

学位論文 博士（学士） 甲

Changes of clinical symptoms in patients with new psychoactive substance (NPS)-related disorders from fiscal year 2012 to 2014: A study in hospitals specializing in the treatment of addiction

「2012年から2014年におけるNPS関連物質使用障害患者の臨床症状の変化、依存症専門治療病院での研究」

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Changes of clinical symptoms in patients with new psychoactive substance (NPS)-related disorders from fiscal year 2012 to 2014: A study in hospitals specializing in the treatment of addiction

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Abstract

Aims: The use of new psychoactive substances (NPS) has become increasingly widespread over the last decade, in Japan and internationally. NPS are associated with a range of increasingly serious clinical, public, and social issues. Political measures to ameliorate the effects of NPS in Japan have focused on tightening regulation rather than establishing treatment methods. The current study sought to compare the neuropsychiatric symptoms of patients with NPS-related disorders across several years. We examined patients who attended specialized hospitals for treating addiction, to elucidate the impacts of legal measures to control NPS.

Methods: Subjects ($n = 864$) were patients with NPS-related disorders who received medical treatment at eight specialized hospitals for treating addiction in Japan between April 2012 and March 2015. Clinical information was collected retrospectively from medical records.

Results: Among psychiatric symptoms, the ratio of hallucinations/delusions decreased over time across 3 years of study (first year vs second year vs third year: 40.1% vs 30.9% vs 31.7%, $P = 0.037$). Among neurological symptoms, the ratio of coma/syncope increased over the 3-year period (7.8% vs 11.0% vs 17.0%, $P = 0.002$), as did the ratio of convulsions (2.8% vs 4.3% vs 9.7%, $P = 0.001$).

Conclusion: The symptoms associated with NPS were primarily psychiatric in the first year, while the prevalence of neurological symptoms increased each year. The risk of death and the severity of symptoms were greater in the third year compared with the first year, as regulation of NPS increased.

KEYWORDS

addiction, government regulation, new psychoactive substance, psychiatric hospital, substance-related disorders

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1 | INTRODUCTION

In recent years, new psychoactive substances (NPS) have become an increasingly serious social problem worldwide.¹⁻⁶ NPS are defined as unknown substances and are typically produced by modifying chemical structures of known substances to circumvent legal control. Because of these chemical structure changes, NPS cannot be detected using existing drug detection tests. Like controlled substances, NPS typically evoke a sense of exaltation and euphoria and can have harmful effects including dependence and toxicity. These new addictive substances were initially sold in stores and via the Internet while clear rules were not yet in place and were easily available for a relatively low cost. In the mid-2000s, the use of NPS rapidly spread worldwide, particularly among young people. In Japan, as the use of NPS increased, they became known as *kiken* (dangerous) drugs.

From 2011, the number of NPS-related consultations dramatically increased at the Japan Poison Information Center^{7,8} and in emergency rooms.⁹ Concomitantly, there were ongoing media reports of NPS causing hallucinatory delusions, disturbances of consciousness, convulsions, and cardiac arrest related to acute poisoning. In addition, reports of car accidents, violence, and suicidal behavior under the influence of NPS increased at an alarming rate. This situation was also reflected in psychiatric practice. In the 2012 survey of the Nationwide Mental Hospital Surveys on Drug-related Psychiatric Disorders (conducted every 2 years), NPS ranked second among the main drugs of abuse of patients with substance-induced mental disorders, after methamphetamines, which have consistently been the main drug of abuse in Japan since the end of wartime.¹⁰ In the next Nationwide Mental Hospital Surveys on Drug-related Psychiatric Disorders survey in 2014, the percentage of patients with substance-induced mental disorders who used NPS as their main drug of abuse had increased further.¹¹

In the past, other legal intoxicants that circumvented legislative controls, such as "magic mushrooms" and 5-Meo-DIPT (5-methoxy-N,N-diisopropyltryptamine; common names: 5-MeO and Foxy), became social problems. These issues were resolved by tightening regulations. However, this regulatory approach has not been successful in the case of NPS and has resulted in a vicious circle; each time the regulations were tightened, new NPS appeared, circumventing the updated regulations. In 2014, almost daily media reports of traffic accidents and other incidents involving NPS users generated a sense of national crisis.

