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ORIGINAL RESEARCH ARTICLE

Suvorexant (Belsomra® Tablets 10, 15, and 20 mg): Japanese Drug-Use Results Survey

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Abstract

Background We report on the results of a Japanese postmarketing drug-use survey of suvorexant (Belsomra®) tablets.

Methods A survey with a ≤6-month observation period after the start of administration was conducted, targeting insomnia patients who were treated with suvorexant for the first time in Japan. Information on the safety and efficacy of the drug product was collected. The evaluation period was July 21, 2015–August 12, 2017, and the target number of patients was 3428.

Results The mean administration period for the safety analysis population of 3248 patients was 113 days. At 6 months after the start of treatment, 48.6% (1577/3248) of the patients had been continually receiving treatment, and 51.4% (1671/3248) of the patients discontinued/dropped out of treatment before 6 months. Among the patients who discontinued/dropped out of the treatment, more than 30% discontinued due to improvement. The mean treatment duration for those who had discontinued treatment for this reason was 62 days. The incidence rate of adverse drug reactions among those in the safety analysis population was 9.7%, and the common adverse drug reactions were somnolence (3.6%), insomnia (1.2%), dizziness (1.1%), and nightmare (0.8%), all of which are described in the product label. No additional noteworthy events were observed. In 2439 patients with a final overall global assessment of sleep judged by physicians, the 'improved' rate was 74.0%. Among 2424 patients who provided a final overall global assessment, the improvement rate was 73.2%, which was comparable with the improvement rate judged by physicians. Regarding clinical effects (based on patient diary data or physician's assessment), reduction in median sleep latency and increase in median total sleep time (reduction from 60 to 50 min and increase from 300 to 360 min compared with baseline, respectively) were observed at 1 week after the start of treatment and onwards, and the effect was maintained after the start of treatment for 6 months. A similar effect was observed irrespective of age groups or reasons for using suvorexant.

Conclusion This survey was an exploratory observational study without a control group; the interpretation of results may require the consideration of factors that may have caused bias in the results, such as demographic characteristics and effects of other drugs. However, the results suggest that suvorexant can be a useful drug in daily clinical practice for treating insomnia.

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Key Points

We report on the results of a Japanese postmarketing drug-use survey of suvorexant (Belsomra® tablets 10, 15, and 20 mg), a new type of anti-insomnia drug that functions as an orexin receptor antagonist.

Suvorexant was well-tolerated and improved clinical outcome in the real-world clinical setting; the incidence rate of adverse drug reactions in the safety analysis population was 9.7%, and suvorexant showed improvement of insomnia in > 70% of patients.

The results suggest that suvorexant can be a useful drug in daily clinical practice for treating insomnia. However, this was an exploratory observational study without a control group; therefore, interpretation of the data may require consideration of factors that could have caused bias in the results.

1 Introduction

Insomnia is a common sleep disorder with a high incidence [1]. In general, γ-aminobutyric acid A ($GABA_A$) receptor agonists, such as benzodiazepines and non-benzodiazepines, and melatonin receptor agonists are used for treatment depending on the symptoms of insomnia and demographic characteristics of the patients. On the other hand, suvorexant (Belsomra® tablets 10, 15, and 20 mg), is a new type of anti-insomnia drug that functions as an orexin receptor antagonist. Suvorexant possesses a different pharmacological activity than conventional anti-insomnia drugs, and inhibits the nuclei of the central nervous system (CNS) arousal system that are under the control of orexin neurons by selectively blocking the receptors (OX1R and OX2R) of orexin, which is a wake-promoting neurotransmitter.

Suvorexant was approved for use in Japan on September 26, 2014, at a dose of 20 mg for adults and 15 mg for elderly patients, after its efficacy and safety were demonstrated by clinical trials [2]. However, suvorexant could be administered to patients with more diverse demographic characteristics than those studied in the original clinical development program after being marketed. Thus, we started a drug-use survey for suvorexant on July 21, 2015, to collect or confirm information on the safety and efficacy of suvorexant for use in daily clinical practice in Japan. In an interim report, safety and efficacy were evaluated from 791 Japanese patients whose survey results were collected from commencement to August 12, 2016, and no additional noteworthy adverse events were observed [3]. In this article, we report the results of the final analysis of the surveys of 3428 Japanese patients collected up to the end date of August 12, 2017.

This survey was performed in compliance with the ministerial ordinance on 'Good Post-marketing Study Practice' (GPSP), which was authorized by the Ministry of Health, Labour and Welfare in Japan (Ordinance No. 171, dated December 20, 2004).

2 Patients and Methods

2.1 Survey Patients

A total of 3428 insomnia patients who received suvorexant for the first time were included in this survey. They were registered by a central registration method at medical institutions that signed a written contract for this survey. Patients were excluded from registration if they were registered beyond the survey period specified in the contract, were double registered, had a history of suvorexant treatment, were contraindicated per the Japanese package insert [4] (such as patients with a history of hypersensitivity to suvorexant, patients who were taking drugs that strongly inhibit cytochrome P450 (CYP) 3A), or took suvorexant to treat insomnia induced by temporary factors. Suvorexant 10 mg was additionally approved for use in Japan on September 13, 2016 and the 10 mg tablets were included in the current study after marketing on December 15, 2016.

2.2 Survey Methods

As indicated in the Japanese package insert [4], Belsomra® was orally administered once daily immediately before bedtime at a dose of 20 mg for adults and 15 mg for elderly patients.

As a general principle, the intended observation period was for 1 month after the initiation of treatment. When patients continued treatment with suvorexant, the observation period was extended until 6 months after initiation. When treatment with suvorexant was completed (discontinued because of improvement in insomnia) or discontinued before 6 months after initiation, a 30-day follow-up period was set after the completion or discontinuation for the collection of information on adverse events. The survey period was July 21, 2015 to August 12, 2017

2.3 Survey Items

Patient sex, age, reason for using suvorexant, duration of insomnia, medical history, complications, diagnosis of narcolepsy (including cataplexy), and narcolepsy-like symptoms before treatment with suvorexant, which are also commonly observed in the general population without

narcolepsy [major symptoms include long-term intolerable drowsiness and dozing off in the daytime lasting for ≥ 3 months, emotional atonia (cataplexy: sudden loss of strength when patients felt deeply delighted, angry, or surprised), hypnagogic hallucinations (visual and auditory hallucinations experienced during sleep onset), or sleep paralysis (inability to move despite awareness during sleep/wake transitions)], were evaluated.

Information on previous therapy for insomnia, other concomitant drugs for the treatment of insomnia, and use of suvorexant (initial dose, duration, reason for discontinuation, etc.) were collected. Drugs listed in the Japanese insomnia treatment guidelines [1], were considered to be drugs for previous therapy or other concomitant drugs for the treatment of insomnia.

Information on safety was collected through a physician's medical interview. Regardless of a possible causal relationship with suvorexant, information on all adverse events after the initiation of suvorexant was collected during the observation period with a physician's assessment of severity and causality.

Information on efficacy, including global improvement and sleep effects (sleep latency and total sleep time), was collected. The overall global improvement assessment by physicians was evaluated at the end of the observation period (1 week, 1 month, 3 months, and 6 months after the initiation of treatment with suvorexant or on the day of completion/discontinuation). A physician in charge made a comprehensive assessment of improvement through a medical interview and categorized results as 'improved,' 'unchanged,' or 'deteriorated' by comparing them with results before initiation. The overall global improvement at 6 months after the initiation of suvorexant or on the day of completion/discontinuation was considered to be 'the final overall global improvement.' Overall global improvement judged by patients was evaluated at the same timepoints as the physician's assessment. Patients assessed improvement by categorizing results as 'improved,' 'unchanged,' or 'deteriorated' compared with results before initiation, and the physician in charge recorded the results during the interview. Information on sleep effects (sleep latency and total sleep time) was collected at the following timepoints: pre-dose and 1 week, 1 month, 3 months, and 6 months after the initiation of treatment with suvorexant, or on the day of completion/discontinuation through a medical interview with/without a patient's sleep diary conducted by the physician in charge.

2.4 Analysis Methods

For the safety assessment, patients were excluded from the analysis if they had an initial visit only (no subsequent visits), a registration violation was found after data collection (e.g., patients who were previously treated with suvorexant; had contraindications mentioned in the Japanese package insert [4]; took suvorexant to treat insomnia induced by temporary factors; and the patient information was different from that at the time of registration), or they did not take suvorexant. Data on adverse drug reactions (adverse events for which a causal relationship with suvorexant could not be ruled out) were evaluated using MedDRA®/J (*Medical Dictionary for Regulatory Activities* (MedDRA®) Japanese translation) version 20.0 Preferred Term (PT). If the same PT was observed more than once in the same patient, the event was counted only once.

Multivariate logistic regression was performed to evaluate demographic characteristics that might have influenced the occurrence of somnolence, which was a noteworthy event in the current survey. Factors that were expected to be medically valid were selected: sex, age, body mass index (BMI), duration of insomnia, co-morbid conditions that may be associated with insomnia (e.g., schizophrenia, depression, manic-depressive illness, anxiety disorder, and dementia), concomitant drugs, and initiation status of suvorexant (i.e., hypnotic naïve, switch, or add-on therapy).

For efficacy assessment, patients were excluded from the analysis if (1) the initial dose was different from that specified in the Japanese package insert [4] (20 mg once daily for adults and 15 mg once daily for elderly patients); (2) no data regarding overall global improvement and sleep effects were obtained; (3) physicians did not assess overall global improvement and sleep effects within 30 days after the end of the observation period; or (4) there was a discrepancy between a physician's judgement and the reason for discontinuation.

