The influence of tightening regulations on patients with new psychoactive substance-related disorders in Japan

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Abstract
Aims: This study aimed to investigate the influence of tightened regulations on new psychoactive substances in patients with disorders related to these drugs in Japan.

Methods: We used a biennial nationwide survey on drug-related psychiatric disorders to examine why individuals who had previously used new psychoactive substances as their primary drug (the drug that had the greatest impact on their psychiatric symptoms) had switched to other drugs, how they had used drugs in the last 12 months and what type of drugs they were now using. We compared the clinical features of these individuals with patients who mainly used new psychoactive substances and had used these drugs at least once in the last 12 months.

Results: A total of 2262 people were included, and 399 had used new psychoactive substances. Of those, 71 people had switched to another drug as primary drug, mostly stimulant drugs (35.2%), hypnotics and anxiolytics (15.5%), and cannabis (14.1%) and used these drugs during the previous 12 months. The majority, 53.3%, had switched “because new psychoactive substances were no longer available.” In total, 25 people mainly used new psychoactive substances. The group that had changed drugs had more experience of using methamphetamine and were more likely to have abused other drugs before using new psychoactive substances. They had often switched to illegal or prescription drugs after regulations had been tightened.

Conclusion: The number of patients abusing new psychoactive substances decreased after drug regulations were tightened, but new psychoactive substance-related problems still exist. It is therefore not enough to tighten regulations. Drug dependence treatment and recovery support are also needed.

KEYWORDS
drug abuse, drug dependence, nationwide survey, new psychoactive substances, regulations

1 INTRODUCTION

New psychoactive substances (NPS) have spread throughout the worldwide drugs’ market.1–6 Their use has become a global phenomenon, existing in some 94 countries as of December 2013.7 In total, 27 million people are thought to be affected by a total of 541 NPS as of December 2014.8 NPS have been a serious social problem in Japan since the mid-2000s.

The term NPS was first coined by the UNODC for substances of abuse that may harm public health, but are not controlled under
current legislation. These drugs are very similar to controlled substances, but their chemical structure has been slightly modified to circumvent drug prohibition laws. They cannot be detected with existing tests, but have similar effects to controlled substances, such as giving a sense of exaltation and euphoria, and can harm the central nervous system, causing dependence and toxic symptoms. Initially, these new addictive substances were sold in stores and on the Internet because there were no clear rules about their sale. They were readily available and also cheaper than controlled substances.

The expanded abuse of these substances was accompanied by a drastic increase in reports about related adverse events in Japan. At the Japan Poison Information Center, the number of NPS-related consultations has dramatically increased since 2011, and there have been reports of people with hallucinations and delusions, disturbances of consciousness, convulsions, and cardiac arrest caused by acute poisoning requiring emergency medical care. In addition to violence and suicidal behavior, reports about car accidents while under the influence of NPS rose at an alarming rate in Japan.

These drugs are now formally known as kiken (or dangerous) drugs in Japan.

As a countermeasure, the Japanese Government began to regulate the use of these substances in the mid-2000s. Since then, regulations have been tightened several times, and efforts have been made to take abusers and vendors of these drugs into custody. A comprehensive designation of illegal drug components was introduced in 2013, and the Japanese Pharmaceutical Affairs Act was revised in November 2014 to increase inspections and sale suspension orders for shops, to stop sales of NPS. In July 2015, it was reported that outlets selling these drugs had been completely eradicated in Japan.

As a result of these actions, many people stopped abusing NPS, but some switched to other drugs. As far as we know, there have been no studies examining the types of drugs now used, or the background and history of drug abuse among these users. The aim of this study was therefore to look at the impact of the tightening of regulations on patients with NPS-related disorders in Japan. It used the Nationwide Mental Hospital Survey on Drug-related Psychiatric Disorders (2016) to look at the clinical features of individuals who have abused these drugs in the past, but have changed to other drugs, and compared them with individuals who still use NPS as their primary drug despite the tighter regulations.