Following the introduction of a new, comprehensive approach in Japan for designating illegal drugs based on similarities in chemical structure (in 2013 and 2014), as well as a revision of the *Pharmaceutical Affairs Act* involving measures that included an order to stop sales and an expansion of the number of shops required to undergo inspections at the end of 2014, the number of NPS sales outlets drastically decreased. In 2015, the disruption caused by NPS rapidly ended.

However, from the perspective of those involved in the provision of specialized treatments for substance-dependent patients, the

psychiatric and neurological symptoms of patients with NPS-related disorders appear to have worsened year-by-year from 2011 to 2014, the period in which regulations were implemented. Thus, it is possible that, as regulations for NPS were tightened, neuropsychiatric symptoms of patients using NPS worsened because of the emergence of new types of NPS. However, quantitative investigation of this issue has been lacking. The present study was conducted to compare neuropsychiatric symptoms of patients with NPS-related disorders during the period in which the regulations for NPS were tightened and to examine the relationship between drug regulation and harm to drug users. To this end, we investigated changes in the psychiatric and neurological symptoms of patients with NPS-related disorders over time, using data from eight medical hospitals specialized in the treatment of addiction.

2 | METHODS

2.1 | Subjects

The subjects in the current study were patients with NPS-related disorders who were treated as outpatients at one of eight Japanese medical hospitals specialized in the treatment of addiction during the period from April 2012 to March 2015 (fiscal year: FY2012–FY2014). Here, "patients with NPS-related disorders" refers to NPS users who were diagnosed with ICD-10 F1 (mental and behavioral disorders due to psychoactive substance use).

The following institutions participated in the study: Saitama Psychiatric Medical Center; National Center Hospital, National Center of Neurology and Psychiatry; Tokyo Metropolitan Matsuzawa Hospital; Kanagawa Psychiatric Center; Mie Prefectural Mental Medical Center; Osaka Psychiatric Medical Center; Okayama Psychiatric Medical Center; and Hizen Psychiatric Center. These institutions are all leading Japanese hospitals specialized in the treatment of addiction.

2.2 | Methods

In the current study, information was collected using a retrospective method, transcribing clinical information from medical records. Specifically, the attending psychiatrist of the target patients at each hospital (or the person who was in charge of the survey at their respective institution [ie, a coauthor of this study] in cases where the attending psychiatrist was no longer present) collected and transcribed information related to the items investigated in the study (excluding personally identifiable information) from medical records obtained at each patient's initial medical examination.

2.3 | Investigated items

The main items we investigated were as follows.

2.3.1 | Basic information

Subject attributes (biological sex, age).

2.3.2 | F1 diagnosis regarding NPS according to the ICD-10 code

All applicable diagnoses were selected from the following: F19.0 acute intoxication, F19.1 harmful use, F19.2 dependence syndrome, F19.3 withdrawal state, F19.4 withdrawal state with delirium, F19.5 psychotic disorder, F19.6 amnesic syndrome, F19.7 residual and late-onset psychotic disorder, and F19.8 other mental and behavioral disorders.

2.3.3 | Simultaneous use of other psychoactive substances

All applicable items were selected from the following: alcohol, stimulant drugs, cocaine, other psychostimulant drugs, hypnotics and anxiolytics, cannabis, toluene, lacquer, and thinner, other volatile solvents (butane, freon gas, and gas dusters), over-the-counter drugs, opioids (heroin, morphine, and other narcotics for medical use), hallucinogens (eg, MDMA, LSD, PCP, and 5-Meo-DIPT), alkyl nitrites (eg, poppers), and other substances.

However, the use of alcohol, and hypnotics and anxiolytics was only assessed as “simultaneous use” if these items were used at a level that was equivalent to “harmful use” and beyond.

