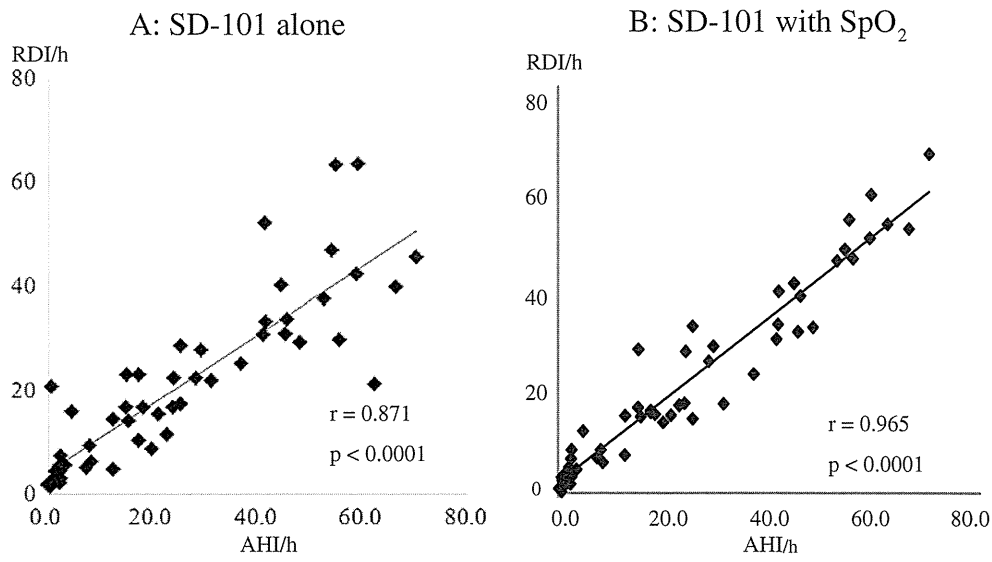

Fig. 2 Pearson correlations between RDI on SD-101 and AHI on PSG. SD-101 alone (**a**) and SD-101 with SpO_2 (**b**) vs. PSG (r=0.871 and 0.965, respectively; p<0.0001 for both)

could not be collected into the SD-101 and the SD-101 data could not be collected from one because the battery ran out on the night of the examination. Thus, we analyzed data from 53 patients.

None of the participants described adverse events. The mean AHI on PSG and the RDI on SD-101 with SpO_2 for the 53 patients (men, 46; women, 7; age, 50.1±13.8 years; BMI, 25.3±3.4 kg/m^2) were 24.5±21.2 and 22.6±17.7/h, respectively. The TST used for calculating AHI on PSG was 412.8±76.9 min (mean±SD), and the sleep efficiency (TST/TIB) was 81.7±14.2 % (Table 1). The TIB used for calculating RDI based on the results from the SD-101 was 510.6 ±29.5 min (mean±SD). The TIB and TST significantly differed (p<0.001), whereas AHI and RDI did not (p=0.91).

The scatter graph in Fig. 2 demonstrates a close and statistically significant correlation coefficient between the AHI obtained from PSG and the RDI from SD-101 alone, and SD-101 with SpO_2 (SD-101 alone: r=0.871, p<0.0001; SD-101 with SpO_2: r=0.965, p<0.0001).

Bland–Altman analysis generally showed close agreement between the AHI and RDI values derived from PSG and from SD-101, respectively. The mean difference in AHI and RDI on the Bland–Altman plot was smaller when generated from the SD-101 with SpO_2 than from the SD-101 alone (1.9 vs. 4.1; Fig. 3).

At an AHI cutoff on PSG of 15 episodes per hour, the screening sensitivity of RDI on the SD-101 with SpO_2 was 96.9 % and the specificity was 90.5 % (Table 2). The positive and negative predictive values were 93.9 and 95 %, respectively. The sensitivity and specificity of RDI at cutoffs of 15 episodes per hour were 87.5 and 85.7 %, respectively, on the SD-101 alone. At an AHI cutoff on PSG of 5 episodes per hour, the screening sensitivity of RDI on the SD-101 with SpO_2 was 100 % and the specificity was

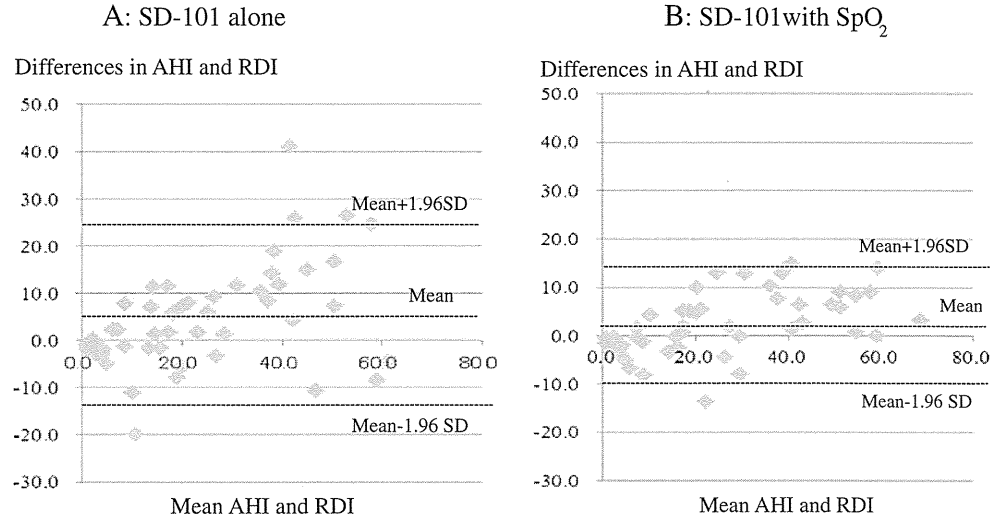

Fig. 3 Bland–Altman plot of RDIs on SD-101 and AHIs on PSG. *Upper* and *lower solid lines* indicate means±1.96 SD

Table 2 Concurrent validity of manual scoring data of SD-101 alone and SD-101 with SpO_2 for apnea–hypopnea indexes of ≥5 and ≥15 on polysomnography

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	FN (%)	FP (%)
RDI (SD-101 alone) ≥5	94.7	60.0	85.7	81.8	5.3	40
RDI (SD-101 alone) ≥15	87.5	85.7	90.3	81.8	12.5	14.3
RDI (SD-101 with SpO_2) ≥5	100	66.7	88.4	100	0	33.3
RDI (SD-101 with SpO_2) ≥15	96.9	90.5	93.9	95	3.1	9.5

RDI respiratory disturbance index, *PPV* positive predictive value, *NPV* negative predictive value, *FN* false negative, *FP* false positive

66.7 % (Table 2). The positive and negative predictive values were 88.4 and 100 %, respectively. The sensitivity and specificity of RDI at cutoffs of 5 episodes per hour were 94.7 and 60 %, respectively, on SD-101 alone.

The AUC of the ROC was >0.96 at a cutoff AHI of ≥15 episodes per hour (Fig. 4). The RDI cutoffs from the SD-101 alone and SD-101 with SpO_2 at AHI cutoffs of 15 per hour were 16.1 and 14.9, respectively.

Discussion

Various studies have attempted to validate the accuracy of devices used to determine the screening capability of PM devices. Some studies have conducted PM and PSG on different days [20, 21]. However, 15–25 % of individuals especially with mild to moderate OSAS are likely to show night-to-night variability, possibly due to the first-night effect including differences in total sleep time, frequency of arousals, and sleep stage distributions [21–23]. Therefore, we simultaneously recorded PSG and SD-101 to accurately evaluate the validity of SD-101 in the present study.

The RDI on the SD-101 closely correlated with the AHI determined by PSG. Bland–Altman plots provided graphic evidence of adequate concordance between the results of the two analyses. Interestingly, the analytical accuracy of the SD-101 was improved by simultaneously measuring SpO_2. One report describing time-matched RDI measurements using the SD-101 alone and the AHI on PSG suggested that the SD-101 has a relatively low ability to detect normal and mild SDB mainly because of the incorrect detection of some body movement as SDB [11]. However, the new SD-101 with SpO_2 sensors might exclude incorrect respiratory events without desaturation, such as body movements.

The findings of the ROC analysis also indicated a cutoff of 14.9 episodes per hour of RDI on SD-101 with SpO_2 to detect 15 episodes per hour of AHI, which is a generally accepted criterion for pathological OSAS in many epidemiological studies [1, 4] and an active indication of a need to treat OSAS [24]. At cutoffs of AHI ≥5 and ≥15, the sensitivity, specificity, positive and negative predictive values, as well as false-negative and false-positive values of the SD-101 were better when AHI on PSG was compared with the RDI on SD-101 plus SpO_2 than with the value from the SD-101 alone. These results indicate that the new system is sufficiently accurate for screening pathological OSAS. The diagnostic accuracy of type 3 PM devices has recently improved and their sensitivity and specificity have reached ≥90 % [25, 26]. Although SD-101 is classified as a type 4 PM device that measures only single or dual physiological variables, the diagnostic accuracy of the new SD-101 system seems essentially compatible with that of type 3 PM devices.

