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Original Article

Relation between morningness–eveningness score and depressive symptoms among patients with delayed sleep phase syndrome

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ABSTRACT

Objectives: Depressive symptoms are observed in a relatively large series of patients with delayed sleep phase syndrome (DSPS). This study was undertaken to investigate the prevalence, characteristics, and factors associated with depressive symptoms among DSPS patients.
Methods: This study targeted 90 consecutive patients (54 men, 27.1 ± 9.2 years old) diagnosed as having DSPS. Demographic and clinical characteristics were assessed at their initial visit, including application of the Zung self-rating depression scale (SDS) and morningness–eveningness questionnaire. A series of logistic regression analyses were conducted to determine the factors associated with depressive symptoms (determined as SDS $\geqslant$ 48).
Results: Sixty-four percent of the DSPS patients were in a moderate or severe depressive state. Diurnal variation, sleep disturbance, fatigue, and psychomotor retardation were the main depressive symptom items on SDS in the DSPS patients. Logistic regression analyses showed that SDS $\geqslant$ 48 was significantly associated with moderate and definite evening chronotype. In contrast, self-reported nocturnal sleep onset and offset times were not associated with depressive symptoms.
Conclusions: There is a high prevalence of depressive symptoms among the DSPS patients. The symptomatic structure of depressive symptoms in this population appears to differ from those of typical depression. Moreover, results of our study suggest that depressive symptoms are more associated with the preference of the evening chronotype rather than sleep–wake phase among DSPS patients.

1. Introduction

Delayed sleep phase syndrome (DSPS), which is more common among adolescents and young adults, is characterized by a habitually delayed sleep–wake schedule as compared to a conventional or socially acceptable one [1–3]. Among the Japanese population, prevalence of DSPS from junior high school to university is estimated as 0.48% [4]; that of adults is estimated as 0.13% [5]. Patients with DSPS sometimes have complicated depressive symptoms [6–10]. However, the prevalence, mechanisms, and symptomatic characteristics of secondary depressive symptoms in patients with DSPS have not been well elucidated.

Relations between a depressive state and evening chronotype assessed by morningness–eveningness questionnaire (MEQ) [11] have been shown in college students [12], healthy subjects aged 18–99 years [13], and patients with major depressive disorder [14,15]. Recently, this relationship was also found in the Japanese adult population aged 20–59 years [16]. Considering that DSPS patients frequently have an evening chronotype, it can be inferred that depressive symptoms among patients with DSPS are associated with the MEQ score or delay of the sleep–wake schedule phase.

In this study, we examined the prevalence and characteristics of depressive symptoms among Japanese DSPS patients. Moreover, we investigated the factors associated with depressive symptoms among this patient population retrospectively, particularly addressing their chronotype and sleep–wake schedule before treatment.

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2. Methods

This study examined 106 consecutive patients (68 men, 38 women, 26.9 ± 9.4 years old (mean ± SD)) who were diagnosed as having DSPS according to the second edition of the International Classification of Sleep Disorders [1] at their initial visit from June 2007 to October 2009. The patients visited the outpatient clinic of the Japan Somnology Center seeking treatment for sleep-related problems, including difficulty falling asleep and waking up at the desired time, disturbed sleep–wake schedule, and/or excessive daytime sleepiness. All the patients were asked to record sleep logs for more than two weeks. Their diagnosis was made by at least two sleep disorder specialist physicians based on clinical interviews and their sleep log. Polysomnographic recordings were also conducted if needed. The ethics committee of the Neuropsychiatric Research Institute approved this study. All participants gave their written informed consent to participate.

In total, 90 patients (54 men, 36 women, 27.1 ± 9.2 years old (mean ± SD)) were included in further analyses after excluding 11 patients who were comorbid with restless legs syndrome (4 patients), obstructive sleep apnea syndrome (6 patients) or secondary insomnia because of atopic dermatitis (1 patient) and an additional 5 other patients who received hypnotic medications and subsequently showed clear improvement of their bed time delay. Exclusion criteria other than these comorbid sleep disorders were not set in the present study.

We retrospectively investigated the subjects' descriptive medical records including age, sex, duration of DSPS morbidity, family history related to eveningness lifestyle [17] in their first-degree relatives, self-reported time of sleep onset and sleep offset, self-reported time spent for sleep (total sleep time), past history of depression, use of antidepressants, and presence or absence of a conventional schedule. The latter was defined as a situation in which one must get up regularly on weekdays to meet an obligatory schedule such as a regular or part-time job, housekeeping, or attending school [8,10,18]. Because eveningness is regulated by some genetic factors [19–23], the family history related to eveningness lifestyle was used to investigate the association between depressive symptoms and genetic susceptibility. In addition, the DSPS patients were examined for their depressive symptoms, daytime sleepiness, and morningness–eveningness chronotype by using the Zung self-rating depression scale (SDS) [24,25], the Epworth sleepiness scale (ESS) [26,27], and the morningness–eveningness questionnaire (MEQ) [11,28], respectively, at their initial visit. The SDS is a self-assessed 20-item scale with 4 points assigned for each [24]. The SDS has 10 positively worded items and 10 negatively worded items. The positively worded items were scored in reverse, and item responses were ranked 1–4 with higher numbers corresponding to a higher severity of each depressive symptom. The raw SDS scores were divided into four levels according to the classification presented by Barrett et al. [29]: little or no symptomatology, 20–39 points; mild depressive state, 40–47 points; moderate depressive state, 48–55 points; and severe depressive state, 56–80 points.

A score of 48 or more points on the SDS is considered pathological [29]. Therefore, factors associated with moderate and severe depressive symptoms (SDS $\geqslant$ 48) were examined by using a series of logistic regression analyses. Sex, age at the time of investigation, duration of DSPS morbidity, family history related to the eveningness lifestyle, presence of a conventional schedule, past history of depression, use of antidepressants, sleep onset time, sleep offset time, sleep duration, ESS, and chronotypes were submitted as independent variables. Age at the time of investigation, duration of DSPS morbidity, sleep onset time, and sleep offset time were used as continuous variables. Sleep duration was categorized as $\leqslant$6, 6–9, and $\geqslant$9 h according to Hartmann et al. [30,31]. The Epworth sleepiness scale score was classified into $\leqslant$10 and $\geqslant$11 according to the criteria of excessive daytime sleepiness [26]. Chronotypes were classified into five based on results of MEQ according to Horne and Östberg [11,28]: definitely morning type (score: 70–86), moderately morning type (score: 59–69), intermediate type (score: 42–58), moderately evening type (score: 31–41), and definitely evening type (score: 16–30). Morning chronotypes were not found among the DSPS patients participating in this study.

All variables were examined initially in univariate models. Multivariate logistic regression analyses were performed for all variables that showed a significant correlation in univariate models to control for confounding factors and to determine the main correlates. Statistical tests of the regression estimates odds ratios (ORs) were based on Wald statistics. Odds ratios and their 95% confidence intervals (CIs) are presented to show the association. One-way analysis of variance (ANOVA) was performed on each score; the total score of SDS among groups was divided by chronotype (intermediate type, moderately evening type, and definitely evening type). All analyses were performed using software (SPSS, V11.5; SPSS Inc., Chicago, IL, USA); a p value of less than 0.05 was inferred as indicating statistical significance. Means ± standard deviations are reported in Section 3.

3. Results

Characteristics of the DSPS patients are presented in Table 1. Sixty-four percent of the DSPS patients were in moderate or severe depressive states. Seventy-seven percent of the DSPS patients were moderately evening type or definitely evening type.

Fig. 1 shows characteristics of depressive symptoms according to the Zung Self-Rating Depression Scale among the DSPS patients. For the 20 items of the SDS, mean scores of 3.0 or higher (this range means that patients have each symptom most of the time or a good part of the time) were observed in diurnal variation (mean = 3.59; 95% CI, 3.44–3.74), sleep disturbance (mean = 3.50; 95% CI, 3.33–3.67), fatigue (mean = 3.48; 95% CI, 3.31–3.64), and psychomotor retardation (mean = 3.00; 95% CI, 2.84–3.16) among the DSPS patients.

Table 2 presents logistic regression results for moderate or severe depressive symptoms in DSPS patients. Univariate logistic regression analyses showed that the presence of family history of

Table 1
Characteristics of the study cohort.

Characteristic	
Age at investigation (years)	27.1 ± 9.2 (range: 13–64)
Sex	
Men	60.0% (n = 54)
Women	40.0% (n = 36)
Use of antidepressants	15.6% (n = 14)
Duration of DSPS morbidity (years)	6.2 ± 6.1 (range: 0–27)
Sleep onset time on weekdays	3:22 ± 1:25 (range: 01:00–08:30)
Sleep offset time on weekdays	10:39 ± 2:45 (range: 06:30–16:30)
Sleep duration on weekdays	7:17 ± 2:12 (range: 03:30–13:30)
SDS score	50 ± 6.6 (range: 31–65)
Depressive state	
Little or no symptomatology	6.7% (n = 6)
Mild depressive state	28.9% (n = 26)
Moderate depressive state	43.3% (n = 39)
Severe depressive state	21.1% (n = 19)
MEQ score	35 ± 7.2 (range: 22–51)
Chronotype	
Intermediate type	23.0% (n = 20)
Moderately evening type	50.6% (n = 44)
Definitely evening type	26.4% (n = 23)

SDS, Zung self-rating depression scale; MEQ, morningness–eveningness questionnaire.