2.3.4 | Diagnosis of comorbid psychiatric disorders according to the ICD-10 Code

All applicable diagnoses were selected from the following: F0: organic, including symptomatic, mental disorders; F2: schizophrenia, schizotypal, and delusional disorders; F3: mood (affective) disorders; F4: neurotic, stress-related and somatoform disorders; F5: behavioral syndromes associated with physiological disturbances and physical factors; F6: disorders of adult personality and behavior; F7: mental retardation; F8: disorders of psychological development; and F9: behavioral and emotional disorders with onset usually occurring in childhood and adolescence.

2.3.5 | Psychiatric and neurological symptoms before and during the first medical examination

A total of seven psychiatric and nine neurological symptoms (for evaluating problematic behavior) were examined. These items were selected through discussion among the co-authors and the principal psychiatrists at each hospital as notable symptoms in clinical settings from the perspective of a specialist and as feasible items for review in the retrospective study.

The collected information was classified into two types of symptoms: symptoms that had been resolved during the first medical examination but which were the reason for visiting the hospital's outpatient department for the treatment of addiction (symptoms reported by patients and their families to be present within a month before the first medical examination), and symptoms that were identified during the first medical examination (symptoms observed during the first medical examination).

We collected data on the following psychiatric and neurological symptoms:

1. *Psychiatric symptoms.* All symptoms in the medical records that were considered to be applicable by the attending psychiatrist were selected from the following: severely depressed state, severe anxiety and tension, hallucinations and delusions, comprehension and/or concentration ability impairment or memory disturbance, uncontrollable violence, suicidal ideation, and suicide attempts.
2. *Neurological symptoms.* All symptoms in the medical records that were considered to be applicable by the attending physician were selected from the following: comas and fainting, convulsions, dysarthria, movement disorders such as weakness of limbs and paralysis, tremors, other types of involuntary movement, sensation disorders such as dysesthesia and loss of sensation, ataxia, and other neurological symptoms.

2.4 | Statistical analysis

In the current study, subjects were divided into three groups (FY2012, FY2013, or FY2014) depending on the fiscal year in which their first medical examination took place, and the rate of each investigated item was compared among these three groups.

For statistical analysis, we used SPSS version 22.0 (IBM, Chicago, IL, USA). For continuous variables, such as age, we performed an analysis of variance (and if significant differences were observed, Bonferroni's post hoc test was performed), and ratios were compared using Pearson's chi-square test.

As a general rule in the two-sided test, the level of significance was set at $P < 0.05$. However, for the chi-square test, which was conducted nine times for diagnosis by ICD-10 F1 subcategory, 14 times for psychiatric symptoms before and during the first medical examination, and 18 times for neurological symptoms before and during the first medical examination among the three groups, Bonferroni correction was performed to prevent type I errors, and the significance level was set at $P < 0.0055$, $P < 0.0035$, and $P < 0.0027$, respectively.

2.5 | Ethical considerations

This study was conducted after receiving approval from the ethics committee of the National Center of Neurology and Psychiatry to which one of the co-authors belongs, and by the ethics committees of all medical facilities at which the survey was conducted.

3 | RESULTS

We examined information collected from a total of 864 subjects with NPS-related disorders at eight hospitals specialized in the treatment of addiction: 105 subjects (12.2% of the sample) from Saitama Psychiatric Medical Center, 76 subjects (8.8%) from the



National Center of Neurology and Psychiatry, 174 subjects (20.1%) from Tokyo Metropolitan Matsuzawa Hospital, 294 subjects (34.0%) from Kanagawa Psychiatric Center, 12 subjects (1.4%) from Mie Prefectural Mental Medical Center, 82 subjects (9.5%) from Osaka Psychiatric Medical Center, 68 subjects (7.9%) from Okayama Psychiatric Medical Center, and 53 subjects (6.1%) from Hizen Psychiatric Center.

3.1 | Profile of subjects

Table 1 shows the profile of the 864 subjects included in this study. In the study sample, 774 subjects were male (89.6%) and 90 were female (10.4%), and the mean age (standard deviation; SD) was 30.7 (8.82) years.

Subjects reporting that they mainly used herbal products were the most frequent (641 subjects [74.2%]), followed by those who used both herbal products and nonherbal products (powder and liquid) (113 subjects [13.1%]), those who mainly used nonherbal products (75 subjects [8.7%]), and cases in which the main mode of NPS use was unknown (35 [4.1%]).