The SD-101 is a noninvasive PM device in which sheet-like sensors placed under the body detect respiratory

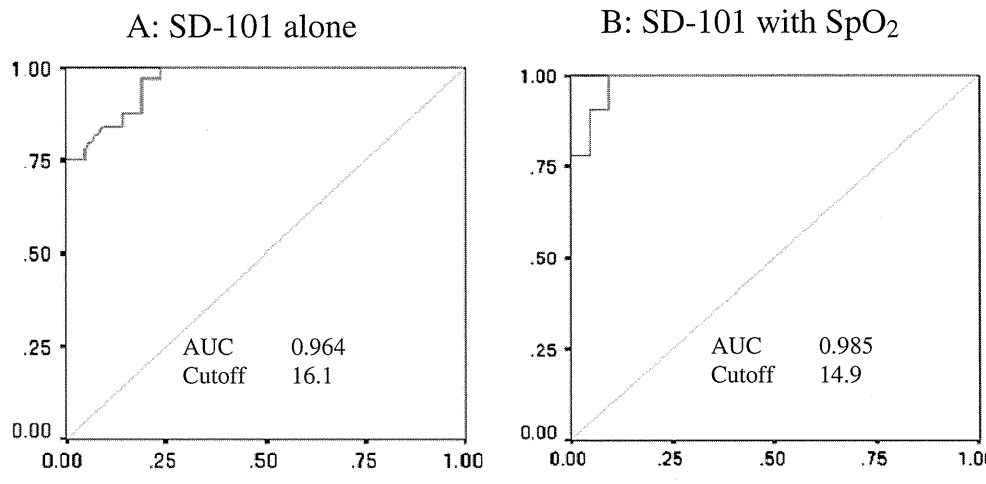

Fig. 4 Receiver operating characteristic curves with RDI on SD-101 alone (**a**) and SD-101 with SpO_2 (**b**) for determining 15 episodes per hour of AHI on PSG

movements. Measurement difficulties, such as disengaging air flow sensors, and body position sensors, did not arise during this study. Type 3 PM devices generally require the positioning of oronasal and respiratory effort sensors, which can cause discomfort [27]. The present results emphasize that the low invasiveness of the SD-101 with SpO_2 measurement confers a greater advantage for OSAS screening than any invasive type 3 or type 4 PM device. Moreover, the essentially equivalent accuracy of the SD-101 with SpO_2 measurement implies that the device could have broader uses among populations with suspected OSAS.

This study has a number of limitations. Firstly, the study population comprised patients with snoring and/or OSAS who were recruited from only two sleep disorder clinics, which might have caused sampling bias. Secondly, the rate of data loss was 16.7 %, which was quite similar to that previously reported for type 3 PM devices [28]. Data losses with this system were mainly caused by disconnection of the cable between the SpO_2 measurement device and the SD-101 rather than errors in attaching sensors or electrodes becoming disengaged during overnight monitoring. Improvements in the sensor cable would be desirable. Thirdly, the Bland–Altman findings revealed that the RDI measured on the SD-101 seemed lower than the AHI values on PSG, and this trend was evident in patients with severe OSAS. This phenomenon is quite consistent with the results of previous studies on type 3 PM devices [29–31] and possibly arose from the difference in the denominators; that is, TIB is clearly longer than TST [32]. When conducting epidemiological surveys of general populations using screening devices, high specificity is desirable to exclude false-positive findings. However, sleep physicians prefer screening tools with high sensitivity in the clinical setting to avoid missing conditions that might lead to a diagnostic underestimation of OSAS. Some investigators have found close agreement between AHI obtained from PM devices with an actigraph and PSG [31, 32]. Simultaneous measurements using the SD-101 and actigraphy that can determine total sleep duration would be necessary to improve the accuracy of SD-101 screening among patients with severe OSAS. Fourthly, none of our patients were extremely obese (BMI>35 kg/m^2). Our findings require confirmation in a study of extremely obese patients.

The SD-101 with SpO_2 measurement appears to offer relatively good performance with high sensitivity and specificity for OSAS screening, and this system is thought to confer a definite advantage for the screening of this disorder.

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NEW RESEARCH

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Is Nocturnal Panic a Distinct Disease Category? Comparison of Clinical Characteristics among Patients with Primary Nocturnal Panic, Daytime Panic, and Coexistence of Nocturnal and Daytime Panic

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Objective: Many patients with panic disorder (PD) experience nocturnal panic attacks. We investigated the differences in demographic variables and symptom characteristics as well as response to treatment among patients with primary day panic (DP), primary nocturnal panic (NP), and the coexistence of DP and NP (DP/NP), and discuss whether NP is a distinct disease category.

Method: One hundred one consecutive untreated patients with PD were enrolled and subsequently divided into the NP, DP, and DP/NP groups. The presence of 13 panic attack symptom items as well as scores on the Panic Disorder Severity Scale (PDSS) and the Pittsburgh Sleep Quality Index (PSQI) were compared among the groups. After 3 months of regular treatment, PDSS scores were assessed again to evaluate treatment response.

Results: Nocturnal panic attacks of the participants were mostly reported to occur in the first tertile of nocturnal sleep. The number of males, onset age, and presence of choking sensation were significantly higher, and the PDSS score was significantly lower in the NP group compared with the other groups. The DP/NP group showed the highest PDSS score, and participants in this group were prescribed the highest doses of medication among all groups. Only diagnostic subcategory was significantly associated with treatment response. The total score for PDSS and PSQI correlated significantly only in the NP group.

Conclusions: DP/NP could be a severe form of PD, while primary NP could be a relatively mild subcategory that may partially share common pathophysiology with adult type night terror.

Keywords: Panic disorder, nocturnal panic, the Panic Disorder Severity Scale (PDSS), the Pittsburgh Sleep Quality Index (PSQI)

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SCIENTIFIC INVESTIGATIONS

Panic disorder (PD) is an anxiety disorder characterized by recurrent daytime panic (DP) attacks (primary DP).[1] However, some patients who fulfill the clinical criteria for PD experience panic attacks mainly during the nocturnal sleep period.[2-4] These nighttime attacks occur without any obvious triggers during periods of sleep-wake transition and are referred to as nocturnal panic (NP) attacks.[5] In general, 18% to 45% of PD patients experience both DP and NP attacks (DP/NP).[6,7] Meanwhile, there are a considerable number of patients who have panic attacks only during the nocturnal sleep period (primary NP). However, most previous reports have not mentioned the clinical characteristics of primary NP, except for one report in which the response to pharmaceutical treatment in such patients was discussed.[7] Mainly due to the lack of this information, the Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (DSM-IV-TR)[8] has not clarified whether NP alone should be included within the PD category. Similarly, the description of PD in the International Classification of Sleep Disorders, 2nd edition,[9] does not address this issue.

Previous studies have suggested that individuals with NP have more frequent panic attacks, more severe anxiety symptomatology,[6,10] and higher rates of comorbid depression, which may lead to an increased risk of suicide compared with those without NP.[11] However, these comparisons were mainly made on patients with DP/NP and those with primary DP. Meanwhile, one study that included both primary NP and DP/NP demonstrated no differences between NP and primary DP in terms of frequency of comorbid depression.[12] Thus, the clinical significance of primary NP as well as that of DP/NP remains unclear, although it is possible that the latter is a severe subcategory of PD.

This study set out to compare clinical characteristics including demographic variables, panic symptom items, severity of

BRIEF SUMMARY

Current Knowledge/Study Rationale: Many patients with panic disorder experience nocturnal panic attack during sleep time (coexistence of day panic and nocturnal panic attacks: DP/NP), and some patients have panic attacks mainly during the nocturnal sleep period (primary nocturnal panic: NP). The aim of this study was to discuss whether NP is a distinct disease category from DP/NP.

Study Impact: NP was differ from DP/NP in demographic and clinical characteristics. Our findings suggest that DP/NP could be a severe form of panic disorder, while NP could be a relatively mild subcategory partially sharing common pathophysiology with adult type night terror.

PD, subjective sleep disturbances, and response to treatment for PD among patients with primary NP, primary DP, and DP/NP. Based on the results, we discuss whether primary NP is a subcategory of PD distinct from DP or DP/NP.

METHODS

Participants

This retrospective study was approved by the ethics committee of the Neuropsychiatric Research Institute, and all patients gave written informed consent to participate.

The study comprised 101 consecutive untreated individuals seeking treatment for panic-anxiety symptoms (56 males, 45 females; mean age 36.9 ± 9.9 years) who visited the outpatient clinic of Japan Somnology Center and Seiwa Hospital, both of which are affiliated with the Neuropsychiatric Research Institute (Tokyo, Japan) from May 2003 to January 2008. Some of the patients (most with primary NP) were referred to our clinic with suspicion of obstructive sleep apnea syndrome (OSAS). However, results of clinical interviews and screening with a portable device as described below indicated that they had neither habitual snoring nor pathological apnea. Based on this, attending physicians judged that the core symptoms of these patients were panic-anxiety rather than OSAS. Eighty-nine of the patients met the diagnostic criteria of PD with and without agoraphobia by the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Forth Edition). The remaining 12 patients (all of them in the NP group) had limited panic attacks with ≤ 3 panic attack symptom items, and none of the NP patients reported experiencing nightmares with the episodes of panic anxiety during sleep.

After diagnosis of PD, all patients received regular pharmacological treatment over 3 months with fixed doses of medication for at least 1 month before the investigation. The treatment drug was determined individually based on the decision of the attending physician. No patients had abnormal findings on physical or laboratory examinations at their first visit, or had a current or previous diagnosis of other psychiatric disorders, psychoactive substance abuse, respiratory disease, cardiovascular disease, thyroid disease, or OSAS.

