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Current state of hypnotic use disorders: Results of a survey using the Japanese version of Benzodiazepine Dependence Self-Report Questionnaire

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Abstract

Aims: Benzodiazepine receptor agonists (BZ-RAs) are frequently prescribed to treat insomnia; however, their long-term use is not recommended. To introduce an appropriate pharmaco-therapy, the current state and background factors of BZ-RAs' dependence must be elucidated. In this study, we developed a Japanese version of the Benzodiazepine Dependence Self-Report Questionnaire (Bendep-SRQ-J) and conducted a study of BZ-RAs' use disorder.

Methods: The Bendep-SRQ-J was created with permission from the original developer. Subjects were inpatients and outpatients receiving BZ-RAs between 2012 and 2013. Clinical data collected were Bendep-SRQ-J scores, sleep disorders for which BZ-RAs were prescribed, physical comorbidities, psychotropic drugs, and lifestyle factors. Logistic analysis was performed to extract factors associated with severe symptoms.

Results: Of the 707 patients prescribed BZ-RAs, 324 had voluntarily tapered or discontinued their drugs. Logistic analysis showed that the total number of drugs administered in the last 6 months correlated with both worsening of symptoms or conditions. This was more notable among younger patients, and the proportion of patients with severe symptoms or conditions increased with the increasing number of drugs.

Conclusion: Using the Bendep-SRQ-J, we elucidated the current state of BZ-RA dependence. Nearly half of the patients were non-compliant. The proportion of patients with severe symptoms or disease conditions increased with the increase in the number of drugs administered. These findings highlight the need for clinicians to be aware

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of the likelihood of benzodiazepine dependence, especially in young patients and patients prescribed multiple hypnotics.

KEYWORDS
benzodiazepine, hypnotics, insomnia, Japanese version of Benzodiazepine Dependence Self-Report Questionnaire, non-compliance

1 | INTRODUCTION

Insomnia is a highly prevalent and serious disorder with far-reaching clinical and socioeconomic consequences. The prevalence of insomnia varies among studies, depending on the definition used,[1] but it has been reported to range from 6% to 30%.[1–7] Chronic insomnia intensifies anxiety/strain experienced due to the symptoms and causes physiological and emotional arousal and compensatory daytime sleepiness, thus compromising daytime quality of life[8–12]. Consequently, insomnia is thought to contribute to workforce and socioeconomic losses by increasing long-term absenteeism and industrial accidents, decreasing performance and productivity, and increasing healthcare costs.[13–16]

Benzodiazepine receptor agonists (BZ-RAs) are frequently used for the treatment of insomnia. BZ-RAs provide anxiolytic, sedative, and hypnotic effects by acting as agonists of gamma-aminobutyric acid (GABA) receptors.[17] According to an epidemiological study of the frequency of BZ-RA prescriptions, 3.66% of the Japanese population (3.02% in men, 4.29% in women) were prescribed hypnotics in 2005.[18] The frequency of BZ-RA prescriptions also increases with age and with increasing numbers of physical comorbidities in both men and women. In 2002, a Canadian survey found that 2.5% to 4.2% of Canadians were taking hypnotics[19], the 3-month prescription rate estimated in both the Japanese and Canadian studies was comparable.

In the United States, a 1985 survey report showed that 2.6% of the population used hypnotics and 4.3% used antidepressants or anxiolytics prescribed as alternatives to hypnotics over a 1-year period.[5] Also, 3.1% of the population used over-the-counter sleep aids.

The known problems and risks of BZ-RAs, which are commonly prescribed for the treatment of insomnia, include carry-over effects, falls due to lightheadedness,[20,21] cognitive decline and amnesia,[22,23] traffic accidents,[24–27] and dependence.[28–31] Thus, BZ-RAs are not recommended for use in middle-aged and elderly patients with chronic insomnia, although they are often the major users.[17,32,33] In addition, high-dose BZ-RAs, concurrent use with multiple drugs, and long-term use are not recommended because of aggravation of BZ-RA side effects. Despite these drawbacks, BZ-RAs have continuously been used on a long-term basis in clinical settings, even though they cause dependence in the broad sense.

Since the early 1960s, BZ-RA dependence has been debated. Because of anxiety over insomnia symptoms and withdrawal symptoms, patients on BZ-RAs continue to use the drugs without having intended to do so, sometimes leading to problems related to drug use, such as non-compliance with treatment regimens and problematic drug use. Thus, BZ-RA-dependence is regarded as a use disorder.