Regarding overall global improvement in sleep, the improvement rate was calculated with the following formula:

$$\frac{\text{Number of patients categorized as"improved"}}{\text{Number of patients assessed for the final overall global improvement}} \times 100.$$

In addition, multivariate logistic regression was performed to search for factors that could affect overall global improvement. In this analysis, 'improved' was categorized as the 'improvement' group, while 'unchanged' and 'deteriorated' were categorized as the 'no improvement' group. Factors that were expected to be medically valid were selected as variables, including sex, age, BMI, duration of insomnia, co-morbid conditions that may be associated with insomnia (e.g., schizophrenia, depression, manic-depressive illness, anxiety disorder, and dementia), concomitant medications, and initiation status of suvorexant.

Regarding sleep effects, the median of sleep latency and total sleep time were calculated from all available data at each timepoint of collection (pre-dose and 1 week, 1 month, 3 months, and 6 months after the initiation of

treatment with suvorexant or on the day of completion/discontinuation).

For safety and efficacy assessments, attention was focused on patient populations with special demographic characteristics described in the Japanese regulatory agency (Pharmaceuticals and Medical Device Agency [PMDA]) review report [5] or the Japanese package insert [4], such as patients with narcolepsy (including cataplexy), respiratory dysfunction, psychiatric disorders, elderly patients, and patients using suvorexant with a concomitant drug for treating insomnia.

To understand the initiation status of suvorexant in daily clinical practice, patients were classified based on the use of other drugs for treating insomnia, as shown in Table 1. The continuation status of patients in each initiation status group (continued, discontinued because of improvement, discontinued due to inadequate effects, discontinued due to no efficacy, discontinued due to the occurrence of adverse events, dropped out due to no subsequent revisit after the second visit) was also summarized.

3 Results

3.1 Composition of Patients

Data from 3428 patients were collected from 884 medical institutions within Japan. Among these patients, 180 were excluded for various reasons, including 158 patients who only had the initial visit and no subsequent visits. In total, 3248 patients were included in the safety analysis population, 2665 of whom were included in the efficacy analysis population; 583 patients were excluded from these analyses, including those who started treatment with suvorexant at an unapproved dose ($N=504$) and those with no overall global improvement or sleep measures information ($N=92$) (Fig. 1).

Table 1 Patients classified based on use of other drugs for insomnia

Classification	Condition
Naïve	Patients who received suvorexant without any history of use of drugs for insomnia (drugs used 50 days or longer before initiation of suvorexant are not considered as drugs used)
Switching	Patients who received suvorexant after discontinuation or dose reduction of existing drug(s) for insomnia within 14 days before initiation of suvorexant
Add-on	Patients who received suvorexant without changing the use of existing drug(s) for insomnia within 14 days before initiation of suvorexant
Others	Patients other than the above

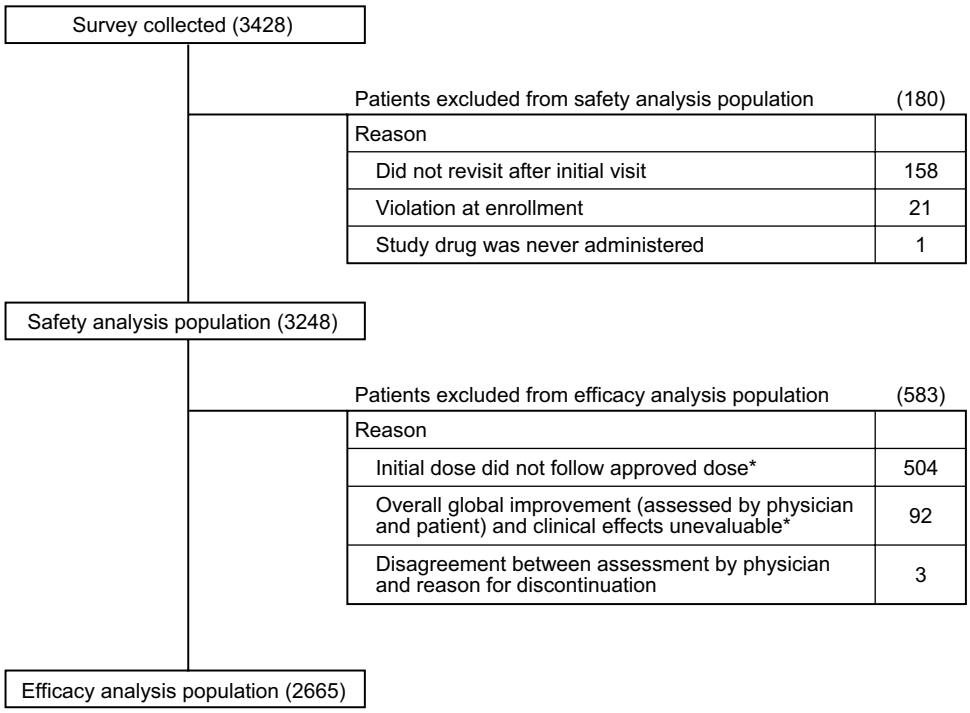


Fig. 1 Composition of patients. *16 patients in the 'Initial dose did not follow approved dose' and 'Overall global improvement (assessed by physician and patient) and clinical effects unevaluable' categories overlapped

3.2 Patient Background

The composition of the 3248 patients in the safety analysis population is shown in Table 2. In total, 1977 patients (60.9%) were females, and the mean age was 62.1 years. Further, 1758 patients (54.1%) were ≥ 65 years (elderly) and 1028 (31.7%) were ≥ 75 years (latter-stage elderly). The most common reason for using suvorexant was difficulty in falling asleep (2429 patients; 74.8%). The duration of insomnia was less than 1 year in 1313 patients (40.4%), at least 1 year and less than 10 years in 1481 patients (45.6%), and at least 10 years in 454 patients (14.0%).

Among patients with special demographic characteristics of interest, there was one patient (0.03%) who was diagnosed with narcolepsy (including cataplexy) before receiving treatment with suvorexant, 141 patients with hepatic function disorder [4.3%, including five patients (0.2%) with severe hepatic function disorder (which was recorded as 'severe' in the survey form)], and 121 patients with respiratory dysfunction (3.7%, including 28 patients (0.9%) with severe respiratory dysfunction). Of the 121 patients with respiratory dysfunction, 73 patients had obstructive sleep apnea (OSA) (26 patients were severe) and 50 patients had chronic obstructive pulmonary disease (COPD) (four patients were severe). In total, 106 patients (3.3%) had structural brain disorder; 1007 (31.0%) had a psychiatric disorder, including 508 patients (15.6%) with depression, 211 (6.5%) with anxiety disorder, 92 (2.8%) with schizophrenia, and 84 (2.6%) with manic-depressive illness; and 144 (4.4%) had dementia. The previous clinical trials of suvorexant [6, 7] specified exclusion criteria and targeted patients with insomnia as the primary disease, while the current survey included patients with a broader background. There were 1277 patients (39.3%) who had received prior drugs for treating insomnia and 888 (27.3%) who received other concomitant drugs for treating insomnia. Regarding the initiation status of suvorexant, 1946 patients (59.9%) were treatment-naïve, 703 patients (21.6%) were switched from other insomnia treatments, and 536 patients (16.5%) were receiving add-on therapy. Although most treatment-naïve patients were treated with only suvorexant [97.3% (1894/1946 patients)], there were some patients who started treatment with suvorexant simultaneously with other insomnia treatments [2.7% (52/1946 patients)]. For those who switched treatment, most had discontinued their prior treatment before they started treatment with suvorexant (complete switch) [68.0% (478/703 patients; 454 patients switched to suvorexant from a single drug)] and some discontinued/reduced treatment or switched to another drug and started treatment with suvorexant (partial switch) [32.0% (225/703 patients)]. For patients who received suvorexant as add-on treatment, most patients added suvorexant to their single treatment (either adding on only suvorexant or adding on suvorexant plus one or more

Table 2 Demographic characteristics (safety analysis population)

Item	Safety analysis set	
	N	%[a]
Overall	3248	
Sex		
Male	1271	39.1
Female	1977	60.9
Age group 1 (years)		
< 15	2	0.1
≥ 15 to < 65	1488	45.8
≥ 65	1758	54.1
Age group 2 (years)		
< 65	1490	45.9
≥ 65 to < 75	730	22.5
≥ 75	1028	31.7
Age group 3 (years)		
< 65	1490	45.9
≥ 65 to < 85	1490	45.9
≥ 85	268	8.3
BMI (kg/m^2)		
< 25.0	1357	41.8
≥ 25.0	497	15.3
Unknown	1394	42.9
Reason for use (multi-count)		
Difficulty falling asleep	2429	74.8
Nocturnal awakening	1596	49.1
Early morning awakening	349	10.7
Others	31	1.0
Duration of insomnia (years)		
< 1	1313	40.4
≥ 1 to < 10	1481	45.6
≥ 10	454	14.0
Medical examination[b]		
Psychiatry	917	28.2
Internal medicine	2004	61.7
Others	327	10.1
Narcolepsy-like events		
No	3113	95.8
Yes	92	2.8
Unknown	43	1.3
Diagnosis of narcolepsy (including cataplexy)		
No	3206	98.7
Suspected	4	0.1
Yes	1	< 0.1
Unknown	37	1.1
Respiratory dysfunction		
No	2866	88.2
Yes	121	3.7
Unknown	261	8.0
Chronic obstructive pulmonary disease (COPD)		
No	3077	94.7

Table 2 (continued)

