biological factors, such as decreased monoamine concentrations in the synaptic cleft, increases in amine sensitivity of the postsynapse, hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis, hippocampal atrophy, and inhibition of neurogenesis (Fava & Kendler, 2000; Krishnan & Nestler, 2008; Nestler et al., 2002). Studies also identify the following risk factors for depression: life stress (Caspi et al., 2003; Risch et al., 2009), being female (Young & Korszun, 2009), and older age (Alexopoulos et al., 2005). In addition, recent studies suggest that diurnal preference (morningness/eveningness, or chronotype), which is a functional component of the biological clock, is also a risk factor.

Studies of patients with depression (Drennan et al., 1991) and patients with bipolar disorder (Ahn et al., 2008; Mansour et al., 2005; Wood et al., 2009) report that for both illnesses patients demonstrated significantly greater associations with evening preference (eveningness) compared to control groups. Another study of patients with depression also reports that increased evening preference is significantly associated with severity of illness (Gaspar-Barba et al., 2009). Associations between the incidence of depressive state and evening preference are also confirmed in studies of healthy persons. Chelminski et al.'s study (1999) of 1617 young college students and Hirata et al.'s study (2007) of 161 medical school students, both investigating associations between chronotype and incidence of depressive symptoms, report that evening-type individuals are likely to experience depressive symptoms. A similar finding is reported by Hidalgo et al. (2009), who conducted a study with 200 subjects and observed an association between the incidence of depressive states and evening preference, but not morning or intermediate preference. Collectively, these results support an association between evening preference and incidence of depression or depressive states. However, they do not adequately substantiate whether evening preference is directly associated with the onset of depression or whether it is associated secondarily through other sleep problems, such as shortened sleep duration caused by delayed sleep timing. Indeed, compared to morning- or intermediate-type subjects, those with extreme evening preference are more

likely to experience delayed sleep onset and wake times (Ishihara et al., 1987; Park et al., 1997), which leads to reduced sleep during weekdays when time is constrained due to school attendance or work, and consequently results in increased daytime sleepiness caused by sleep debt (Taillard et al., 1999). These persisting sleep insufficiencies could serve as a risk for depressive state (Meerlo et al., 2008; Novati et al., 2008).

Many previous studies exploring the association between evening preference and depressive states have issues of small sample size and biases in subject attributes, including age, and they do not adequately examine differences in sleep properties across chronotypes, which are primary confounding factors. Therefore, these associations have not yet been adequately substantiated. Thus, the objective of this study is to investigate whether there is a direct association between evening preference and depressive states, adjusting for various sleep parameters accompanying differences in chronotype, such as insufficient sleep (sleep debt), sleep duration, sleep quality, and sleep timing.

METHODS

Participants and Survey Methods

Participants were 1814 Japanese persons who were working at universities or medical institutions, or were members of their families (age range, 10 to 97 yrs), and who consented to participate. Because the structure of sleep remarkably changes in children and adolescents or those over 60 yrs of age (Carrier et al., 1997; Ohayon et al., 2004), subjects <19 or >60 yrs were excluded due to the effects of age. Thus, the final sample consisted of 1170 subjects, ranging in age from 20 to 59 yrs (male/female = 493/677; mean age ± SD = 38.5 ± 12.3 yrs) for analysis.

The questionnaire survey was administered to all qualified subjects and comprised the Morningness-Eveningness Questionnaire (MEQ) developed by Horne and Ostberg (1976) to assess diurnal preference, the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) to assess sleep parameters, and the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977) to assess mood states. Subjects were asked to complete the questionnaires within the 3 h between 09:00 and 12:00 h on a weekday. For those working shifts (at least once a week, 45.5%; average frequency/wk, 1.10 times), surveys were administered in the morning after ≥3 consecutive days of daytime work, asking them to think about the situation of consecutive daytime work. Written consent was obtained from all participants following explanations about the study and its purposes. The study was approved by the Institutional Review Board of the National Center of Neurology and Psychiatry, and met the international standards for ethical chronobiological research on human beings (Portaluppi et al., 2008).