2 METHODS

2.1 Data source

The Nationwide Mental Hospital Survey on Drug-related Psychiatric Disorders is the only complete study of patients with substance-induced mental health problems in Japan. It has been conducted every other year since 1987, using almost the same methodology, to gather information about drug abuse and drug-dependent people in Japan. Various strategies against drug abuse have been developed based on its results. The survey includes all medical facilities with psychiatric wards in Japan and covers any individuals diagnosed with F1 of the ICD-10 (“Mental and behavioral disorders due to psychoactive substance use”) at the time of the survey but to whom F10 does not apply (ie, all “patients with substance-induced disorders due to the use of psychoactive substances other than alcohol”), who were treated as an inpatient or outpatient at one of the target sites during the 2 months from September 1 to October 31 in the year of the survey.

The 2016 survey used the same method as in previous years. All target sites were notified in writing about the aim and method of the survey and were asked to cooperate with the survey and inform their patients about it. As a general rule, patients were only interviewed if they had given verbal consent. A survey request letter, survey information leaflet, and survey form were sent by mail to each target site, and the attending physician was asked to fill out the survey form for patients with substance-induced mental health problems who fulfilled the requirements described above.

The survey items included demographic data (gender, age), highest level of education (high school graduate or higher/less than high school graduate), employment at the time of the survey, criminal record (history of drug-related crimes, non-drug-related crimes, or detention in a correctional facility), history of drug use, drug use status during the last 12 months, drug of abuse (their “primary drug,” or the drug that is believed by their doctors to have the greatest impact on their psychiatric symptoms at the time of the survey), and diagnosis of drug use (lower-level diagnosis of ICD-10 classification F1).

The 2016 survey also included questions on “whether the patient had switched to another drug as primary drug at the time of this survey after using NPS as primary drug in the past.” Those to which this applied were asked to select all items that applied about the reason why they had changed to a different drug from: “Because NPS were no longer available,” “Because I had personal experience that NPS can cause severe health problems, and therefore did not want to use them anymore,” “Because the punishment for use of NPS is now more severe, and I did not want to be put into prison,” “Because I became afraid of using NPS after hearing, eg, in the news that they can cause severe health problems,” and “Others.”

Patients who did not want to participate in the survey were reported as “Refused to participate in this survey.” If it was difficult to interview patients because of their medical condition or they had already been discharged from hospital, then data were used from their medical records, and it was not considered necessary to obtain consent.

2.2 Subjects

The subjects of this study were anyone who had switched to another drug as their primary drug after using NPS as their primary drug in the past, and had used another drug as their primary drug during the 12 months before the survey. This group is known in this study as the “switch group.” The subjects also included a group of participants who used NPS as their primary drug, and had used these drugs during the previous 12 months (“NPS group”).
2.3 Procedure

The following points were examined for each individual in the switch group:

1. Drug of abuse (primary drug) at the time of the survey.
2. The reason for switching to other drugs (multiple answers possible) was checked to examine the effect of the tighter regulations.
3. Comparison between the switch group and others with NPS-related disorders. We compared the switch group with 25 survey participants who used NPS as their primary drug, and had used these drugs during the previous 12 months. We looked at three areas:
   a. Attributes (gender, age, educational background, employment rate, history of being taken into custody or arrested for drug-related crimes, history of being taken into custody or arrested for other crimes, history of confinement in a correctional facility, alcohol-related problems [diseases, rather than harmful alcohol use] at the time of the survey, and history of psychiatric hospitalization because of drug problems);
   b. The drugs used during their lifetime; and
   c. Whether their first drug use had been NPS.

2.4 Statistical analysis

We used Pearson’s chi-square test to compare the two groups because we examined only qualitative variables. In a two-sided test, the level of significance was set at less than 5%. Multiple comparisons were required to compare all items related to lifetime experience with each drug between the two groups, so the test had to be repeated 12 times. We therefore used the Bonferroni correction, and the level of significance was set at less than 0.42% (0.05/12 or approximately 0.0042).

2.5 Ethical considerations

The conduct of this investigative study was approved by the ethics committee of the National Center of Neurology and Psychiatry (Approval No. A2016-002).