Item	Safety analysis set	
	N	%[a]
Yes	50	1.5
Unknown	121	3.7
Obstructive sleep apnea (OSA)		
No	2919	89.9
Yes	73	2.2
Unknown	256	7.9
Severe respiratory dysfunction		
No	2959	91.1
Yes	28	0.9
Unknown	261	8.0
Hepatic function disorder		
No	2984	91.9
Yes	141	4.3
Unknown	123	3.8
Severe hepatic function disorder		
No	3120	96.1
Yes	5	0.2
Unknown	123	3.8
Structural brain disorder		
No	3142	96.7
Yes	106	3.3
Psychiatric disorder		
No	2182	67.2
Yes	1007	31.0
Unknown	59	1.8
Schizophrenia		
No	3095	95.3
Yes	92	2.8
Unknown	61	1.9
Depression		
No	2680	82.5
Yes	508	15.6
Unknown	60	1.8
Manic-depressive illness		
No	3103	95.5
Yes	84	2.6
Unknown	61	1.9
Anxiety disorder		
No	2976	91.6
Yes	211	6.5
Unknown	61	1.9
Dementia		
No	3043	93.7
Yes	144	4.4
Unknown	61	1.9
Medical history		
No	2498	76.9
Yes	543	16.7
Unknown	207	6.4
Prior medication		
No	1946	59.9
Yes	1277	39.3
Unknown	25	0.8
Concomitant medication		
No	982	30.2
Yes	2241	69.0
Unknown	25	0.8
Concomitant insomnia medication		
No	2335	71.9
Yes	888	27.3
Unknown	25	0.8
Initiation status		
Naïve	1946	59.9
Switch	703	21.6
Add-on	536	16.5
Others	63	1.9

BMI body mass index

[a]Total for each item will not be 100% due to rounding

[b]Psychiatric and psychosomatic medicines are given as 'psychiatry'

other drugs) [85.8% (460/536 patients)], but some patients [14.2% (76/536 patients)] added suvorexant to their multiple treatments (add-on to multiple drugs) (Fig. 2). The mean initial dose of suvorexant was 16.9 mg, and the mean treatment period was 113 days.

3.3 Safety

Among the 3248 patients in the safety analysis population, 377 adverse drug reactions (adverse events for which a causal relationship with suvorexant could not be ruled out based on the clinician's assessment) were observed in 315 patients (9.7%) (Table 3). The most common adverse drug reactions were somnolence (117 patients; 3.6%), insomnia (40 patients; 1.2%), dizziness (35 patients; 1.1%), and nightmare (27 patients; 0.8%), none of which was considered serious. Most adverse drug reactions were resolved or resolving; 169 were resolved, 33 were resolving, ten were not resolved, and seven were unknown. In total, 8.0% (260/3428; Fig. 4) of patients discontinued suvorexant after an adverse event. A total of 13 serious adverse drug reactions were reported in eight patients (0.2%; two events of delirium, one each of agitation, dissociative disorder, irritability, suicidal ideation,

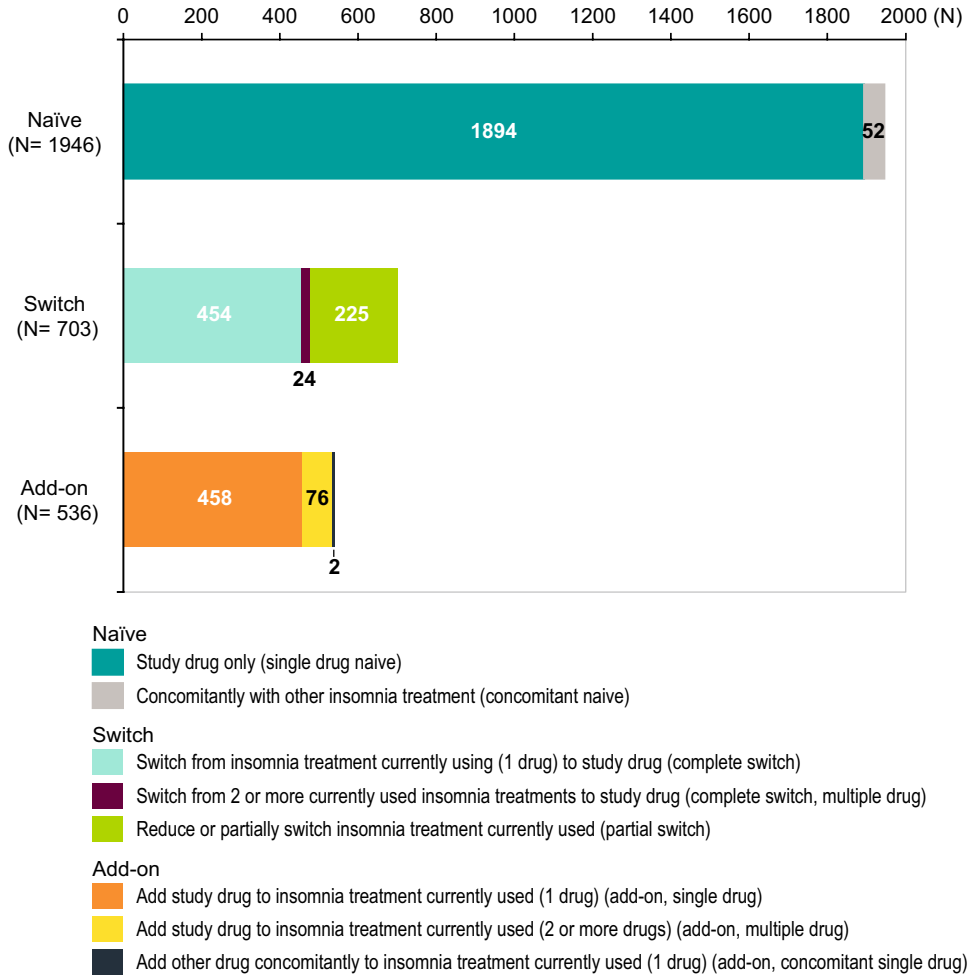


Fig. 2 Initiation status of suvorexant (safety analysis population). Data for 63 patients in the "Others" category of Table 1 not shown

coughing, dyspnea, pneumonia aspiration, falling, femoral neck fracture, subdural hematoma, and traumatic intracranial hemorrhage). All serious adverse drug reactions were resolved or resolving except in three patients [one with dissociative disorder (outcome: unknown), one with falling (not resolved), and one with traumatic intracranial hemorrhage and subdural hematoma (resolved with sequelae)]. After the end of this survey, the causal relationship for subdural hematoma and traumatic intracranial hemorrhage with suvorexant were ruled out by the reporting physician.

Regarding adverse drug reactions that necessitated evaluation in the PDMA review report [5] or were stated in the Japanese package insert [4], two patients experienced adverse drug reactions that were reported to affect potentially hazardous machinery operation (e.g., driving) (one patient with disturbance in attention and one with somnolence), but no accidents or associated injuries occurred. Narcolepsy-like events occurred in five patients with sleep paralysis, two with falls, and one with hypnagogic hallucination. Parasomnia, abnormal sleep-related events, and sleepwalking occurred in 27 patients with nightmare, seven with abnormal dreams, one with REM sleep abnormality, and one with sleep talking. Suicidal ideation occurred in one patient. There were no adverse drug reactions related to suicidal behavior or dependency (i.e., alcohol or drug dependence). All outcomes were recovering or recovered except for unknown outcome for nightmare (one case) and abnormal dreams (two cases), and unrecovered outcome for sleep paralysis (one case), fall (one case), and nightmare (two cases).

Among the 180 patients who were excluded from the safety analysis population, one case of malaise occurred in one patient; the patient recovered.

Multivariate logistic regression analysis revealed that concomitant drug use and duration of insomnia were factors that affected the occurrence of somnolence, which was intensively investigated in this survey (Table 4). Patients who used concomitant drugs had a higher risk of somnolence than those who did not use them (odds ratio 3.007, 95% confidence interval CI 1.307–6.918; $p = 0.010$). On the other hand, patients with a duration of insomnia of ≥ 10 years had a lower risk of somnolence than those with

Table 3 Incidence of adverse drug reactions and other events (safety analysis population)

Items	Cumulative results of drug-use survey
Number of patients in the safety analysis population	3248
Number of patients with adverse drug reactions	315
Number of adverse drug reaction events	377
Rate of occurrence	9.70%

Type of adverse drug reactions	Patients with adverse drug reactions	
	N	%
Mental disorder	100	3.08
Abnormal dreams	7	0.22
Agitation	1	0.03
Delirium	2	0.06
Depression	1	0.03
Disorientation	1	0.03
Dissociative disorder	1	0.03
Hallucination	1	0.03
Hallucination, visual	2	0.06
Hypnagogic hallucination	1	0.03
Initial insomnia	9	0.28
Insomnia	40	1.23
Irritability	1	0.03
Middle insomnia	6	0.18
Nervousness	1	0.03
Nightmare	27	0.83
REM sleep abnormality	1	0.03
Sleep talking	1	0.03
Suicidal ideation	1	0.03
Nervous system disorders	185	5.70
Disturbance in attention	1	0.03
Dizziness	35	1.08
Dyslalia	1	0.03
Head discomfort	2	0.06
Headache	12	0.37
Hypersomnia	6	0.18
Paresthesia	1	0.03
Sedation	4	0.12
Sleep paralysis	5	0.15
Sleep phase rhythm disturbance	1	0.03
Somnolence	117	3.60
Cognitive disorder	1	0.03
Restless legs syndrome	1	0.03
Poor quality sleep	4	0.12
Angiopathy	2	0.06
Hot flush	2	0.06
Respiratory, thoracic and mediastinal disorders	4	0.12
Cough	1	0.03
Dyspnea	1	0.03
Pneumonia aspiration	1	0.03
Rhinitis allergic	1	0.03
Sleep apnea syndrome	1	0.03
Gastrointestinal disorders	15	0.46
Abdominal discomfort	1	0.03
Diarrhea	3	0.09
Gastritis	1	0.03
Nausea	9	0.28
Salivary hypersecretion	1	0.03
Skin and subcutaneous tissue disorders	8	0.25
Cold sweat	1	0.03
Drug eruption	1	0.03
Eczema	1	0.03
Hyperhidrosis	1	0.03
Night sweats	1	0.03
Pruritus	2	0.06
Rash	2	0.06
Renal and urinary disorders	1	0.03
Pollakiuria	1	0.03
General disorders and administration site conditions	42	1.29
Asthenia	1	0.03
Discomfort	1	0.03
Face edema	1	0.03
Feeling abnormal	11	0.34
Feeling cold	1	0.03
Hangover	7	0.22
Malaise	17	0.52
Edema peripheral	2	0.06
Thirst	3	0.09
Investigation	1	0.03
Blood glucose increased	1	0.03
Injury, poisoning and procedural complications	3	0.09
Fall	2	0.06
Femoral neck fracture	1	0.03
Subdural hematoma[a]	1	0.03
Traumatic intracranial hemorrhage[a]	1	0.03

[a]In a patient who experienced subdural hematoma and traumatic intracranial hemorrhage, the causal relationship to the survey drug was denied by the additional information given by the physician after completion of the survey

a duration of insomnia of < 1 year (odds ratio 0.308, 95% CI 0.112–0.845; $p = 0.022$).