Determination of Diurnal Preferences

Diurnal preference was evaluated by the MEQ. This questionnaire is composed of 19 items with the total score ranging from 16 to 86 points, higher scores indicating an inclination to morning preference and lower scores indicating an inclination to evening preference. Validity of the Japanese version of the MEQ was confirmed by Ishihara et al. (1984).

Evaluation of Subject Sleep Properties

Sleep parameters were calculated from the MEQ and PSQI. The PSQI is a questionnaire that screens sleep disorders from habitual sleep patterns over a 1-month period, and uses a cut-off score of 5.5 points (Buysse et al., 1989). A survey using the Japanese version of the PSQI with this cut-off score reported 85.7% sensitivity and 86.6% specificity for primary insomnia (Doi et al., 2000).

As indicators of desired sleep properties, the following variables were calculated from the MEQ subscales: Desired Sleep Onset Time (dSOT), Desired Wake Time (dWT), and Desired Sleep Time (dSPT; defined as the elapsed interval from dSOT to dWT). As indicators of actual sleep properties, the following variables were calculated from the PSQI subscales: Actual Bed Time (aBT), Actual Sleep Onset Time (aSOT), Actual Wake Time (aWT), and Actual Sleep Time (aSPT; defined as the elapsed interval from aSOT to aWT). As indicators for sleep debt, the following delta (Δ) variables were calculated, subtracting actual sleep properties from desired sleep properties: $\Delta SPT = dSPT - aSPT$; $\Delta SOT = dSOT - aSOT$; and $\Delta WT = dWT - aWT$. As indicators for sleep quality, the following rank data were used: nocturnal awakening (Q5-d), subjective sleep quality (Q6), and daytime sleepiness (Q8).

Evaluation of Depressive States

Depressive states were evaluated based on total CES-D scores. Following the cutoff values determined by Radloff (1977), scores ≥ 16 were identified as indicating the incidence of depressive states. In the Japanese version used in this study, the same cut-off value of 16 was also identified (Shima et al., 1985).

Statistical Analysis

Pearson's correlation coefficients were used to determine the degree of association between age and MEQ scores. In addition, chi-square tests were used for comparisons of ratio data of males and females and shift-workers across chronotypes, and one-way analysis of variance (ANOVA)

was used for age comparisons. As for the effect size index, Cramer's V in the chi-square tests and partial eta-squared (η_p^2) in the ANOVA were calculated. With the number of row or column equaling 2, the value of 0.1 for Cramer's V represents a small effect size, 0.3 a medium effect, and 0.5 a large effect size (Cohen, 1988).

One-way analysis of covariance (ANCOVA) adjusted for sex, age, and shiftwork was used for comparisons of sleep parameters (dSOT, dWT, dSPT, aSOT, aWT, aSPT, ΔSPT, ΔSOT, ΔWT, nocturnal awakening, subjective sleep quality, and daytime sleepiness) across chronotypes and for comparisons of CES-D scores. Then, multiple comparisons using the Bonferroni method were conducted on those with observed main effects, and significance probabilities were determined with appropriately adjusted p values (Wright, 1992). As for the effect size index, partial eta-squared (η_p^2) in a model with covariates was calculated.

In a logistic regression with the incidence of depressive states (CES-D scores $\geq$16) as dependent variables, the following independent variables were entered into the regression models using the forced entry method: demographic variables (sex, age, and presence of shiftwork), chronotype, and sleep parameters (aSPT, aSOT, aWT, ΔSPT, nocturnal awakening, subjective sleep quality, and daytime sleepiness). Regarding sex and shiftwork, "male" and "not shiftwork" were regarded as the reference categories. The aSPT, aSOT, and aWT variables were each divided into three categories, and levels at the mean scores were regarded as the reference categories. The ΔSPT variable was divided into two categories, "sufficient" (in the situation when aSPT is longer than dSPT) and "insufficient" (in the situation when aSPT is shorter than dSPT), with "sufficient" as the reference category. The nocturnal awakening and daytime sleepiness variables were divided into two categories: "low" ("Not during the past month" [=0], or "Less than once a week" [=1]), and "high" ("Once or twice a week" [=2], or "Three or more times a week" [=3]), with "low" as the reference category. The subjective sleep quality variable was divided into two categories: "good" ("Very good" [=0], or "Fairly good" [=1]), and "bad" ("Very bad" [=2], or "Fairly bad" [=3]), with "good" as the reference category.