Against this background, it is anticipated that long-term administration of hypnotics is a risk factor for substance use disorder. It is therefore desirable to introduce an appropriate drug tapering/discontinuation program for patients who have been taking hypnotics for a prolonged period. To establish an appropriate discontinuation program, it is important to elucidate and accurately evaluate the current state and background factors of hypnotic use disorder. To date, no studies have reported data that accurately describe the incidence and severity of hypnotic use disorder in Japan. This is partly due to a lack of clinically useful criteria for assessing the severity of this disorder in Japanese patients.

Several self-report questionnaires have been developed for assessing BZ-RA dependence, including the Composite International Diagnostic Interview,[34] Schedules for Clinical Assessment in Neuropsychiatry,[35] and Benzodiazepine Dependence Questionnaire[36], but all the criteria have some deficits. Consequently, the Benzodiazepine Dependence Self-Report Questionnaire (Bendep-SRQ)[37] was developed as a multidimensional tool for comprehensive assessment of BZ-RA dependence.

Studies on Bendep-SRQ have been reported and these studies investigated the characteristics of patients with cravings for BZ-RAs;[38] risk factors for BZ-RA dependence;[39] cross-validation, predictive validity, and change in Bendep-SRQ scores over time;[40] the dependence potential of antidepressants compared with benzodiazepines;[41] and cross-validation of the Bendep-SRQ.[42,43] However, these studies were not conducted in Japan, and so Japanese patients have not been studied.

In light of the above, we developed the Japanese version of Bendep-SRQ (Bendep-SRQ-J) and conducted a multicenter collaborative study to clarify the current state of BZ-RA use disorder in Japan.

2 | METHODS

2.1 | Development of the Bendep-SRQ-J

With permission from the developer of the original Bendep-SRQ, we translated the questionnaire into Japanese, back-translated it,

and made inquiries about medications, before developing the final Japanese version.

The Bendep SRQ[37] consists of 20 questions in 4 dimensions: (1) preoccupation with drug availability, (2) problematic drug use, (3) non-compliance with treatment regimen, and (4) withdrawal symptoms. This study also included withdrawal insomnia as a fifth dimension to evaluate the withdrawal symptoms unique to hypnotics. All patients answered 15 questions in dimensions 1-3, and patients who had previously tapered drugs also answered questions in dimensions 4 and 5. Each dimension has a cutoff point, and the severity of symptoms/conditions is classified into 3-5 grades (Figure S1).

2.2 | Self-administered questionnaire survey

In this multicenter collaborative study, a self-administered cross-sectional survey was conducted with inpatients and outpatients receiving drug therapy with BZ-RA hypnotics or anxiolytics at 14 participating medical institutions over a period of 3 months, between August 2012 and March 2013. Additionally, patient information was obtained from primary care physicians, including the sleep disorder necessitating the prescription of BZ-RAs, physical comorbidities, psychotropic drugs prescribed during a period of 180 days (6 months) prior to the survey, and lifestyle factors including alcohol consumption.

2.3 | Definition of drugs

BZ-RAs were classified as hypnotics when prescribed to provide sedative-hypnotic effects at night or as anxiolytics (BZ-A) when prescribed to provide anxiolytic effects during the day. BZ-RA hypnotics were classified as BZ-hypnotics (BZ-H), which are drugs with a benzodiazepine (BZ) backbone in their chemical structure or as non-BZ-hypnotics (non-BZ-H) for those without a BZ backbone that have high selectivity for the α1 subunit (zopiclone, eszopiclone, and zolpidem). The distinction between non-BZ-H and BZ-H was made in this study because there is a lower incidence of withdrawal symptoms and lower risk of developing dependence with non-BZ-H.[44] In addition, patients were divided by drug category and were analyzed separately to reveal the differences in actual drug use and risk factors.

2.4 | Statistical analysis

Bendep-SRQ scores and patient background factors were compared in order to extract background factors for BZ-RA use disorder. Also, to extract factors associated with severe or extremely severe symptoms/conditions in each dimension, logistic regression analysis was performed using the following as independent variables: sex, age (20-44, 45-64, or 65-90 years), presence/absence of mental or physical disorder, drug category (BZ-H, non-BZ-H, or BZ-A), daily drug dose (<10 mg or ≥10 mg of BZ-H, non-BZ-H, or BZ-A), and the total number of drugs administered in the last 3 months (1, 2, or ≥3 drugs). To reveal the specific features of BZ-H, non-BZ-H, and BZ-A, the clinical data of patients receiving each of these monotherapies were extracted and analyzed separately in logistic analysis. Statistical analysis was conducted using the IBM SPSS Statistics software (Ver. 22).

