Prevalence of and Factors Associated With Sleep-Related Eating Disorder in Psychiatric Outpatients Taking Hypnotics

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ABSTRACT

Objective: To clarify the prevalence and clinical features of sleep-related eating disorder (SRED) in psychiatric outpatients taking hypnotics as well as factors associated with the disorder.

Methods: From February 1, 2012, to February 29, 2012, a cross-sectional study was undertaken. A questionnaire addressing demographics, the Japanese version of the Pittsburgh Sleep Quality Index (PSQI), presence of abnormal behavior during sleep focusing on SRED and sleepwalking, and duration of hypnotic medication and subjective side effects of the drug was distributed to psychiatric outpatients who were taking hypnotics at the time of the survey.

Results: Of 1,318 patients taking hypnotics, 1,048 patients (79.5%) provided valid responses, and 88 of them (8.4%) had experienced SRED. The SRED group was significantly younger, had a significantly higher total PSQI score, and took higher bedtime diazepam-equivalent doses of hypnotics than the non-SRED group ($P < .01$ for all comparisons). In the SRED group, subjective side effects due to hypnotics were present at significantly higher proportions than in the non-SRED group. Multiple logistic regression analysis showed that younger age (adjusted odds ratio [aOR] = 0.98, 95% CI = 0.96–0.99, $P = .021$), taking 2 or more kinds of antipsychotics (aOR = 3.41, 95% CI = 1.93–6.05, $P < .001$), and the bedtime diazepam-equivalent dose of a hypnotic (aOR = 1.03, 95% CI = 1.01–1.05, $P = .039$) were significantly associated with the experience of SRED.

Conclusion: The prevalence of SRED in psychiatric outpatients taking hypnotics is elevated, particularly in younger patients, and the hypnosedative effects of the drugs could be responsible for the occurrence of the disorder in this population.

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Sleep-related eating disorder (SRED) is a condition presenting with abnormal eating and drinking behaviors typically in a partially-fully unconscious state at the transition from non–rapid eye movement sleep to arousal during nocturnal sleep.[1] This disorder is classified as a parasomnia in the third edition of the International Classification of Sleep Disorders (ICSD).[2] Because only 2 decades have passed since the disease concept of SRED was established, awareness of this disorder has remained low not only in the general population, but also among physicians including psychiatrists. Given this situation, certain cases of SRED have been misdiagnosed as bulimia nervosa having binge-eating episodes that are exacerbated mostly near the middle of the night.[3,4]

Generally, episodes of SRED appear most commonly in the first half of nocturnal sleep (within about 1 to 3 hours after falling asleep), and food uncontrollably ingested during an episode primarily contains a great amount of fat and carbohydrates.[1,5] Body weights of patients are likely to be increased owing to SRED, and they may feel abdominal bloating in the morning with anorexia as a result of the abnormal nighttime eating behavior. Some patients also may develop depressive symptoms due to self-disgust over these eating behaviors.[5,6] Considering these adverse effects on daily life, establishment of an accurate diagnosis of SRED, possible promoting factors, and adequate treatment, as well as preventive measures, appear to be important issues.

Reportedly, 60%–84% of individuals affected with SRED are female,[3] and this female predominance is quite similar to the trend for the prevalence of daytime eating disorders in general. It is possible, therefore, that a female-specific psychological or physical basis could be involved in the mechanism of SRED, as is the case with daytime eating disorders. The onset of SRED is mostly in adolescence or young adulthood.[3] The prevalence rate of SRED in the general population has been reported to be about 1%,[1] but the rate was as high as 4.6% in a survey of 217 students in a university extension school in the United States.[7] Taking these factors into consideration, SRED could be considered a condition most likely to occur in young female patients.