SPSS version 11.5J (SPSS) was used for statistical analysis, setting 5% for all critical probability levels.

RESULTS

Diurnal Preferences

A distribution with negative skewness and kurtosis (Figure 1) represented the distribution of the MEQ scores (mean ± SD, 52.6 ± 9.3; range, 21–81; skewness, −0.155; kurtosis, −0.378). Correlations between age and MEQ

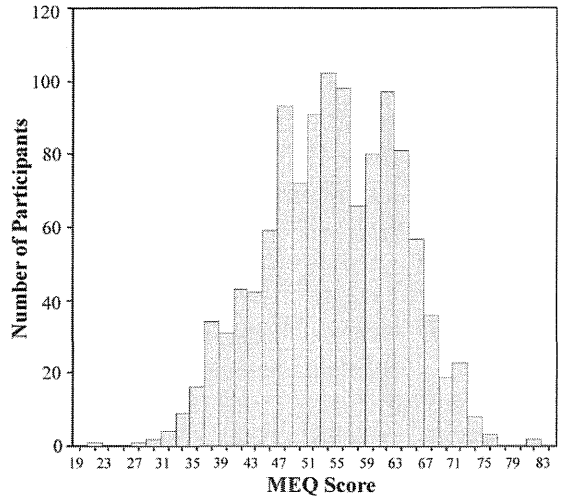

FIGURE 1 Frequency distribution of morningness-eveningness questionnaire (MEQ) score in our Japanese population sample. Horizontal axis indicates MEQ scores, and vertical axis indicates number of participants.

scores showed statistically significant positive correlations ($r = .498$, $p < .001$). Based on MEQ scores, subjects were divided into the following five chronotypes according to a 5-point (7%–24%–38%–24%–7%) grading method (Cajori, 1914): Extreme evening type (EE: 21–38 points), Evening type (E: 39–48 points), Intermediate type (I: 49–58 points), Morning type (M: 59–65 points), and Extreme morning type (MM: 66–81 points).

Table 1 shows subject mean ages and proportions of sex and shiftworkers by chronotype. Mean age increased significantly with shifts in the chronotype from EE to MM ($F(4, 1165) = 83.858$, $p < .001$, $\eta_p^2 = 0.224$). Concerning sex proportions, the I chronotype had the largest female proportion, and the proportion of males increased toward both ends of the morning/evening continuum ($\chi^2(4) = 33.696$, $p < .001$, $V = 0.170$). The evening-type groups had greater proportions of shiftworkers compared to morning-type groups ($\chi^2(4) = 38.237$, $p < .001$, $V = 0.185$).

TABLE 1 Demographic characteristics of the experimental subjects by chronotype

	Whole	Extreme Evening Type (EE)	Evening Type (E)	Intermediate Type (I)	Morning Type (M)	Extreme Morning Type (MM)
Number	1170	335	214	494	78	49
Sex (% Male)	42.1	50.7	36.4	36.6	42.3	63.3
Age (yrs)	38.46 ± 0.36	30.85 ± 0.59	36.09 ± 0.73	41.96 ± 0.48	47.37 ± 1.22	51.29 ± 1.54
Shiftwork (% Shiftworker)	45.5	57.5	51.0	38.3	36.6	25.0

Sleep Properties

Sleep properties (aBT, dSOT, dWT, aSOT, aWT) of the five chronotypes are shown in Figure 2. As preference shifted from morning (MM) to evening (EE), dSOT ($F(4, 1112) = 115.490$, $p < .001$, $\eta_p^2 = 0.294$) and dWT ($F(4, 1112) = 121.261$, $p < .001$, $\eta_p^2 = 0.304$) showed significant delays with means of 200 and 225 min, respectively. Similarly, aBT ($F(4, 1112) = 74.427$, $p < .001$, $\eta_p^2 = 0.212$), aSOT ($F(4, 1112) = 80.955$, $p < .001$, $\eta_p^2 = 0.226$), and aWT ($F(4, 1112) = 49.308$, $p < .001$, $\eta_p^2 = 0.151$) showed significant delays with means of 150, 160, and 95 min, respectively.