2.5 | Ethical considerations

The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. Committee of National Center of Neurology and Psychiatry, Approval No. A2012-065. All informed consent was obtained from the subjects.

3 | RESULTS

3.1 | Background characteristics

Surveys were returned by 922 patients treated with BZ-RAs, of whom 215 provided invalid data such as unclear or unrealistic responses. Table 1 shows the background characteristics of the patients. Of the 707 patients with valid responses, 198, 99, and 115 (412 in total) were receiving monotherapy with BZ-H, non-BZ-H, or BZ-A, respectively.

Table 2 shows drugs belonging to the BZ-H, non-BZ-H, and BZ-A categories and the number of patients on each drug. Of the 707 patients treated with BZ-RAs, 324 (45.8%) had previously tapered/discontinued their drug use, and 187 (45.4%) of the 324 patients were receiving monotherapy with BZ-H (n = 86), non-BZ-H (n = 49), or BZ-A (n = 52).

3.2 | Severity of Bendep-SRQ dimensions and withdrawal symptoms and insomnia

Among all patients (N = 707), the Bendep-SRQ dimensions of preoccupation with drug availability, medication non-compliance, and problematic drug use were severe in 32.4%, 29.0%, and 32.4%, respectively. Among patients who had previously tapered/discontinued their drug use (n = 324), withdrawal symptoms were severe in 10.8% and withdrawal insomnia was severe in 30.9%.

3.3 | Factors associated with severe/extremely severe symptoms/conditions in each dimension

1. All subjects (N = 707, Table 3).

Age < 44 years had a significant correlation with severe or extremely severe non-compliance with treatment regimen,

TABLE 1 Patient background information

Subjects	All patients	Patients on Bz-RAs-H	Patients on non-Bz-RAs-H	Patients on Bz-RAs-A
All Patients				
Number of patients, n	707	198	99	115
Age, y				
Mean age (SD)	53.2 (16.5)	52.9 (17.0)	52.9 (18.8)	53.1 (15.4)
Range	20-90	20-87	21-88	22-86
Sex, n (%)				
Men (%)	322 (45.5)	90 (45.5)	50 (50.5)	53 (46.1)
Women (%)	385 (54.5)	108 (54.5)	49 (49.5)	62 (53.9)
Number of drugs, n				
Mean	2	1.4	1.1	1.2
Dose of Bz-RAs, mg				
Mean	9.6	6.5	4.2	6.5
Comorbidity, n (%)				
Mental disorder	460 (65.1)	136 (68.7)	43 (43.4)	76 (66.1)
Physical disorder	261 (36.9)	57 (28.8)	47 (47.5)	49 (42.6)
Patients with a history of drug tapering				
Number of patients, n				
Number (% to total)	324 (45.8)	86 (43.4)	49 (49.5)	52 (45.2)
Age, y				
Mean age (SD)	53.3 (16.5)	50.62 (17.1)	54.84 (17.0)	54 (16.4)
Range	20 to 90	21 to 84	22 to 85	20 to 90
Sex, n (%)				
Men (%)	156 (48.1)	45 (52.3)	25 (51.0)	22 (42.3)
Women (%)	168 (51.9)	41 (47.7)	24 (49.0)	30 (57.7)
Number of drugs, n				
Mean	2	1.4	1.1	1.3
Dose of Bz-RAs, mg				
Mean	9.3	8.2	4.2	7
Comorbidity, n (%)				
Mental disorder	205 (63.3)	54 (62.8)	22 (44.9)	33 (63.5)
Physical disorder	125 (38.6)	27 (31.4)	25 (51.0)	24 (46.2)

Abbreviation: BZ-A, benzodiazepine agonistic anxiolytics; Bz-H, benzodiazepine agonistic hypnotics; Non-BZ-H, benzodiazepine agonistic hypnotics without benzodiazepine chemical structure.

problematic drug use, withdrawal symptoms, and withdrawal insomnia. Presence of physical disorder had a significant correlation with severe or extremely severe non-compliance with treatment regimen. Additionally, there was a significant correlation between use of ≥3 drugs and severe or extremely severe symptoms/conditions in all dimensions. Use of 2 drugs also correlated with severe or extremely severe preoccupation with drug availability, problematic drug use, and withdrawal symptoms. Total dose of BZ-RAs administered in the last 3 months was not associated with severe or extremely severe symptoms/conditions in any of the dimensions.