With regard to OSAS, all patients were screened with a portable device (Stardust, Respironics; Murrysville, PA, USA) including 4 channels (airflow monitoring with pressure sensor, respiratory movements, oxyhemoglobin saturation, and heart rate) for 1 night.[13] All patients had a respiratory disturbance index < 5/h, and only a few had episodes of airflow limitation.

The disease course of PD was evaluated by psychiatrists with expertise in sleep disorders who performed detailed interviews with patients and their bed partners, if necessary. NP attacks were determined when a patient experienced an abrupt and uncomfortable sensation and fear immediately upon waking from nocturnal sleep, when symptoms were not attributable to frightening dreams, external interruptions, or other sleep disorders such as nightmares, night terrors, sleep paralysis, hypnopompic hallucinations, or choking associated with sleep apnea.[14]

We divided the patients into 3 groups with the main purpose of differentiating NP and NP/DP. Patients with primary DP in whom the rate of frequency of NP attacks to total panic attacks was less than 25% during the 3 months before the first visit, as noted by themselves and/or their bed partners, were placed in the DP group (n = 41). Patients with primary NP in whom the rate of the frequency of NP attacks to total panic attacks was ≥ 75% were placed in the NP group (n = 40), and patients with coexistence of DP and NP (rate of frequency of NP attacks was from 25% to 50% of all panic attacks) were placed in the DP/NP group (n = 20). No patient had a rate of frequency of NP attacks to total panic attacks of 50% to 75%.

Measurements

Before starting treatment, patients were interviewed regarding the occurrence of 13 panic attack symptoms listed by the DSM-IV-TR. The items were (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization or depersonalization; (10) fear of losing control or going crazy; (11) fear of dying; (12) paresthesia; and (13) chills or hot flashes. The Panic Disorder Severity Scale (PDSS), a self-rating scale, was used by patients to assess the severity of PD with 7 items scored on a scale of 0 to 4 and total score ranging from 0 to 28.[15] This scale has sufficiently high reliability, with a Cronbach α of 0.86; a total score > 16 corresponds to severe panic disorder in the Japanese version.[16] Subjective sleep conditions were assessed using the self-rating Pittsburgh Sleep Quality Index (PSQI).[17] The PSQI is an effective instrument to evaluate subjective sleep disturbance by measuring 7 domains. Scoring is based on a 0 to 3 scale for each domain. A global sum score (ranging 0 to 21) ≥ 5.5 indicates a poor sleep quality in Japanese (Cronbach α = 0.77) individuals.[18]

Patients with NP were asked about the distribution of NP attacks in the first, second, and third tertiles of their nocturnal sleep. As with DP attacks, the frequency of NP attacks were assessed and expressed using the score on item 1 (frequency of panic attacks) on the PDSS (e.g., 0: no panic attacks, 1: < 1 attack per week and ≤ 1 attack per day, 2: 1-2 attacks per week and/or many attacks per day, 3: ≥ 2 attacks per week and ≤ 1 attack per day, 4: ≥ 1 attack per day, more days than not).

After 3 months of treatment for PD, PDSS was evaluated again in all patients to determine their therapeutic response. As an indicator of treatment response, we calculated the reduction rate of PDSS with treatment ([pre-treatment PDSS total score] – [post-treatment PDSS total score] / [pre-treatment PDSS total score]).

Medication

All patients were treated pharmacologically. No types of psychotherapies such as cognitive behavioral therapy were used during the study. The following drugs were used: selective serotonin reuptake inhibitors, including paroxetine (10 to 40 mg/day), fluvoxamine (25 to 100 mg/day), and sertraline (25 to 50 mg/day); tricyclic antidepressants (25 to 75 mg/day of imipramine or amitriptyline); benzodiazepine anxiolytics including alprazolam (0.4 to 1.6 mg/day), ethyl loflazepate (1 to 2 mg/day), lorazepam (0.5 to 3 mg/day), clotiazepam (5 to 30 mg/day), and etizolam (0.5 to 3 mg/day); and benzodiazepine or benzodiazepine agonist hypnotics including triazolam (0.125 to 0.25 mg/day), flunitrazepam (1 to 2 mg/day), brotizolam

Table 1—Descriptive variables by group

	DP (n = 41)			DP/NP (n = 20)			NP (n = 40)		
Characteristic	**M**	**SD**	**%**	**M**	**SD**	**%**	**M**	**SD**	**%**
Female			56.1			55.0			27.5†
Onset age (year)	30.6[a,**]	6.8		26.5[a,**]	7.5		40.4	9.5	
Duration of PD morbidity	2.0[a,*]	1.1		3.8	6.2		4.3	2.5	

DP, day panic group; DP/NP, the coexistence of day panic and nocturnal panic; NP, primary nocturnal panic. †Post hoc cell contribution test showed a significantly lower rate of female ($p < 0.05$). [a]vs NP, *$p < 0.05$, **$p < 0.01$.

(0.25 mg/day), zopiclone (7.5 to 10 mg/day), and zolpidem (5 to 10 mg/day). The daily doses of antidepressants were calculated according to the imipramine-equivalent dose, and those of anxiolytics and hypnotics were calculated on the basis of diazepam-equivalent dose.[19]

Data Analysis

Continuous variables including demographics were compared among groups using analysis of variance (ANOVA) followed by post hoc Bonferroni corrections. Statistical analyses of categorical variables (gender, distribution of NP in each tertile of nocturnal sleep period, and presence of each panic attack symptom) among groups were made using the χ^2 test with cell contribution rate test as the post hoc rest error test. The post hoc cell contribution rate test is a form of standardized rest-error test that provides significance information among groups when the absolute value exceeds 1.96. Backwards stepwise multiple regression analysis was used to investigate factors associated with the reduction rate in PDSS score after treatment. Diagnostic subcategories which were dummy coded with d1 (pure NP or not; 0: DP and DP/NP, 1: NP) and d2 (pure DP or not; 0: NP and DP/NP, 1: DP), self-reported onset age of the disorder, gender, pretreatment total scores of PDSS and PSQI, and daily dosage of medication (antidepressants, anxiolytics, and hypnotics) were included as independent variables. The correlation between PDSS and PSQI scores in the 3 groups was estimated using Spearman rank correlation coefficient. A p value < 0.05 was considered statistically significant. Data analyses were made using SPSS version 10 (SPSS Inc., Chicago, IL, USA).

RESULTS

Descriptive Variables

Based on detailed clinical interviews, it was confirmed that the first attacks occurred during the nocturnal sleep period in all NP patients, and during the daytime in DP and DP/NP patients. The NP group included a significantly larger number of male patients than DP and DP/NP groups (**Table 1**). The self-reported age of onset of PD was significantly different among groups (df: 2, F-value: 33.3, $p < 0.01$), and post hoc test revealed that the onset age in the NP group was significantly higher than that in the other 2 groups. Duration of PD morbidity was also significantly different among groups (df: 2, F-value: 5.07, $p < 0.05$), and the duration in NP group was significantly longer than in the DP group. In the DP/NP group, the duration did not differ significantly from the other 2 groups.

Distribution of NP Attacks during Sleep

NP attacks were reported to occur predominantly in the first tertile of nocturnal sleep in both the NP group (32/40, 80%) and the DP/NP group (14/20, 70%). The distribution of tertiles in which attacks mainly occurred did not differ significantly between these 2 groups (first/second/third tertile: NP = 32/6/2, DP/NP = 14/5/1, $p = 0.64$).

Presence of Panic Attack Symptoms before Treatment

Chi-square test revealed that the presence of all PD symptoms except palpitations, sweating, sensation of shortness of breath or smothering, and paresthesias significantly differed among the groups before treatment. Rest error test revealed that the NP group had the highest rate of feelings of choking (DP: 23/41, DP/NP: 15/20, NP: 35/40; $p < 0.01$; $\chi^2(2) = 10.06$, $p < 0.01$). However, in this group, symptoms of trembling or shaking, chest pain or discomfort, nausea or abdominal distress, feeling dizzy, derealization or depersonalization, fear of losing control or going crazy, fear of dying, and chills or hot flashes were lowest. On the other hand, the DP group had a significantly higher rate for symptoms of trembling or shaking (DP: 18/41, DP/NP: 8/20, NP: 6/40), chest pain or discomfort (DP: 24/41, DP/NP: 12/20, NP: 9/40), nausea or abdominal distress (DP: 12/41, DP/NP: 5/20, NP: 2/40), feeling dizzy (DP: 20/41, DP/NP: 8/20, NP: 6/40), fear of losing control or going crazy (DP: 24/40, DP/NP: 12/20, NP: 9/40), fear of dying (DP: 27/41, DP/NP: 14/20, NP: 11/40), and chills or hot flashes (DP: 18/41, DP/NP: 6/20, NP: 7/40) compared with the other groups. In the DP/NP group, the rate of derealization or depersonalization was significantly higher than in the other groups (DP: 17/41, DP/NP: 12/20, NP: 7/40). In terms of the total number of symptoms, the NP group showed a significantly lower number than the other 2 groups (DP: 6.7 ± 1.8, DP/NP: 7.1 ± 2.2, NP: 4.3 ± 2.2; df: 2, F-value: 25.55, $p < 0.01$, $p < 0.01$ vs DP, $p < 0.01$ vs DP/NP, respectively).