Sleep properties (dSPT, aSPT, ΔSPT, ΔSOT, ΔWT), nocturnal awakening, subjective sleep quality, and daytime sleepiness of the five chronotypes are shown in Table 2. As preference shifted toward evening, aSPT was significantly shortened ($F(4, 1112) = 9.216$, $p < .001$, $\eta_p^2 = 0.032$), whereas dSPT showed no significant differences across all five groups

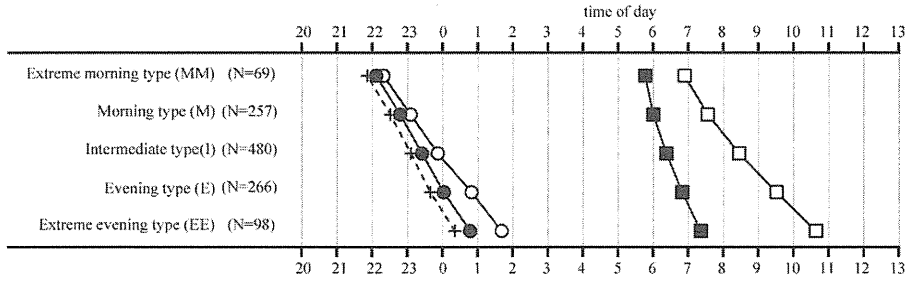

FIGURE 2 Sleep onset time and wake time by chronotype. Horizontal axis indicates time-of-day. Closed circle, open circle, closed box, open box, and dashed line indicate actual sleep onset time (aSOT), desired sleep onset time (dSOT), actual wake time (aWT), desired wake time (dWT), and actual bedtime (aBT), respectively.

TABLE 2 Sleep properties in the experimental subjects by chronotype

	Extreme evening type (EE)	Evening type (E)	Intermediate type (I)	Morning type (M)	Extreme morning type (MM)
Number	98	266	480	257	69
aBT (h:min)	0:21 ± 0:07	23:39 ± 0:04	23:06 ± 0:03	22:31 ± 0:04	21:51 ± 0:08
dSPT (h)	8.96 ± 0.17	8.69 ± 0.10	8.59 ± 0.07	8.47 ± 0.10	8.59 ± 0.21
aSPT (h)	6.57 ± 0.13	6.79 ± 0.08	6.96 ± 0.06	7.21 ± 0.08	7.66 ± 0.16
ΔSPT (min)	143.23 ± 10.34	114.00 ± 6.30	97.75 ± 4.51	75.29 ± 6.40	55.65 ± 12.81
ΔSOT (min)	53.97 ± 7.50	47.47 ± 4.57	26.73 ± 3.27	17.81 ± 4.64	12.14 ± 9.30
ΔWT (min)	197.20 ± 8.79	161.47 ± 5.36	124.48 ± 3.84	93.10 ± 5.44	67.79 ± 10.89
Nocturnal awakening	2.25 ± 0.12	2.28 ± 0.07	2.32 ± 0.05	2.39 ± 0.07	2.19 ± 0.14
Subjective sleep quality	1.47 ± 0.07	1.32 ± 0.04	1.11 ± 0.03	0.89 ± 0.04	0.85 ± 0.09
Daytime sleepiness	1.76 ± 0.08	1.66 ± 0.05	1.43 ± 0.04	1.38 ± 0.05	1.27 ± 0.10

($F(4, 1112) = 1.616$, $p = .168$, $\eta_p^2 = 0.006$). Consequently, a significant increase in ΔSPT for the EE group relative to the MM group was observed ($F(4, 1112) = 10.412$, $p < .001$, $\eta_p^2 = 0.028$), with a mean 87-min increase. Although ΔSOT ($F(4, 1112) = 7.603$, $p < .001$, $\eta_p^2 = 0.027$) and ΔWT ($F(4, 1112) = 36.327$, $p < .001$, $\eta_p^2 = 0.116$) both increased significantly as evening preferences became stronger, the ΔWT difference between the MM and EE groups (mean, 129 min) was more remarkable than that of ΔSOT (mean, 42 min).