1. Patients receiving monotherapy with BZ-A (n = 115, Table 4).

Presence of physical disorder had a significant correlation with severe or extremely severe non-compliance with treatment regimen. Total dose of BZ-RAs in the last 3 months was not associated with severe or extremely severe symptoms/conditions in any of the dimensions. No withdrawal symptoms are listed because there were no cases of severe dependence. The distributions of severalty among the 52 participants were very mild 42, mild 5, moderate 5, severe 0.

TABLE 2 Drugs in the Bz-RAs-H, non-Bz-RAs-H, and Bz-RAs-A categories and the number of patients on each drug

Bz-RAs-H (n = 198)		Non-Bz-RAs-H (n = 99)		Bz-RAs-A (n = 115)	
Brotizolam	149 (48)	Eszopiclone	18 (1)	Alprazolam	54 (23)
Clonazepam	22 (4)	Zolpidem	158 (58)	Bromazepam	34 (9)
Cloxazolam	1 (-)	Zopiclone	63 (23)	Chlordiazepoxide	4 (-)
Diazepam	1 (-)	Clonazepam	44 (13)		
Estazolam	15 (2)	Clotiazepam	14 (6)		
Etizolam	36 (11)	Cloxazolam	7 (2)		
Flunitrazepam	139 (27)	Diazepam	22 (3)		
Flurazepam	1 (-)	Etizolam	60 (28)		
Haloxazolam	1 (-)	Loflazepate	36 (7)		
Loflazepate	5 (-)	Lorazepam	45 (8)		
Lormetazepam	10 (2)	Lormetazepam	1 (-)		
Nimetazepam	1 (-)	Medazepam	1 (-)		
Nitrazepam	37 (18)	Tofisopam	1 (-)		
Quazepam	18 (2)				
Rilmazafone	17 (3)				
Triazolam	40 (13)				

Note: (), number of patients receiving monotherapy with this drug.

Abbreviations: BZ-A, benzodiazepine agonistic anxiolytics; Bz-H, benzodiazepine agonistic hypnotics; Non-BZ-H, benzodiazepine agonistic hypnotics without benzodiazepine chemical structure.

1. Patients receiving monotherapy with BZ-H (n = 198, Table 5).

Age < 44 years had a significant correlation with severe or extremely severe non-compliance with treatment regimen, problematic drug use, and withdrawal insomnia. Use of ≥3 drugs correlated significantly with severe or extremely severe preoccupation with drug availability, while use of 2 drugs had a significant correlation with severe or extremely severe withdrawal insomnia. Total dose of BZ-RAs in the last 3 months was not associated with severe or extremely severe symptoms/conditions in any of the dimensions.

1. Patients receiving monotherapy with non-BZ-H (n = 99, Table 6).

Age < 44 years correlated significantly with severe or extremely severe problematic drug use. Presence of physical disorder correlated significantly with severe or extremely severe preoccupation with drug availability. Additionally, use of 2 drugs had a significant correlation with severe or extremely severe preoccupation with drug availability, non-compliance with treatment regimen, and problematic drug use. Total dose of BZ-RAs in the last 3 months was not associated with severe or extremely severe symptoms/conditions in any of the dimensions.

Incidence of withdrawal insomnia based on the number of drugs administered.

The investigation of withdrawal insomnia appearing in 324 patients who had previously tapered/discontinued their drug use revealed that an incidence of 20.5% in patients taking 1 drug, 27.20% in those taking 2 drugs, and 54.40% in those taking ≥3 drugs, indicating that the proportion of patients with severe or extremely severe withdrawal insomnia increased with the increasing number of drugs. Compared with those receiving monotherapy with BZ-H, non-BZ-H, or BZ-A, patients taking 2 drugs had a higher incidence of severe or extremely severe withdrawal insomnia. However, no statistical analysis was performed on patients taking ≥3 drugs due to the small sample size.

4 | DISCUSSION

In this study, using the Bendep-SRQ-J, a rating scale for BZ-RA dependence, we investigated the current state of BZ-RA dependence among patients treated at sleep disorder outpatient clinics in Japan. The results showed that approximately 30% of patients had a severe or extremely severe preoccupation with drug availability, non-compliance with treatment regimen, and problematic drug use. Of all patients receiving drug therapy with BZ-RAs, 45% had previously tapered/discontinued their drug use. The frequency of withdrawal symptoms by the number of drugs administered in this patient population was approximately 20% in patients taking 1 drug and 40% in those taking multiple drugs. Approximately 10% and 30% of the patients had severe or extremely severe withdrawal symptoms and withdrawal insomnia, respectively.