Some reports have shown that the prevalence of SRED among individuals with mental illness is higher than that in the general population.[6,8] As for the reason for this phenomenon, not only the impact of the symptoms of mental illness, but also the effects of any psychotropic drugs being taken need to be considered. In particular, with the belief that previously reported cases of SRED were mostly common in people taking zolpidem,[9–11] an ultrashort-acting benzodiazepine agonist hypnotic, it appears quite likely that administration of hypnotics contributes to the appearance of SRED. However, conclusive information about the prevalence and risk factors of the occurrence of SRED in the population of psychiatric patients taking hypnotics has not yet been reported.[8,12]

In order to clarify these issues, we conducted a cross-sectional epidemiologic study on SRED in psychiatric outpatients regularly taking hypnotics. In the present study, we investigated the prevalence

Clinical Points

- Information about the prevalence and risk factors for the occurrence of SRED in the population of psychiatric patients taking hypnotics has not yet been reported.
- The prevalence rate of SRED in this population was 8.4%, which is thought to be higher than that in the general population. Younger age and usage of multiple hypnotics and antipsychotics were associated with the experience of SRED.
- Multiple kinds of hypnotics and antipsychotics should be used cautiously to prevent the presence of SRED.

and symptomatic characteristics of SRED and relevant factors contributing to the presence of SRED in this population.

METHODS

The present study was performed as a part of a survey of the current status of side effects due to hypnotics among patients in the outpatient clinic of Tokyo Medical University. We started the survey after obtaining approval of the Ethics Committee of Tokyo Medical University Hospital. When conducting this survey, attending psychiatrists fully explained the main purpose of the study to eligible patients and obtained written informed consent from all the participants.

In this study, to compare the prevalence rate of SRED between patients taking or not taking benzodiazepine hypnotics at the time of the survey, a self-administered questionnaire was distributed to 1,971 patients who visited the Mental Health Department of Tokyo Medical University Hospital as outpatients between February 1, 2012, and February 29, 2012. Of these cases, 431 patients were excluded from the subsequent analyses because their responses were either not obtained or not valid. Consequently, 1,540 patients with valid responses were included in the analyses.

Considering the likely comorbidity of SRED and sleepwalking,[13] questions about recurrent episodes of the presence of the following abnormal behaviors were asked: eating something or preparing a meal while asleep and sleepwalking or sitting up while still asleep.[14] When we made this a questionnaire item, we referred to Munich Parasomnia Screening[15] and the criteria item for SRED on ICSD-3.[2] We inquired about the frequency of these behaviors, categorized as "very often," "sometimes," "occasionally," and "no." These abnormal behaviors during sleep were categorized as "present" if the participant answered with "very often," "sometimes," or "occasionally." Persons screening positive for SRED were also asked to provide answers about the time period in which SRED episodes were likely to occur (roughly how many hours after sleep onset).

Subsequently, patients who were taking benzodiazepines at the time of the survey were asked to answer a questionnaire to clarify associated factors of SRED in psychiatric outpatients taking hypnotics. Nightly users of hypnotics were defined as "taking hypnotics." Finally, 1,048 patients (response rate: 79.5%) were included in the analysis.

The self-reported questionnaire items used for the present study included age, sex, height and weight, presence of cohabitating family, presence of rotating shift work, educational degree (university graduation or otherwise), and other demographic background items, as well as an assessment of sleep difficulty using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI).[16,17] The PSQI comprises 7 items as follows: C1 (sleep quality), C2 (sleep latency), C3 (sleep duration), C4 (sleep efficiency), C5 (sleep disturbances), C6 (use of sleep medication), and C7 (daytime dysfunction) and a total score. A total score of 5.5 points is the cutoff point for having sleep difficulty.[16,17] The validity and reliability of the Japanese version of PSQI were previously established.[17] The items for duration of hypnotics medication (less than 1 month, 1 to less than 6 months, 6 months to less than 1 year, 1 to less than 5 years, and 5 years or longer) and usual timing of the medication were also set, as were the items for presence of bedtime alcohol ingestion and presence of common subjective side effect symptoms of hypnotics (dizziness, fatigue, sleepiness, amnesia, and headache).[18]

Mental illness diagnoses (schizophrenia, depression, bipolar disorder, anxiety disorders, and others) based on the *Diagnostic and Statistical Manual of Mental Disorders, Text Revision* (*DSM-IV-TR*) were collected for each case from the attending physician, and information about the currently prescribed psychotropics (antipsychotics, antidepressants, and benzodiazepines) was collected from the database of the institution's medical care system. Among the study participants, there were no patients having drug dependence.