Regarding the diagnosis by ICD-10 F1 subcategory, subjects who were diagnosed with F19.2 dependence syndrome were the most frequent (714 subjects [82.6%]), followed by subjects who were diagnosed with F19.5: psychotic disorder (271 subjects [31.4%]), subjects who were diagnosed with F19.0: acute intoxication (68 subjects [7.9%]), subjects who were diagnosed with F19.1: harmful use (63 subjects [7.3%]), subjects who were diagnosed with F19.7: residual and late-onset psychotic disorder (14 subjects [1.6%]), subjects who were diagnosed with F19.6: amnesic syndrome (seven subjects [0.8%]), subjects who were diagnosed with F19.3: withdrawal state (six subjects [0.7%]), and subjects who were diagnosed with F19.4: withdrawal state with delirium (five subjects [0.6%]).

A total of 198 patients (22.9%) also used other psychoactive substances. Alcohol was the most frequently used (116 subjects [13.4%]), followed by hypnotics and anxiolytics (72 subjects [8.3%]), indicating that unregulated substances were the most commonly used. This was followed by cannabis (15 subjects [1.7%]), stimulant drugs (nine subjects [1.0%]), over-the-counter drugs (four subjects [0.5%]), other psychostimulant drugs, toluene, lacquer, and thinner, and other volatile solvents (eg, butane, freon gas) (two subjects each [0.2%]), and opioids (eg, heroin, morphine, other narcotics for medical use) (one subject [0.1%]).

Comorbid psychiatric disorders were observed in 134 subjects (15.5%). Specifically, F3: mood (affective) disorders were the most frequently observed (41 subjects [4.7%]), followed by F4: neurotic, stress-related and somatoform disorders (34 subjects [3.9%]), and F2: schizophrenia, schizotypal, and delusional disorders (21 subjects [2.4%]).

3.2 | Symptom features

Table 2 shows the psychiatric and neurological symptoms experienced by the 864 subjects included in this study (symptoms observed

before the first medical examination and symptoms observed during the first medical examination).

The most frequently observed psychiatric symptoms were hallucinations and delusions (observed before the first medical examination: 460 subjects [53.2%], observed during the first medical examination: 295 subjects [34.1%]), followed by comprehension and/or impaired concentration ability, or memory disturbance (observed before the first medical examination: 400 subjects [46.3%], observed during the first medical examination 270 subjects [31.3%]).

In contrast, the most frequently developed neurological symptoms were comas and fainting (104 subjects [12.0%] observed before the first medical examination, four subjects [0.5%] observed during the first medical examination), followed by convulsions (49 subjects [5.7%] observed before the first medical examination, 49 subjects [5.7%] observed during the first medical examination) and tremors (44 subjects [5.1%] observed before the first medical examination; 44 subjects [5.1%] observed during the first medical examination) at the same rate.

3.3 | Changes in symptoms depending on the fiscal year of the first medical examination

Table 3 shows the results obtained from a comparison of the diagnosis by the ICD-10 F1 subcategory made in FY2012–FY2014 with psychiatric and neurological symptoms observed at the time treatment was started in the same fiscal year.

No significant differences were observed when comparing age and sex ratios (percentage of males) in each fiscal year. In addition, no significant differences were observed between fiscal years regarding the form in which NPS products were mainly used, the percentage of the combined use of other psychoactive substances, or the percentage of other comorbid psychiatric disorders.

Differences between each fiscal year were found regarding the diagnosis of the ICD-10 F1 subcategory, and psychiatric and neurological symptoms observed before or during the first medical examination. First, regarding the ICD-10 F1 subcategory, significant differences were observed for F19.1: harmful use (4.3% vs 4.6% vs 12.7%, $P < 0.001$) and F19.5: psychotic disorder (38.7% vs 28.7% vs 27.0%, $P = 0.005$). These differences were also confirmed after performing the Bonferroni correction.