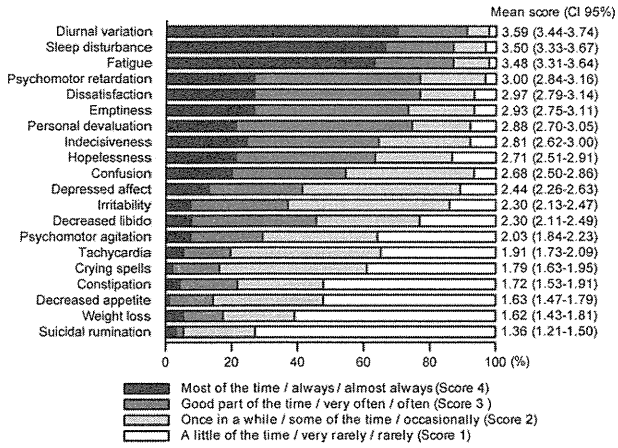

Fig. 1. Characteristics of depressive symptoms according to the Zung self-rating depression scale among the DSPS patients.

eveningness lifestyle, moderately evening type, and definitely evening type exhibited significant association with moderate to severe depressive symptoms. The sleep onset time and sleep offset time were not associated with depressive symptoms in DSPS patients. All significant variables in the univariate models (family history of eveningness symptoms and chronotypes) were analyzed using a multivariate model to control for confounding factors and to determine the main correlates of SDS ⩾ 48 among the DSPS patients. Results show that moderate to severe depressive symptoms were significantly associated only with moderately evening type and definitely evening type.

Table 3 presents results of comparison of SDS scores and sleep phase among the groups categorized by chronotype. One-way ANOVA and post hoc comparisons for the total score of SDS demonstrated that the definitely evening chronotype showed a higher depressive score than the intermediate chronotype. Subsequently, we performed a one-way ANOVA followed by post hoc comparisons after excluding sleep-related SDS items (items 2 and 4) to exclude the possibility that this finding was only an epiphenomenon derived from the DSPS symptoms themselves. Results show that the definitely evening chronotype showed a significantly higher score than the intermediate type. The times of sleep onset and offset did not differ among the three chronotype groups.

4. Discussion

This study was aimed at examination of the prevalence, characteristics, and associated factors for depressive symptoms among patients with DSPS. Using an SDS scale, 64.4% of the DSPS patients were estimated as having moderate or severe depressive symptoms (moderate, 43.3%; severe, 21.1%). Among the Japanese general population, Chida et al. [32] found a moderate or severe depressive state among the 13.7% of the population aged 20–79 years in Iwate prefecture, Japan. The same prevalence was replicated in a report by Yamazaki et al. [33], in which moderate or severe depressive symptoms were observed in 14.0% of 4500 people from the entire population of Japan aged 16 years or older, selected

Table 2
Univariate and multivariate logistic regression results for associated factors for moderate or severe depressive symptoms (SDS ⩾ 48) in delayed sleep phase syndrome (DSPS).

Factor	Total	SDS ⩾ 48		Univariate model		Multivariate model*	
		n	%	Odds ratio (95% CI)	*P*	Adjusted odds ratio (95% CI)	*P*
Sex							
Female	36	26	72.2	1.00 (Ref.)			
Male	54	32	59.3	0.56 (0.23–1.39)	0.21		
Age at investigation (years)[a]	90	58	64.4	0.99 (0.94–1.04)	0.63		
Duration of DSPS morbidity (years)[a]	90	58	64.4	1.00 (0.93–1.07)	0.98		
Family medical history of eveningness symptoms							
No	73	43	58.9	1.00 (Ref.)		1.00 (Ref.)	
Yes	17	15	88.2	5.23 (1.11–24.59)	0.04	7.82 (0.95–64.20)	0.06
Presence of conventional schedule[b]							
No	21	13	61.9	0.91 (0.33–2.50)	0.85		
Yes	67	43	64.2	1.00 (Ref.)			
History of depression							
No	74	47	63.5	1.00 (Ref.)			
Yes							
Use of antidepressants							
No	76	49	64.5	1.00 (Ref.)			
Yes	14	9	64.3	0.99 (0.30–3.26)	0.99		
Sleep onset time[c]	90	58	64.4	1.01 (0.75 – 1.36)	0.97		
Sleep offset time[c]	90	58	64.4	1.16 (0.98 – 1.37)	0.08		
Sleep duration							
⩽6 h	34	17	50	0.43 (0.16 – 1.18)	0.10		
6–9 h	33	23	69.7	1.00 (ref)			
⩾9 h	23	18	78.3	1.57 (0.45 – 5.40)	0.48		
Epworth sleepiness scale							
⩽10	53	33	62.3	1.00 (Ref.)			
⩾11	36	24	66.7	1.21 (0.50–2.95)	0.67		
Chronotypes							
Definitely evening type	23	18	78.3	5.40 (1.42–20.52)	0.01	4.56 (1.16–17.89)	0.03
Moderately evening type	44	32	72.7	4.00 (1.31–12.18)	0.02	3.27 (1.04–10.28)	0.04
Intermediate type	20	8	40.0	1.00 (Ref.)		1.00 (Ref.)	

CI, confidence interval; Ref., reference category.
[a] Odds ratios correspond with increment for each step of a year.
[b] Presence or absence of conventional schedule is defined as a situation in which one must get up regularly on a weekday to meet schedule of jobs including a regular or part-time job, housekeeping, or going to school.
[c] Odds ratios correspond with increment for each step of an hour.
* This model included family history of eveningness symptoms and chronotypes as dependent variables.

Table 3
Comparison of SDS scores and sleep phase among groups categorized by chronotype.

	Intermediate type	Moderately evening type	Definitely evening type	ANOVA	
				$F(2, 84)$	P
N	20	44	23		
Total SDS score	46.5 ± 7.3[a]	50.5 ± 5.2	51.8 ± 7.2[b]	4.28	<0.05
Total SDS score except for sleep-related items	40.0 ± 6.8[a]	43.3 ± 5.2	44.5 ± 6.6[b]	4.28	<0.05
Sleep onset time	3:19 ± 1:21	3:23 ± 1:30	3:27 ± 1:26	0.05	0.95
Sleep offset time	9:56 ± 2:24	11:08 ± 2:59	10:17 ± 2:35	1.55	0.22

[a,b]Different superscripts indicate significant difference among chronotypes ($P < 0.05$).

using stratified random sampling. Although our sample might have been biased because of patient recruitment from a single sleep disorder clinic, the rate of patients with DSPS having depressive symptoms is clearly higher than that among the Japanese general population. This result corroborates the results of previous studies, all of which show that patients with DSPS have a high prevalence of depression [6–10].

Although patients with DSPS are expected to score in the clear eveningness range of MEQ, the sensitivity and specificity of the scale for substantiating clinical diagnosis of DSPS have not been evaluated [34]. As expected, our DSPS patients did not include the morningness chronotype, and a large proportion (77.0%) of the patients showed the evening chronotype. However, interestingly, 23.0% of the patients showed an intermediate chronotype. In addition, although reported prevalence of delayed sleep–wake phase is higher for the evening chronotype compared to the intermediate chronotype in the general population [16,35], this relationship was not observed among DSPS patients in the present study, as shown in Table 2. This finding raises the possibility that a certain number of DSPS patients are in a situation in which their circadian rhythm is delayed in spite of a lack of deviation of the chronotype (probably because of extraneous factors).

This study revealed higher mean scores of SDS sub-items in DSPS patients for diurnal variation, sleep disturbance, fatigue, and psychomotor retardation. Romera et al. [36] demonstrated that among their patients with major depression, SDS items showing a 3 or higher mean score were observed in psychomotor retardation, confusion, indecisiveness, emptiness, and depressed affect. In contrast, these items, except for psychomotor retardation, showed low scores of less than 3.0 among the DSPS patients in this study. This difference in depressive symptoms construction between major depression and comorbid depression with DSPS suggests that secondary depression attributable to DSPS might show different symptomatic structures of the disorder.

It was noteworthy that the moderate or severe depressive symptoms in the DSPS patients were more closely associated with the evening chronotype than with the intermediate chronotype. Moreover, the total score of SDS was higher in the definitely evening chronotype group than in the intermediate group, even after sleep-related items were excluded from the analyses. This result is consistent with previous studies showing a significant association between depressive states and evening chronotypes [12–16]. One possible underlying mechanism of the relationship is the psychological background associated with the evening chronotype. Reportedly, persons with evening chronotype have more attention problems and poor school achievement and are more emotionally upset. They have a higher likelihood of using substances such as alcohol, caffeine, or tobacco; more neurotic personality; and decreased daytime functioning as compared to those with an intermediate and/or morning chronotype [37–41]. These psychological characteristics of the evening chronotype might contribute to the linkage between depressive symptoms and evening chronotype among DSPS patients. For a second possible mechanism, the genetic basis of the association between chronotype and depressive symptoms should be considered. Polymorphisms of clock-related genes such as *Clock* [19,20], *Per2* [21], and *Per3* [22,23] are associated with the evening chronotype evaluated with MEQ. On the other hand, previous studies have demonstrated the association between mood disorder and polymorphisms of *Clock* [42,43], *Per2* [44], and *Per3* [45,46]. In light of these findings, the evening chronotype might be related to the occurrence of depressive symptoms among the DSPS population based on their molecular background.