PDSS and PSQI Scores before Treatment

The total PDSS score and all sub-item scores of the PDSS were significantly different among the groups (**Table 2**). Post hoc tests revealed that all the sub-item scores as well as the total score in the DP/NP group were significantly higher than in the NP group. Scores for frequency of panic attacks, anticipatory anxiety, agoraphobic fear and avoidance, and total score were also significantly higher in the DP/NP group than in the DP group. The NP group showed significantly lower scores than the DP group in terms of agoraphobic fear and avoidance, interoceptive fear and avoidance, impairment of

Table 2—PDSS scores before treatment

	DP		DP/NP		NP	
	M	SD	M	SD	M	SD
1:Frequency of panic attacks	2.4	0.7	3.0[a,*;b,*]	0.7	2.4	0.7
2:Distress during panic attacks	2.1	0.7	2.5[b,*]	1.0	1.8	0.7
3:Anticipatory anxiety	2.0	0.7	2.5[a,*;b,**]	0.8	1.8	0.7
4:Agoraphobic fear and avoidance	1.7	0.9	2.4[a,*;b,**]	0.6	1.2[a,**]	0.7
5:Interoceptive fear and avoidance	2.2	0.8	2.2[b,**]	0.8	0.4[a,**]	0.5
6:Impairment of work functioning	1.1	0.8	1.2[b,**]	0.9	0.1[a,**]	0.3
7:Impairment of social functioning	0.9	0.8	1.3[b,**]	0.8	0.1[a,**]	0.2
Total Score	12.4	2.4	15.0[a,**;b,**]	2.8	7.7[a,**]	2.3

DP, day panic group; DP/NP, day panic and nocturnal panic group; NP, nocturnal panic group. [a]vs DP, [b]vs NP, *p < 0.05, **p < 0.01.

Table 3—PSQI scores (pre-treatment scores)

	DP		DP/NP		NP	
	M	SD	M	SD	M	SD
C1:Subjective sleep quality	1.3	0.7	1.7[a,**]	0.7	1.0	0.9
C2:Sleep latency	0.7	0.6	1.2	0.9	1.0	0.8
C3:Sleep duration	1.0	0.9	1.5	0.8	1.1	0.8
C4:Habitual sleep efficiency	0.7	0.8	0.9	0.7	0.4	0.6
C5:Sleep disturbances	0.9[a,**]	0.9	0.7[a,**]	0.7	1.5	0.8
C6:Use of sleeping medicine	0.6	1.0	0.9	1.3	0.6	1.0
C7:Daytime dysfunction	0.7	0.8	0.8	0.9	0.7	0.9
Total Score	5.9	3.0	7.6	2.5	6.2	3.1

DP, day panic group; DP/NP, day panic and nocturnal panic group; NP, nocturnal panic group. [a]vs NP, *p < 0.05, **p < 0.01.

Table 4—Daily doses of medication

	DP		DP/NP		NP	
	M	SD	M	SD	M	SD
Doses of antidepressants (mg)	85.6	19.4	116.1[a,**;b,**]	27.0	41.4[a,**]	16.3
Doses of anxiolytics (mg)	10.7	9.1	14.8[b,**]	10.5	1.9[a,**]	3.0
Doses of hypnotics (mg)	1.5	2.5	4.6[a,**;b,**]	3.8	0.1[a,*]	0.6

DP, day panic group; DP/NP, day panic and nocturnal panic group; NP, nocturnal panic group. The dose equivalents of psychotropic drugs were calculated according to the report by Inagaki A et al.[16] The doses of antidepressants are presented in mg basis of imipramine, and those of anxiolytics and hypnotics are presented in mg basis of diazepam. [a]vs DP, [b]vs NP, *p < 0.05, **p < 0.01.

work functioning, impairment of social functioning, and total score. On the comparison result of PDSS (after excluding the 12 patients with limited panic attacks), the total PDSS score of NP (7.7 ± 2.3) was also lower than DP and DP/NP ($p < 0.01$, $p < 0.01$, respectively).

The total PSQI score did not differ significantly among the groups (**Table 3**). However, the scores of subjective sleep quality (C1), habitual sleep efficiency (C4) and sleep disturbance (C5) differed significantly among the 3 groups. Post hoc Bonferroni testing showed that the score of C5 was higher in NP group than in DP group and DP/NP group, and that DP/NP group showed higher score of subjective sleep quality (C1) than that of NP group (**Table 3**). As with the PDSS score, the total score of PSQI did not differ among these 3 groups (excluding the 12 patients with limited panic attacks). The total scores for PDSS and PSQI correlated significantly in the NP group ($r = 0.59$, $p < 0.001$), but not in the other groups (DP group, $r = 0.30$, $p = 0.06$; DP/NP group, $r = 0.14$, $p = 0.59$).

Medications and Treatment Response

As shown in **Table 4**, the final daily doses of antidepressants, anxiolytics, and hypnotics differed significantly among the groups. Multiple comparisons by the Bonferroni test indicated that the DP/NP group received significantly higher daily doses of antidepressants and hypnotics than the other 2 groups. As for anxiolytics, the daily dose was not significantly different between the DP/NP group and DP group ($p = 0.16$), but was significantly lower in the NP group compared with the other 2 groups ($p < 0.01$ vs DP/NP, $p < 0.01$ vs DP).

After 3 months of treatment, all groups showed significant improvements in PDSS total score ($p < 0.01$ DP, $p < 0.01$ DP/NP, $p < 0.01$ NP) (**Table 5**). ANOVA revealed significant differences among groups for the reduction rate in PDSS score

Table 5—Change in PDSS score with treatment

	Pre-treatment PDSS score		Post-treatment PDSS score		Reduction rate (%)†	
	M	SD	M	SD	M	SD
DP	12.4	2.4	6.8	2.5	43.8[a,*]	20.7
DP/NP	15.0	2.8	8.1	2.6	45.6[a,*]	14.7
NP	7.7	2.2	1.7	1.7	76.6	25.9

DP, day panic group; DP/NP, day panic and nocturnal panic group; NP, nocturnal panic group. †Reduction rate = ([pre-treatment score] – [post-treatment score]) / [pre-treatment score]. [a]vs NP, *p < 0.01.

(df: 2, F-value: 25.92, p < 0.01), with the NP group showing a significantly greater reduction in score than the other 2 groups (p < 0.01). No significant difference in the reduction rate was found between the DP/NP group and DP group.

Stepwise multiple regression analysis showed that only the diagnostic subcategory (pure NP was dummy coded as d1) was significantly associated with the reduction rate in PDSS score (p < 0.01, B-hat = -0.32, with intercept B-hat = 0.76, p < 0.01)

DISCUSSION

This study investigated differences in clinical features among three panic disorder subcategories stratified based on presence/absence of nocturnal or daytime panic attack. The results revealed significant differences in demographics, severity of the disorder, and response to pharmacological treatment among the groups.

Several epidemiological studies have shown that the prevalence of PD is higher in females than in males, and that the mean age of onset of PD is in the 20s and 30s.[20,21] These demographic characteristics were recognized in the DP group and DP/NP group in our study. However, of note, the NP group showed a clear male predominance and significantly later age of onset than the other two groups. The patients with OSAS, which develops most frequently in middle-aged males, occasionally wake up with choking sensation during nocturnal sleep. However, OSAS was completely ruled out in the participants of the present study by examination with a portable device together with thorough clinical interviews. In addition, we excluded the possibility of upper airway resistance syndrome based on a lack of flow limitation on the air flow pressure sensor of the portable device.[22] Moreover, the NP group had a significantly longer self-reported duration of the disorder than previously reported by Levitan,[23] but had a milder severity of the disorder evaluated with the PDSS score at their first visit compared with the other two groups, even after excluding 12 patients with limited panic attacks, suggesting that a majority of NP patients remain stable in mild severity and symptoms do not become progressively more severe. Taking these findings together, primary NP can be considered a mild subcategory of PD with slow progression that is likely to occur among a middle-aged male population.

Many previous studies have indicated that PD patients with NP attacks experience significantly more frequent and severe panic symptoms[6,11,24] and more depressive and other psychiatric symptoms.[25] However, in contrast to the findings in this study, sociodemographic characteristics did not differ between patients with and without NP attacks in these studies.[4,6,11,24,25] The reason for this discrepancy is unknown. However, in most previous studies, the definition of NP was primarily made based on the answer to a one-item screening questionnaire such as "Have you ever been woken from your sleep by a panic attack?"[14] Thus, it is possible that NP reported in previous studies included many patients with DP/NP who actually may have had a younger age of onset and a female predominance with higher PD severity, as seen in the present study.

Nocturnal panic attacks have been reported to occur during NREM sleep, especially during delta sleep.[2] However, no study has ascertained the distribution of panic attacks among tertiles of nocturnal sleep. Interestingly, most patients with NP or DP/NP in the present study reported that their NP attacks occurred mainly in the first tertile. Although we did not perform polysomnographic evaluations of sleep structure among the patients, in general, delta sleep occurs mainly in the early part of sleep.[26] Thus, our results could be consistent with the previous report showing that NP attacks are likely to occur during delta sleep.[2] With regard to the nocturnal distribution of events, NP in our patients seemed to share common characteristics with sleep terrors, which occur during the transition period of arousal from slow wave sleep, mainly in the early part of the night. These two disorders also share common symptoms, such as autonomic symptoms including tachycardia, acute respiratory distress, sweating, and intense fear.[27] It has been reported that a considerable number of patients with sleep panic have a history of sleep terrors in their early childhood,[28] and that respiratory symptoms frequently appear during episodes of night terrors in adults.[29] Given these findings, it is possible that the pathophysiological mechanism of sleep panic attacks is related to that of adult type sleep terrors, although there is a clear difference in that patients are fully aroused and conscious during sleep panic episodes, while night terror occurs under the condition of clouded consciousness. Further research comparing polysomnographic variables and subjective symptoms between NP and adult type sleep terror is needed to clarify this issue.