A χ^2 test was used to compare the prevalence of SRED between patients who were taking benzodiazepine hypnotics or not. Subsequently, patients who were taking benzodiazepine hypnotics were allocated into 2 groups, those screening positive for SRED and those screening negative for SRED (NSRED). A χ^2 test was used to compare the 2 groups in terms of sex, presence of cohabitating family, educational degree, presence of shift work, presence of bedtime alcohol drinking habit, and categories of psychiatric diagnoses. A χ^2 test followed by residual analysis was used to compare the number of participants taking hypnotics with different half-lives (individuals taking ultrashort-acting, short-acting, intermediate-acting, long-acting, and 2 or more kinds of hypnotics) and to compare the number taking each type of antipsychotic (individuals not taking antipsychotics, those taking first-generation antipsychotics, those taking second-generation antipsychotics, and individuals taking 2 or more kinds of antipsychotics) among the groups with and without SRED. Similarly, continuous variables such as age, degree of obesity manifested as body mass index (BMI), total score of the PSQI, and diazepam-equivalent daily doses of hypnotics[19] being taken were compared between the 2 SRED/NSRED groups using a *t* test. Regarding the presence of subjective side effects due to hypnotics, the participants were divided into the following 2 categories: "very often" or "sometimes" was categorized as positive for each symptom, and "rarely" or "never" as negative for the symptom. The

Table 1. Comparison of Demographic Variables Between the Participants With and Without SRED

Variable	Total Participants (N = 1,048)	Participants With SRED (n = 88)	Participants Without SRED (n = 960)	*P* Value
Age at the time of investigation (y)[a]	51.1 ± 16.1	46.4 ± 12.3	51.4 ± 15.1	.001[b]
Sex (male/female)	525/523	37 (42.0%)/51 (58.0%)	488 (50.8%)/472 (49.2%)	.120[c]
BMI (kg/m^2)[a]	23.0 ± 4.3	24.0 ± 5.1	23.1 ± 4.3	.210[b]
Living alone (yes/no)	788/254	60 (68.2%)/27 (30.7%)	728 (75.8%)/227(23.6%)	.151[c]
Educational history (college education/no)	463/562	28 (31.8%)/60 (68.2%)	435 (45.3%)/612 (63.8%)	.085[c]
Shift work (yes/no)	110/896	13 (14.8%)/71 (80.7%)	97 (10.1%)/825 (92.1%)	.198[c]
Alcohol drinking habit (yes/no)	43/932	2 (2.3%)/83 (94.3%)	41 (4.3%)/849 (91.1%)	.241[c]

[a]Values are expressed as mean ± SD.
[b]Student *t* test was used for the comparison of continuous variables.
[c]χ^2 test was used for the comparison of categorical variables.
Abbreviations: BMI = body mass index, SRED = sleep-related eating disorder.

percentages of the number of participants positive for subjective side effect symptoms were compared between the SRED/NSRED groups by the χ^2 test.

Next, using the presence of SRED as a dependent variable, associated factors were investigated through logistic regression analyses. In the analyses, age, sex, BMI, educational degree, presence of shift work, presence of cohabitating family, presence of alcohol drinking habit at bedtime, diagnoses of psychiatric disorders based on the *DSM-IV-TR*, presence of taking antipsychotics, antidepressants or antiepileptics, and diazepam-equivalent doses of hypnotics were put into a univariate or multivariate model as independent variables. In the series of logistic regression analyses, variables that showed significant association in univariate analyses were put into a multivariate model. SPSS version 11.5 (SPSS Inc, Tokyo, Japan) was used for all the statistical analyses. Significance level was set at $P < .05$.

RESULTS

Of the 1,048 participants who were taking benzodiazepine hypnotics, 88 patients (8.4%) responded with "very often," "sometimes," or "occasionally" regarding "I either eat something or cook something while still asleep" (SRED group), and 960 patients (91.6%) had no SRED (NSRED group). Of the 492 patients who were not taking benzodiazepine hypnotics, 16 patients (3.3%) responded with "very often," "sometimes," or "occasionally" regarding "I either eat something or cook something while still asleep," and 492 (96.7%) patients had no SRED. The rate of SRED in patients who were taking hypnotics was significantly higher than that in patients who were not taking hypnotics ($P < .001$).