3 RESULTS

In total, 1241 (78.7%) of the 1576 target sites completed the 2016 Nationwide Mental Hospital Survey on Drug-related Psychiatric Disorders. Of the 2303 subjects from whom data were collected, 2262 (1637 male [72.4%], 623 female [27.5%], and two other [0.1%]) were included in the survey, of whom 399 (17.6%) had used NPS. Of these, 98 (4.3%) fulfilled the requirement “that they had switched to another drug as primary drug at the time when this survey was conducted after using NPS as their primary drug in the past.” A total of 71 (8.4%) had abused their existing primary drug during the last 12 months and were designated as the switch group. A total of 101 people (4.5%) had used NPS as their main drug, and of these, 25 (1.1%) had used these drugs in the last 12 months and were designated as NPS group.

In the switch group, the most frequently used primary drug type at the time of the survey was methamphetamine (25 individuals, 35.2%), followed by hypnotics and anxiolytics (11 people, 15.5%), cannabis, volatile solvents, and multiple substances (10 people, 14.1%, each), and commercially available drugs (five people, 7.0%). The most frequent reason why individuals in the switch group had changed to another primary drug was “Because NPS were no longer available” (38 people, 53.3%), followed by “Others” (17 people, 23.9%), “Because I had personal experience that NPS can cause severe health problems, and therefore did not want to use them anymore” (16 people, 22.5%), “Because the punishment for use of NPS is now more severe, and I did not want to be put into prison” (14 people, 19.7%), and “Because I became afraid of using NPS after hearing, eg, in the news that they can cause severe health problems” (nine people, 12.7%).

A comparison of the attributes that were examined is shown in Table 1. The 25 individuals in the NPS group included 24 males (96.0%) and one female (4.0%), and the 71 in the switch group included 56 males (78.9%) and 15 females (21.1%). There were therefore significantly more females in the switch group (P = 0.048).

There were no significant differences between groups in terms of age, educational level or percentage with a job at the time of the survey. There were also no significant differences in the percentage of individuals with a history of being taken into custody or arrested for drug-related crimes (NPS group: 10 people [40.0%], switch group: 35 people [49.3%]). There were, however, significant differences in the percentage with a history of being taken into custody or arrested for other crimes (NPS group: 10 people [40.0%], switch group: 21 people [29.6%]). The percentage of individuals with a history of confinement in a correctional facility (24 people [33.8%] vs four [16.0%]) and the percentage of individuals with alcohol-related problems at the time of the survey (NPS group: six people [24.0%], switch group: 19 people [26.8%]) were not significantly different between the groups, and neither was the percentage of individuals with a history of psychiatric hospitalization because of drug problems (NPS group 20: people [80.0%], switch group: 58 people [81.7%]).

A comparison of lifetime experience of each drug is shown in Table 2. In the NPS group, cannabis was the most popular drug (10 people [40.0%]), followed by methamphetamine and MDMA (3,4-methylenedioxymethamphetamine; six people, 24.0%, each), hypnotics and anxiolytics (five people, 20.0%), cocaine (four people, 16.0%), volatile solvents and hallucinatory drugs other than MDMA (three people, 12.0%, each), and heroin (one person, 4.0%). In the switch group, methamphetamine (52 people, 73.2%) and cannabis (49 people, 69.0%) were the most popular, followed by volatile solvents (24 people, 33.8%), hypnotics and anxiolytics (22 people, 31.0%), and MDMA (21 people, 29.6%). The switch
group therefore showed higher percentages with experience of methamphetamine, cannabis, and volatile solvents. After Bonferroni correction, however, only lifetime experience of methamphetamine use showed any significant difference between groups ($P < 0.001$).

The first drug used by the largest proportion of the NPS group had been NPS (12 people, 48.0%), followed by cannabis (five people, 20.0%), and methamphetamine (four people, 16.0%). One person had used each of volatile solvents, hypnotics and anxiolytics, others, and unknown as their first drug. In the switch group, most people (28, 39.4%) had taken cannabis as their first drug, followed by NPS (14 people, 19.7%), volatile solvents (10 people, 14.1%), and methamphetamine (eight people, 11.3%). Three people had their first drug experience with each of MDMA and commercially available drugs.