This study revealed a high incidence of voluntary drug discontinuation. A previous survey of international comparisons of awareness of hypnotics has shown that Japanese people have particularly high levels of anxiety and psychological resistance toward hypnotics,

TABLE 3 Factors associated with severe/extremely severe symptoms/conditions in each dimension (all patients, n = 707)

	Preoccupation with drug availability		Non-compliance with treatment regimen		Problematic drug use		Withdrawal symptoms (n = 324)		Withdrawal insomnia (n = 324)	
	Exp(B) 95% CI	Significance (*P* value)	Exp(B) 95% CI	Significance (*P* value)	Exp(B) 95% CI	Significance (*P* value)	Exp(B) 95% CI	Significance (*P* value)	Exp(B) 95% CI	Significance (*P* value)
Age 20-44 y										
Age 45-64 y	0.847 (0.573, 1.251)	.404	0.591* (0.395, 0.883)	.010	0.601* (0.410, 0.881)	.009	0.355* (0.149, 0.844)	.019	0.527* (0.287, 0.967)	.039
Age 65-90 y	0.816 (0.534, 1.247)	.347	0.477* (0.305, 0.746)	.001	0.463* (0.301, 0.712)	.000	0.383* (0.145, 1.013)	.053	0.416* (0.211, 0.819)	.011
Sex, men/women	1.079 (0.777, 1.497)	.651	1.058 (0.752, 1.488)	.746	1.069 (0.771, 1.482)	.691	1.074 (0.520, 2.218)	.848	0.821 (0.490, 1.377)	.455
Total number of drugs administered, 1 drug										
Total number of drugs administered, 2 drugs	1.623* (1.099, 2.395)	.015	1.470* (0.975, 2.217)	.066	1.702* (1.154, 2.510)	.007	3.822* (1.289, 11.326)	.016	1.529 (0.819, 2.855)	.182
Total number of drugs administered, ≥ 3 drugs	2.786* (1.859, 4.177)	.000	2.970* (1.957, 4.508)	.000	2.359* (1.567, 3.550)	.000	7.620* (2.730, 21.270)	.000	4.665* (2.503, 8.692)	.000
Total dose (Dzp equivalent) administered daily, <10 mg										
Total dose (Dzp equivalent) administered daily, ≥10 mg	1.287 (0.882, 1.879)	.191	1.196 (0.807, 1.773)	.373	0.860 (0.595, 1.244)	.424	1.088 (0.446, 2.653)	.853	1.384 (0.778, 2.464)	.269
Presence/absence of mental disorder	0.762 (0.530, 1.095)	0.142	0.858 (0.587, 1.254)	.430	0.735 (0.511, 1.058)	.097	2.652 (0.971, 7.243)	.057	0.816 (0.457, 1.459)	.493
Presence/absence of physical disorder	1.315 (0.917, 1.885)	.136	1.763* (1.210, 2.567)	.003	1.150 (0.800, 1.653)	.452	0.797 (0.336, 1.889)	.606	1.024 (0.578, 1.812)	.936

Note: Samples were analyzed using the logistic regression analysis.

Abbreviation: CI, confidence interval.

*Statistically significant factor.

TABLE 4 Factors associated with severe/extremely severe symptoms/conditions in each dimension (patients on Bz-RAs-A only, n = 115)