It is possible that internal desynchronization of circadian rhythm due to DSPS can contribute to the occurrence of depressive symptoms [6]. However, in our DSPS patients, the times of sleep onset and offset were not associated with depressive symptoms; this finding may indicate that the depressive symptoms were more closely associated with the preference for the evening chronotype than with the sleep–wake phase. Kitamura et al. [16] demonstrated that the evening chronotype is associated with depressive symptoms independent of sleep–wake timing among the Japanese adult population. Moreover, they observed no significant associations between depressive state and sleep–wake timing. Results of our study indicate that evening chronotype was more closely associated with depressive symptoms than sleep–wake timing among not only the general population but also DSPS patients.

DSPS patients frequently fail in conforming to conventional work schedules and other social demands [34], and they are likely to be urged to confront occupational or educational difficulties [47]. Consequently, these social problems could play an important role in developing depressive symptoms [10]. Thus, we presumed that the absence of a conventional schedule is associated with depressive symptoms. However, this study did not find any association between depressive symptoms and conventional schedule. It is difficult to explain why there was no relationship between depressive symptoms and absence of conventional schedule. Further research on this issue with a prospective design is necessary.

Our study did not find an association between depressive symptoms and a history of depression or use of antidepressants among DSPS patients. This result might suggest a poor treatment response of depressive symptoms to antidepressants among DSPS patients. For these patients, chronobiological treatment such as bright light exposure and/or melatonin administration could be applicable in reducing their depressive symptoms because these treatments have been known to be beneficial for improving depressive symptoms among DSPS patients [10,48].

This study presents some limitations. First, we were unable to compare the chronotype, sleep–wake phase, and score of SDS between DSPS patients and healthy controls in this study. Second, the causal relation between the chronotype and depressive symptoms in DSPS patients could not be investigated because this study was a cross-sectional retrospective study. Further studies addressing not only the chronotype but also the melatonin secretion profile and polymorphisms in circadian clock-related genes are necessary to clarify this issue. Third, self-reported nocturnal sleep onset and offset times in the DSPS patients were evaluated in the present study. Because actigraphy enables a reasonably accurate estimation of sleep and wakefulness patterns [49], an investigation

of the relationship between actigraphically measured sleep–wake pattern and depressive symptoms in DSPS patients would provide us with more detailed information.

In conclusion, the results demonstrated that 64.4% of DSPS patients in this study had moderate or severe depressive symptoms. But depressive symptoms in DSPS patients were associated significantly with the evening chronotype rather than the sleep–wake phase (as found in major depression).

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: doi:10.1016/j.sleep.2010.12.017.

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ORIGINAL ARTICLE

A meta-analysis on the treatment effectiveness of cognitive behavioral therapy for primary insomnia

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Abstract

Previous meta-analyses have shown the effectiveness of cognitive behavioral therapy for insomnia (CBT-I). However, conclusive information about therapeutic effects (especially during follow-up), effect sizes of objective sleep parameters and self-rating scales, and the problem of publication bias has not been obtained. We conducted a meta-analysis focusing on these issues. We identified 14 randomized controlled studies published between 1990 and 2009 that fulfilled our selection criteria. Intra-group comparison of CBT-I and comparison between CBT-I and control groups were performed on these studies. The intra-group comparison revealed that the effect sizes of CBT-I for subjective sleep variables from sleep diaries were medium to large at the end point of treatment, and these effect sizes were favorably maintained on follow-up. A between-group comparison revealed that CBT-I was more effective than the control for subjective sleep variables at the end of treatment and that its effectiveness was also recognized on follow-up. With regard to self-rating scales, as compared to the control group, the effect sizes in the CBT-I group were medium to large both at the end of treatment and on follow-up. However, there were problems of publication bias in some of the subjective or objective sleep variables. The abovementioned results support the effectiveness of CBT-I for the treatment and prevention of relapse of primary insomnia despite the existence of a certain publication bias.

Key words: cognitive behavioral therapy, insomnia, meta-analysis, publication bias, randomized controlled trial.

INTRODUCTION

Insomnia has been estimated to be prevalent in about one-fifth of the general adult population.[1] Several population-based studies have revealed that 25–35% of subjects experienced occasional or mild insomnia,[2,3] and that 10–15% of the insomniac population showed a chronic course.[2,4,5] For the treatment of primary insomnia, two effective methods have been widely accepted: pharmacotherapy, and cognitive behavioral therapy for insomnia (CBT-I). Although pharmacotherapy is commonly used for the treatment of insomnia, recurrence of symptoms shortly after drug discontinuation is frequently observed.[6] However, it has been reported that CBT-I is effective for improving insomnia symptoms in 70–80% of patients, and also has long-term effects on the prevention of recurrence.

To the best of our knowledge, there have been four meta-analyses on the effectiveness of cognitive

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behavioral techniques for primary insomnia.[7–10] In these analyses, effect sizes for subjective sleep measures such as sleep onset latency (SOL), number of awakenings, wake time after sleep onset (WASO), and sleep quality from pre- to post-treatment were moderate to large. However, the results of these meta-analyses could not clarify treatment outcome with CBT-I in detail, in terms of the following important points.

Firstly, it was unclear whether the effectiveness of CBT-I was sustained long after the end of the treatment. To clarify this, comparisons of the effectiveness of CBT-I and control groups, including placebo use and/or waiting list, should be made both at the end of the treatment phase and at the point of follow-up investigation. Secondly, previous meta-analyses used only sleep diaries, but changes in objective sleep measures including polysomnographic (PSG) findings and/or actigraphic (ACT) findings as well as subjective rating scales such as the Pittsburgh Sleep Quality Index (PSQI)[11] have not been systematically investigated. Thirdly, the problem of file-drawer studies, that is, publication bias[12,13] had not been taken into consideration in previous meta-analyses on CBT-I. Selection bias is known to occur in meta-analyses because studies with results that are significant, interesting, from large well-funded studies, or of higher quality are more likely to be submitted, published, or published more rapidly than work without such characteristics. Sutton *et al.*[14] have emphasized that evaluation of publication bias should be made routinely in any systematic review.

This study set out to examine the therapeutic effectiveness of CBT-I, using meta-analysis focused on the above issues. Presently, CBT-I has become commonly implemented through a variety of techniques (stimulus control, sleep restriction, relaxation, cognitive therapy, sleep hygiene education, and so on). Considering this trend, we selected studies which implemented multicomponent CBT-I for the present meta-analysis.

METHODS

Population and sample

Published studies were identified through computer searches (using the keywords "insomnia" and "treatment") of the PsycINFO and MEDLINE databases during the period from 1990 to 2009. We checked all the extracted studies according to the following six criteria: (i) the interventions were made only for the treatment of primary insomnia; (ii) statistical values (mean and standard deviation or standard error) were described; (iii) study results were written in English; (iv) randomized controlled design was used; (v) they were published; and (vi) CBT-I was implemented using the previously indicated treatment techniques. Based on these criteria, 14 studies were selected from 213 studies and used for the analyses (Table 1).

Design

First, we calculated mean effect size from the baseline to the endpoint of treatment or from the baseline to follow-up investigation within the group in which subject patients had received CBT-I. We analyzed effect sizes with regard to SOL, total sleep time (TST), total wake time (TWT), WASO, early-morning awakening (EMA), time in bed (TIB), and sleep efficiency (SE) from the findings of sleep diaries (14 studies), PSGs (6 studies)or ACTs (4 studies).

Second, we calculated effect size (Cohen's *d*-value)[15] to compare the above parameters between the CBT-I and control groups both at the end point of treatment and on follow-up. For comparison, the group of patients with primary insomnia who had not received any specific treatment during the study period was defined as the control group. The control group came from 6 studies in which placebo controls were used,[16–21] 5 studies in which a waiting list was set as the control,[22–26] 1 study in which treatment as usual (TAU) by general practitioners was used,[27] and 2 remaining studies in which only CBT-I technique information was offered to the subject patients.[28,29] In addition, the CBT-I group came from the 9-individual format and 5-group format (Table 1).

After analyzing effect sizes with regard to the above-indicated sleep parameters, we analyzed the effect sizes of subjective sleep disturbance manifested on the PSQI,[11] the Insomnia Symptom Questionnaire (ISQ),[30] and the Sleep Impairment Index (SII),[31] and psychological status measured with the Dysfunctional Beliefs and Attitudes about Sleep scale (DBAS),[32] the Beck Depression Inventory (BDI),[33] the State-Trait Anxiety Inventory (STAI),[34] the Self-Efficacy Scale (SES),[35] and the Profile of Mood States (POMS).[36] We also calculated the combined effect size of the insomnia and psychological indices. These analyses were performed with comparison between both the baseline and the endpoint of treatment, and between the baseline and the point of follow-up investigation in the CBT-I group. The comparison between the CBT-I and control groups

Table 1 Characteristics of randomized controlled trials of cognitive behavioral therapy for primary insomnia