Both subjective sleep quality ($F(4, 1112) = 16.546$, $p < .001$, $\eta_p^2 = 0.056$) and daytime sleepiness ($F(4, 1112) = 6.749$, $p < .001$, $\eta_p^2 = 0.024$) scores increased as evening preference became stronger. However, no significant differences across chronotypes were observed in nocturnal awakening ($F(4, 1112) = 0.581$, $p = .677$, $\eta_p^2 = 0.002$).

Depressive States and Chronotypes

The proportion of subjects whose CES-D scores were ≥16 and group means are shown for each chronotype in Figure 3. The proportions of subjects whose CES-D scores were ≥16—indicating the presence of depressive state—were greater as evening preference became stronger ($\chi^2(4) = 41.736$, $p < .001$, $V = 0.189$). About half (46.9%) of the EE group appeared to show depressive states. CES-D scores increased as evening preference became stronger ($F(4, 1112) = 6.117$, $p < .001$, $\eta_p^2 = 0.022$), with a mean score of 15.85 ± 0.814 (SD) in the EE group, which was close to the cutoff value of 16. Results from multiple comparisons

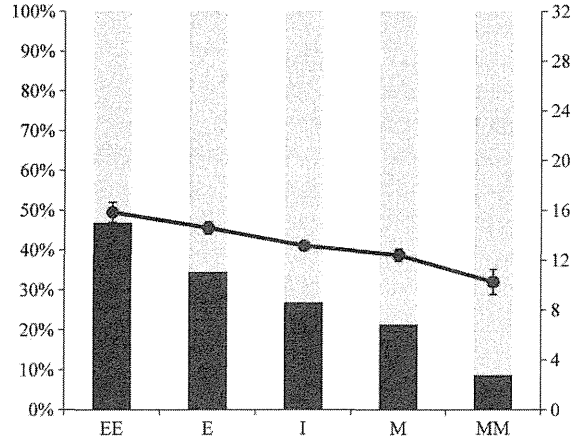

FIGURE 3 Proportions of subjects whose Center for Epidemiological Studies Depression Scales (CES-D) scores ≥16, and mean CES-D scores, by chronotype. Horizontal axis indicates chronotype: EE (Extreme Evening type), E (Evening type), I (Intermediate type), M (Morning type), and MM (Extreme Morning type). Black columns represent proportions of subjects whose CES-D scores ≥16 in five chronotypes (left axis). Closed circles with bars represent mean CES-D scores and standard error of means (SEM).

revealed significant differences between the EE and I, M and MM, and E and M or MM groups (all $p < .05$). No significant differences were observed between groups I, M, and MM, respectively.

Correlated Factors for Depressive States

Findings of the logistic regression analysis with the incidence of depressive states as the dependent variable are shown in Table 3. Statistically significant associations were observed between the increased incidence of depressive states and the following: belonging to the EE chronotype (odds ratio [OR] = 1.926), nocturnal awakening (OR = 1.844), subjective sleep quality (OR = 2.471), daytime sleepiness (OR = 1.895), and being female (OR = 1.391). In contrast, the following showed statistically significant associations with the decreased incidence of

TABLE 3 Correlated factors for the incidence of depressive states

		CES-D score (≥16)		Adjusted OR (95% CI)		*P*
Age	20–29	145	(35.1 %)			0.135
	30–39	47	(24.9 %)	.664	(0.433–1.018)	0.060
	40–49	66	(25.4 %)	.768	(0.508–1.162)	0.212
	50–59	70	(22.7 %)	.649	(0.424–0.994)	0.047
Sex	Male	118	(23.9 %)			
	Female	210	(31.0 %)	1.391	(1.026–1.886)	0.033
Shiftwork	Not shiftworker	152	(24.9 %)			
	Shiftworker	163	(32.0 %)	1.138	(0.853–1.520)	0.380
Chronotype	Intermediate type (I)	129	(26.9 %)			0.029
	Extreme morning type (MM)	6	(8.7 %)	.342	(0.124–0.941)	0.038
	Morning type (M)	55	(21.4 %)	.830	(0.546–1.261)	0.383
	Evening type (E)	92	(34.6 %)	1.230	(0.841–1.801)	0.286
	Extreme evening type (EE)	46	(46.9 %)	1.926	(1.120–3.311)	0.018
aSPT	6–7 h	118	(31.6 %)			0.216
	<6 h	69	(31.8 %)	.677	(0.434–1.055)	0.085
	>7 h	141	(24.3 %)	1.016	(0.678–1.522)	0.938
aSOT	23:00 to 23:59	110	(26.3 %)			0.186
	Before 23:00	72	(20.3 %)	.844	(0.547–1.303)	0.445
	After 24:00	146	(36.8 %)	1.408	(0.927–2.140)	0.109
aWT	6:00 to 6:29	82	(24.6 %)			0.279
	Before 6:00	64	(26.4 %)	1.340	(0.858–2.094)	0.198
	After 7:30	182	(30.6 %)	.883	(0.586–1.330)	0.551
Δ SPT	Sufficient	36	(25.2 %)			
	Insufficient	292	(28.4 %)	1.056	(0.664–1.677)	0.819
Nocturnal awakening	Low	131	(20.6 %)			
	High	196	(36.9 %)	1.844	(1.367–2.487)	0.000
Subjective sleep Quality	Good	174	(20.3 %)			
	bad	153	(49.5 %)	2.471	(1.792–3.407)	0.000
Daytime Sleepiness	Low	251	(24.9 %)			
	High	76	(47.8 %)	1.895	(1.286–2.791)	0.001