In the subsequent analysis of patients who were taking hypnotics, the SRED group had a significantly lower age than the NSRED group ($P = .001$). The SRED group also had a significantly higher total score of the PSQI ($P < .001$) and significantly higher diazepam-equivalent doses of hypnotics ($P = .001$).

Between the groups with and without SRED, there was a significant difference in the rate of individuals taking respective hypnotics by half-life categories ($P < .001$). Residual analysis revealed that the rate of individuals taking 2 or more kinds of hypnotics was significantly higher in the SRED group ($P < .05$). Compared with the NSRED group, the SRED group also had a significantly higher proportion of those taking multiple kinds of hypnotics. The breakdown of drugs used among the 39 persons with SRED who were taking a single kind of hypnotic was as follows: zolpidem (n = 7, 17.9%), zopiclone (n = 3, 7.7%), triazolam (n = 3, 7.7%), brotizolam (n = 5, 12.8%), etizolam (n = 6, 15.4%), lormetazepam (n = 3, 7.7%), nitrazepam (n = 5, 12.8%), and flunitrazepam (n = 7, 17.9%). Regarding concurrent medication, there was a significant difference in the rate of individuals having SRED among the groups with respective types of antipsychotic users ($P < .001$). Residual analysis revealed that the rate of individuals having SRED in the group without antipsychotic medication was significantly lower ($P < .05$) and that the rate was significantly higher in the group with medication of 2 or more kinds of antipsychotics ($P < .01$). No significant differences were noted between the SRED/NSRED groups in terms of gender distribution, BMI, proportion of those living alone, educational history, presence of shift work, presence of bedtime alcohol drinking, distribution of psychiatric diagnoses, or the number of individuals with combined use of antidepressants or antiepileptics (Tables 1 and 2).

In the SRED group, the frequency of SRED behavior was "very often" for 13 cases (14.8%), "sometimes" for 26 cases (29.5%), and "occasionally" for 49 cases (55.7%). As for the nocturnal distribution of the behavior episodes, 33 patients (37.5%) answered that SRED occurred during the first half of sleep, 15 (17.0%) during the second half of sleep, and the answer of "unknown" was reported by 40 (45.5%). Forty-two patients (47.7%) affirmed having sleepwalking symptoms other than eating behaviors.

The percentages of individuals who answered having each of the hypnotic drug side effects (dizziness, fatigue, sleepiness, amnesia, and headache) "very often" or "sometimes" were compared between the SRED and NSRED groups (Table 3). Compared with the NSRED group, the SRED group had higher percentages of positive responses for all the subjective side effects.

Univariate analysis on the associated factors of SRED revealed that younger age (odds ratio [OR] = 0.98; 95% CI, 0.96–0.99; $P = .003$), taking 2 or more kinds of antipsychotics (OR = 4.60; 95% CI, 2.69–7.85; $P < .001$), and larger diazepam-equivalent daily doses of hypnotics (OR = 1.04; 95% CI,

Table 2. Comparison of Clinical Descriptive Variables Between Participants With and Without SRED

Variable	Total Participants (N = 1,048)	Participants With SRED (n = 88)	Participants Without SRED (n = 960)	*P* Value
Psychiatric diagnosis				.259[a]
Schizophrenia	224	26 (29.5%)	198 (20.6%)	
Major depression	409	32 (36.4%)	377 (39.3%)	
Bipolar disorder	81	6 (6.8%)	75 (7.8%)	
Anxiety disorder	158	10 (11.4%)	148 (15.4%)	
Others	174	14 (15.9%)	160 (16.7%)	
PSQI total score (points)[b]	8.5 ± 4.0	11.9 ± 3.8	8.3 ± 3.9	< .001[c]
Benzodiazepine dose (mg)[b,d]	10.9 ± 9.0	13.7 ± 10.4	10.3 ± 8.9	.001[c]
Half-life categories of hypnotics				< .001[a]
Ultrashort-acting	138	12 (13.6%)	146 (15.2%)	
Short-acting	231	12 (13.6%)	219 (22.8%)	
Intermediate-acting	158	13 (14.8%)	120 (12.5%)	
Long-acting	3	0 (0%)	3 (0.3%)	
Two kinds or more	438	49 (55.7%)*	389 (40.5%)	
Combination use of other psychotropic drugs				
Antipsychotic drugs				< .001[a]
No user	632	37 (42.0%)	595 (62.0%)*	
FGA	119	9 (10.2%)	110 (11.5%)	
SGA	171	14 (15.9%)	157 (16.4%)	
Two kinds or more	126	28 (31.8%)**	98 (10.2%)	
Antidepressants (yes/no)	589/459	49 (55.7%)/39 (44.3%)	540 (56.3%)/420 (43.8%)	.502[a]
Antiepiletics (yes/no)	171/877	19 (21.6%)/69 (78.4%)	152 (15.8%)/808 (84.2%)	.108[a]