Author	Sample and design	Diagnosis	Mean age	Duration of insomnia (years)	Dropout rate of CBT	Treatment components	Number of sessions	Follow-up	Outcome		
									Sleep diary	PSG or Actigraphy	Self-report
Morin *et al.*, 1993[24]	CBGT = 12 WLC = 12	ICSD-I	Total = 67.1	NR	NR	SHE, SR, SC, CT	8	Y (3-,12-months)	Y	Y	NR
Mimeault *et al.*, 1999[23]	BT = 18 BTPC = 18 WLC = 18	ICSD-I DSM-IV	BT = 49.83 BTPC = 45.61 WLC = 56.94	14.1	18%	SHE, SR, SC, CT, RLX	6	Y (3-months)	Y	NR	Y
Morin *et al.*, 1999[18]	CBGT = 18 PCT = 17 COMB = 19 PL = 18	ICSD-I DSM-IV	CBGT = 64.4 PCT = 64.1 COMB = 65.2 PL = 64.9	16.8	0%	SHE, SR, SC, CT	8	Y (3-,12-,24-months)	Y	Y	NR
Edinger *et al.*, 2001[16]	CBT = 23 PL = 25	DSM-III-R	CBT = 55.8 PL = 55.7	13.6	8%	SHE, SR, SC	6	Y (6-months)	Y	Y	Y
Rybarczyk *et al.*, 2002[25]	CBGT = 11 WLC = 13	NR	CBGT = 66.5 WLC = 71.4	5.3	NR	SHE, SR, SC, CT, RLX	8	Y (4-months)	Y	Y	Y
Jacobs *et al.*, 2004[17]	CBT = 15 PCT = 15 COMB = 18 PL = 15	ICSD-I DSM-IV	CBT = 47.1 PCT = 45.4 COMB = 49.1 PL = 46.6	9.6	7%	Modified SR, Modified SC, RLX	6	Y (1-,3-,6-,12-months)	Y	Y	NR
Ström *et al.*, 2004[26]	CBT = 30 WLC = 51	ICSD-I DSM-IV	CBT = 46.2 WLC = 43.9	10.6	33%	SHE, SR, SC, CT	5	NR	Y	NR	Y
Perlis *et al.*, 2004[19]	M + CBT = 10 M + PL = 8	ICSD-I	M + CBT = 35.0 M + PL = 42.4	NR	0%	SHE, SR, SC, CT	8	NR	Y	NR	NR
Jansson *et al.*, 2005[29]	CBGT = 64 CTL = 72	NR	CBGT = 50 CTL = 49	7.9	NR	SHE, SR, SC, CT, PI	6	Y (12-months)	Y	NR	Y
Sivertsen *et al.*, 2006[20]	CBT = 18 PCT = 16 PL = 12	DSM-IV	CBT = 59.8 PCT = 61.3 PL = 61.8	14.1	0%	SHE, SR, SC, CT, RLX	6	Y (6-months)	Y	Y	NR
Wu *et al.*, 2006 [21]	CBT = 19 PCT = 17 COMB = 18 PL = 17	ICSD-I DSM-IV	Total = 38	NR	0%	SHE, SR, SC, CT	8	Y (3-,8-months)	Y	Y	Y
Espie *et al.*, 2007[27]	CBGT = 107 TAU = 94	ICSD-R DSM-IV	CBGT = 54.4 TAU = 54.1	11.1	11%	SHE, SR, SC, CT, RLX	5	Y (6-months)	Y	Y	Y
Edinger *et al.*, 2007[22]	CBT1s = 16 CBT2s = 18 CBT4s = 24 CBT8s = 17 WLC = 11	DSM-IV	CBT1s = 52.4 CBT2s = 55.9 CBT4s = 55.5 CBT8s = 57.0 WLC = 54.7	NR	8%	SHE, SC	1 2 4 8	Y (6-months)	Y	Y	Y
Edinger *et al.*, 2009[28]	CBT = 16 SHE = 18	DSM-IV-TR	CBT = 56.9 SHE = 55.0	CBT = 11.0 SHE = 8.0	NR	SHE, SC, SR, taped CT	4	Y (6-months)	Y	Y	Y

BT, bibliotherapy; BTPC, bibliotherapy and phone call; CBGT, cognitive behavioral group therapy; CBT, cognitive behavioral therapy; COMB, combined CBT with PCT; CT, cognitive therapy; CTL, control; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICSD, International Classification of Sleep Disorders; M, modafinil; N, no; NR, not reported; PCT, pharmacotherapy; PI, paradoxical intention; PL, placebo; PSG, polysomnogram; RLX, relaxation; SC, stimulus control; SHE, sleep hygiene education; SR, sleep restriction; TAU, treatment as usual; WLC, waiting-list control; Y, yes.

was also made both at the end of treatment and on follow-up.

Analyses

In the analyses, the effect sizes and failsafe indices were calculated using Tougou computer software (Nakanishiya Press, Kyoto, Japan) as in the study by Ishikawa.[37] The number of file-drawer studies was calculated with the formula advocated by Rosenthal[38] (number of file-drawer studies = $5k + 10$; k = number of research studies used for meta-analysis). In this study, when an effect size showed a positive value, the effectiveness of treatment at the end of treatment or on follow-up in comparison to the baseline in the CBT-I group, and the relative effectiveness of CBT-I in comparison to the control conditions, were determined.

RESULTS

Therapeutic effect of CBT-I both at the end of treatment and on follow-up

Tables 2 and 3 show within-subject changes in subjective and objective sleep parameters among the CBT-I trial studies. Mean effect sizes (ES_M) for each variable calculated from sleep diaries ranged from medium to large with regard to SOL (ES_M = 0.67), TWT (ES_M = 1.09), WASO (ES_M = 0.70), EMA (ES_M = 0.74), TIB (ES_M = 0.80), and SE (ES_M = 0.89), and effect sizes of those indices except for TIB were sustained at the point of follow-up investigation (Table 3). Regarding TST, effectiveness at the end of treatments was small (ES_M = 0.32), but the value on follow-up increased to a medium level (ES_M = 0.58). TWT, WASO, EMA, and SE from the results of PSG and/or ACT at the end of treatment (1.18, 0.57, 0.47, and 0.47, respectively) and SOL and SE on follow-up (0.58 and 0.43, respectively) also demonstrated effect sizes ranging from medium to large. Regarding SOL, effect size at the end of treatment did not reach significant levels, while the value on follow-up was medium.

The effectiveness of CBT-I differed between subjective and objective evaluations of some variables. Both SOL and TST improved on patients'; sleep diaries (ES_M = 0.67 and 0.32, respectively), but effectiveness on PSG and/or ACT did not reach significant levels at the end of treatment (ES_M = 0.23 and 0.03, respectively). On follow-up, especially, TST on the results of PSG and/or ACT did not reach a significant level (ES_M = 0.28), although the value increased in sleep diaries (ES_M = 0.58–0.95).

CBT-I group versus control group

We compared the treatment effectiveness of the CBT-I and control groups. The results at the end of treatment are shown in Table 4, and those on follow-up are shown in Table 5. At the end of treatment, sleep diaries demonstrated effect sizes ranging from medium to large for SOL, TWT, WASO, EMA, TIB, and SE (0.44, 0.59, 0.75, 1.09, 0.71, and 0.86, respectively). Moreover, the effects of SOL, WASO, and SE were sustained at least until the 12-month point of follow-up (0.45, 0.47, and 0.54, respectively). Although improvement of TST evaluated from sleep diaries was not significant at the end of treatment (d = –0.00; Table 4), the size of its effect, although small, was significant at both 3-month and 12-month points of follow-up (0.36 and 0.42, respectively; Table 5).

The results of the above variables on PSG or ACT also showed medium effect sizes for TWT (d = 0.73), WASO (d = 0.42), and SE (d = 0.53) at the end of treatment, and for SOL (d = 0.59), TST (d = 0.71), and SE (d = 0.78) on follow-up.

The efficacy of self-rating indices

We examined the effectiveness of CBT-I on the above-indicated self-rating measures evaluating the severity of insomnia or psychological status (Table 6). Effect sizes were calculated for insomnia measures and psychological measures by comparison between the baseline and the end-of-treatment scores, between the baseline and the follow-up scores, and between the scores of the CBT-I and control groups both at the end of treatment and on follow-up investigation. Within the CBT-I group, the results of insomnia and psychological measures both at the end of treatment (PSQI: ES_M = 0.83, ISQ: ES_M = 1.28, BDI: ES_M = 0.56, and DBAS: ES_M = 1.17) and on follow-up (PSQI: ES_M = 1.13, BDI: ES_M = 0.55, and DBAS: ES_M = 1.09) demonstrated that effect sizes ranged from medium to large (Table 6). In comparison to the control group, the effect sizes of the CBT-I group at the end of treatment (PSQI: d = 0.48, ISQ: d = 2.16, BDI: d = 1.30, and DBAS: d = 1.04) and on follow-up (PSQI: d = 0.77 and DBAS: d = 0.83) were medium to large. Insomnia and psychological indices demonstrated that effect sizes ranged from medium to large (Table 6).