In the present study, primary NP patients had fewer panic attack symptom items than patients in other groups. However, feelings of choking occurred in a significantly larger number of patients in the NP group than in the other groups. This finding is compatible with previous reports, suggesting that respiratory symptoms such as choking or shortness of breath are specifically common in NP.[30,31] Thus, a respiratory symptom during sleep may be a primary symptom in the NP group.

The milder form of PD in the NP group compared with the other groups was thought to be attributable to the lower score for agoraphobic or interoceptive fear and avoidance and lower scores for both impairment of work functioning and social functioning in this group. The reasons for these findings are unclear.

Overall, primary NP patients did not have a tendency toward disturbance in initiation and/or maintenance of sleep (insomnia), although they experienced attacks mainly during sleep. However, the severity of panic symptoms during sleep time in the NP group as manifested on the PDSS was significantly correlated with sleep disturbance measured with the PSQI. Considering that there was no significant correlation between PDSS and PSQI in either DP or DP/NP patients, the PD severity-dependent aggravation of sleep disturbance may be a specific clinical characteristic of primary NP.

In the present study, all three groups showed an improvement of PD symptoms with standard treatment including antidepressants, anxiolytics, and hypnotics. However, the dosages of antidepressants and benzodiazepine anxiolytics as well as hypnotics used for the treatment were significantly lower in the NP group than in the DP and DP/NP groups. Moreover, the reduction rate of PDSS with the treatment in this group was significantly higher than that of the other groups. In addition, among the descriptive variables, only the diagnosis of primary NP *per se* was significantly associated with a higher reduction rate of PDSS, possibly suggesting a better treatment response in this group. These findings could indicate that primary NP is most responsive to treatment among the three groups.

On the other hand, similar to the findings of a study by Agargun and Kara,[11] the DP/NP group in our study showed the highest values in terms of number of panic attack symptoms and total PDSS score. Moreover, among the three groups, the DP/NP group received the highest doses of both antidepressants and hypnotics as treatment. These findings strongly impress that DP/NP is the most severe and treatment-resistant subcategory of PD.

This study has several limitations. First, since the Japan Somnology Center mainly treats patients with sleep-related disorders, referral bias could exist. Thus, the sample of NP in our study might not be a representative of the general NP population. Second, there might be recall bias, especially regarding subjective distribution of panic attacks in subjects. Third, the assessment of depressive symptoms may be necessary because depression is frequently comorbid with panic attacks and would affect the severity of panic symptoms. Fourth, this study was an observation-based study, and we need further study with simultaneous measurement of autonomic system markers and polysomnographic recordings to investigate of the nature of the physiological change that occurs during episodes of NP.

In conclusion, NP attacks are likely to occur in the first tertile of the nocturnal sleep period both in NP and DP/NP. However, primary NP is thought to be a mild and treatment-responsive subgroup of PD, while DP/NP patients showed severe PD symptoms and the worse treatment response. Identification of these two NP categories would be helpful for making better treatment plans.

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NEW RESEARCH

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Efficacy and Safety of Adjunctive Modafinil Treatment on Residual Excessive Daytime Sleepiness among Nasal Continuous Positive Airway Pressure-Treated Japanese Patients with Obstructive Sleep Apnea Syndrome: A Double-Blind Placebo-Controlled Study

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Study Objectives: This double-blind study evaluated the efficacy and safety of modafinil for treating excessive daytime sleepiness in Japanese patients with obstructive sleep apnea syndrome (OSAS).

Methods: Patients with residual excessive sleepiness (Epworth Sleepiness Scale [ESS] ≥ 11) on optimal nasal continuous positive airway pressure (nCPAP) therapy (apnea-hypopnea index ≤ 10) were randomized to either 200 mg modafinil (n = 52) or placebo (n = 62) once daily for 4 weeks. Outcomes included baseline-week 4 changes in ESS total score, sleep latency on maintenance of wakefulness test (SL-MWT), nocturnal polysomnography, Pittsburgh Sleep Quality Index (PSQI), and safety.

Results: All 114 randomized patients completed the study. Mean change in ESS total score (-6.6 vs -2.4, p < 0.001) and SL-MWT (+2.8 vs -0.4 minutes, p = 0.009) were significantly greater with modafinil than with placebo. ESS total score decreased from > 11 to < 11 at the final assessment in 69.2% of modafinil-treated patients and 30.6% of placebo-treated patients (p < 0.001). Corresponding rates at week 1 were 57.7% and 33.9% (p = 0.014). Changes in nocturnal polysomnography, PSQI, and apnea-hypopnea index from baseline to the final assessment were similar in both groups. Adverse drug reactions occurred in 36.5% and 22.6% of patients in the modafinil and placebo groups, respectively (p = 0.146).

Conclusions: Once-daily modafinil was effective and well tolerated for managing residual daytime sleepiness in Japanese OSAS patients with residual excessive daytime sleepiness on optimal nCPAP therapy.

Clinical Trial Registration: JapicCTI-No.090777

Keywords: Randomized clinical trial, daytime sleepiness, Epworth Sleepiness Scale, modafinil, nasal continuous positive airway pressure, maintenance of wakefulness test, obstructive sleep apnea, safety

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SCIENTIFIC INVESTIGATIONS

Obstructive sleep apnea syndrome (OSAS) is a chronic condition characterized by recurrent episodes of upper airway collapse that occur during sleep. OSAS frequently causes nocturnal intermittent hypoxemia, sympathetic activation and fragmented/disrupted sleep.[1] Studies of Caucasian and Asian populations have consistently estimated that the prevalence of OSAS associated with excessive daytime sleepiness ranges from 3% to 7% in adult men and from 2% to 5% in adult women.[2] In Japan, Nakaya-Ashida et al.[3] reported that the prevalence of moderate to severe sleep disordered breathing (respiratory disturbance index ≥ 15) was 22.3% in male workers aged 23-59 years.

Factors predisposing to OSAS include obesity, advanced age, male sex, and craniofacial abnormalities.[4,5] The diagnosis of OSAS generally requires objective measurement of obstructive respiratory events and the presence of characteristic symptoms, such as excessive daytime sleepiness and unrestored nocturnal sleep that could not be better explained by other factors.[6] Severe OSAS is often associated with vascular morbidities,[7,8] cognitive impairment, occupational and vehicular accidents attributable to excessive daytime sleepiness, and worse quality of life than unaffected individuals.[9]

Management of OSAS requires the use of nasal continuous positive airway pressure (nCPAP) therapy, a first-line treatment, which acts as a pneumatic splint to maintain patency of

BRIEF SUMMARY

Current Knowledge/Study Rationale: Very few studies, and none in Asian patients, have examined the effects of modafinil on subjective or objective sleep measures in patients with residual sleepiness on optimal nCPAP.

Study Impact: Treatment with 200 mg modafinil once daily improved residual daytime sleepiness in Japanese patients with OSAS on optimal nCPAP compared with placebo.

the upper airway. nCPAP therapy is widely accepted to reduce excessive sleepiness and to improve daytime functioning and self-reported health status.[10-12] However, despite the reported improvements of respiratory events, clinically significant excessive sleepiness persists in some patients on optimal nCPAP. In some of these patients, the residual sleepiness may reflect the presence of other sleep disorders, including narcolepsy, behaviorally induced sleep insufficiency syndrome and periodic limb movement disorders.[13] In other patients, this outcome may be caused by hypoxia-induced cerebral metabolic changes.[14] In a recent study in France, 6.0% (95% confidence interval [CI] 3.9-8.0) of OSAS patients who were optimally treated with nCPAP had evidence of residual excessive sleepiness.[15] Considering the potential adverse outcomes that may affect the health and safety of the patients, residual sleepiness requires prompt attention.

The Standards of Practice Committee of the American Academy of Sleep Medicine recommends use of the wake-promoting agent modafinil in nCPAP-treated patients without other identifiable causes for their residual sleepiness.[16] Modafinil differs from other amphetamine-like wake-promoting agents, such as methamphetamine and methylphenidate, in its chemical structure and mechanisms of action.[17-20] Modafinil mainly interacts with the dopamine transporter,[21,22] and affects the γ-amino butyric acid (GABA)-ergic, serotonergic, glutaminergic, noradrenergic, and histaminergic neurotransmitter systems,[22-26] which may contribute to its wake-promoting activity. Double-blind placebo-controlled clinical studies on nCPAP-treated patients with residual sleepiness associated with OSAS have revealed that modafinil significantly improved objectively determined sleep latency, overall subjective severity of sleepiness, health-related quality of life, and functional status, and that it was well tolerated.[27-29] To date, however, no studies have examined the effects of modafinil on residual excessive sleepiness in Japanese patients with OSAS on optimal nCPAP treatment. Furthermore, although central nervous system stimulants may theoretically disturb nocturnal sleep,[30] previous studies have not documented the effects of modafinil on subjective or objective nocturnal sleep measures.

Therefore, in the present study, we evaluated the effects of modafinil on the efficacy and safety of modafinil in Japanese patients with OSAS and excessive daytime sleepiness despite optimal therapeutic use of nCPAP. We also examined the effects of modafinil on subjective and objective measures of nocturnal sleep in these patients.