No significant differences were observed for the psychiatric symptoms observed before or during the first medical examination. Although a strong tendency for hallucinations and delusions was observed in FY2012 compared with other fiscal years (40.1% vs 30.9% vs 31.7%, $P = 0.037$), no significant difference was observed after Bonferroni correction.

Comparison of neurological symptoms revealed a significant difference in comas and fainting (observed before the first medical examination) (7.8% vs 11.0% vs 17.0%, $P = 0.002$), convulsions (observed before the first medical examination) (2.8% vs 4.3% vs 9.7%, $P = 0.001$), and tremors (observed before the first medical examination and observed during the first medical examination; 9.6% vs 2.8% vs 3.0%, $P < 0.001$: 5.0% vs 1.4% vs 0.3%, $P < 0.001$) after

TABLE 1 Profile of investigated subjects (demographic variables, fiscal year at the time of medical examination, and the status of *kiken* drug use, abused products, ICD-10 F1 subcategory, other substances abused, and comorbid psychiatric disorders during the first medical examination)

	Mean	SD
Age (y)	30.7	8.82
	Number of patients	Percentage
Sex		
Male	774	89.6
Female	90	10.4
Year of first medical examination		
FY2013	282	32.6
FY2013	282	32.6
FY2014	300	34.7
Product used		
Mainly used herbal products	641	74.2
Mainly used nonherbal products (powder and liquid)	75	8.7
Used both types of products	113	13.1
Unknown	35	4.1
Diagnosis by ICD-10 F1 subcategory		
(F19.0) Acute intoxication	68	7.9
(F19.1) Harmful use	63	7.3
(F19.2) Dependence syndrome	714	82.6
(F19.3) Withdrawal state	6	0.7
(F19.4) Withdrawal state with delirium	5	0.6
(F19.5) Psychotic disorder	271	31.4
(F19.6) Amnesic syndrome	7	0.8
(F19.7) Residual and late-onset psychotic disorder	14	1.6
(F19.8) Other mental and behavioral disorders	0	0.0
Used in combination with other psychoactive substances	198	22.9
Breakdown of all abused substances		
Alcohol	116	13.4
Stimulant drugs	9	1.0
Cocaine	0	0.0
Other psychostimulant drugs	2	0.2
Hypnotics and anxiolytics	72	8.3
Cannabis	15	1.7
Toluene, lacquer, and thinner	2	0.2
Other volatile solvents (butane, freon gas, gas dusters)	2	0.2

(Continues)

TABLE 1 (Continued)

	Number of patients	Percentage
Commercially available antitussives, cough, and cold preparations	4	0.5
Opioids (heroin, morphine, other narcotics for medical use)	1	0.1
Hallucinogens (MDMA, LSD, PCP, 5-Meo-DIPT, etc.)	0	0.0
Alkyl nitrites (poppers, etc.)	0	0.0
Other substances	0	0.0
Presence of comorbid psychiatric disorder(s)	134	15.5
Breakdown of comorbid psychiatric disorders		
F0: Organic, including symptomatic, mental disorders	2	0.2
F2: Schizophrenia, schizotypal and delusional disorders	21	2.4
F3: Mood [affective] disorders	41	4.7
F4: Neurotic, stress-related, and somatoform disorders	34	3.9
F5: Behavioral syndromes associated with physiological disturbances and physical factors	1	0.1
F6: Disorders of adult personality and behavior	15	1.7
F7: Mental retardation	11	1.3
F8: Disorders of psychological development	18	2.1
F9: Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	7	0.8

performing the Bonferroni correction. The results revealed that tremors were observed more frequently in FY2012, while comas and fainting, as well as convulsions, were observed more frequently in FY2014.