Incidence rates of adverse drug reactions according to demographic characteristics are shown in Table 5, and

Table 4 Analysis of factors potentially influencing an adverse drug reaction of somnolence (safety analysis population)

Item	*N*	Adverse drug reaction of somnolence		Univariate			Multivariate		
		Number of patients	%	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value
Overall	3248	117	3.6						
Sex									
Male	1271	46	3.6	1			1		
Female	1977	71	3.6	0.992	0.680–1.447	0.967	0.857	0.512–1.434	0.558
Age (years)									
< 65	1490	76	5.1	1			1		
≥ 65 to < 85	1490	34	2.3	0.434	0.288–0.655	< 0.001	0.659	0.373–1.163	0.150
≥ 85	268	7	2.6	0.499	0.228–1.094	0.083	0.497	0.140–1.766	0.280
BMI (kg/m^2)									
< 25.0	1357	47	3.5	1			1		
≥ 25.0	497	18	3.6	1.047	0.602–1.821	0.870	0.921	0.517–1.639	0.779
Duration of insomnia (years)									
< 1	1313	54	4.1	1			1		
≥ 1 to < 10	1481	53	3.6	0.865	0.588–1.274	0.463	0.598	0.338–1.056	0.076
≥ 10	454	10	2.2	0.525	0.265–1.040	0.065	0.308	0.112–0.845	0.022
Schizophrenia									
No	3095	113	3.7	1			1		
Yes	92	4	4.3	1.200	0.433–3.325	0.726	0.327	0.044–2.450	0.277
Depression									
No	2680	88	3.3	1			1		
Yes	508	29	5.7	1.783	1.159–2.744	0.008	1.127	0.583–2.182	0.722
Manic-depressive illness									
No	3103	110	3.5	1			1		
Yes	84	7	8.3	2.474	1.115–5.487	0.026	1.669	0.476–5.854	0.423
Anxiety disorder									
No	2976	106	3.6	1			1		
Yes	211	11	5.2	1.489	0.787–2.816	0.221	1.298	0.531–3.168	0.567
Dementia									
No	3043	113	3.7	1			1		
Yes	144	4	2.8	0.741	0.270–2.038	0.562	0.708	0.160–3.137	0.649
Concomitant medication									
No	982	19	1.9	1			1		
Yes	2241	98	4.4	2.318	1.410–3.810	< 0.001	3.007	1.307–6.918	0.010
Initiation status									
Naïve	1946	59	3.0	1			1		
Switch	703	33	4.7	1.575	1.020–2.434	0.041	1.504	0.793–2.854	0.212
Add-on	536	21	3.9	1.304	0.785–2.166	0.305	1.147	0.553–2.380	0.713

BMI body mass index, *CI* confidence interval

patients with a background of special interest and the adverse drug reactions that occurred in those patients are indicated in Sects. 3.3.1–3.3.4.

3.3.1 Patients with Narcolepsy Including Cataplexy

No adverse drug reaction was observed in one patient with narcolepsy diagnosed before the initiation of suvorexant. Among four patients with narcolepsy suspected before the initiation of suvorexant, an adverse drug reaction of poor

Table 5 Adverse drug reactions by demographic characteristic (safety analysis population)

Items	*N*	Number of patients with events	Number of events	Rate of occurrence (%)
Overall	3248	315	377	9.7
Sex				
Male	1271	129	147	10.1
Female	1977	186	230	9.4
Age group 1 (years)				
< 15	2	0	0	0.0
≥ 15 to < 65	1488	168	206	11.3
≥ 65	1758	147	171	8.4
Age group 2 (years)				
< 65	1490	168	206	11.3
≥ 65 to < 75	730	63	76	8.6
≥ 75	1028	84	95	8.2
Age group 3 (years)				
< 65	1490	168	206	11.3
≥ 65 to < 85	1490	126	147	8.5
≥ 85	268	21	24	7.8
BMI (kg/m^2)				
< 25.0	1357	135	160	9.9
≥ 25.0	497	52	66	10.5
Unknown	1394	128	151	9.2
Reason for use (multi-count)				
Difficulty falling asleep	2429	217	264	8.9
Nocturnal awakening	1596	176	215	11.0
Early morning awakening	349	43	52	12.3
Others	31	8	10	25.8
Duration of insomnia (years)				
< 1	1313	116	139	8.8
≥ 1 to < 10	1481	149	181	10.1
≥ 10	454	50	57	11.0
Medical examination[a]				
Psychiatry	917	127	157	13.8
Internal medicine	2004	150	171	7.5
Others	327	38	49	11.6
Narcolepsy-like events				
No	3113	303	361	9.7
Yes	92	9	11	9.8
Unknown	43	3	5	7.0
Diagnosis of narcolepsy (including cataplexy)				
No	3206	311	373	9.7
Suspected	4	1	1	25.0
Yes	1	0	0	0.0
Unknown	37	3	3	8.1
Respiratory dysfunction				
No	2866	274	332	9.6
Yes	121	10	10	8.3
Unknown	261	31	35	11.9
Chronic obstructive pulmonary disease (COPD)				
No	3077	301	361	9.8
Yes	50	2	2	4.0
Unknown	121	12	14	9.9
Obstructive sleep apnea (OSA)				
No	2919	275	333	9.4
Yes	73	8	8	11.0
Unknown	256	32	36	12.5
Severe respiratory dysfunction				
No	2959	282	340	9.5
Yes	28	2	2	7.1
Unknown	261	31	35	11.9
Hepatic function disorder				
No	2984	276	331	9.2
Yes	141	22	25	15.6
Unknown	123	17	21	13.8
Severe hepatic function disorder				
No	3120	297	355	9.5
Yes	5	1	1	20.0
Unknown	123	17	21	13.8
Structural brain disorder				
No	3142	307	367	9.8
Yes	106	8	10	7.5
Psychiatric disorder				
No	2182	166	190	7.6
Yes	1007	144	181	14.3
Unknown	59	5	6	8.5
Schizophrenia				
No	3095	296	350	9.6
Yes	92	13	20	14.1
Unknown	61	6	7	9.8
Depression				
No	2680	239	282	8.9
Yes	508	70	88	13.8
Unknown	60	6	7	10.0
Manic-depressive illness				
No	3103	298	356	9.6
Yes	84	11	14	13.1
Unknown	61	6	7	9.8
Anxiety disorder				
No	2976	282	332	9.5
Yes	211	27	38	12.8
Unknown	61	6	7	9.8
Dementia				
No	3043	300	358	9.9
Yes	144	9	12	6.3
Unknown	61	6	7	9.8

Table 5 (continued)

Items	*N*	Number of patients with events	Number of events	Rate of occurrence (%)
Medical history				
No	2498	224	268	9.0
Yes	543	69	82	12.7
Unknown	207	22	27	10.6
Prior medication				
No	1946	132	157	6.8
Yes	1277	182	219	14.3
Unknown	25	1	1	4.0
Concomitant medication				
No	982	47	57	4.8
Yes	2241	267	319	11.9
Unknown	25	1	1	4.0
Concomitant insomnia medication				
No	2335	192	225	8.2
Yes	888	122	151	13.7
Unknown	25	1	1	4.0
Initiation status				
Naïve	1946	132	157	6.8
Switch	703	110	137	15.6
Add-on	536	68	76	12.7
Others	63	5	7	7.9

BMI body mass index

[a]Psychiatric and psychosomatic medicines are given as 'psychiatry'

quality sleep (non-severe, recovered) occurred in one patient (0.03%).

3.3.2 Elderly Patients

Among patients aged ≥ 65 years, adverse drug reactions that occurred in ≥ 5 patients were somnolence (41 patients; 2.3%), dizziness (24 patients; 1.4%), insomnia (23 patients; 1.3%), nightmare (11 patients; 0.6%), headache (6 patients; 0.3%), and nausea and feeling abnormal (5 patients each; 0.3%). The incidence rate of adverse drug reactions in elderly patients [8.4% (147/1758 patients)] was lower than that in non-elderly patients under the age of 65 years [11.3% (168/1490 patients)]. The incidence rate of adverse drug reactions in latter-stage elderly patients aged ≥ 75 years was 8.2% (84/1028 patients), which was lower than the incidence rates in patients under the age of 65 years and those aged between 65 and 74 years (11.3% (168/1490 patients) and 8.6% (63/730 patients), respectively).