[a]χ^2 test was used for the comparison of categorical variables.
[b]Values are expressed as mean ± SD.
[c]Student *t* test was used for the comparison of continuous variables.
[d]Benzodiazepine dose = mean dose in mg diazepam-equivalent doses.
*$P < .05$.
**$P < .01$.
Abbreviations: FGA = first-generation antipsychotic, PSQI = Pittsburgh Sleep Quality Index, SGA = second-generation antipsychotic, SRED = sleep-related eating disorder.

Table 3. Comparison of the Number of Participants in Each Category for Subjective Side Effects due to Benzodiazepines[a]

Side Effect	Total Participants (N = 1,048)	Participants With SRED (n = 88)	Participants Without SRED (n = 960)	*P* Value
Dizziness (yes/no)	154/782	29 (33.0%)/52 (59.1%)	125 (13.0%)/730 (76.0%)	<.001[b]
Fatigue (yes/no)	341/608	47 (53.4%)/37 (42.0%)	294 (30.1%)/571 (59.5%)	<.001[b]
Sleepiness (yes/no)	360/584	46 (52.3%)/39 (44.3%)	314 (32.7%)/545 (56.8%)	<.001[b]
Amnesia (yes/no)	112/835	33 (37.5%)/51 (58.0%)	79 (8.2%)/784 (81.7%)	<.001[b]
Headache (yes/no)	145/804	21 (23.9%)/64 (72.7%)	122 (12.7%)/740 (77.1%)	.004[b]

[a]Answers "always" and "sometimes" were categorized as "yes"; "rarely" and "no" were categorized as "no."
[b]The χ^2 test was used for the comparison of categorical variables.
Abbreviation: SRED = sleep-related eating disorder.

1.02–1.06; $P < .001$) were significantly associated with the presence of SRED. When these items were modeled as independent variables in a multivariate regression analysis, the results showed that having a younger age (adjusted OR [aOR] = 0.98; 95% CI, 0.96–0.99; $P = .021$), taking 2 or more kinds of antipsychotics (aOR = 3.41; 95% CI, 1.93–6.05; $P < .001$), and larger diazepam-equivalent daily doses of hypnotics (aOR = 1.03; 95% CI, 1.01–1.05; $P = .039$) appeared as factors significantly associated with the disorder (Table 4).

DISCUSSION

In the present study, the prevalence rate of SRED in the psychiatric outpatient population taking hypnotics was 8.4%, which is quite comparable to the rate reported by Hwang et al[12] in an epidemiologic study targeting a similar population in Taiwan. The prevalence of SRED in psychiatric outpatients taking sedative hypnotics may be higher than that in the general population[7] despite the lack of a control/nonpsychiatric cohort in the present study.

Among the psychiatric patients with SRED in the present study, 40% or more experienced symptoms at least once weekly; 14.8% experienced symptoms daily. Several reports have shown that cases with SRED have complications or have a history of sleepwalking.[13] A previous study suggested that there were several clinical commonalities, such as a past history of sleepwalking, a similar timing of parasomnia episode particularly during the first half of the night, numerous arousals from stage N3 sleep, a similarly altered level of daytime sleepiness, and anxiety symptoms, between SRED and sleepwalking.[20] In the present study, more than 40% of the cases with SRED also answered that they had other somnambulistic symptoms. This finding supports the idea that sleepwalking and SRED share a common pathophysiology including disordered sleep-awake transition even in psychiatric patients taking hypnotics.