depressive states: belonging to the MM chronotype (OR = 0.342) and being in the 50–59 age group (OR = 0.649). In addition, no significant associations were observed between the incidence of depressive states and the following: shiftworking, actual sleep time (aSPT), actual sleep timing (aSOT and aWT), and sleep debt (ΔSPT).

DISCUSSION

In this study, we investigated associations between diurnal preference and incidence of depressive states, after adjusting for confounding factors, including sleep parameters, which greatly influence mood adjustment. In fact, the sleep parameters of subjects in this study varied considerably across chronotypes. As evening preference increased, actual sleep onset and wake time were significantly delayed. However, the magnitude of delay in the actual wake time of subjects with evening chronotypes was remarkably smaller than that for subjects with morning chronotypes due to social constraints, such as going to work (Figure 3, Table 2). This led to shortened sleep time in chronotypes with stronger evening preference, on average by ~1 h in the EE group compared to the MM group.

The results of logistic regression analysis with the incidence of depressive states as a dependent variable clearly demonstrated that EE preference was associated with increased incidence of depressive states (OR = 1.926) and that MM preference was associated with the decreased incidence of depressive states (OR = 0.342), even after adjusting for differences in sleep parameters across the chronotypes.

Daytime sleepiness (OR = 1.895) was also associated with the increased incidence of depressive states. However, sleep debt (ΔSPT), which was thought to be a likely cause for daytime sleepiness, was not significantly associated with incidence of depressive states. This finding could be explained by the fact that some types of depression, e.g., atypical depression or seasonal affective disorder, are accompanied with hypersomnia without sleep debt (Kaplan & Harvey, 2009). Alternatively, individual susceptibility to sleep debt, rather than degree of sleep debt, itself, might contribute to an increased risk for depressive states. Indeed, inter-individual differences in required sleep time are considerable, and influences on insufficient sleep vary by individual (Leproult et al., 2003; Tucker et al., 2007; Van Dongen et al., 2004, 2005). Given that there is increased risk for depressive states in those individuals whose homeostasis is disturbed by sleep debt, in the evaluation of risk factors it is essential to consider individual sensitivity to and capacity to absorb sleep debt on top of objective sleep duration. A study by Kaneita et al. (2006) supports this argument and demonstrates that subjective sleep satisfaction (and sleep duration) is an independent risk factor for depressive states as defined by CES-D score.

Our study results also suggest that the following factors were associated with the incidence of depressive states: being female (OR = 1.391), having nocturnal awakening (OR = 1.844), and poor subjective sleep quality (OR = 2.471). These findings are in agreement with those of previous studies reporting that women have a high risk for depression (Young & Korszun, 2009) and that insomnia is highly concomitant with depression (Ford & Kamerow, 1989; Thase, 1999).