3.3.3 Patients with Respiratory Dysfunction

Adverse drug reactions occurred in 8.3% (10/121 patients) of patients with respiratory dysfunction: five patients with somnolence and one each with insomnia, dizziness, pruritus, feeling abnormal, and hangover. All events were not serious, and the patients recovered. No adverse drug reaction related to respiratory depression was observed.

Adverse drug reactions occurred in 7.1% (2/28 patients) of patients with severe respiratory dysfunction. In severe OSA patients, there was one incidence each of insomnia and pruritus that were not serious. The patients recovered from both events.

3.3.4 Patients with Psychiatric Disorders

The incidence of adverse drug reactions in patients with psychiatric disorder(s) was 14.3% (144/1007 patients), higher than the 7.6% incidence in patients without psychiatric disorder(s) (166/2182 patients). Adverse drug reactions that occurred in five or more patients with psychiatric disorder(s) were somnolence (56 patients), insomnia (20 patients), dizziness (18 patients), malaise (11 patients), and nightmare (ten patients). The outcomes were as follows: 88, recovered; 17, recovering; four, not recovered; and six, outcome unknown. For each psychiatric disorder, the rate of patients experiencing adverse drug reactions with/without co-morbid schizophrenia was 14.1% (13/92 patients)/9.6% (296/3095 patients), with/without co-morbid depression was 13.8% (70/508 patients)/8.9% (239/2680 patients), with/without manic-depressive illness was 13.1% (11/84 patients)/9.6% (298/3103 patients), and with/without anxiety disorder was 12.8% (27/211 patients)/9.5% (282/2976 patients).

Of the 144 patients with a psychiatric disorder who experienced adverse drug reactions, 86.1% (124/144 patients) were also taking CNS-active medications versus 13.9% (20/144 patients) not taking these medications.

3.4 Efficacy

3.4.1 Overall Global Improvement

In the 2439 patients who had a final overall global physician assessment, the proportion of patients judged by the physician to be 'improved' (improvement rate) was 74.0% (1806/2439 patients). The proportions of patients judged to be 'unchanged' and 'deteriorated' were 22.2% (542/2439 patients) and 3.7% (91/2439 patients), respectively (Table 6). In the 2424 evaluable patients who had a final overall global self-assessment, the proportion who judged themselves to be 'improved' (improvement rate) was 73.2% (1775/2424 patients), similar to the results assessed by the physician.

Table 6 Final overall global improvement by demographic characteristic (physician's assessment) (efficacy analysis population)

Items	Number of patients by characteristic	Improved patients		Unchanged patients		Deteriorated patients	
		N	%	*N*	%	*N*	%
Overall	2439	1806	74.0	542	22.2	91	3.7
Sex							
Male	943	686	72.7	218	23.1	39	4.1
Female	1496	1120	74.9	324	21.7	52	3.5
Age group 1 (years)							
< 65	997	731	73.3	226	22.7	40	4.0
≥ 65	1442	1075	74.5	316	21.9	51	3.5
Age group 2 (years)							
< 65	997	731	73.3	226	22.7	40	4.0
≥ 65 to < 75	565	417	73.8	128	22.7	20	3.5
≥ 75	877	658	75.0	188	21.4	31	3.5
Age group 3 (years)							
< 65	997	731	73.3	226	22.7	40	4.0
≥ 65 to < 85	1213	898	74.0	273	22.5	42	3.5
≥ 85	229	177	77.3	43	18.8	9	3.9
BMI (kg/m^2)							
< 25.0	1046	782	74.8	233	22.3	31	3.0
≥ 25.0	377	276	73.2	82	21.8	19	5.0
Unknown	1016	748	73.6	227	22.3	41	4.0
Reason for use (multi-count)							
Difficulty falling asleep	1826	1356	74.3	410	22.5	60	3.3
Nocturnal awakening	1222	908	74.3	262	21.4	52	4.3
Early morning awakening	261	190	72.8	59	22.6	12	4.6
Others	22	16	72.7	5	22.7	1	4.5
Duration of insomnia (years)							
< 1	968	756	78.1	189	19.5	23	2.4
≥ 1 to < 10	1124	814	72.4	262	23.3	48	4.3
≥ 10	347	236	68.0	91	26.2	20	5.8
Medical examination[a]							
Psychiatry	689	492	71.4	167	24.2	30	4.4
Internal medicine	1515	1139	75.2	320	21.1	56	3.7
Others	235	175	74.5	55	23.4	5	2.1
Narcolepsy-like events							
No	2344	1746	74.5	513	21.9	85	3.6
Yes	63	43	68.3	16	25.4	4	6.3
Unknown	32	17	53.1	13	40.6	2	6.3
Diagnosis of narcolepsy (including cataplexy)							
No	2404	1784	74.2	531	22.1	89	3.7
Suspected	2	1	50.0	1	50.0	0	0.0
Yes	1	0	0.0	1	100.0	0	0.0
Unknown	32	21	65.6	9	28.1	2	6.3
Respiratory dysfunction							
No	2151	1611	74.9	461	21.4	79	3.7
Yes	102	78	76.5	22	21.6	2	2.0
Unknown	186	117	62.9	59	31.7	10	5.4
Chronic obstructive pulmonary disease (COPD)							
No	2306	1711	74.2	508	22.0	87	3.8
Yes	44	37	84.1	7	15.9	0	0.0
Unknown	89	58	65.2	27	30.3	4	4.5

Table 6 (continued)

Items	Number of patients by characteristic	Improved patients		Unchanged patients		Deteriorated patients	
		N	%	*N*	%	*N*	%
Obstructive sleep apnea (OSA)							
No	2197	1647	75.0	471	21.4	79	3.6
Yes	60	43	71.7	15	25.0	2	3.3
Unknown	182	116	63.7	56	30.8	10	5.5
Severe respiratory dysfunction							
No	2230	1670	74.9	479	21.5	81	3.6
Yes	23	19	82.6	4	17.4	0	0.0
Unknown	186	117	62.9	59	31.7	10	5.4
Hepatic function disorder							
No	2254	1680	74.5	491	21.8	83	3.7
Yes	106	75	70.8	27	25.5	4	3.8
Unknown	79	51	64.6	24	30.4	4	5.1
Severe hepatic function disorder							
No	2356	1752	74.4	517	21.9	87	3.7
Yes	4	3	75.0	1	25.0	0	0.0
Unknown	79	51	64.6	24	30.4	4	5.1
Structural brain disorder							
No	2357	1740	73.8	529	22.4	88	3.7
Yes	82	66	80.5	13	15.9	3	3.7
Psychiatric disorder							
No	1642	1246	75.9	343	20.9	53	3.2
Yes	756	534	70.6	185	24.5	37	4.9
Unknown	41	26	63.4	14	34.1	1	2.4
Schizophrenia							
No	2321	1728	74.5	507	21.8	86	3.7
Yes	76	52	68.4	21	27.6	3	3.9
Unknown	42	26	61.9	14	33.3	2	4.8
Depression							
No	2012	1500	74.6	441	21.9	71	3.5
Yes	386	280	72.5	87	22.5	19	4.9
Unknown	41	26	63.4	14	34.1	1	2.4
Manic-depressive illness							
No	2333	1742	74.7	505	21.6	86	3.7
Yes	64	38	59.4	23	35.9	3	4.7
Unknown	42	26	61.9	14	33.3	2	4.8
Anxiety disorder							
No	2243	1669	74.4	492	21.9	82	3.7
Yes	154	111	72.1	36	23.4	7	4.5
Unknown	42	26	61.9	14	33.3	2	4.8
Dementia							
No	2279	1692	74.2	505	22.2	82	3.6
Yes	118	88	74.6	23	19.5	7	5.9
Unknown	42	26	61.9	14	33.3	2	4.8
Medical history							
No	1875	1398	74.6	413	22.0	64	3.4
Yes	403	286	71.0	98	24.3	19	4.7
Unknown	161	122	75.8	31	19.3	8	5.0

Table 6 (continued)

Items	Number of patients by characteristic	Improved patients		Unchanged patients		Deteriorated patients	
		N	%	*N*	%	*N*	%
Prior medication							
No	1446	1136	78.6	281	19.4	29	2.0
Yes	976	659	67.5	256	26.2	61	6.3
Unknown	17	11	64.7	5	29.4	1	5.9
Concomitant medication							
No	727	572	78.7	136	18.7	19	2.6
Yes	1695	1223	72.2	401	23.7	71	4.2
Unknown	17	11	64.7	5	29.4	1	5.9
Concomitant insomnia medication							
No	1756	1336	76.1	364	20.7	56	3.2
Yes	666	459	68.9	173	26.0	34	5.1
Unknown	17	11	64.7	5	29.4	1	5.9
Initiation status							
Naïve	1446	1136	78.6	281	19.4	29	2.0
Switch	538	344	63.9	151	28.1	43	8.0
Add-on	410	292	71.2	101	24.6	17	4.1
Others	45	34	75.6	9	20.0	2	4.4

Totals will not be 100% due to rounding

BMI body mass index

[a]Psychiatric and psychosomatic medicines are given as 'psychiatry'

Even if the population who were excluded because the initial dose, as stated in the Japanese package insert [4] (adult: 20 mg once daily; elderly: 15 mg once daily), was not administered were included in the analysis, the proportion of patients judged by the physician to be 'improved' (improvement rate) was similar to that already described.