	Preoccupation with drug availability		Non-compliance with treatment regimen		Problematic drug use		Withdrawal symptoms (n = 52)		Withdrawal insomnia (n = 52)	
	Exp(B) 95% CI	Significance (*P* value)	Exp(B) 95% CI	Significance	Exp(B) 95% CI	Significance (*P* value)	Exp(B) 95% CI	Significance (*P* value)	Exp(B) 95% CI	Significance (*P* value)
Age 20-44 y										
Age 45-64 y	0.824 (0.269, 2.527)	.735	0.715 (0.231, 2.211)	.560	1.108 (0.397, 3.087)	.845	– (-, -)	-	1.307 (0.123, 13.947)	.824
Age 65-90 y	1.163 (0.322, 4.198)	.817	0.453 (0.110, 1.866)	.273	0.849 (0.243, 2.971)	.798	– (-, -)	-	0.466 (0.025, 8.539)	.607
Sex, men/women	1.131 (0.442, 2.891)	.797	0.849 (0.327, 2.207)	.737	1.274 (0.529, 3.069)	.589	– (-, -)	-	3.041 (0.266, 34.761)	.371
Total number of drugs administered, 1 drug										
Total number of drugs administered, 2 drugs	0.512 (0.099, 2.655)	.425	0.932 (0.219, 3.963)	.924	1.954 (0.552, 6.912)	.299	– (-, -)	-	2.955 (0.308, 28.380)	.348
Total number of drugs administered, ≥ 3 drugs	0.000 (0.000, 0.000)	.999	2.277 (0.116, 44.571)	.588	6 527 426 393.976 (0.000, 0.000)	.999	– (-, -)	-	0.000 (0.000, 0.000)	1.000
Total dose (Dzp equivalent) administered daily, < 10 mg										
Total dose (Dzp equivalent) administered daily, ≥ 10 mg	2.520 (0.878, 7.234)	.086	1.067 (0.376, 3.032)	.903	0.854 (0.337, 2.164)	.739	– (-, -)	-	0.195 (0.016, 2.367)	.199
Presence/absence of mental disorder	0.481 (0.124, 1.875)	.292	1.667 (0.448, 6.202)	.446	2.228 (0.648, 7.654)	.203	– (-, -)	-	0.535 (0.031, 9.254)	.667
Presence/absence of physical disorder	0.681 (0.196, 2.371)	.546	4.238* (1.171, 15.342)	.028	1.639 (0.529, 5.080)	.392	– (-, -)	-	1.125 (0.059, 21.482)	.938

Note: Samples were analyzed using the logistic regression analysis. Statistical significance was not calculated because there were no corresponding patients.

Abbreviation: CI, confidence interval.

*Statistically significant factor; statistical significance was not calculated because there were no corresponding patients.

TABLE 5 Factors associated with severe/extremely severe symptoms/conditions in each dimension (patients on Bz-RAs-H only, n = 198)

	Preoccupation with drug availability		Non-compliance with treatment regimen		Problematic drug use		Withdrawal symptoms (n = 86)		Withdrawal insomnia (n = 86)	
	Exp(B) 95% CI	Significance (*P* value)	Exp(B) 95% CI	Significance (*P* value)	Exp(B) 95% CI	Significance (*P* value)	Exp(B) 95% CI	Significance (*P* value)	Exp(B) 95% CI	Significance (*P* value)
Age 20-44 y										
Age 45-64 y	0.747 (0.346, 1.613)	.457	0.380* (0.167, 0.866)	.021	0.294* (0.135, 0.640)	.002	0.000 (0.000)	.997	0.501 (0.152, 1.649)	.255
Age 65-90 y	0.887 (0.383, 2.055)	.780	0.291* (0.110, 0.768)	.013	0.200* (0.079, 0.505)	.001	0.000 (0.000)	.997	0.189* (0.044, 0.812)	.025
Sex, men/women	0.910 (0.473, 1.753)	.779	0.751 (0.373, 1.512)	.423	1.291 (0.659, 2.532)	.456	2.288 (0.374, 14.012)	.371	0.629 (0.230, 1.720)	.367
Total number of drugs administered, 1 drug										
Total number of drugs administered, 2 drugs	1.936 (0.913, 4.102)	.085	1.303 (0.579, 2.932)	.523	1.274 (0.575, 2.823)	.551	1.740* (0.258, 11.757)	.570	3.998* (1.164, 13.737)	.028
Total number of drugs administered, ≥ 3 drugs	4.217 (1.267, 14.032)	.019	0.706 (0.138, 3.617)	.676	1.403 (0.368, 5.343)	.620	6.891* (0.439, 108.161)	.169	4.657* (0.695, 31.205)	.113
Total dose (Dzp equivalent) administered daily, < 10 mg										
Total dose (Dzp equivalent) administered daily, ≥ 10 mg	0.787 (0.348, 1.779)	.565	0.993 (0.413, 2.388)	.988	0.491 (0.218, 1.103)	.085	0.385 (0.057, 2.597)	.327	0.577 (0.182, 1.832)	.351
Presence/absence of mental disorder	1.090 (0.523, 2.268)	.819	0.880 (0.400, 1.937)	.751	0.707 (0.332, 1.505)	.368	2.449 (0.242, 24.818)	.449	0.616 (0.215, 1.769)	.368
Presence/absence of physical disorder	1.187 (0.542, 2.599)	.668	1.557 (0.672, 3.609)	.301	1.140 (0.503, 2.584)	.754	3.417 (0.480, 24.339)	.220	2.156 (0.658, 7.071)	.205

Note: Samples were analyzed using the logistic regression analysis.

Abbreviation: CI, confidence interval.