Publication bias

In comparison to the baseline, sleep variables with failsafe index values larger than those of file-drawer studies

Table 2 Effect size from baseline to end of treatment

Outcomes	Tx	Baseline		End-treatment		Follow-up		*k*	ES_M	95% CI	File-drawer studies (*k*)	Fail-safe index ($P = 0.05$)
		Mean	SD	Mean	SD	Mean	SD					
Subjective evaluation from sleep diaries												
SOL	CBT-I	44.11	18.56	24.11	8.13	28.56	10.00	10	0.67*	0.48–0.81	60	174.32
	control	46.71	16.14	39.62	15.26	46.93	12.25					
TST	CBT-I	315.28	75.57	357.95	15.56	373.31	22.93	13	0.32*	0.15–0.47	75	51.50
	control	346.67	31.46	353.01	28.54	351.93	29.77					
TWT	CBT-I	130.61	24.38	77.69	17.41	80.17	19.68	5	1.09*	0.73–1.24	35	63.72
	control	138.39	22.11	124.47	23.14	–	–					
WASO	CBT-I	79.13	22.55	40.16	16.77	47.09	20.83	10	0.70*	0.50–0.84	60	182.24
	control	75.09	19.10	64.99	23.71	76.33	24.97					
EMA	CBT-I	51.49	6.87	31.93	9.30	37.08	1.73	4	0.74*	0.41–0.99	30	23.72
	control	47.51	2.56	43.09	5.29	–	–					
TIB	CBT-I	486.75	9.14	440.26	46.85	461.62	46.27	3	0.80*	0.40–1.09	25	14.65
	control	483.81	31.16	480.93	18.19	–	–					
SE	CBT-I	57.24	17.13	83.03	3.43	81.95	4.54	12	0.89*	0.69–0.98	70	439.87
	control	71.45	4.49	73.31	3.85	71.43	3.06					
Objective measures from PSG and/or ACT												
SOL	CBT-I	20.62	17.20	14.08	7.00	12.73	6.62	6	0.23	0.02–0.44	40	7.68
	control	28.14	17.46	33.95	19.85	38.67	21.18					
TST	CBT-I	365.29	25.94	365.58	33.19	377.53	30.26	9	0.03	0.22–0.27	55	–9.00
	control	362.13	33.89	352.08	51.61	376.27	79.14					
TWT	CBT-I	118.50	11.38	90.00	26.02	107.02	37.89	3	1.18*	0.90–1.39	25	17.30
	control	123.20	26.80	111.41	15.97	–	–					
WASO	CBT-I	80.01	14.55	55.04	21.45	87.65	24.54	6	0.57*	0.36–0.75	40	55.90
	control	69.45	18.44	6.93	20.13	85.70	26.59					
EMA	CBT-I	12.14	3.59	13.47	0.90	–	–	2	0.47*	0.01–0.91	20	0.27
	control	22.14	8.40	20.04	10.80	–	–					
SE	CBT-I	77.10	3.47	81.14	4.94	79.03	7.46	10	0.47*	0.29–0.64	60	89.64
	control	78.36	3.73	74.80	11.07	76.13	4.20					

An underline indicates that the value of file-drawer studies was larger than that of the fail-safe index. *$P < 0.05$. ACT, actigraphic evaluation; CBT-I, cognitive behavioral therapy for insomnia; CI, confidence interval; EMA, early morning awakening; ES_M, mean effect size; *k*, number of studies; PSG, polysomnogram; SE, sleep efficiency; SOL, sleep onset latency; TIB, time in bed; TST, total sleep time; TWT, total wake time; Tx, treatment; WASO, wake after sleep onset.

Table 3 Effect sizes of sleep variables from baseline to follow-up

Outcomes	Assessment	*k*	ES_M	95% CI	File-drawer studies (*k*)	Fail-safe index (*P* = 0.05)
Subjective evaluation from sleep diaries						
SOL	overall	9	0.57*	0.39–0.72	55	111.21
	3-month	4	0.76*	0.38–1.06	30	18.85
	6-month	4	0.47*	0.23–0.68	30	15.24
	12-month	3	0.65*	0.34–0.91	25	15.73
TST	overall	9	0.58*	0.40–0.73	55	148.55
	3-month	4	0.62*	0.25–0.93	30	13.91
	12-month	3	0.95*	0.61–1.14	25	29.65
TWT	overall	3	0.83*	0.35–1.17	25	12.17
WASO	overall	8	0.59*	0.40–0.74	50	110.34
	3-month	3	0.68*	0.24–1.03	25	9.68
	12-month	3	0.91*	0.58–1.10	25	25.77
EMA	overall	2	0.66*	0.11–1.11	20	5.93
SE	overall	10	0.82*	0.62–0.93	60	310.29
	3-month	5	1.07*	0.69–1.25	35	62.76
	6-month	4	0.57*	0.16–0.77	30	33.15
	12-month	4	1.14*	0.78–1.26	30	68.76
Objective measures from PSG and/or ACT						
SOL	overall	3	0.58*	0.14–0.96	25	1.71
TST	overall	4	0.28	0.11–0.65	30	−3.70
SE	overall	4	0.43*	0.33–0.79	30	−0.81

Overall means that all follow-up data at 1-,3-,4-,6-,8-,12-, and 24-months were combined. An underline indicates that the value of file-drawer studies was larger than that of the fail-safe index. *$P < 0.05$. ACT, actigraphic evaluation; CI, confidence interval; EMA, early morning awakening; ES_M, mean effect size; FU, follow-up; *k*, number of studies; PSG, polysomnogram; SE, sleep efficiency; SOL, sleep onset latency; TST, total sleep time; TWT, total wake time; WASO, wake after sleep onset.

Table 4 Effect size of CBT-I versus control groups at the end of treatment for sleep variables

Outcomes	*k*	*d*	95% CI	File-drawer studies (*k*)	Fail-safe index (*P* = 0.05)
Subjective evaluation from sleep diaries					
SOL	10	0.44*	0.26–0.61	60	56.00
TST	13	−0.00	0.16–0.17	75	−12.93
TWT	5	0.59*	0.29–0.85	35	17.28
WASO	10	0.75*	0.54–0.89	60	256.35
EMA	4	1.09*	0.73–1.24	30	54.50
TIB	3	0.71*	0.36–0.99	25	16.82
SE	12	0.86*	0.66–0.95	70	410.58
Objective measures from PSG and/or ACT					
SOL	5	0.24	0.01–0.46	35	14.62
TST	10	0.13	0.06–0.31	60	7.74
TWT	3	0.73*	0.25–1.11	25	12.38
WASO	7	0.42*	0.21–0.61	45	50.25
SE	10	0.53*	0.34–0.69	60	142.69

An underline indicates that the value of file-drawer studies was larger than that of the fail-safe index. *$P < 0.05$. CBT-I, cognitive behavioral therapy for insomnia; ACT, actigraphic evaluation; CI, confidence interval; CTL, control; *d*, Cohen's effect size (1988); EMA, early morning awakening; *k*, number of studies; PSG, polysomnogram; SE, sleep efficiency; SOL, sleep onset latency; TIB, time in bed; TST, total sleep time; TWT, total wake time; Tx, treatment; WASO, wake after sleep onset.

Table 5 Effect sizes of CBT-I versus control groups on follow-up for sleep variables

Outcomes	Assessment	*k*	*d*	95% CI	File-drawer studies (*k*)	Fail-safe index ($P = 0.05$)
Subjective evaluation from sleep diaries						
SOL	overall	7	0.40*	0.21–0.57	45	30.60
	3-month	2	0.00	0.53–0.54	20	−1.98
	12-month	2	0.45*	0.13–0.75	20	0.43
TST	overall	7	0.21*	0.03–0.39	45	14.72
	3-month	3	0.36*	0.09–0.78	25	−0.79
	12-month	4	0.42*	0.13–0.70	25	7.87
WASO	overall	6	0.34*	0.15–0.52	40	18.72
	3-month	2	0.55*	0.03–1.06	20	0.26
	12-month	3	0.47*	0.15–0.76	25	7.56
SE	overall	8	0.43*	0.25–0.59	50	49.48
	3-month	3	0.81*	0.35–1.15	25	90.10
	12-month	3	0.54*	0.23–0.80	25	10.95
Objective measures from PSG and/or ACT						
SOL	overall	2	0.59*	0.08–1.02	20	2.28
TST	overall	2	0.71*	0.21–1.12	20	0.94
SE	overall	2	0.78*	0.27–1.17	20	1.29

Overall means that all follow-up data at 1-,3-,4-,6-,8-,12-, and 24-months were combined. An underline indicates that the value of file-drawer studies was larger than that of the fail-safe index. *$P < 0.05$. CBT-I, cognitive behavioral therapy for insomnia; CI, confidence interval; CTL, control; *d*, Cohen's effect size (1988); *k*, number of studies; SE, sleep efficiency; SOL, sleep onset latency; TST, total sleep time; Tx, treatment; WASO, wake after sleep onset.

(*i.e.* without publication bias) at the end of treatment were SOL (174.32 *vs* 60), TWT (63.72 *vs* 35), WASO (182.24 *vs* 60), and SE (439.87 *vs* 70), and SOL (111.21 *vs* 55), TST (148.55 *vs* 55), WASO (110.34 *vs* 50), and SE (310.29 *vs* 60) on follow-up. In comparisons of CBT-I to control groups, sleep variables without publication bias were WASO (256.35 *vs* 60), EMA (54.50 *vs* 30), and SE (410.58 *vs* 70) at the end of treatment and only SE (90.10 *vs* 25) on follow-up.

In comparison to the baseline, self-rating scales with fail-safe index values larger than those of file-drawer studies were the PSQI, the DBAS, the integrated insomnia index, and the integrated psychological index, both at the end of treatment (33.41 *vs* 25, 46.63 *vs* 35, 105.28 *vs* 35, and 46.63 *vs* 35, respectively) and on follow-up (56.90 *vs* 25, 83.44 *vs* 30, 70.78 *vs* 30, and 71.95 *vs* 35, respectively). In comparisons of CBT-I to control groups, self-rating scales without publication bias were the ISQ, BDI, DBAS, integrated insomnia index, and integrated psychological index at the end of treatment (34.51 *vs* 20, 30.18 *vs* 25, 57.02 *vs* 30, 94.14 *vs* 35, 193.67 *vs* 95, respectively), and the DBAS (47.23 *vs* 45) on follow-up.