METHODS

Study Design

This randomized, double-blind, placebo-controlled, parallel-group study was conducted at 37 sites specialized in sleep disorders in Japan between May 2009 and December 2009. The study included a screening visit, an observation period ≥ 15 days, and a 4-week double-blind treatment period. The protocol and the informed consent form were reviewed and approved by the internal review board at each institution. All patients provided written informed consent to participate in this study.

Patients

Patients evaluated in this study were required to be receiving effective nCPAP therapy to rule out inadequate or incorrect nCPAP use as a cause of their residual sleepiness. Patients with sleep disorders other than OSAS were excluded from the study. The main inclusion criteria for eligible patients in this study were as follows: men and women aged 20-70 years; confirmed diagnosis of OSAS; and the presence of subjective excessive sleepiness (i.e., Epworth Sleepiness Scale [ESS] total score ≥ 11)[31] despite optimal use of nCPAP; having received nCPAP therapy for ≥ 3 months and being willing and able to continue its use during the study period; the use of nCPAP for ≥ 70% of nights for ≥ 4 h/night[32] for 14 days before the baseline visit; and an apnea-hypopnea index (AHI) ≤ 10 determined by nocturnal polysomnography (PSG) during the observation period. Definitive diagnosis of OSAS or other sleep disorders was made using PSG data obtained before randomization based on Rechtschaffen and Kales criteria[33] and American Sleep Disorders Association arousal criteria.[34] The data were scored according to American Association of Sleep Medicine criteria.[35] Patients who met any of the following criteria were excluded from this study: diagnosis of other sleep disorders (e.g., narcolepsy, periodic limb movement disorders, and central sleep apnea); pregnant, potentially pregnant, or lactating women; presence of arrhythmias, angina, and clinically significant cardiac, respiratory, cardiovascular diseases, psychiatric disorders (e.g., depression[36]), or hypertension with systolic blood pressure ≥ 160 mm Hg and diastolic blood pressure ≥ 100 mm Hg,[37] as specified in the exclusion criteria of the U.S. OSAS study.[29] Patients who were concomitantly administered prohibited drugs, such as central nervous system stimulants, sedative medications, antidepressants, antiepileptic drugs, acetazolamide, warfarin, monoamine oxidase inhibitors, or antimigraine drugs, within 2 weeks before the start of the study, were also excluded. Patients fulfilling these criteria were identified by the physicians and invited to participate in the study at the physician's request.

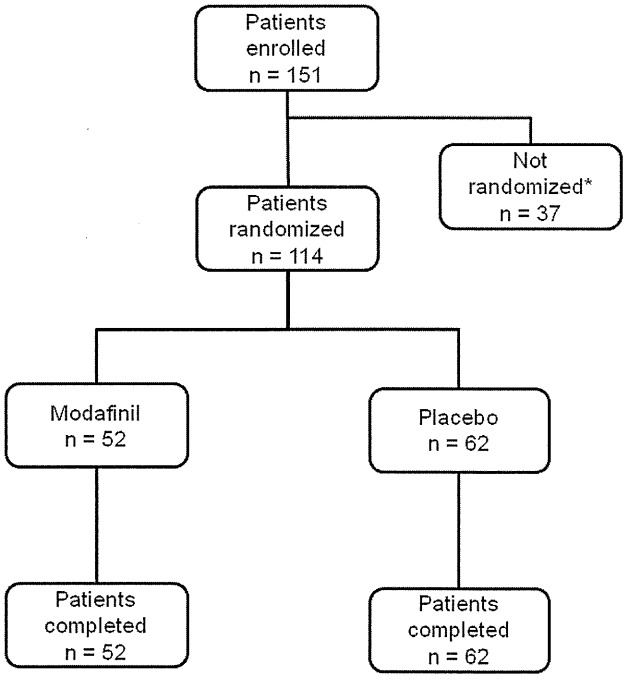
Randomization and Dosing

Patients were randomly assigned in a blocked randomization manner to receive 2 tablets of 100 mg modafinil (total dose, 200 mg/day) or placebo once daily in the morning, to be administered before or after meals. Randomization was performed using a computer-generated random number list prepared by an independent contract research organization. Clinicians contacted the organization via telephone to obtain the randomization sequence for each patient.

Efficacy Measures

Efficacy assessments were conducted at the start (i.e., baseline) and at Weeks 1 and 4 of the double-blind treatment period. The primary efficacy measure was ESS score at Week 4 of treatment. The secondary efficacy measure was mean sleep latency on the maintenance of wakefulness test (MWT).[38,39] The MWT was conducted in a subset of patients (modafinil, n = 22; placebo, n = 28) at baseline and at Week 4 of the double-blind period on the days immediately after nocturnal PSG. Each MWT session lasted 20 min. Because of the methodology, the MWT was only performed at study sites with the facilities required to conduct the test. Some patients at these facilities were unable

Figure 1—Patient disposition



*37 patients were not randomized to the study for the following reasons: 35 patients did not meet the eligibility criteria, one patient withdrew consent, and one patient gave up on the starting dose because of changes in work schedule.

to do the MWT because of the burden associated with the test. Other secondary variables were ESS score at each visit, and the total score of Japanese version of Pittsburgh Sleep Quality Index (PSQI),[40] which represents the severity of subjective sleep disturbance, and sleep parameters measured by nocturnal PSG at baseline and Week 4. PSG and MWT were conducted in an inpatient setting.

Safety

Safety was assessed by evaluating adverse drug reactions (ADRs) as well as the results of general laboratory tests (blood and urine), physiological variables (blood pressure and pulse rate), 12-lead electrocardiograms, and physical examinations. ADRs were defined as any unfavorable or unintended symptom or disease that was considered to be associated with the study drug during the study period.

Statistical Analysis

Continuous demographic variables were compared using the 2-sample *t*-test. Categorical variables were compared using the Fisher exact test. The efficacy population (n = 114) was defined as patients who received ≥ 1 dose of modafinil and underwent ≥ 1 post-baseline evaluation for any efficacy or safety variable during the treatment period. The changes in efficacy variables (ESS and MWT) from baseline to the final assessment (Week 4) were compared between the modafinil and placebo groups using analysis of covariance with the baseline value as a covariate. To verify the efficacy of modafinil administration, the point estimate and 2-sided 95% (CI) of the difference between the modafinil and placebo groups were calculated using the least squares mean (LS mean) method. Statistical tests were performed at a significance level of 5% using SAS System (Release 9.1.3, SAS Institute Inc., Cary, NC, USA). Changes in other secondary variables (PSQI and nocturnal PSG) from baseline were also compared between the modafinil- and placebo-treated groups. Safety data are summarized using descriptive statistics.

Table 1—Patient characteristics

Characteristic	Placebo (n = 62)	Modafinil (n = 52)	p-value*
Age, years	50.5 ± 9.2	49.0 ± 10.4	0.399
Sex, n (%)			0.330
Male	61 (98.4)	49 (94.2)	
Female	1 (1.6)	3 (5.8)	
BMI, kg/m^2	27.3 ± 3.5	27.9 ± 4.3	0.441
ESS, total score	14.6 ± 3.1	14.3 ± 2.7	0.553
AHI during nCPAP	2.6 ± 2.6	2.8 ± 2.7	0.740
Duration of nCPAP use per night, h	6.0 ± 0.6	6.1 ± 1.0	0.495

Data are means ± SD or n (%). *The p-values were determined using the 2-sample *t*-test for continuous variables or the Fisher exact test for categorical variables. BMI, body mass index; ESS, Epworth Sleepiness Scale; AHI, apnea-hypopnea index; nCPAP, nasal continuous positive pressure.

RESULTS

Subjects

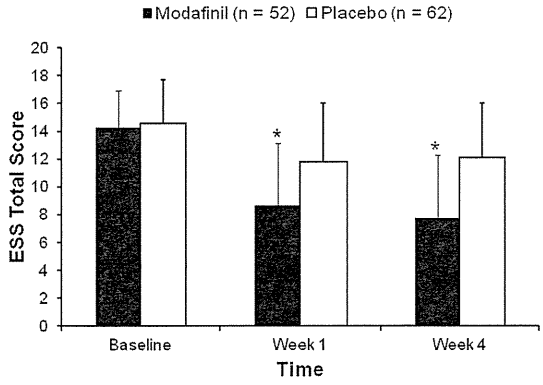
A total of 114 patients were randomized—52 patients to modafinil and 62 patients to placebo. All 114 patients completed the study (**Figure 1**). There were no differences between the 2 groups in terms of demographic and baseline characteristics (**Table 1**). Males accounted for > 94% of the patients in both groups. Before starting treatment with the study drug, the patients in both groups had moderate levels of residual sleepiness, with mean total ESS scores ≥ 14 despite effective nCPAP therapy; mean AHI was ≤ 10 in both groups. The mean duration of nCPAP use per night was 6.1 ± 1.0 and 6.0 ± 0.6 h in the modafinil and placebo groups, respectively (**Table 1**). Concomitant diseases included hypertension (modafinil, n = 13 [25%]; placebo, n = 20 [32%]) and hyperlipidemia (modafinil, n = 4 [8%]; placebo, n = 14 [23%]).

Subjective Sleepiness

Mean ESS total scores were determined at baseline and at the final assessment in both groups. The mean changes in ESS total score from baseline to the final assessment were -6.61 in the modafinil group and -2.44 in the placebo group (LS mean). The between-group difference of -4.17 (95% CI -5.66 to -2.69) was therefore significantly greater with modafinil than with placebo ($p < 0.001$). The change in mean ESS total score at 1 week after starting treatment was also significantly greater in the modafinil group than in the placebo group ($p < 0.001$; **Figure 2**).