The physician-assessed global improvement rates in patient groups of special interest were as follows:

1. Elderly patients: the improvement rate was 73.3% in those < 65 years. Among elderly patients, improvement rates were 74.5% (≥ 65 years), 75.0% (≥ 75 years), and 77.3% (≥ 85 years).
2. Insomnia symptoms as the reason for using suvorexant: the improvement rates for those patients with difficulty falling asleep, nocturnal awakening, or early morning awakening were 74.3%, 74.3%, and 72.8%, respectively.
3. Duration of insomnia and use of prior drugs for insomnia as well as other concomitant drugs for insomnia: in terms of the duration of insomnia, the improvement rates were 78.1%, 72.4%, and 68.0% for patients whose duration of insomnia was < 1 year, ≥ 1 to < 10 years, and ≥ 10 years, respectively. The improvement rates were 67.5% with prior drug use for insomnia and 78.6% without any prior drug use for insomnia. In terms of whether other concomitant drugs were used for insomnia, the improvement rates were 68.9% with the use of other concomitant drugs and 76.1% without the use of other concomitant drugs.
4. Patients with psychiatric disorders: in terms of having or not having a psychiatric disorder, the improvement rates were 70.6% with a psychiatric disorder and 75.9% without a psychiatric disorder. Regarding the types of psychiatric disorder, the improvement rates in patients with/without schizophrenia were 68.4%/74.5%, with/without depression were 72.5%/74.6%, with/without manic-depressive illness were 59.4%/74.7%, and with/without anxiety disorder were 72.1%/74.4%.

Duration of insomnia, use of concomitant medication, and initiation status of suvorexant were identified as factors that affect physician-judged overall global improvement based on the multivariate logistic regression analysis results (Table 7). The probability of efficacy in patients with a duration of insomnia of less than 1 year was higher than that of patients with a duration of insomnia of ≥ 1 to < 10 years and of ≥ 10 years. On the other hand, the probability of efficacy was lower in patients who used

Table 7 Analysis of factors potentially influencing overall global improvement (physician's assessment) (efficacy analysis population)

Item	*N*	Overall global improvement		Univariate			Multivariate		
		Improved patients	Improvement rate (%)	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value
Overall	2439	1806	74.0						
Sex									
Male	943	686	72.7	1			1		
Female	1496	1120	74.9	1.116	0.928–1.343	0.245	1.126	0.876–1.447	0.355
Age (years)									
< 65	997	731	73.3	1			1		
≥ 65 to < 85	1213	898	74.0	1.037	0.858–1.255	0.705	1.163	0.876–1.543	0.296
≥ 85	229	177	77.3	1.239	0.882–1.739	0.217	1.172	0.720–1.906	0.524
BMI (kg/m^2)									
< 25.0	1046	782	74.8	1			1		
≥ 25.0	377	276	73.2	0.923	0.706–1.205	0.554	0.973	0.736–1.285	0.846
Duration of insomnia (years)									
< 1	968	756	78.1	1			1		
≥ 1 to < 10	1124	814	72.4	0.736	0.602–0.900	0.003	0.741	0.553–0.994	0.045
≥ 10	347	236	68.0	0.596	0.454–0.783	< 0.001	0.600	0.404–0.890	0.011
Schizophrenia									
No	2321	1728	74.5	1			1		
Yes	76	52	68.4	0.743	0.454–1.217	0.238	0.781	0.417–1.464	0.441
Depression									
No	2012	1500	74.6	1			1		
Yes	386	280	72.5	0.902	0.706–1.152	0.407	1.051	0.730–1.512	0.790
Manic-depressive illness									
No	2333	1742	74.7	1			1		
Yes	64	38	59.4	0.495	0.298–0.823	0.007	0.736	0.364–1.490	0.395
Anxiety disorder									
No	2243	1669	74.4	1			1		
Yes	154	111	72.1	0.888	0.617–1.278	0.522	1.405	0.848–2.329	0.187
Dementia									
No	2279	1692	74.2	1			1		
Yes	118	88	74.6	1.018	0.665–1.556	0.936	1.077	0.610–1.904	0.797
Concomitant medication									
No	727	572	78.7	1			1		
Yes	1695	1223	72.2	0.702	0.571–0.864	< 0.001	0.716	0.520–0.987	0.041
Initiation status									
Naïve	1446	1136	78.6	1			1		
Switch	538	344	63.9	0.484	0.390–0.601	< 0.001	0.675	0.496–0.920	0.013
Add-on	410	292	71.2	0.675	0.527–0.865	0.002	0.863	0.603–1.238	0.424

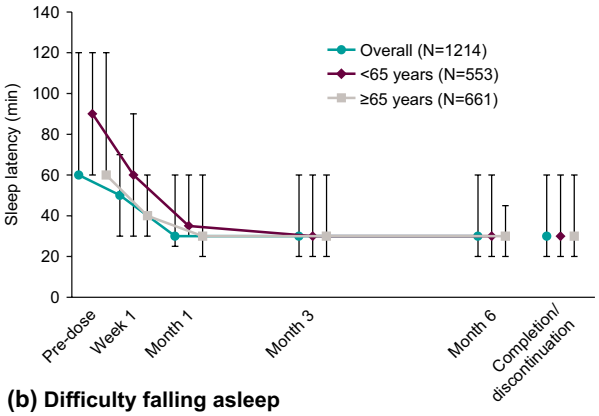
BMI body mass index, *CI* confidence interval

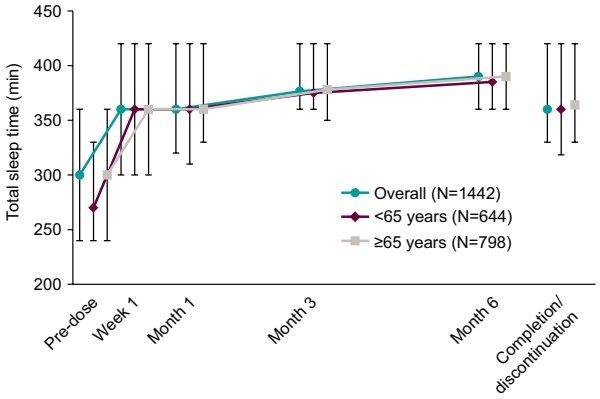
concomitant medications and who switched drugs. Similar results to those described for the physician's judgement were observed in the analysis for overall global improvement judged by the patients.

3.4.2 Sleep Measures

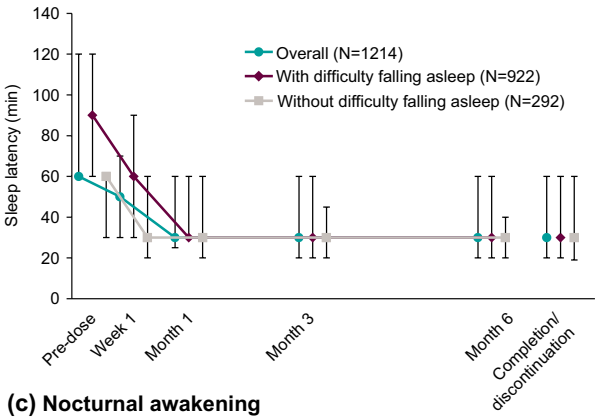
Changes in median sleep latency and total sleep time by age group and reason for using suvorexant are shown in Fig. 3. (Data from physician interviews with/without a patient's sleep diary were used for the analysis.)