DISCUSSION

Considering recent trends, we investigated the effectiveness of multicomponent CBT for primary insomnia, both at the end of treatment and on follow-up, by conducting a meta-analysis on previous randomized controlled trials. As a result, we confirmed the findings of earlier meta-analyses which supported the effectiveness of various kinds of cognitive behavioral interventions on chronic insomnia.[7,8] Moreover, we succeeded in confirming the therapeutic effectiveness of CBT-I even during follow-up periods. In addition, this study is the first meta-analysis to reveal the effectiveness of CBT-I both on objective sleep measures and self-rating measures.

Most of the weighted effect sizes of sleep parameters evaluated from sleep diaries were greater than 0.5 throughout the comparisons, both between baseline and at the end of treatment, and between baseline and on follow-up, indicating a medium to large treatment effectiveness. In addition, the effect size of TST became larger after the 12-month follow-up than the value at the end of treatment. This is in line with the report by Morin *et al.*[17] in which the effectiveness of CBT-I on sleep

Table 6 Effect sizes of CBT-I for self-rating measures

Outcomes	*k*	ES_M	95% CI	File-drawer studies (*k*)	Fail-safe index ($P = 0.05$)
Baseline to end of treatment					
Insomnia index	5	0.94*	0.68–1.06	35	105.28
PSQI	3	0.83*	0.56–1.00	25	33.41
ISQ	2	1.28*	0.75–1.46	20	17.96
Psychological index	5	1.03*	0.68–1.19	35	46.63
BDI	3	0.56*	0.18–0.88	25	1.90
DBAS	4	1.17*	0.76–1.31	30	102.62
Baseline to follow-up					
Insomnia index	4	1.13*	0.82–1.21	30	70.78
PSQI	3	1.13*	0.81–1.22	25	56.90
Psychological index	5	0.88*	0.51–1.12	35	71.95
BDI	3	0.55*	0.26–0.81	25	13.41
DBAS	4	1.09*	0.75–1.21	30	83.44

Outcomes	*k*	*d*	95% CI	File-drawer studies (*k*)	Fail-safe index ($P = 0.05$)
CBT-I versus CTL at the end of treatment					
Insomnia index	5	0.93*	0.67–1.06	35	94.14
PSQI	3	0.48*	0.23–0.71	25	12.33
ISQ	2	2.16*	1.53–2.78	20	34.51
Psychological index	7	0.71*	0.51–0.86	45	193.67
BDI	3	1.30*	0.81–1.43	25	30.18
DBAS	4	1.04*	0.68–1.21	30	57.02
CBT-I versus CTL on follow-up					
PSQI	2	0.77*	0.48–0.97	20	16.97
DBAS	3	0.83*	0.52–1.04	25	52.58

Insomnia index included all the insomnia scales including PSQI, ISQ, and SII. Psychological index included all the psychological scales including DBAS, SES, BDI, STAI, and POMS. An underline indicates that the value of file-drawer studies was larger than that of fail-safe index. *$P < 0.05$. BDI, Beck Depression Inventory; CBT-I, cognitive behavioral therapy for insomnia; CI, confidence interval; CTL, control; *d*, Cohen's effect size (1988); DBAS, Dysfunctional Belief s About Sleep Scale; ES_M, mean effect size; *k*, number of studies; ISQ, Insomnia Symptoms Questionnaire; PSQI, Pittsburgh Sleep Quality Index.

disturbance further improved over time, even after discontinuation of the treatment. The reason for this is unclear; however, CBT-I could be superior to pharmacotherapy in that the effectiveness on most of the symptoms of insomnia is sustained even after discontinuation of the treatment.

Regarding objective measures, effect sizes of WASO, TWT, EMA, and SE were different between baseline and at the end of treatment, and those of SOL and SE were different between baseline and on follow-up. These findings suggest that CBT-I relieves disturbance of onset and maintenance of sleep objectively. However, there was no significant improvement in objective TST both between baseline and at the end of treatment, and between baseline and on follow-up. This could suggest that there is a difference in subjective and objective findings in this measure; insomniacs are likely to underestimate their subjective sleep time, or to overestimate their insomnia symptoms, especially before treatment. Given this, our results might suggest that CBT-I is effective for the improvement of their subjective sleep misperceptions without changing actual sleep length.

In comparisons between the CBT-I and control groups, it was revealed that CBT-I was more effective than the control groups for subjectively measured SOL, TWT, WASO, EMA, TIB, and SE at the end of treatment, and that the effectiveness for some of these measures was sustained even on follow-up. From these findings, CBT-I for insomnia symptoms was thought to be clearly superior to the control group.

For insomnia and psychological measures, improvements of CBT-I on these measures were clearly superior

to the control group at the end of treatment. The results of improvement of insomnia measures, including the PSQI and the ISQ were thought to correspond to the above-indicated changes in sleep parameters with the treatment.

The improvement of psychological measures including the BDI and the DBAS after CBT-I is of clinical interest. The existence of chronic insomnia symptoms is well known as a risk factor for developing depression.[39,40] It has also been reported that CBT-I significantly improved SOL, WASO, TST, SE, and sleep quality together with depression scores, both at the end of treatment and at 3-month follow-up, in insomnia sufferers with mild depression.[41] The coadministration of hypnotic drugs with antidepressant treatment has been also reported to improve not only insomnia symptoms but also depressive symptoms in depressed patients.[42] The result of the present meta-analysis strongly supports the assumption that CBT-I could alleviate the depressive symptoms of insomnia sufferers following the improvement of insomnia symptoms.

Previous studies have indicated that sleep-related dysfunctional beliefs (*e.g.* "I think that I need eight hours of sleep to function well during the day") is responsible for the formation of persistent insomnia,[43] and decreases in the DBAS score brought about by CBT-I reflect the action mechanisms of treatment.[44]

The DBAS was developed to quantify the degree of dysfunctional beliefs, but no previous meta-analyses have focused on the effectiveness of CBT-I on the DBAS. We would like to emphasize that CBT-I might improve insomnia symptoms mainly based on the correction of sleep-related dysfunctional beliefs manifested on the DBAS.

Previous meta-analyses[7,8,10] showed that CBT-I packaged with evidence-based cognitive behavioral techniques could be expected to be effective not only for the treatment of primary insomnia. However, publication bias has not been taken into consideration in previous studies. In this study, the effectiveness of CBT-I was confirmed only in a small number of sleep measures after excluding publication bias. Further accumulation of data is necessary to avoid the influence of file-drawer studies.

This study has some limitations. First, the ages of the participants in each study were not considered. A previous study by Irwin *et al.*[10] made a comparison of the efficacy of behavioral intervention for primary insomnia in participants with a mean age less than 55 years and in those with a mean age more than 55 years; the result showed that the effect size of each sleep parameter with treatment was different in each of these two age groups. In the present work, analysis on effectiveness for age cohorts was not conducted. Second, the studies we used included those with individual CBT-I and those with group format CBT-I. Although Bastien *et al.*[45] reported that there was no significant difference in effectiveness between the two formats, future study of comparisons of the efficacy between individual CBT-I and group CBT-I is necessary.

In conclusion, our meta-analysis showed that CBT-I improves not only nocturnal sleep problems but also daytime depressive mood, both at the end of treatment and on follow-up. However, publication bias is clearly evident in a certain number of sleep variables. CBT-I can be recommended for patients with primary and chronic insomnia; however, we should be cautious about the possibility of overestimating the efficacy of the treatment.

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Original Article

Quality of life in patients with narcolepsy with cataplexy, narcolepsy without cataplexy, and idiopathic hypersomnia without long sleep time: Comparison between patients on psychostimulants, drug-naïve patients and the general Japanese population

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ABSTRACT

Objective: To assess the quality of life of patients with narcolepsy with cataplexy (NA–CA), narcolepsy without cataplexy (NA w/o CA), and idiopathic hypersomnia without long sleep time (IHS w/o LST) who were taking psychostimulant medication, and to ascertain which factors (including psychosocial and environmental variables) influence quality of life in this population.
Methods: In total, 185 patients who had received regular treatment were enrolled in the study (NA–CA, $n = 83$; NA w/o CA, $n = 48$; IHS w/o LST, $n = 54$). Patients were asked to complete questionnaires including the Short Form-36 Health Survey (SF-36), the Epworth Sleepiness Scale (ESS), and items concerning psychosocial and environmental variables.
Results: All three diagnostic groups had significantly lower scores for most SF-36 domains compared with the Japanese normative data, and the ESS score was significantly reduced with treatment. Multiple logistic regression analyses revealed that several SF-36 domains were associated with the ESS score; autonomy in controlling own job schedule, experience of divorce or break up with a partner due to symptoms, experience of being forced to relocate or being dismissed due to symptoms, and perception of support from others.
Conclusions: The severity of subjective sleepiness and psychological and environmental variables influenced quality of life in patients with these hypersomnias of central origin.

1. Introduction

Excessive daytime sleepiness (EDS), including hypersomnias of central origin, affects 9–17% of the general population [1–4]. Narcolepsy is quite rare, with a prevalence of approximately 0.02–0.05% in Western countries [5–7]. The highest reported prevalence is 0.16%, and this was reported in a Japanese population [8]. However, narcolepsy has clear impacts on the functions of daily life. Several previous studies have demonstrated relationships between hypersomnias of central origin (especially narcolepsy), severe limitations and difficulties in everyday life activities (including school, work, interpersonal relationships, and social activities) [9,10], and decreased quality of life (QOL) [11–16]. It has been recently reported that drug-naïve patients suffering from narcolepsy with cataplexy (NA–CA), narcolepsy without cataplexy (NA w/o CA), and idiopathic hypersomnia without long sleep time (IHS w/o LST) have poorer QOL compared with the general population, and that the severity of subjective sleepiness is not related to the degree of decline of QOL among these patients [17].