4 | DISCUSSION

Most of the 864 subjects in the current study were male (89.6%), and the mean age was 30.7 years. During the first medical examination, more than 30% of patients suffered from hallucinations and delusions, or exhibited comprehension and/or concentration ability impairments or memory disturbances. These psychiatric symptoms were considered by the attending psychiatrist to be caused by NPS. Regarding neurological symptoms, although some patients developed serious neurological symptoms, such as comas, fainting, and



TABLE 2 Psychiatric and neurological symptoms observed before/during the first medical examination in the 864 subjects included in this study

	Observed before the first medical examination		Observed during the first medical examination	
	Number of patients	Percentage	Number of patients	Percentage
Psychiatric symptoms observed before/during the first medical examination				
Severely depressed state	140	16.2	66	7.6
Severe anxiety and tension	222	25.7	157	18.2
Hallucinations and delusions	460	53.2	295	34.1
Comprehension and/or concentration ability impairment, or memory disturbance	400	46.3	270	31.3
Uncontrollable violence	293	34.5	139	16.1
Suicidal ideation	92	10.6	48	5.6
Suicide attempt	44	5.1	5	0.6
Neurological symptoms observed before/during the first medical examination				
Comas and fainting	104	12.0	4	0.5
Convulsions	49	5.7	2	0.2
Dysarthria	37	4.3	9	1.0
Movement disorders, such as weakness of limbs and paralysis	34	3.9	11	1.3
Tremors	44	5.1	44	5.1
Other types of involuntary movement	1	0.1	1	0.1
Sensation disorders, such as numbness of limbs and loss of sensation	25	2.9	14	1.6
Ataxia	23	2.7	6	0.7
Other neurological symptoms	31	3.6	31	3.6

convulsions before the first medical examination, these symptoms had largely resolved by the time of the first medical examination. Patients with such severe neurological symptoms were likely to have been transported to the emergency department of a medical facility that treats patients with physical symptoms, explaining why they visited a hospital specialized in the treatment of addiction.

Importantly, the current results revealed that the psychiatric and neurological symptoms of patients with NPS-related disorders, observed before the first medical examination or during the first medical examination, differed between fiscal years, and that adverse health impacts resulting from the use of NPS became more serious year-by-year. Although no differences were observed in age and sex ratios between years, or in the form in which NPS products were mainly used, in FY2012 a higher rate of patients was diagnosed with psychotic disorder, while in FY2014 more patients tended to exhibit neurological symptoms, such as comas, fainting, and convulsions. Psychotic disorders as well as comas, fainting, and convulsions are

all serious medical symptoms. However, in terms of lethality and the likelihood of causing a life-threatening crisis, neurological symptoms such as comas, fainting, and convulsions are more serious than psychiatric symptoms such as psychotic disorder. This suggests the possibility that NPS spreading in FY2014 contained higher amounts of high-risk compounds than NPS spreading in FY2012.

Counterintuitively, it is also possible that the tightening of regulations caused the producers of NPS to begin using unknown compounds, further jeopardizing the health of NPS users. After judging that the earlier approach (imposing ex post facto restrictions on a new illegal compound after detecting the emergence of that compound) was leading to a vicious circle, the Japanese government decided to introduce a new, comprehensive approach for designating illegal drug components, under which it preemptively regulated compounds with the same chemical structures as those of controlled compounds. Synthetic cannabinoids (compounds similar to tetrahydrocannabinol [THC]) were initially the main component of herbal



TABLE 3 (Continued)