Although the physiological mechanisms linking evening preference with susceptibility to the induction of depressive states are not fully understood, cumulative insights from molecular genetic studies suggest there are functional associations between diurnal preference, regulatory function of the biological clock, and mood adjustment (Artioli et al., 2007; Barnard & Nolan, 2008; Kripke et al., 2009; Lamont et al., 2007; McClung, 2007; Mendlewicz, 2009). Determination of diurnal preference is greatly associated with the circadian period (τ) of the biological clock. Correlations are observed between diurnal preference and τ, where individuals with morning preference are likely to have shorter τ and those with evening preference are likely to have longer τ (Duffy et al., 2001). Determination of τ is largely affected by the transcriptional/translational regulatory network among clock genes, which forms biological rhythms. Polymorphism of clock genes such as *Per3* (Archer et al., 2003) and *Clock* (Katzenberg et al., 1998; Mishima et al., 2005) is reported to be associated with evening preference. Studies of bipolar disorder report that linkage disequilibrium is observed in the particular haplotype of *Bmal1* and *Per3* (Nievergelt et al., 2006), and polymorphism of *Bmal1* and *Timeless* genes (Mansour et al., 2006). Another study of bipolar disorder reports that patients with T3111C polymorphism of the *Clock* gene have higher rates of recurrence (Benedetti et al., 2003). A modulator of clock genes, glycogen synthase kinase 3 beta (GSK3β), is considered a target of the mood stabilizer lithium (Gould & Manji, 2005). In addition, a *Clock* mutant mouse model with behaviors similar to manic states of bipolar disorder is being developed (McClung et al., 2005; Roybal et al., 2007). This series of findings strongly suggests that there might be a functional linkage among diurnal preference, regulatory function of the biological clock, and mood adjustment.

Another series of chronobiological studies also suggest that evening preference might affect mood adjustment by modifying the mutual phase relationship between sleep and other physiological rhythms. Compared to subjects with morning preference, those with evening preference have phase delays in the core body temperature and melatonin circadian rhythms (Bailey & Heitkemper, 2001; Kerkhof & Van Dongen, 1996; Liu et al., 2000), which leads to a relative delay in these physiological rhythms against sleep phase (internal desynchronization) (Baehr et al., 2000; Duffy et al., 1999; Mongrain et al., 2004). Persistent internal

desynchronization could cause depressive states (Germain & Kupfer, 2008). A similar case of internal desynchronization is observed in patients with seasonal affective disorder, who experience depressive symptoms in the winter when daylight time is short (Lewy et al., 1987).

Evening preference is also reported to be associated with personality, which influences mood state. Compared to morning-chronotype subjects, evening-chronotype subjects are likely to have a more neurotic personality (Tonetti et al., 2009). Also, many patients with delayed sleep phase syndrome (DSPS)—where sleep timing is extremely delayed in a phenotype of extreme evening preference—tend to be introspective, defensive, nervous, depressive, and lacking in control of emotional expression (Shirayama et al., 2003). These dispositions might form the foundations for greater incidence of depressive states.

This study has several limitations. First, the incidence of depressive states was examined using an operational definition based on a CES-D cut-off score ≥ 16; the etiologies of depressive states using that definition could include not only mood disorders but also other mental illnesses accompanied with depressive symptoms, and life event–inducing transient depressive reactions. Second, we did not obtain a sufficient number of participants with extreme evening chronotype ($N = 7$) when using the Horne and Ostberg's categorization to our study subjects. Therefore, we chose the 5-point grading method to make each category have a certain ratio (7%–24%–38%–24%–7%). We further analyzed our data using the Taillard's criteria (2004), and confirmed that the main results and effect size by the 5-point grading method in this study and those by Taillard's criteria to be identical (data not shown). Third, because the Japanese version of MEQ has different factor structures and semantic differences in part of the items in comparison with the English version (Smith et al., 1991), the external validity was limited. Therefore, it should be noted that a certain consideration is necessary for applying these results to the other cultural populations.

The findings of this study demonstrate that evening preference, independent of sleep parameters, such as sleep time, sleep quality, sleep timing, and sleep debt, is associated with depressive states. Nevertheless, although a causative relationship between them cannot be definitively substantiated, this study provides the important insight that the biological clock systems that regulate diurnal preference are functionally associated with mood adjustment, and such association might consequently increase susceptibility to the induction of mood disorders. More studies are needed to further investigate the pathophysiological mechanisms linking evening preference with the incidence of depressive states.

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

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