Treatment with psychostimulant medication has been widely accepted as the first-line treatment for patients with the above-mentioned hypersomnias. Some studies have shown that treatment with psychostimulant medication improves both EDS and

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QOL [15,18]. However, it has not been determined whether treatment with psychostimulant medication improves QOL to a normal level in patients with hypersomnia. As QOL is a comprehensive and multidimensional concept, it can reflect not only health status but also psychological, social, and environmental variables of an individual's life, including lifestyle and social support. Therefore, such variables should be taken into consideration when evaluating QOL. However, to the authors' knowledge, no studies have considered environmental variables when investigating the association between hypersomnia and QOL in treated patients with hypersomnias of central origin.

The aims of this cross-sectional study were: (1) to assess QOL among treated patients with NA–CA, NA w/o CA, and IHS w/o LST compared with drug-naive patients [17] and Japanese normative data; and (2) to investigate the impact of psychostimulant medication and psychosocial and environmental variables on QOL.

2. Methods

The present study was approved by the Ethics Committee of the Neuropsychiatric Research Institute. Informed consent was obtained from all participants.

2.1. Participants

Among consecutive eligible patients (aged $\geqslant$ 20 years) who visited the outpatient clinic of the Japanese Somnology Centre between May 2007 and March 2009, patients who met the following two inclusion criteria were enrolled in this study: (1) a diagnosis of NA–CA, NA w/o CA, or IHS w/o LST based on the diagnostic criteria in the Second Edition of the International Classification of Sleep Disorders [19]; and (2) regular treatment with psychostimulant medication for EDS with more than one year of follow-up after fixation of the dose [mean duration of treatment 35.4 ± 20.3 months]. Moreover, patients with any of the following four conditions were excluded: (1) apnoea–hypopnoea index > 5/h and/or periodic limb movement index > 15/h on nocturnal polysomnography (PSG); (2) possible circadian rhythm sleep disorders or behaviourally induced insufficient sleep syndrome judged from sleep diaries; (3) possible comorbidities of psychiatric disorders (including mood disorders and other major medical illnesses); and (4) habitually taking drugs or substances with psychotropic effects. Before starting treatment, diagnoses were made for all participants according to the above criteria by at least two board-certified psychiatrists specializing in sleep disorders.

Consequently, 183 patients (83 patients with NA–CA, 48 patients with NA w/o CA, and 54 patients with IHS w/o LST) were enrolled in the study. All subjects with NA w/o CA or IHS w/o LST underwent overnight PSG followed by a standard multiple sleep latency test (MLST) [20] for diagnosis of the disorders. Of the 83 NA–CA subjects, 50 did not undergo MSLT but had both typical cataplexy and a sleep-onset rapid eye movement period (SOREMP) on overnight PSG. The remaining patients with NA–CA and those with NA w/o CA had at least two SOREMPs and less than 8 min of mean sleep latency on MSLT. Patients with IHS w/o LST had less than 8 min of mean sleep latency and one SOREMP or less on MLST. Due to an insufficient number of patients, patients with IHS with LST ($n = 5$) were not included in this study.

For comparison, 137 newly diagnosed and drug-naïve patients with NA–CA ($n = 28$), NA w/o CA ($n = 27$), and IHS w/o LST ($n = 82$) who had participated in a previous study [17] were included for analysis in the present study. Thirteen of these patients (7%) also participated in the present study.

2.2. Measures

The participants were asked to complete a questionnaire that included an instrument assessing QOL, an instrument evaluating subjective sleepiness, and questions regarding sociodemographic and psychosocial variables. Additional clinical information including demographic variables was also obtained from the participants' medical records.

2.2.1. Medical outcomes study Short Form-36

QOL was assessed using the Japanese version of the Short Form-36 Health Survey questionnaire (SF-36, Version 1.2), a self-administered questionnaire that has been widely used and validated in the general Japanese population [21–23]. The questionnaire consists of 36 questions divided into eight domains that represent different aspects of QOL: (1) physical functioning (PF), (2) role limitations due to physical problems (RP), (3) role limitations due to emotional problems (RE), (4) social functioning (SF), (5) mental health (MH), (6) energy/vitality (VT), (7) bodily pain (BP), and (8) general health (GH).

2.2.2. Epworth Sleepiness Scale

Subjective sleepiness was assessed at the first visit to the outpatient clinic and at the time of the survey using the Epworth Sleepiness Scale (ESS) [24]. The ESS is a widely accepted self-completion questionnaire designed to evaluate the level of sleepiness during daily life. Participants were asked to score the possibility of falling asleep in eight different situations (0 = would never doze; 3 = high chance of dozing, final score range 0–24) [24].

2.2.3. Clinical information and sociodemographic variables

Clinical information obtained included age, gender, age at onset of hypersomnia, length of subjective hypersomnia morbidity, and prescribed medications for the treatment of hypersomnia or cataplexy. Furthermore, questionnaires regarding sociodemographic and psychosocial variables were designed specifically for the present study. Sociodemographic variables included marital status, number of family members in the household, and occupation. The questionnaires also inquired whether hypersomnia had caused problems in different aspects of life, such as relationships and work. Questions about the experience of divorce or a break up with a partner due to symptoms, and the experience of being forced to relocate or being dismissed due to symptoms, were included. In addition, specific questions about autonomous control of job schedule, including the ability to take naps, and questions about perceived support from family, friends, superiors, or coworkers were embedded [25,26].

2.3. Statistical analysis

First, demographic, sociodemographic and clinical variables were compared between the treated patients and the drug-naïve patients. The *t*-test was used to compare continuous variables, and the Chi-squared test was used to compare categorical variables.

Furthermore, demographic, sociodemographic, and clinical variables were compared between the treated patients in the three diagnostic groups (NA–CA, NA w/o CA, and IHS w/o LST). One-way analysis of variance (ANOVA), followed by post-hoc analysis using Scheffe's test, was used to compare continuous variables, and Chi-squared test was used to compare categorical variables. Moreover, in order to assess treatment effectiveness among the treated patients, the paired *t*-test was used to compare ESS scores between pre- and post-treatment periods.

The scores for the eight subscales of the SF-36 were converted into a Japanese norm-based score according to gender and age (standardized *t* score transformation with a mean of 50 ± 10)

Table 1
Descriptive variables of treated patients and drug-naive patients.

Characteristics	Treated patients				Comparison between three diagnostic groups of treated patients	Drug-naive patients[a]				Comparison between treated patients and drug-naive patients
	Overall	NA–CA	NA w/o CA	IHS w/o LST		Overall	NA–CA	NA w/o CA	IHS w/o LST	
Number of participants	185	83	48	54		137	28	27	82	
Gender (%)										
Male	55.1	51.8	52.1	63.0	n.s.	48.2	35.7	37.0	56.1	n.s.
Female	44.9	48.2	47.9	37.0		51.8	64.3	63.0	49.3	
Age (years)										
Mean (SD)	32.6 ± 8.3	33.2 ± 9.8	30.5 ± 6.0	33.3 ± 7.0	n.s.	31.2 ± 9.2	33.2 ± 13.0	28.6 ± 8.6	31.4 ± 7.6	n.s.
Age at onset (years)										
Mean (SD)	17.9 ± 7.1	17.9 ± 8.2	16.0 ± 4.9	19.5 ± 6.7[b]	0.044	18.6 ± 6.7	18.8 ± 7.0	17.8 ± 4.2	18.8 ± 7.2	n.s.
Duration of disease morbidity (years)										
Mean (SD)	14.6 ± 7.7	15.0 ± 7.7	14.6 ± 7.0	14.0 ± 8.3	n.s.	12.6 ± 8.5	14.4 ± 12.3	11.0 ± 8.7	12.5 ± 6.6	0.021
Marital status (%)										
Married	20.0	21.3	13.6	23.5	n.s.	26.3	17.9	11.1	34.1	n.s.
Not married	80.0	78.7	86.4	76.5		73.7	82.1	88.9	65.9	
Number of family members (%)										
⩾1	56.2	62.7	47.9	53.7	n.s.	60.6	75.0	40.7	62.2	n.s.
0		33.5	24.1	43.8	38.9		32.8	21.4	48.1	31.7
Missing	10.3	13.3	8.3	7.4		6.6	3.6	11.1	6.1	
Occupation (%)										
Employed (full time)	72.4	59.0	83.3	83.3	0.017	64.7	60.7	55.6	68.3	n.s.
Employed (part time)	11.9	16.9	8.3	7.4		11.0	14.3	22.2	6.1	
Housewife	2.7	4.8	0	1.9		7.4	10.7	7.4	6.1	
Student	10.9	16.8	4.2	7.4		15.4	14.3	11.1	17.1	
Missing	2.2	2.4	4.2	0		1.5	0	3.7	2.4	
ESS score (before treatment)										
Mean (SD)	16.0 ± 4.0	16.6 ± 3.6	16.5 ± 4.2	14.7 ± 4.2[c]	0.021	14.8 ± 3.3	16.9 ± 2.8	14.5 ± 2.7[i]	14.1 ± 3.3[j]	n.s.
ESS score (after treatment)										
Mean (SD)	12.8 ± 5.1[d]	14.1 ± 4.7[e]	12.8 ± 5.7[f]	11.0 ± 4.6[g,h]	0.002					
Medication type (%)										
Stimulant and anticataplexy	9.7	21.7	0	0	<0.001					
Stimulant only	90.3	78.3	100.0	100.0						
Stimulant medication type (%)										
Modafinil only	17.8	15.7	18.8	20.4	n.s.					
Methylphenidate only	17.3	18.1	25.0	9.3						
Pemoline only	29.7	24.1	27.1	40.7						
Two medications or more	35.1	42.2	29.2	29.6						

NA–CA, narcolepsy with cataplexy; NA w/o CA, narcolepsy without cataplexy; IHS w/o LST, idiopathic hypersomnia without long sleep time; ESS, Epworth Sleepiness Scale; n.s., not significant; SD, standard deviation.