	2012		2013		2014		F/ χ^2	P-value
	Number of patients	Percentage	Number of patients	Percentage	Number of patients	Percentage		
Hallucinations and delusions (During 1st med. exam.)	113	40.1	87	30.9	95	31.7	6.584	0.037
Comprehension and/or concentration ability impaired, or memory disturbance (Before 1st med. exam.)	134	47.5	127	45.0	139	46.3	0.350	0.840
Comprehension and/or concentration ability impaired, or memory disturbance (During 1st med. exam.)	94	33.3	86	30.5	90	30.0	0.862	0.650
Uncontrollable violence (Before 1st med. exam.)	91	32.3	91	32.3	116	38.7	3.547	0.170
Uncontrollable violence (During 1st med. exam.)	43	15.2	44	15.6	52	17.3	0.541	0.763
Suicidal ideation (Before 1st med. exam.)	30	10.6	28	9.9	34	11.3	0.301	0.860
Suicidal ideation (During 1st med. exam.)	15	5.3	17	6.0	16	5.3	0.178	0.915
Suicide attempt (Before 1st med. exam.)	14	5.0	9	3.2	21	7.0	4.377	0.112
Suicide attempt (During 1st med. exam.)	1	0.4	1	0.4	3	1.0	1.418	0.492
Neurological symptoms observed before/during the first medical examination								
Comas and fainting (Before 1st med. exam.)	22	7.8	31	11.0	51	17.0	12.047	0.002^a
Comas and fainting (During 1st med. exam.)	1	0.4	1	0.4	2	0.7	0.414	0.813
Convulsions (Before 1st med. exam.)	8	2.8	12	4.3	29	9.7	14.244	0.001^a
Convulsions (During 1st med. exam.)	1	0.4	1	0.4	0	0.0	1.066	0.587
Dysarthria (Before 1st med. exam.)	15	5.3	13	4.6	9	3.0	2.017	0.365
Dysarthria (During 1st med. exam.)	3	1.1	2	0.7	4	1.3	0.551	0.759
Movement disorders, such as weakness of limbs and paralysis (Before 1st med. exam.)	12	4.3	9	3.2	13	4.3	0.615	0.735
Movement disorders, such as weakness of limbs and paralysis (During 1st med. exam.)	4	1.4	1	0.4	6	2.0	3.201	0.202
Tremors (Before 1st med. exam.)	27	9.6	8	2.8	9	3.0	17.407	<0.001^a
Tremors (During 1st med. exam.)	14	5.0	4	1.4	1	0.3	15.682	<0.001^a
Other types of involuntary movement (Before 1st med. exam.)	1	0.4	0	0.0	0	0.0	2.066	0.356
Other types of involuntary movement (During 1st med. exam.)	0	0.0	0	0.0	0	0.0	—	—
Sensation disorders, such as numbness of limbs and loss of sensation (Before 1st med. exam.)	7	2.5	6	2.1	12	4.0	2.066	0.356

(Continues)

TABLE 3 (Continued)

	2012		2013		2014		F/ χ^2	P-value
	Number of patients	Percentage	Number of patients	Percentage	Number of patients	Percentage		
Sensation disorders, such as numbness of limbs and loss of sensation (During 1st med. exam.)	5	1.8	4	1.4	5	1.7	0.117	0.943
Ataxia (Before 1st med. exam.)	11	3.9	7	2.5	5	1.7	2.852	0.240
Ataxia (During 1st med. exam.)	1	0.4	1	0.4	4	1.3	2.720	0.257
Other neurological symptoms (Before 1st med. exam.)	9	3.2	11	3.9	11	3.9	0.213	0.899
Other neurological symptoms (During 1st med. exam.)	3	1.1	2	0.7	5	1.7	1.197	0.550

Bold indicate significant P value.
^a <0.05; Pearson's chi-square test.

NPS and were targeted by comprehensive regulations in March 2013. Subsequently, in January 2014, comprehensive regulations came into force for methamphetamine-like compounds (cathinone derivatives), which are found in powder-type and liquid-type NPS. It is highly likely that as a result of these regulations, from April 2014, NPS began to contain compounds that were neither synthetic cannabinoids nor cathinone derivatives. Thus, these new compounds may have been more dangerous than those used previously. According to the White Paper on Police 2015, the number of traffic-related law violations related to NPS was zero in 2010 and 2011, then markedly increased to 40 violations in 2012, and as many as 160 violations in 2014.¹² Thus, the shift from psychiatric to neurological symptoms observed in NPS abusers in this study may reflect changes in drug compounds.

Furthermore, in the current study, we observed an increase in the number of patients who fell into the ICD-10 F1: harmful use criteria (a subcategory of dependence syndrome) in FY2014. This might indicate the circumstances under which the increasing number of patients visited specialized medical facilities before they became drug dependent because they had developed serious neurological symptoms and could not continue to use these drugs until they reached the subcategory of dependence syndrome.