*Statistically significant factor.

TABLE 6 Factors associated with severe/extremely severe symptoms/conditions in each dimension (patients on Non-Bz-RAs-H only, n = 99)

	Preoccupation with drug availability		Non-compliance with treatment regimen		Problematic drug use		Withdrawal symptoms (n = 86)		Withdrawal insomnia (n = 86)	
	Exp(B) 95% CI	Significance (*P* value)	Exp(B) 95% CI	Significance (*P* value)	Exp(B) 95% CI	Significance (*P* value)	Exp(B) 95% CI	Significance (*P* value)	Exp(B) 95% CI	Significance (*P* value)
Age 20-44 y										
Age 45-64 y	0.863 (0.238, 3.134)	.823	0.797 (0.249, 2.551)	.702	0.971 (0.310, 3.038)	.959	0.000 (0.000, 0.000)	.997	0.639 (0.104, 3.934)	.629
Age 65-90 y	1.695 (0.524 5.487)	.378	0.457 (0.135, 1.548)	.209	0.218* (0.055 0.869)	.031	0.000 (0.000 0.000)	.997	0.392 (0.046 3.333)	.391
Sex, men/women	2.019 (0.756, 5.394)	.161	1.528 (0.589, 3.962)	.384	0.904 (0.337, 2.421)	.840	15 815 493.150(0.000, 0.000)	.997	0.983 (0.226, 4.279)	.981
Total number of drugs administered, 1 drug										
Total number of drugs administered, 2 drugs	9.947* (1.684, 58.743)	.011	5.136 (1.059, 24.906)	.042	5.892 (1.077, 32.238)	.041	0.000 (0.000, 0.000)	.999	1.739* (0.105, 28.757)	.699
Total number of drugs administered, ≥ 3 drugs	– (-, -)	-	– (-, -)	-	– (-, -)	-	– (-, -)	-	– (-, -)	-
Total dose (Dzp equivalent) administered daily, <10 mg										
Total dose (Dzp equivalent) administered daily, ≥10 mg	1.414 (0.514, 3.893)	.503	1.100 (0.408, 2.964)	.851	1.508 (0.538, 4.229)	.435	14 266 459.370(0.000, 0.000)	.997	1.345 (0.299, 6.045)	.699
Presence/absence of mental disorder	0.945 (0.331, 2.695)	.916	1.313 (0.477, 3.618)	.598	0.374 (0.128, 1.094	.073	6 336 719.714 (0.000, 0.000)	.996	1.419 (0.269, 7.492)	.680
Presence/absence of physical disorder	3.252* (1.143, 9.250)	.027	1.775 (0.646, 4.880)	.266	1.280 (0.456, 3.589)	.639	0.000 (0.000, 0.000)	.997	1.203 (0.248, 5.833)	.818

Note: Samples were analyzed using the logistic regression analysis.

Abbreviation: CI, confidence interval.

*Statistically significant factor; statistical significance was not calculated because there were no corresponding patients.

which apparently contribute as background factors to the high incidence of voluntary drug discontinuation among Japanese individuals.

Compared with older age groups, patients aged 20-44 years (younger patients) had more severe or extremely severe use problems, such as non-compliance with treatment regimen and problematic drug use. The findings of this cross-sectional study do not reveal any causal relationship among the severe symptoms/conditions, but previous studies have pointed out that physical dependence (formation of tolerance) is a risk factor for BZ-RA dependence. For example, according to studies using clinical data suggesting tolerance to BZ-RAs, the prescribed dose of BZ-RAs did not increase over time generally, but gradually did so among younger patients.[45,46] However, because no correlation was observed between dependence symptoms and BZ-RA dose in the present study, it is difficult to think that waning of efficacy due to development of drug tolerance is a direct cause of drug use disorder. Although there are not certain data about the rate of comorbidity, the group of patients aged 20-44 years tended to have some form of comorbid mental health issue, such as anxiety. We speculate that they may be anxious due to recurring anxiety or insomnia and that this may contribute to psychological dependence on hypnotics.

As for patients taking BZ-A, younger age was not associated with severe or extremely severe symptoms/conditions in any of the dimensions. However, this does not necessary mean that the risk of dependence is lower with BZ-A than with BZ-H or non-BZ-H. A failure to reveal risk factors for BZ-RA anxiolytics among patients taking BZ-A in this study could suggest that compared with the severity of insomnia, the severity of mental disorders such as anxiety disorder and somatic symptom disorder, both of which are the target of BZ-A, was milder because these patients were treated at clinics specialized in sleep disorders. Indeed, most patients were on the recommended dose of BZ-A (a table will be developed to show the data), and it is likely that only a small number of patients had severe symptoms, were taking higher doses, or were taking it for an extended period.