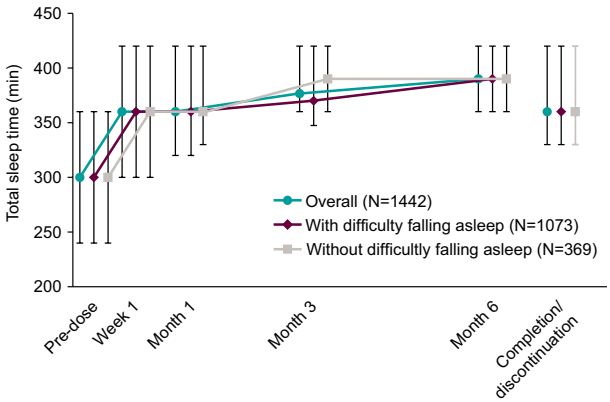
(a) Age group



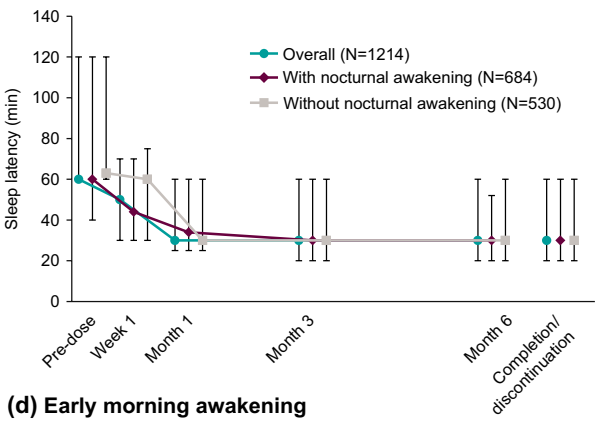


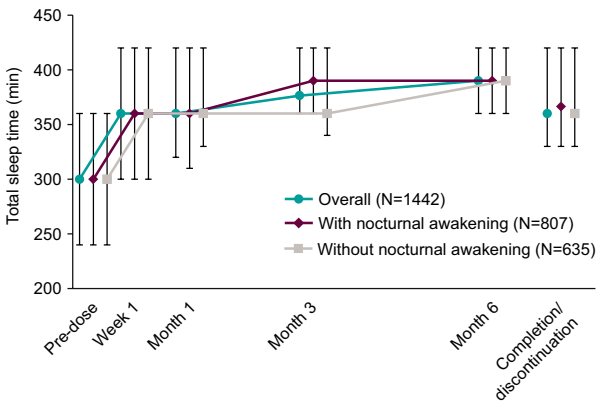
(b) Difficulty falling asleep



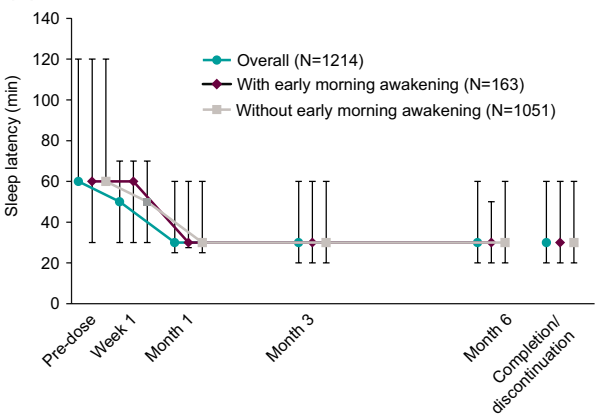


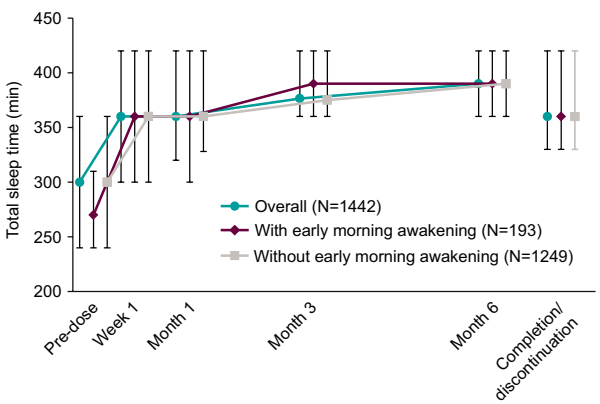
(c) Nocturnal awakening





(d) Early morning awakening





◂**Fig. 3** Change in sleep latency and total sleep time (efficacy analysis population) by **a** age group; **b** difficulty falling asleep; **c** nocturnal awakening; and **d** early morning awakening. Data are presented as median and interquartile range

The median sleep latency was 60 min at pre-dose, 50 min at Week 1, 30 min at Month 1, and this reduction in sleep latency was then maintained up to Month 6. In terms of age groups, reduced sleep latency was observed from Week 1 and was maintained from Month 1 to Month 6 in patients < 65 years and those ≥ 65 years.

The median total sleep time per night changed from 300 min at pre-dose to 360 min at Week 1 and was subsequently maintained at no less than 360 min up to Month 6. In terms of age groups, the median sleep time started lengthening at Week 1, and did not return to the pre-dose value up to Month 6 in patients aged < 65 and ≥ 65 years.

Regarding reasons for using suvorexant, reduction in the median sleep latency was observed at all timepoints in all groups (i.e., patients with difficulty in falling asleep, those with difficulty in falling asleep and early morning awakening, those with difficulty in falling asleep and nocturnal awakening, and those with difficulty in falling asleep, early morning awakening, and nocturnal awakening). Reduced sleep latency was maintained in patients across all reasons for using suvorexant up to Month 6, with no clear differences in changes between the reasons for use. Similarly, lengthening of total sleep time was observed in patients across all reasons for using suvorexant at all observation timepoints and was maintained up to Month 6.

3.5 Continuation Status of Suvorexant in Each Initiation Status Group

The continuation status of suvorexant in each initiation status group is shown in Fig. 4. At 6 months after the start of treatment, 48.6% (1577/3248) of the patients had been continually receiving treatment and 51.4% (1671/3248) had discontinued/dropped out of treatment before 6 months.

Among patients who discontinued or dropped out from treatment, the percentage of patients who discontinued treatment because of improvement was the highest [17.1% (555/3248 patients)]. With respect to the initiation status of suvorexant, the percentage of patients who completed treatment because of improvement was the highest in naïve patients [22.3% (434/1946 patients)]. On the other hand, among switched patients, many discontinued treatment because of inadequate effects [14.9% (105/703 patients)] and adverse event occurrence [13.2% (93/703 patients)].

Among the reasons for discontinuation, the mean duration of treatment was as follows: 61.7 days for improvement in insomnia, 45.2 days for inadequate effects, 30.5 days for no efficacy, 32.2 days for the occurrence of adverse events, 52.3 days for dropout due to no subsequent revisit after the second visit, and 56.9 days for other reasons.

Regarding the initiation of treatment in patients who discontinued treatment due to improvement, the mean duration of treatment was 57.0 days for naïve patients, 79.2 days for switched patients, and 77.2 days for add-on patients.

Moreover, for patients who received add-on treatment, 12.1% (65/536 patients) ended, reduced the number of, or reduced the dose of the prior medications.

4 Discussion

We conducted this survey to evaluate the safety and efficacy of suvorexant use in daily clinical practice in Japan. In this report, data from 3428 patients were collected from 884 medical institutions. Among the safety analysis population, more than half of patients were elderly (31.7% were ≥ 75 years and 8.3% were ≥ 85 years). In addition, this population included patients with a variety of demographic characteristics, such as those with psychiatric disorders and dementia, who were excluded from the clinical trials. These observations suggest that this survey population reflects the conditions of patients in a real-world clinical practice setting. Among the safety analysis population, 59.6% of patients had insomnia for at least 1 year and 14.0% had insomnia for at least 10 years. Although 59.9% of patients were treatment-naïve, many patients received prior medications for insomnia or received other concomitant medications for insomnia.

Regarding safety, the incidence rate of adverse drug reactions was 9.7% (serious adverse drug reactions: 0.2%) and the common adverse drug reactions were somnolence, insomnia, dizziness, and nightmare, all of which are included the product label [4]. In terms of outcomes, > 90% of patients were recovered or recovering. In total, 8.0% of patients in the survey discontinued the use of suvorexant due to adverse events, although some patients continued the use of suvorexant after adverse drug reactions and their adverse drug reactions and were resolved and resolving. The relatively high proportion of patients who discontinued suvorexant after adverse events (8.0%) compared with the overall incidence rate of adverse drug reactions (9.7%) may indicate than in a survey setting patients tend to report adverse drug reactions that are significant for them. In the suvorexant clinical trials, more patients reported adverse drug reactions (46.5%) but relatively few discontinued due to them (3.0%) [6]. While insomnia is not specified as an adverse drug reaction in the Japanese package insert, insomnia is the indication for use of suvorexant, and these reports may well reflect insufficient efficacy in some patients. Regarding somnolence, which was intensively investigated in the current survey and is the most commonly occurring adverse

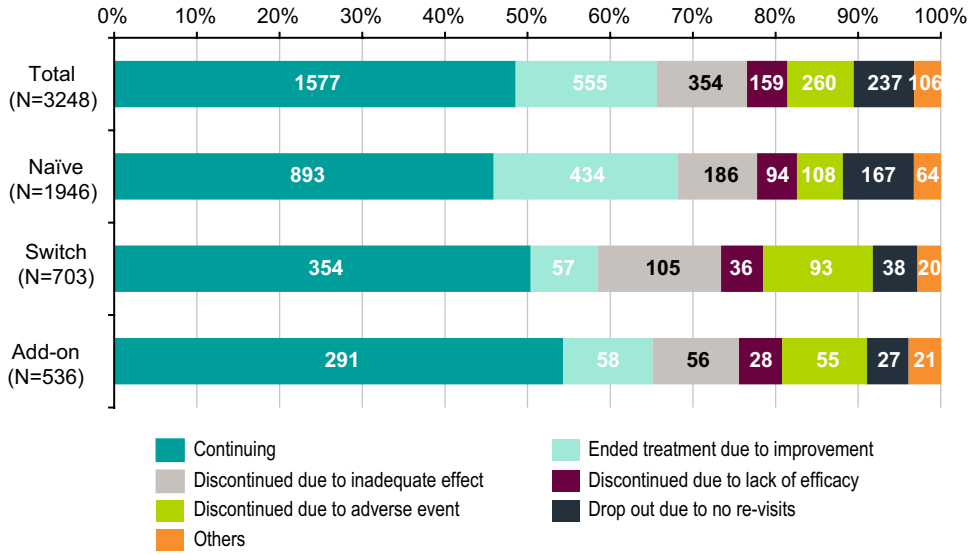


Fig. 4 Continuation status of suvorexant (safety analysis population). "Total" includes 63 patients in the "Others" category of Table 1

drug reaction, multivariate logistic regression analysis was conducted to identify the demographic characteristics that affect the occurrence of such reactions. As a result, the use of concomitant medications and the duration of insomnia were identified as factors. We did not analyze the effects of different types of concomitant medications, but, given that 27% of patients were using insomnia treatments other than suvorexant, it is possible that concomitant administration of these and other CNS-suppressant drugs (such as antidepressants) influenced the occurrence of somnolence. Additionally, it is possible that many refractory insomnia patients were included in the survey population with a longer duration of insomnia; this could have lowered the occurrence of somnolence in these patients.

Regarding adverse drug reactions that necessitated evaluation in the PDMA review report [5] or were stated in the Japanese package insert [4], two patients experienced adverse drug reactions that were reported to affect potentially hazardous machinery operation (e.g., driving); narcolepsy-like events occurred in five patients with sleep paralysis, two with falls, and one with hypnagogic hallucination; parasomnia, abnormal sleep-related events, and sleepwalking occurred in 27 patients with nightmare, seven with abnormal dreams, one with REM sleep abnormality, and one with sleep talking; and suicidal ideation occurred in one patient. More than 80% of the outcomes of those adverse drug reactions were recovering or recovered. No adverse drug reactions related to suicidal behavior and dependency were observed.

The influence of demographic characteristics was assessed for narcolepsy (including cataplexy) patients, elderly patients, patients with respiratory dysfunction, and patients with psychiatric disorder.

There were no adverse drug reactions in the only patient who was diagnosed with narcolepsy prior to suvorexant treatment. On the other hand, a non-serious adverse drug reaction occurred in one of four patients who were suspected of having narcolepsy. The Japanese package insert of suvorexant states that suvorexant should be administered with caution in patients with narcolepsy or cataplexy [4]. However, the occurrence or aggravation of narcolepsy as a result of administration of suvorexant was not reported in the patients in the current survey.