A comparison of those whose first drug experience had been with NPS, and other drugs is shown in Table 3. In the switch group, most subjects had taken drugs other than NPS first, and there was a significant difference between the groups (NPS group: 13 people, 52.0%, switch group: 57 people, 80.3%).

### Table 1 Comparison of attributes between the NPS group and the switch group (N = 96)

|              | NPS group (n = 25) | Switch group (n = 71) | Pearson’s chi-squared test Asymp. Sig. (2-sided) |
|--------------|-------------------|----------------------|-----------------------------------------------|
| Gender       |                   |                      |                                               |
| Male         | Frequency         | 24                   | 56                                             |
|              | %                 | 96.0                 | 78.9                                          |
| Female       | Frequency         | 1                    | 15                                             |
|              | %                 | 4.0                  | 21.1                                          |
| Current age  |                   |                      |                                               |
| 10-19 y of age | Frequency      | 0                    | 1                                              |
|              | %                 | 0.0                  | 1.4                                           |
| In their 20s | Frequency         | 5                    | 25                                             |
|              | %                 | 20.0                 | 35.2                                          |
| In their 30s | Frequency         | 15                   | 31                                             |
|              | %                 | 60.0                 | 43.7                                          |
| In their 40s | Frequency         | 4                    | 10                                             |
|              | %                 | 16.0                 | 14.1                                          |
| In their 50s | Frequency         | 1                    | 4                                              |
|              | %                 | 4.0                  | 5.6                                           |
| In their 60s | Frequency         | 0                    | 0                                              |
|              | %                 | 0.0                  | 0.0                                           |
| In their 70s or older | Frequency | 0                  | 0                                              |
|              | %                 | 0.0                  | 0.0                                           |
| High school graduate or higher (Yes) | Frequency | 14                   | 39                                             |
|              | %                 | 56.0                 | 54.9                                          |
| Had a job/was employed at the time of the survey | Frequency | 9                    | 19                                             |
|              | %                 | 36.0                 | 26.8                                          |
| History of being taken into custody or arrested for drug-related crimes (Yes) | Frequency | 10                   | 35                                             |
|              | %                 | 40.0                 | 49.3                                          |
| History of being taken into custody or arrested for other crimes (Yes) | Frequency | 2                    | 21                                             |
|              | %                 | 8.0                  | 29.6                                          |
| History of confinement in a correctional facility (Yes) | Frequency | 4                    | 24                                             |
|              | %                 | 16.0                 | 33.8                                          |
| Currently suffers from alcohol-related problems (Yes) | Frequency | 6                    | 19                                             |
|              | %                 | 24.0                 | 26.8                                          |
| History of psychiatric hospitalization for drug problems (Yes) | Frequency | 20                   | 58                                             |
|              | %                 | 80.0                 | 81.7                                          |

*<0.05: Pearson’s chi-square test.
Table 2: Comparison of lifetime experience with each drug (N = 96)

| Lifetime experience with each drug | NPS group (n = 25) | Switch group (n = 71) | Pearson’s chi-squared test Asymp. Sig. (2-sided) |
|-----------------------------------|-------------------|----------------------|-----------------------------------------------|
| Methamphetamine                  | Frequency 6 52    | % 24.0 73.2          | <0.001*                                       |
|                                   |                   |                      |                                               |
| Volatile solvents                 | Frequency 3 24    | % 12.0 33.8          | 0.037                                         |
| Cannabis                          | Frequency 10 49   | % 40.0 69.0          | 0.010                                         |
| Cocaine                           | Frequency 4 7     | % 16.0 9.9           | 0.407                                         |
| Heroin                            | Frequency 1 2     | % 4.0 2.8            | 0.770                                         |
| MDMA                              | Frequency 6 21    | % 24.0 29.6          | 0.594                                         |
| Hallucinatory drugs               | Frequency 3 12    | % 12.0 16.9          | 0.562                                         |
| MDMA                              | % 12.0 16.9       |                      |                                               |
| Hypnotics and anxiolytics         | Frequency 5 22    | % 20.0 31.0          | 0.293                                         |
| Analgesic agents (non-opioid      | Frequency 0 2     | % 0.0 2.8            | 0.396                                         |
| commercially available drugs      |                   |                      |                                               |
| Drugs used for the treatment of ADH| Frequency 0 2     | % 0.0 2.8            | 0.396                                         |
| Others                            | Frequency 0 2     | % 0.0 2.8            | 0.396                                         |

*<0.0042: Bonferroni correction; 0.005/12 or approximately 0.0042.