[a] Data from the authors' previous research (2008).
[b] Vs NA w/o CA, $P = 0.044$, Scheffe's test.
[c] Vs NA–CA, $P = 0.036$, Scheffe's test.
[d] Vs before treatment, $P < 0.001$, paired t-test.
[e] Vs before treatment, $P < 0.001$, paired t-test.
[f] Vs before treatment, $P < 0.001$, paired t-test.
[g] Vs before treatment, $P < 0.001$, paired t-test.
[h] Vs NA–CA, $P = 0.002$, Scheffe's test.
[i] Vs NA–CA, $P = 0.022$, Scheffe's test.
[j] Vs NA–CA, $P = 0.001$, Scheffe's test.

[23]. Scores below 50 indicate that health status is below the average for the general Japanese population. This method enables comparison of the magnitude of impact among the eight subscales, which in turn reflects the recommendation of the Japanese Manual of the SF-36 [23]. Scores of treated patients were compared with those of drug-naïve patients [17] and then compared with the national normative data.

Factors associated with QOL of treated patients were examined with the aid of a series of logistic regression analyses. The dependent variables were the eight subscale scores of the SF-36, which were dichotomized at the mean of each subscale score. The independent variables were: gender; age; duration of disease morbidity; ESS score at time of the survey; experience of divorce or break up with a partner due to symptoms; experience of being forced to relocate or being dismissed due to symptoms; autonomy over control of job schedule, including the ability to take naps; and perceived support from family, friends, superiors, or coworkers. All independent variables were initially examined in univariate regression models. To control for confounding variables and to determine the main correlates, multiple logistic regression

Table 2
Sociodemograhic variables of treated patients.

Characteristics	Overall	NA–CA	NA w/o CA	HS w/o LST	Comparison between three diagnostic group
Autonomy in controlling own job schedule					
Yes	70.1	60.8	76.1	78.8	n.s.
No	29.9	39.2	23.9	21.2	
Support from others (family, friends, superiors or coworkers)					
Yes	63.8	71.1	50.0	64.8	n.s.
No	36.2	28.9	50.0	35.2	
Experience of divorce or break up with partner due to symptoms (%)					
Yes	10.2	11.9	4.2	13.0	n.s.
No	89.8	88.1	95.8	87.0	
Experience of being forced to relocate or being dismissed due to symptoms (%)					
Yes	30.3	36.1	25.0	25.9	n.s.
No	69.7	63.9	75.0	74.1	

NA–CA, narcolepsy with cataplexy; NA w/o CA, narcolepsy without cataplexy; IHS w/o LST, idiopathic hypersomnia without long sleep time; n.s., not significant.

analyses were performed for all variables. Statistical tests of the regression estimates were based on Wald statistics. Odds ratios (OR) and 95% confidence intervals (CI) were calculated in order to show associations.

3. Results

3.1. Participant characteristics

The descriptive variables for the main demographic, sociodemographic, and clinical features of the treated patients and drug-naïve patients [17] are shown in Table 1. No significant differences were found between these two groups, except for duration of disease morbidity ($t = 2.326$, $P = 0.021$).

In the treated patients, ANOVA showed that the age of onset differed significantly between the three diagnostic groups ($F[2182] = 3.12$, $P = 0.044$). Scheffe's post-hoc test showed that the age of onset was significantly younger in patients with NA w/o CA compared with those with IHS w/o LST ($P = 0.044$). In total, 90.3% of subjects were only receiving medical treatment for daytime sleepiness, and 9.7% were receiving medical treatment for both hypersomnia and cataplexy at the time of the survey. Among the patients with NA–CA, 21.7% were receiving both stimulant and anticataplectic medications.

The ESS score before treatment differed significantly between the three diagnostic groups of treated patients ($F[2182]=3.94$, $P = 0.021$). Post-hoc tests revealed that the ESS score before treatment was significantly higher in the patients with NA–CA compared with those with IHS w/o LST ($P = 0.036$). However, the ESS scores were not significantly different between the patients with NA–CA and those with NA w/o CA, and between the patients with NA w/o CA and those with IHS w/o LST.

Paired t-tests revealed that ESS scores in the treated patients reduced significantly after treatment ($t = 7.19$, $P < 0.01$), and this was seen in all three diagnostic groups (NA–CA, $t = 3.82$, $P < 0.001$; NA w/o CA, $t = 4.00$, $P < 0.001$; IHS w/o LST, $t = 4.94$, $P < 0.001$). ANOVA revealed that the ESS scores after treatment differed significantly between the three diagnostic groups ($F[2182]=6.58$, $P = 0.002$). Post-hoc tests showed that the ESS score after treatment was significantly higher in the patients with NA–CA compared to those with IHS w/o LST ($P = 0.002$). However, there were no significant differences in the scores between the patients with NA–CA and those with NA w/o CA, and between the patients with NA w/o CA and those with IHS w/o LST.

3.2. Impact on sociodemographic status

Of the treated patients (Table 2), 70.1% had the autonomy to control their job schedule, including the ability to take naps; 63.8% perceived that they received support from their family, friends, superiors or coworkers; 30.3% had been forced to relocate or had been dismissed because of their symptoms; and 10.2% had divorced or broken up with a partner because of their symptoms.

Table 3
Short Form-36 profiles of treated patients in comparison with drug-naive patients and national normative data: mean ± standard deviation.

	Treated patients	Drug-naive patients*	*P*-value †	*P*-value‡
Overall	$n = 185$	$n = 137$		
PF	53.2 ± 6.9	51.2 ± 8.4	0.036	<0.001
RP	40.4 ± 9.1	36.1 ± 24.5	n.s.	<0.001
BP	51.0 ± 10.3	51.0 ± 11.1	n.s.	n.s.
GH	46.9 ± 10.1	47.3 ± 10.8	n.s.	<0.001
VT	45.3 ± 10.6	43.8 ± 9.7	n.s.	<0.001
SF	46.4 ± 11.7	43.9 ± 12.6	n.s.	<0.001
RE	43.7 ± 7.4	36.5 ± 22.6	<0.001	<0.001
MH	48.2 ± 9.9	44.6 ± 10.6	0.003	0.017
NA–CA	$n = 83$	$n = 28$		
PF	52.4 ± 8.2	53.4 ± 6.1	n.s.	0.010
RP	39.8 ± 8.7	38.7 ± 23.6	n.s.	<0.001
BP	52.8 ± 10.0	53.9 ± 9.1	n.s.	0.013
GH	47.3 ± 10.4	47.9 ± 8.2	n.s.	0.021
VT	46.3 ± 11.9	45.7 ± 9.4	n.s.	0.006
SF	46.1 ± 12.3	43.1 ± 12.0	n.s.	0.005
RE	44.0 ± 7.5	39.9 ± 25.6	n.s.	<0.001
MH	47.9 ± 11.1	45.3 ± 11.6	n.s.	n.s.
NA w/o CA	$n = 48$	$n = 27$		
PF	54.7 ± 4.7	51.4 ± 5.7	n.s.	<0.001
RP	41.5 ± 11.6	33.0 ± 28.4	n.s.	<0.001
BP	49.9 ± 10.7	53.0 ± 9.7	n.s.	n.s.
GH	47.9 ± 10.5	49.0 ± 12.6	n.s.	n.s.
VT	44.7 ± 9.1	44.0 ± 9.6	n.s.	<0.001
SF	45.7 ± 11.5	45.3 ± 12.7	n.s.	0.013
RE	43.2 ± 9.2	33.4 ± 22.3	0.037	<0.001
MH	46.9 ± 9.5	45.3 ± 11.1	n.s.	0.029
IHS w/o LST	$n = 54$	$n = 82$		
PF	52.9 ± 6.1	50.5 ± 9.7	n.s.	0.001
RP	40.2 ± 6.9	36.2 ± 23.6	n.s.	<0.001
BP	49.4 ± 10.2	49.4 ± 12.0	n.s.	n.s.
GH	45.5 ± 9.3	46.5 ± 10.9	n.s.	<0.001
VT	44.4 ± 10.0	43.1 ± 9.9	n.s.	<0.001
SF	47.7 ± 11.0	43.7 ± 12.9	n.s.	n.s.
RE	43.7 ± 5.1	36.4 ± 21.7	0.004	<0.001
MH	50.1 ± 7.9	44.2 ± 10.2	<.001	n.s.

NA–CA, narcolepsy with cataplexy; NA w/o CA, narcolepsy without cataplexy; IHS w/o LST, idiopathic hypersomnia without long sleep time; PF, physical health; RP, role limitations due to physical problems; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role limitations due to emotional problems; MH, mental health; n.s., not significant.
* Data from the authors' previous research (2008).
† Treated patients vs drug-naive patients.
‡ Treated patients vs national normative data.