Table 4. Logistic Regression Analysis on the Associated Factors for the Presence of SRED

Variable	Univariate Odds Ratio (95% CI)[a]	*P* Value	Multivariate Adjusted Odds Ratio (95% CI)[a]	*P* Value
Age at the time of investigation (y)	0.98 (0.96–0.99)	.003	0.98 (0.96–0.99)	.021
Sex (male: female)	Male: (ref)			
	1.43 (0.92–2.22)	.116		
BMI (kg/m^2)	1.05 (1.00–1.01)	.065		
Educational history (college education: no)	No: (ref)			
	0.56 (0.13–2.35)	.065		
Engaged in shift work (yes: no)	No: (ref)			
	0.64 (0.34–1.20)	.167		
Living alone (yes: no)	No: (ref)			
	1.44 (0.90–2.33)	.133		
Alcohol drinking habit (yes: no)	No: (ref)			
	0.53 (0.19–1.48)	.226		
Psychiatric diagnoses				
Schizophrenia	Schizophrenia: (ref)			
Major depression	0.65 (0.38–1.12)	.117		
Bipolar disorder	0.61 (0.24–1.54)	.295		
Anxiety	0.52 (0.24–1.10)	.087		
Others	0.67 (0.34–1.32)	.244		
Combination use of other psychotic drugs				
Antipsychotic drugs (yes: no)	No: (ref)			
FGA	1.32 (0.62–2.80)	.477		
SGA	1.43 (0.76–2.72)	.522		
Two kinds or more	4.60 (2.69–7.85)	< .001	3.41 (1.93–6.05)	< .001
Antidepressants (yes: no)	No: (ref)			
	0.98 (0.63–1.52)	.918		
Antiepileptics (yes: no)	No: (ref)			
	1.46 (0.86–2.5)	.164		
Diazepam-equivalent dose (mg)	1.04 (1.02–1.06)	< .001	1.03 (1.01–1.05)	.039

[a]Relative risks approximated with odds ratios.
Abbreviations: BMI = body mass index, CI = confidence interval, FGA = first-generation antipsychotic, PSQI = Pittsburgh Sleep Quality Index, SGA = second-generation antipsychotic, SRED = sleep-related eating disorder.

Reportedly, most eating episodes are likely to occur in the first half of the night owing to a concentrated appearance of slow-wave sleep, which may become the physiological basis of disordered sleep-awake transition, among general SRED cases.[21] However, interestingly, quite a few of the SRED cases in the present study experienced symptoms during the second half of nocturnal sleep. The reason for this phenomenon is unclear; however, it appears possible that the hypnosedative action of hypnotics or concurrent psychotropic drugs being taken by the participants could be carried over to the second half of the night, leading to the delayed appearance of eating episodes in the later hours of the night.

Many studies have shown the prevalence rate of SRED to be higher in women[3]; however, there was no gender difference in the rate of persons having SRED in the present study. Moreover, logistic regression analyses revealed that being female was not a significantly associated factor for the presence of SRED. One possible reason for the absence of a sex difference is that the SRED episodes in the patients of this study appeared to be dependent on the usage of hypnotics. Given this, there is a possibility of some other differences in the clinical features between primary SRED and drug-induced SRED. On the other hand, being younger was significantly associated with the presence of SRED among the patients in the present study, similarly to a previous study.[12] This finding suggests that even secondary SRED in psychiatric outpatients possibly related to taking hypnotics and other psychiatric medications may appear to have a similar physiological background to SRED in the general population.[22]

As stated above, zolpidem has been reported as the most common causative drug of nighttime unconscious and abnormal behaviors, including SRED.[9–11] However, of note in the present study, zolpidem did not appear to be a specific drug responsible for the presence of SRED among persons receiving hypnotic monotherapy. Meanwhile, the rate of individuals positive for SRED was significantly higher in patients taking multiple kinds of hypnotics than in those taking a single kind of hypnotic. The result of multivariate logistic analysis also revealed that the diazepam-equivalent daily dose of hypnotic was significantly associated with the presence of SRED. Taking these findings together, it could be inferred that SRED is more likely to occur when the dosage of any benzodiazepine hypnotic is increased, including administration of multiple kinds of benzodiazepine drugs. Considering this, the phenomenon that there have been many reported cases in which SRED occurred with zolpidem usage most likely comes simply from the fact that the drug has been the most frequently prescribed hypnotic worldwide.[23] Psychiatrists should be encouraged to be proactive in warning and asking patients on hypnotic medications about the presence and/or future emergence of SRED.