The incidence rate of adverse drug reactions in latter-stage elderly patients aged ≥ 75 years was 8.2%, which was lower than the incidence rates in patients under the age of 65 years and those aged between 65 and 74 years (11.3% and 8.6%, respectively). Although no safety concern regarding elderly patients was identified in the clinical trial, the Japanese package insert states that suvorexant should be administered with caution in elderly patients due to the fact that elderly individuals generally have deteriorated physiological functions [4]. However, elderly patients did not exhibit a high incidence rate of adverse drug reactions in this survey.

In phase I clinical trials of suvorexant, no obvious safety issue on respiratory function was observed in patients with mild to moderate COPD or OSA [8, 9], and no adverse drug reaction related to respiratory depression was observed in this survey, even though some patients with severe COPD or OSA were included.

The incidence rate of adverse drug reactions in patients with psychiatric disorder(s) was almost two times the rate reported in patients without psychiatric disorder(s) (14.3% vs. 7.6%, respectively). Among patients with a psychiatric disorder and experiencing an adverse drug reaction, the

majority (86.1%) were taking other CNS-active medications, as compared to those with a psychiatric disorder and not taking these medications (13.9%). Note that the Japanese package insert states that suvorexant should be used with careful administration in patients concomitantly taking CNS depressants [4].

Multivariate logistic regression results did not detect diagnoses of schizophrenia, depression, manic-depressive illness, and anxiety disorder as risk factors for somnolence, which occurred at the highest rate in patients.

Based on these results, we conclude that the occurrence of adverse drug reactions in daily clinical practice was similar to that observed in clinical trials and that no additional noteworthy findings in terms of the safety of suvorexant have been observed thus far.

In the efficacy assessment, the 'improved' rate based on the judgement by the physician and patient were 74.0% and 73.2%, respectively, which was not clinically or significantly different. We also evaluated subgroups of special interest, including elderly patients, reason for using suvorexant, duration of insomnia, use of prior drugs and concomitant drugs for insomnia, and patients with psychiatric disorders.

In terms of age group, the improvement rates were 74.5% (aged ≥ 65 years), 75.0% (aged ≥ 75 years), and 77.3% (aged ≥ 85 years). These values were not significantly different from the improvement rate of the entire population (74.0%).

In terms of reason for using suvorexant, the improvement rates were not significantly different among patients with difficulty in falling asleep, those with nocturnal awakening, and those with early morning awakening. The consistent improvement rate was observed irrespective of the symptoms of insomnia.

Patients with longer durations of insomnia, those using prior drugs for insomnia, and those using other concomitant drugs for insomnia showed a tendency to have lower improvement rates. We speculate that these populations included patients with refractory insomnia, leading to the low improvement rate.

Regarding patients with/without psychiatric disorder(s), the improvement rate was lower in patients with psychiatric disorder(s) (70.6%) than those without psychiatric disorder(s) (75.9%). As a potential reason for this observation, it is speculated that many refractory insomnia patients were included in patients with psychiatric disorder(s); in fact, the proportions of patients with ≥ 10 years' duration of insomnia, those using prior drugs, and those using concomitant drugs for insomnia were higher in patients with psychiatric disorder(s) than those without psychiatric disorder(s) (20.9% (158/756 patients) vs. 11.3% (186/1642 patients), 58.1% (439/756 patients) vs. 32.2% (528/1642 patients), and 44.2% (334/756 patients) vs. 19.8% (325/1642 patients), respectively).

Multivariate logistic regression was performed, considering confounding factors that could affect overall global improvement. The probability of efficacy was higher in patients with a duration of insomnia of < 1 year than in those with a longer duration (≥ 1 to < 10 years or ≥ 10 years). In addition, the probability of efficacy was lower in patients who used concomitant medications and who switched treatment. On the other hand, specific psychiatric disorders (schizophrenia, depression, manic-depressive illness, and anxiety disorder) and dementia were not detected as factors that affect overall global improvement.

Patients who had been recently diagnosed with insomnia have the tendency to improve following treatment with suvorexant. On the other hand, the improvement rate was lower in patients with a longer duration of insomnia or those treated with concomitant medications, probably because many of these patients had refractory insomnia with a prolonged symptom. Regarding switched patients, they discontinued or reduced the amount of prior medication before the initiation of suvorexant; therefore, the total number of anti-insomnia drugs after initiation of suvorexant was likely the same or decreased. For naïve patients and those receiving add-on treatment, the total number of anti-insomnia drugs was increased. Such a change in the number of drugs could have led to a difference in overall global improvement between switched patients, add-on patients, and naïve patients.

Regarding clinical effects, reduction in median sleep latency and lengthening of median total sleep time were observed in both non-elderly and elderly patients after the start of treatment. Similar results were observed in the analysis focusing on reasons for using suvorexant. Efficacy was confirmed regardless of age and reason for use, showing consistency in the results of assessment by the physician and the patients.

Regarding the continuation status of suvorexant in each initiation status group, the proportion of patients who discontinued or dropped out from treatment before 6 months was 51.4%. We confirmed that 33.2% (555/1671 patients) of these patients discontinued treatment because of improvement. With respect to initiation status of suvorexant, the percentage of patients who discontinued treatment because of improvement was particularly high for naïve patients (41.2% of naïve patients that discontinued or dropped out from treatment).

According to Japanese treatment guidelines [1], patients should reduce the amount of hypnotics or cease treatment as immediately as possible after remission from insomnia. In

this survey, we observed patients who completed insomnia treatment and those who were able to reduce the amount of concomitant drugs for insomnia. This suggests that treatment with suvorexant may be helpful for reduction or cessation of such drugs.

The authors acknowledge several limitations regarding the study. Notably, this survey was an exploratory observational study without a control group. In addition, it is possible there were many confounding factors such as variations in the demographic characteristics, baseline characteristics of insomnia, existence of co-morbidities, and use of concomitant drugs. Thus, the interpretation of our results may require consideration.

5 Conclusions

In this postmarketing survey study of suvorexant use in Japan, no new safety concerns were identified. In addition, an improvement rate of 74.0% was achieved by a population with more diverse demographic characteristics than that assessed in previous clinical trials [6, 7]. Reduction in sleep latency and lengthening of total sleep time were also observed after 1 week of treatment, and the effect was maintained for 6 months. Thus, these data support the use of suvorexant in daily clinical practice for treating insomnia.

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Compliance with Ethical Standards

Conflict of interest Yuko Asai, Hideki Sano, Makoto Miyazaki, Mika Iwakura, Yoshikazu Maeda, and Mitsuyoshi Hara are employees of MSD K.K., Tokyo, Japan.

Reference

1. MHLW (Ministry of Health, Labour and Welfare) Comprehensive Research Project on Scientific Research/Countermeasures Concerning Persons with disabilities "Study group on clinical guidelines for proper use and dosage decrease/discontinuation of hypnotics" and The Japanese Society of Sleep Research/Working group for formulating guidelines on hypnotics use version, Clinical Guidelines for Proper Use and Withdrawal of Hypnotics; 2013 **(in Japanese)**. http://www.jssr.jp/data/pdf/suiminyaku-guideline.pdf. Accessed 23 Nov 2017.
2. MSD K.K. Belsomra tablets interview form. Revised November 2016. 6th ed. Tokyo: MSD K.K.; 2016 **(in Japanese)**. http://www.info.pmda.go.jp/go/interview/1/170050_1190023F1024_1_007_1F. Accessed 28 Nov 2018.
3. Asai Y, Miyazaki M, Iwakura M, Hara M. The interim report about the drug use—results survey of orexinergic receptor antagonist, Belsomra, in patients with insomnia. Jpn J Sleep Med. 2017;11(2):249–63.
4. MSD K.K. Belsomra tablets package insert. Revised November 2016. 5th ed. Tokyo: MSD K.K.; 2016 **(in Japanese)**. http://www.info.pmda.go.jp/downfiles/ph/PDF/170050_1190023F1024_1_11.pdf. Accessed 28 Nov 2018.
5. Pharmaceuticals and Medical Devices Agency. Belsomra tablets 15 mg and 20 mg Review Report. Tokyo: MSD K.K.; 14 Sep 2014 **(in Japanese)**. http://www.pmda.go.jp/drugs/2014/P201400117/170050000_22600AMX01302_A100_4.pdf. Accessed 28 Nov 2018.
6. Herring WJ, Connor KM, Ivgy-May N, Snyder E, Liu K, Snavely DB, et al. Suvorexant in patients with insomnia: Results from two 3-month randomized controlled clinical trials. Biol Psychiatry. 2016;79(2):136–48. https://doi.org/10.1016/j.biopsych.2014.10.003.
7. Uchimura N, Hisada S, Takahashi K, Tsumori K, Shimamoto T, Herring WJ. Evaluation of efficacy and safety of suvorexant, an orexin receptor antagonist, in patients with insomnia as a primary disease—comparison of Japanese and overall population/non Japanese multiregional clinical trial III randomized, double-blind, placebo-controlled trial on efficacy. Jpn J Sleep Med. 2015;9(3):395–411.
8. Sun H, Palcza J, Rosenberg R, Kryger M, Siringhaus T, Rowe J, et al. Effects of suvorexant, an orexin receptor antagonist, on breathing during sleep in patients with chronic obstructive pulmonary disease. Respir Med. 2015;109(3):416–26. https://doi.org/10.1016/j.rmed.2014.12.010.
9. Sun H, Palcza J, Card D, Gipson A, Rosenberg R, Kryger M, et al. Effects of suvorexant, an orexin receptor antagonist, on respiration during sleep in patients with obstructive sleep apnea. J Clin Sleep Med. 2016;12(1):9–17. https://doi.org/10.5664/jcsm.5382.