The patients whose ESS total scores were ≥ 11 at baseline and decreased to < 11 at the final assessment were defined as

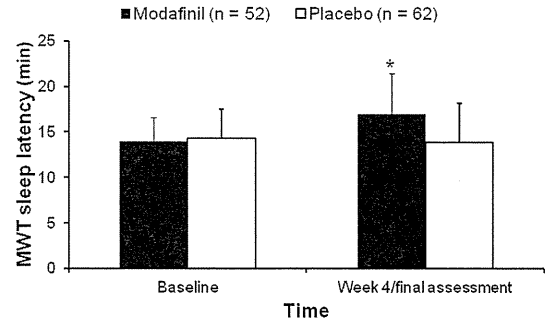
Figure 2—Mean Epworth Sleepiness Scale total score at baseline, and after 1 and 4 weeks of treatment with modafinil or placebo



	Modafinil (n = 52)	Placebo (n = 62)	Statistical analysis*
Week 1	-5.71 ± 0.58	-2.74 ± 0.53	F = 14.189 p < 0.001
Week 4	-6.61 ± 0.55	-2.44 ± 0.51	F = 30.970 p < 0.001

The least significant mean change from baseline ± standard error is shown in the table. *The p-values were determined by analysis of covariance.

Figure 3—Mean maintenance of wakefulness test sleep latency at baseline and after 4 weeks of treatment with modafinil or placebo



	Modafinil (n = 52)	Placebo (n = 62)	Statistical analysis*
Baseline	13.95 ± 5.48	14.33 ± 4.55	
Week 4/final assessment	16.92 ± 3.22	13.85 ± 5.13	p < 0.001

*The p-value was determined by analysis of covariance.

responders with normalization of ESS. Overall, 69.2% of patients (36/52) treated with modafinil and 30.6% of patients (19/62) treated with placebo were classified as responders. The Fisher exact test showed that a significantly higher percentage of patients treated with modafinil were classified as responders compared with patients treated with placebo ($p < 0.001$). The corresponding response rates at week 1 were 57.7% (30/52) and 33.9% (21/62) ($p = 0.014$).

Objective Sleepiness

Fifty patients (modafinil, n = 22; placebo, n = 28) underwent the MWT. There were no differences in patient characteristics, including baseline ESS total score, between patients who did or did not undergo the MWT ($p = 0.292$). Mean sleep latencies determined by MWT at baseline and at the final assessment in both groups are shown in **Figure 3**. The LS mean change in MWT sleep latency from baseline to the final assessment was 2.8 min in the modafinil group and -0.40 min in the placebo group. The between-group difference of 3.2 min (95% CI 0.8 to 5.6) was statistically significant, showing greater effects of modafinil versus placebo ($p = 0.009$).

Objective and Subjective Measures of Nocturnal Sleep

Summary statistics for sleep parameters were determined in 101 patients who underwent nocturnal PSG at baseline and at the final assessment (modafinil, n = 45; placebo, n = 56). As shown in **Table 2**, there were no significant differences in the changes in any nocturnal PSG parameters between the 2 groups.

The total PSQI score decreased from 6.3 ± 2.7 at baseline to 4.8 ± 2.2 at the final assessment in the modafinil group, as compared with a change from 6.1 ± 2.3 to 5.4 ± 1.7 in the placebo group. The mean difference in total PSQI score between the 2 groups for the change from baseline to the final assessment was -0.7 points (95% CI: -1.5 to 0.0 points) and was not statistically significant.

Safety Outcomes

ADRs were reported by 19 patients (36.5%) in the modafinil group and 14 patients (22.6%) in the placebo group. There were no significant differences in the rate of ADRs between the 2 groups ($p = 0.146$; Fisher exact test). The most frequent ADRs in the modafinil group were headache (n = 6, 11.5%), insomnia (n = 2, 3.8%), and palpitation (n = 2, 3.8%). The most frequent ADRs in the placebo group were headache (n = 4, 6.5%) and upper abdominal pain (n = 2, 3.5%) (**Table 3**). All of these ADRs were mild or moderate in severity, and no deaths or other serious adverse events were reported. None of the patients withdrew from the study because of ADRs.

Regarding the time of onset of ADRs, the frequency of ADRs was greatest within 7 days after starting treatment in both the modafinil group (15/19 patients who experienced ADRs) and the placebo group (10/14 patients).

Laboratory test abnormalities included increased γ-glutamyl transpeptidase in one patient in each group; increased alkaline phosphatase in one patient in each group; increased alanine aminotransferase and increased thyroid stimulating hormone in one patient each in the modafinil group; the presence of urinary glucose and decreased white blood cell count in one patient each treated with placebo; and multiple liver enzyme abnormalities (increased aspartate aminotransferase, alanine aminotransferase, and γ-glutamyl transpeptidase) in one patient treated with placebo. Decreased body weight (from 77.0 kg at baseline to 73.0 kg at week 4 of the treatment period) was observed in one patient treated with modafinil. Sinus tachycardia (at Week 1 of the treatment period) and sinus bradycardia (at Week 4 of the treatment period) were observed in one patient each in the modafinil group. Ventricular extrasystole (at Week 1 of the treatment period) was observed in one patient treated with placebo. No clinically relevant abnormalities were ob-

Table 2—Comparison of nocturnal PSG indices at baseline and after 4 weeks of treatment with modafinil and placebo

	Placebo (n = 56)		Modafinil (n = 45)		
Characteristic	**Baseline**	**Week 4**	**Baseline**	**Week 4**	**p-value***
Total sleep time (TST), min	425.2 ± 60.9	421.7 ± 61.4	417.4 ± 55.2	432.3 ± 65.0	0.054
Sleep efficiency (TST/TIB), %	85.0 ± 11.2	85.4 ± 11.2	84.4 ± 10.7	86.2 ± 9.7	0.377
Sleep latency, min	8.8 ± 12.4	11.4 ± 14.8	10.2 ± 16.8	9.3 ± 17.0	0.290
Stage 1, %TST	16.0 ± 6.7	13.7 ± 7.7	16.9 ± 10.7	15.7 ± 10.2	0.871
Stage 2, %TST	56.7 ± 8.4	58.0 ± 9.9	56.4 ± 12.3	58.3 ± 13.0	0.466
Stage 3, %TST	4.2 ± 5.5	5.6 ± 6.6	4.4 ± 5.7	3.6 ± 4.7	0.154
Stage 4, %TST	1.3 ± 3.7	1.3 ± 2.9	1.3 ± 3.1	1.7 ± 4.3	0.345
Stage 3-4, %TST	5.4 ± 7.1	7.0 ± 8.2	5.6 ± 7.7	5.3 ± 7.9	0.531
REM, %TST	21.9 ± 6.4	21.4 ± 5.8	21.1 ± 6.4	20.7 ± 5.5	0.505
Wake (WASO/SPT), %	12.28 ± 10.5	10.9 ± 9.0	12.1 ± 8.4	9.3 ± 6.8	0.264
AHI	2.6 ± 2.6	2.6 ± 2.8	2.8 ± 2.7	2.6 ± 2.7	0.500

Data are means ± SD. *Two-sample *t*-test to compare the change from baseline to Week 4 between the modafinil and placebo groups. TIB, time in bed; WASO, wake after sleep onset; SPT, sleep period time; AHI, apnea-hypopnea index.

served in the other variables, including laboratory tests, blood pressure, pulse rate, body weight, or electrocardiogram.

DISCUSSION

This study was the first Asian study to investigate the efficacy of modafinil for treating residual sleepiness in patients with nCPAP-treated OSAS using both subjective and objective measures. In this study, residual sleepiness was defined as excessive daytime sleepiness in patients who were compliant with OSAS treatment but had subjective sleepiness without any other identifiable cause of sleepiness, applying enrollment criteria identical to those in studies in the United States.[27,29] The degree of residual sleepiness at baseline, as represented by the ESS total score, of the patients enrolled in this study, was also comparable to that in the US studies.[27,29]

The use of the MWT was limited to a subgroup of patients in this study; hence, a subjective measure of sleepiness (the ESS) was used as the primary efficacy parameter. Consequently, in this 4-week study, the improvement in ESS total score was significantly greater in the modafinil group than in the placebo group. Four weeks of treatment with modafinil normalized the ESS total score in approximately two-thirds of the patients. In terms of ESS total score, significant improvements of excessive daytime sleepiness in the modafinil group were observed at the first post-treatment evaluation, i.e., one week after starting treatment, compared with the placebo group. Overall, the mean ESS total scores were normalized (to < 11) within 1 week of modafinil administration in 57.7% of patients, increasing to 69.2% at week 4. Modafinil also improved sleep latency determined by the MWT, representing the patient's ability to maintain wakefulness.

As described above, modafinil exerts its wake-promoting activities by targeting several neurotransmitter systems, rather than a specific molecule or specific neurotransmitter system. Thus, the effects of modafinil on residual sleepiness in OSAS patients are at least partly attributable to its nonspecific pharmacological actions.