Lam et al[8] reported that the presence of SRED or sleepwalking was associated with major depression, whereas

Winkelman et al[2] reported that the prevalence of SRED was higher in cases with eating disorder symptoms than in the control population. Different from these 2 previous reports, the present study did not reveal any specific mental illness associated with the presence of SRED. However, participants in the present study included almost no cases of eating disorders (n = 7, 0.67% of total sample), and the risk of the development of SRED in patients with eating disorder requires further accumulation and investigation of larger numbers of patients with the disorder.

Interestingly, multiple kinds of antipsychotic usage were significantly associated with the presence of SRED in the patients of the present study. With respect to this, several case reports have shown that SRED occurred during the administration of olanzapine or quetiapine.[24,25] Possible mechanisms for this phenomenon have been speculated to involve the hypnosedative or orexinergic action of antipsychotics.[26] However, the present results revealed that the presence of SRED was associated with the usage of multiple kinds of antipsychotics, but not with the types of antipsychotics. Thus, it is important not to use multiple kinds of antipsychotics, but possibly a particular kind of antipsychotic at a higher dose, in combination with hypnotics to reduce the risk of SRED.

In the present study, subjective symptoms of hypnotics use (dizziness, fatigue, sleepiness, amnesia, and headache) were all present more frequently among the cases with SRED than those without, suggesting that secondary SRED due to benzodiazepine hypnotics may be comorbid with other subjective side effects of hypnotics. This finding could imply that attention should be paid to the possibility that hypnotics use may be responsible for the occurrence of SRED in psychiatric patients with both comorbid SRED and subjective side effect symptoms due to usage of hypnotics.

There are several limitations to the present study. First, the present study examined patients who visited a single medical institution; therefore, it is not clear whether the participants are representative of psychiatric patients taking hypnotics in general. Moreover, there were only a few patients with a primary diagnosis of substance abuse including alcohol, prescription medication, and illegal drugs that might have an impact on the presence of SRED in the patients. Second, the presence or absence of SRED was determined on the basis of responses to a self-administered questionnaire from the patients themselves; it is not definitive whether SRED was adequately detected with the questionnaire. Although the results of this study showed no significant difference in the rate of SRED between patients living alone and those having family members, we should have investigated whether patients had a bed partner who could more clearly identify the presence of SRED. In addition, in this questionnaire survey, we did not define frequency and its time period reference. Moreover, it was not possible to distinguish secondary SRED due to other sleep disorders such as restless leg syndrome, periodic limb movements disorder, or obstructive sleep apnea syndrome because polysomnography was not conducted in the SRED-positive cases in the present study. Third, as the present study was conducted as a cross-sectional sample, it was impossible to identify a causal relationship between the presence of SRED and its associated factors, such as a temporal relationship between the presence of SRED and the start of the medication with hypnotics. In addition, we did not evaluate a history of parasomnia of the patients in childhood that is thought to contribute to the risk of developing SRED. Fourth, we did not evaluate night eating disorder. Because night eating disorder is likely to present with similar and overlapping symptoms of SRED, the disorder might have confounded the results of the present study. Fifth, we did not use any psychopathological measures such as a structured interview and questionnaire. There may be confounding factors of psychiatric condition for the presence of SRED.

The present study confirmed that SRED is relatively frequent in psychiatric outpatients taking hypnotics. A larger dose of benzodiazepine hypnotic and usage of multiple antipsychotics were shown to be associated with the presence of SRED. In the future, a more detailed comparison study should be carried out in psychiatric outpatients as regards the presence of SRED in patients taking hypnotics compared with patients not taking hypnotics, to further dissect the factors contributing to the development of SRED in this population. For better understanding of the precise mechanism of SRED in psychiatric patients, we want to emphasize the necessity of a prospective future follow-up study on the changes in SRED symptoms along with changes in both treatment content and illness severity through the clinical course.

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Drug names: diazepam (Valium and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), triazolam (Halcion and others), zolpidem (Ambien, Edluar, and others).

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