4.1 | Relationship between dose and Bendep-SRQ-J score

Previous studies have shown that the risk factors for BZ-RA dependence include long-term use,[47,48] high dose,[48,49] comorbidity with mental disorder[48], severe insomnia[49], and alcohol dependence.[49] However, despite our expectations, no correlation was observed between BZ-RA dose and severity of benzodiazepine dependence [[Bendep-SRQ-J scores]] in this study.

This suggests that the Bendep-SRQ-J might not accurately assess withdrawal symptoms because it is a self-administered questionnaire. For example, anxiety, frustration, and insomnia are the major symptoms of BZ-RA withdrawal,[50] but they are also symptoms already present in patients with insomnia (the disorder requiring BZ-RAs). Another possible reason why no correlation was found between dose and withdrawal symptoms was that the subjects in this study did not take multidrug combinations of BZ-H, non-BZ-H, and BZ-A. Multidrug combination is a risk factor for drug use disorder, but in this study, multidrug cases across drug classes were excluded.

4.2 | Relationship between number of drugs administered and Bendep-SRQ-J score

In this study, a correlation was observed between the number of drugs administered during the last 6 months and high Bendep-SRQ-J scores. Patients taking multiple drugs had a strong tendency toward drug use disorder and dependence, compliance issues, and a high rate of withdrawal symptoms. As is clear from the data showing the lack of correlation with drug dose, multiple drug use was mainly attributable to drug switching in the short term. In this study, we did not cover the reasons for drug switching, and therefore the background factors remain unclear. However, it is possible that anxiety and insomnia, both of which are the target disorders of BZ-RAs, were intractable. Moreover, patients might have requested more effective drugs due to severe anxiety over their symptoms. In such cases, it is easy to imagine that patients are strongly dependent on their drugs, likely leading to non-compliance with the treatment regimen or problematic drug use. Third, physicians might have switched drugs at a faster pace than necessary in response to the patient's request. Drug prescriptions lacking clinical evidence may become a remote cause of high-dose prescriptions or multiple prescriptions, in addition to interfering with the improvement of treatment efficacy.

4.3 | Limitations

Because this was a cross-sectional study, we were unable to investigate changes over time. Additionally, patients on multiple drugs across different drug categories were not included in the analysis. Although patients on multiple drugs are regarded as a problem in actual clinical practice, these patients were excluded in this study, and so these results should be applied with caution in clinical settings.

5 | CONCLUSION

Using the Bendep-SRQ-J, we elucidated the current state of BZ-RA use disorder in this study. Approximately 45% of the patients receiving drug therapy with BZ-RAs had voluntarily tapered/discontinued their drug use in the past, revealing problems associated with non-compliance with the treatment regimen. Additionally, the number of drugs administered during the last 6 months significantly contributed to worsening of the preoccupation with drug availability, drug use disorder (non-compliance with treatment regimen and problematic drug use), withdrawal symptoms, and withdrawal insomnia. These findings were notable among younger patients, and the proportion of patients with severe symptoms/conditions increased with an increase in the number of drugs administered.

In contrast, no correlation was observed between BZ-RA dose and dimensions of the Bendep-SRQ-J. The findings highlight the need for clinicians to be aware of the likelihood of benzodiazepine dependence, specifically in young patients and patients prescribed multiple hypnotics.

CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Mai Yamamoto and Minori Enomoto analyzed the data and prepared the manuscript. Ken Inada collected and interpreted the data and prepared the manuscript. Kazuo Mishima involved in planning, design, and supervision of research; collected the data; and prepared the manuscript. Masayuki Miyamoto, Mitsunari Habukawa, Hideto Niino, Tsuyoshi Kitajima, Masahiro Takeshima, Hidenao Yamashita, Yuichi Inoue, Takahisa Hirose, Motohiro Ozone, Mayumi Suzuki, Yuichi Kamei, and Katsuji Nishimura collected the data and reviewed the manuscript.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

The protocol for this research project has been approved by Ethics Committee of National Center of Neurology and Psychiatry, Approval No. A2012-065.

INFORMED CONSENT

All informed consent was obtained from the subjects.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

The study is not registered because all the data were obtained before 2013.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. The IRB did not grant the deposit of raw data in a publicly accessible data archive or repository at the time of approval since the procedure was not included in the study protocol or informed consent document.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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