The present study evaluated adjunctive once-daily administration of 200 mg modafinil. Another placebo-controlled study

Table 3—Adverse events occurring in two or more patients in either treatment group

Adverse event	Placebo (n = 62)	Modafinil (n = 52)	p-value*
Headache	4 (6.5)	6 (11.5)	0.508
Upper abdominal pain	2 (3.2)	0 (0)	0.499
Insomnia	0 (0)	2 (3.8)	0.206
Palpitation	0 (0)	2 (3.8)	0.206

Values are number of patients (%). *Fisher exact test.

evaluated this dose and a higher dose (400 mg once daily) in a comparable patient population.[29] Interestingly, when the efficacy data for the 200 mg doses in both studies were compared, the changes in ESS score from baseline to Week 4 of treatment were -6.52 ± 5.04 (n = 52) and -3.20 ± 4.25 (n = 95) in our study and in the US study,[29] respectively. The respective changes in MWT sleep latency were 2.97 ± 5.25 (n = 22) and 1.20 ± 4.33 (n = 84). These data suggest that the response to 200 mg/day modafinil is greater in Japanese patients than in US patients, which may indicate slight differences in pharmacokinetic profiles among different ethnicities, as already reported among other ethnic groups.[41,42] Differences in the pharmacokinetic profiles, including the absorption and distribution of modafinil, may also be attributable to the differences in body size between Japanese and US patients, as the mean BMI of patients treated with 200 mg modafinil was 27.9 ± 4.3 kg/m^2 in our study versus 36.2 ± 7.6 kg/m^2 in the US study.[29] Alternatively, excess obesity is known to exacerbate daytime sleepiness,[43,44] possibly resulting in more severe symptoms or less apparent improvements in symptoms in US patients than in Japanese patients. Additionally, differences in the timing or content of the morning meal may partly explain the differences in clinical outcomes between these studies. Nevertheless, the precise reasons for this difference between Japanese and US patients are unclear, and this study was conducted to evaluate safety and efficacy in Japanese OSA patients and not to elucidate the difference between US and Japanese patients. However, the trends in posi-

tive outcomes for patient-reported sleepiness and objectively determined sleep latency in the present study were similar to those reported in the US study.[29]

Of note, in this study of Japanese patients, treatment with modafinil did not significantly affect sleep parameters in terms of nocturnal PSG findings or total PSQI score. Therefore, the administration of modafinil in the morning did not seem to adversely affect the structure or quality of nocturnal sleep.

Generally, modafinil was well tolerated. The safety and tolerability findings of the current study are consistent with those of other double-blind placebo-controlled studies.[27,29] Headache, insomnia, and palpitation were the most common ADRs in modafinil-treated patients. However, modafinil therapy was not associated with clinically significant changes in blood pressure or heart rate relative to placebo. Furthermore, there were no serious adverse events in either group in this study.

Some limitations of this study should be mentioned. First, most of the patients in this study were male, and there are some differences in the pharmacokinetics of modafinil between males and females.[41,42,45] Second, we only included patients with OSAS on nCPAP. The efficacy of modafinil should therefore be evaluated in OSAS patients with residual sleepiness on other treatments.

In conclusion, residual daytime sleepiness was improved in Japanese patients with OSAS treated with 200 mg modafinil once daily. We found significant improvements in ESS total scores at 1 week after starting modafinil that were maintained until the end of the 4-week study. Modafinil may be an effective and well-tolerated adjunct treatment for the chronic management of residual daytime sleepiness in patients with OSAS who experience excessive daytime sleepiness despite regular nCPAP use.

ABBREVIATIONS

ADR, adverse drug reactions
AHI, apnea-hypopnea index
CI, confidence interval
ESS, Epworth Sleepiness Scale
GABA, γ-aminobutyric acid
LS, least squares
nCPAP, nasal continuous positive airway pressure
OSAS, obstructive sleep apnea syndrome
PSG, polysomnography
PSQI, Pittsburgh Sleep Quality Index
SL-MWT, sleep latency on maintenance of wakefulness test

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Regular Article

Reliability, validity, and responsiveness of the Japanese version of International Restless Legs Syndrome Study Group rating scale for restless legs syndrome in a clinical trial setting

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Aim: This study was conducted to verify the reliability, validity, and responsiveness of the Japanese version of the International Restless Legs Syndrome Study Group Rating Scale for restless legs syndrome (J-IRLS) as a sub-study of a clinical trial of pramipexole against restless legs syndrome.

Methods: After evaluating the test–retest reliability, concurrent validity and construct validity were analyzed. The responsiveness of J-IRLS was confirmed by evaluating the correlations between the changes in J-IRLS total score after treatment, Clinical Global Impression Improvement Scale (CGI-I), and Patient Global Impression.

Results: Test–retest reliability of J-IRLS was good (intra-class correlation coefficient, 0.877; 95% confidence interval, 0.802–0.925). The correlation coefficient of J-IRLS total score and CGI-S score for the first and second visit was 0.804 and 0.796, respectively (both $P < 0.0001$). Factor analysis of J-IRLS items alone identified a two-factor structure. Exploratory analysis on 10 items of J-IRLS together with the Japanese version of the Pittsburgh Sleep Quality Index revealed that several items on the Japanese version of the Pittsburgh Sleep Quality Index appeared as the third factor. The correlations of CGI-I and Patient Global Impression with change in J-IRLS total score after treatment were highly significant.

Conclusions: Reliability, validity, and responsiveness of J-IRLS were considered adequate. The scale is highly applicable both for evaluating the severity of restless legs syndrome and for assessing drug efficacy.

Key words: Japanese version of International Restless Legs Syndrome Study Group rating scale for restless legs syndrome, Japanese version of Pittsburgh Sleep Quality Index, reliability, restless legs syndrome, validity.

RESTLESS LEGS SYNDROME (RLS) is a disorder characterized by unpleasant leg sensations and an irresistible urge to move the legs that occurs mainly at night.[1] The prevalence of RLS in Western populations is estimated at 5–15%,[2–4] and a relatively smaller prevalence of the disorder in the Japanese population has been reported.[5,6]

The International Restless Legs Syndrome Study Group Rating Scale for restless legs syndrome (IRLS)[7] was developed as a useful tool for assessing the subjective severity of the disorder, and has become the first-choice method to evaluate the severity of RLS in

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Western countries. Reports have confirmed the high reliability, validity, and responsiveness of the original English version of IRLS.[7,8] However, utility of the Japanese version of IRLS (J-IRLS) has not yet been elucidated. Moreover, IRLS contains only one item for evaluating the insomnia symptom (item 4) even though insomnia is the most problematic symptom of RLS.[9] In addition, the relation between the findings of IRLS and widely accepted scales for assessing subjective sleep disturbance, such as the Pittsburgh Sleep Quality Index (PSQI),[10] has not been well elucidated.

To clarify these issues, the present study was designed to ascertain the test–retest reliability, validity, and responsiveness of J-IRLS and to estimate the correlation between J-IRLS and PSQI-J.

METHODS

Subjects

This study was performed as a sub-study of a randomized, double-blind, placebo-controlled study of the efficacy of pramipexole against RLS in Japan.[11] In that study, male and female patients aged 20–80 years with a diagnosis of primary RLS made according to the essential criteria of the International Restless Legs Syndrome Study Group (IRLSSG)[12] by a sleep disorder expert physician were enrolled. All eight institutions participating in the pramipexole study participated in this sub-study after obtaining approval by the local ethics committee, and all authors of the pramipexole study report agreed to publish the results of this study. Fifty-nine individuals aged 20–78 years who were diagnosed as having idiopathic RLS were enrolled in this sub-study. The presence of any other movement disorders or sleep disorders was ruled out by at least two sleep disorder expert physicians. All patients gave written informed consent before entering the study. Descriptive variables of 59 patients recruited are shown in Table 1.

Analyses of both reliability and validity of J-IRLS were performed during the screening phase of the above pramipexole study in all patients who consented to participate in the study. After excluding three patients, including two patients who did not answer the Japanese version of the PSQI (PSQI-J)[13] and one patient who dropped out shortly after screening, assessment of the construct validity of J-IRLS by examining its correlation with PSQI-J was performed in 56 patients at baseline of the treatment phase of the pramipexole study. Fifteen patients did not meet inclusion criteria (J-IRLS total score >15) for entering the treatment phase, and four patients did not complete treatment. As a result, we evaluated the responsiveness of change in IRLS over 6 weeks' treatment with either pramipexole or placebo by investigating its correlation with the changes in both the original English version of the Clinical Global Impression-Improvement (CGI-I), an estimate of physician's global impression about the improvement of RLS symptoms, and the original English version of the Patient Global Impressions (PGI), which assesses patients' subjective improvement of symptoms over time, in a total of 37 patients.

Table 1. Demographic variables of subjects

Number of subjects	59
Age, years	
Mean ± SD (range)	52.9 ± 16.6 (20–78)
Sex, % (*n*)	
Male	54.2 (32)
Female	45.8 (27)
Age at onset of symptoms, years	
Mean ± SD (range)	52.4 ± 16.5 (20–78)
Time since diagnosis, years	
Mean ± SD (range)	0.38 ± 0.91 (0–4.9)
Treatment history, % (*n*)	
Treated	42.4 (25)
De novo	57.6 (34)
CGI 'Severity of Illness', % (*n*)	
Normal, not at all ill	10.2 (6)
Borderline ill	11.9 (7)
Mildly ill	22.0 (13)
Moderately ill	16.9 (10)
Markedly ill	27.1 (16)
Severely ill	11.9 (7)

CGI, Clinical Global Impression.

J-IRLS

J-IRLS was generated based on the original IRLS (V2.1) after obtaining permission from the IRLSSG through MAPI Research Trust. Linguistic validation of J-IRLS was performed as follows. First, Japanese sleep disorder experts prepared version 1 of the draft J-IRLS by translating the original English IRLS into Japanese. Version 1 was then back-translated into English by native-English-speaking translators; thereafter translation-related issues were addressed and neces-