The present results highlight the significance of this issue for public health, indicating the limited effectiveness of the government's measures for preventing drug abuse, which solely focus on stopping the supply of drugs. Although previous measures interrupting the supply of legal intoxicants by tightening regulations were successful to some extent in the case of magic mushrooms and 5-Meo-DIPT, the measures that were taken for preventing the abuse of NPS cannot be considered successful. As pointed out by Matsumoto et al¹³ in a survey that included psychiatric hospitals across Japan, although no changes in the percentage of patients with dependence syndrome were observed among patients with stimulant drug-induced disorders between 2012 and 2014, among patients with NPS-related disorders, significant increases were observed in both the percentage of patients with dependence syndrome and those with barriers to occupational functioning. These findings also indicate that the government's approach was inadequate, focusing on stopping the supply of drugs by tightening regulations but paying little attention to reducing the demand for drugs by providing treatment to drug-dependent patients.

Importantly, although the problem of NPS abuse appeared on the surface to have improved from 2015, a significant increase in the number of cannabis control law offenders who were put into custody was observed from FY2014.¹² Thus, it would be unsurprising for drug abusers suffering dependence syndrome to search for other drugs if their preferred drugs became unavailable. In addition, if individuals began to use "illegal" drugs falling under drug prohibition laws, they would be less likely to visit a medical facility because of fear that the police would be informed, resulting in reduced access to medical care.

Thus, effective measures for preventing drug abuse in Japan should involve the development and expansion of medical



resources for the treatment of addiction, in conjunction with measures to reduce the demand for drugs by establishing a medical care system in which drug users can undergo treatment without fearing legal consequences, such as notification of the police or detention.

The present study involved several limitations that should be considered. First, our data collection was conducted retrospectively, relying on medical records. Thus, the information obtained would be expected to be less accurate than that of prospective studies.

Second, we only evaluated the symptoms of individuals who visited hospitals. Therefore, the symptoms of individuals who did not visit a hospital facility were not considered in this study. Third, we did not collect information concerning the quantities of drugs used by patients or the frequency of use and did not evaluate the severity of dependence among all patients. Fourthly, our study could not examine the components of NPS used by patients in each year. Therefore, we can only guess that NPS has become more dangerous in FY 2014 than FY 2012. Finally, the symptoms and psychiatric diagnoses relied solely on information obtained by the attending psychiatrist when interviewing the patient. Therefore, the validity of the information might be limited to some extent, because psychiatric and neurological symptoms were not confirmed with structured interviews.

Despite these limitations, to our knowledge, the current survey examined the largest sample of patients with NPS-related disorders visiting Japan's main specialized hospitals to date and is the only survey focusing on the treatment of NPS-related disorders over time.

The current study elucidated changes in the symptoms of patients with NPS-related disorders depending on the fiscal year during which they underwent medical examination for the first time and investigated the health-related impacts of tightened drug regulations based on data from 864 patients with NPS-related disorders who visited eight hospitals specializing in the treatment of addiction. Information was collected retrospectively based on medical records, and patients' psychiatric and neurological symptoms were compared with those observed in the fiscal year of their first medical examination. The results revealed that, while in FY2012 adverse health effects resulting from the use of NPS were mainly psychiatric symptoms, in FY2014 NPS users were more likely to develop neurological symptoms. These findings suggest the possibility that NPS in FY2014 (after drug-related regulations had been tightened) contained more dangerous and toxic compounds than those in FY2012. Thus, our results indicate that, rather than only adopting measures to stop the supply of drugs, comprehensive measures for preventing drug abuse, including measures focused on reducing the demand for drugs, are required.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors have been personally and actively involved in substantive work contributing to this report, and hold themselves jointly and individually responsible for its content. DF mainly drafted the manuscript; TM designed the study and TM and DF analyzed data; TM, DF, YT, YK, SS, NN, SI, TS, TM, and TC collected data, and DF and TM drafted tables and parts of the manuscript.

DATA REPOSITORY

We offer Data S1.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

This study conducted by the ethics committee of the National Center of Neurology and Psychiatry (Approval No. A 2015-033).

INFORMED CONSENT

We consulted that this study is nonintrusive and low risk, judged that the method of acquiring patient information by opt-out is appropriate and obtained approval by the ethics committee. We provided information to patients and protected patient information. All hospitals posted a poster to inform the patients of this research to be displayed at the hospital. We put information on this study on the website (https://www.ncnp.go.jp/guide/ethics_result.html).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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