Table 3: Comparison of first-time drug experience (N = 96)

| Drug used when taking drugs for the very first time | NPS group (n = 25) | Switch group (n = 71) | Pearson’s chi-squared test Asymp. Sig. (2-sided) |
|---------------------------------------------------|-------------------|----------------------|-----------------------------------------------|
| New psychoactive substances                       | Frequency 12 14    | % 48.0 19.7          | 0.006*                                        |
| Other drugs or unknown                            | Frequency 13 57    | % 52.0 80.3          |                                               |

*<0.05: Pearson’s chi-square test.

4 | DISCUSSION

When NPS were recognized as a serious social problem in Japan, regulations were tightened to reduce their supply. However, the effect of these tightened regulations on abusers of these drugs was unclear. This is the only study of which we are aware that has identified and explored the clinical features of individuals who have switched from NPS to other drugs of abuse as a result of regulations. It has also showed how the tightening of regulations resulted in changes to patients with NPS-related disorders in psychiatric care by comparing individuals that have abused these drugs in the past but now switched to other drugs of abuse, with individuals who have continued to abuse NPS after regulatory changes.

The 2012 Nationwide Mental Hospital Survey on Drug-related Psychiatric Disorders added items on NPS to help hospitals to cope with the rapid increase in patients with disorders induced by these drugs. NPS were immediately the second-most popular primary drugs of abuse after methamphetamine, which continues to cause major problems in clinical psychiatry in Japan. Patients using NPS as their primary drug and who had used these drugs during the last 12 months accounted for 14.5% of all eligible subjects. In the 2014 survey, NPS again ranked second, and the percentage of patients using these as their primary drug of abuse increased from 16.3% to 23.7%. Patients using these as their primary drug, and who had used them during the previous 12 months accounted for 22.5% of all eligible subjects, and NPS were the most popular drugs used during the previous 12 months (used by 25.0% of all eligible subjects; multiple items could be selected). In 2014, therefore, NPS might have been the drug type that caused the greatest problems in clinical practice with regard to drug abuse and dependence. The situation of Europe was similar. In the same year, for example, a survey targeted 13 128 young adults aged 15-24 across the 28 EU Member States. In total, 8% of respondents reported lifetime use of NPS, with 3% reporting use in the last year. This was an increase from the 5% reporting lifetime use in a similar survey in 2011.

In the 2016 survey in Japan, the percentage of subjects using NPS as their primary drug of abuse had greatly decreased from 23.7% (2014 survey) to 4.5%, and the percentage of these who had used these drugs during the previous 12 months had also fallen, from 22.5% (2014 survey) to just 1.1%. This shows that the number of patients with NPS-related disorders decreased between 2014 and 2016, and this is believed to be the result not only of tightened regulations after the stepwise enforcement of the comprehensive designation of illegal drug components in 2013, but also because of the revision of the Pharmaceutical Affairs Act, which was enacted at the end of 2014 (“Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices”) and which eventually lead to the clearance of sale outlets for these drugs. A similar phenomenon was observed in the United Kingdom (England and Wales). In a survey in 2014/2015, after control measures had been introduced, use in the previous year of a form of NPS among young people aged 16-24 was estimated at 1.9%, down from 4.4% in 2010/2011. To respond to the proliferation of NPS, many countries have regulated these substances. The World Health Organization provides information on drug dependence, to guide the regulation of drugs in different countries.

In this study, the switch group had mostly switched from NPS to methamphetamine, followed by hypnotics and anxiolytics, cannabis, and volatile solvents. More than half of the respondents answered that the reason they had changed to a different drug was “Because
NPS were no longer available.” Fewer than 20% said “Because the punishment for use of NPS is now more severe, and I did not want to be put into prison.” This suggests that more than 70% had changed their main drug as a result of tighter regulations, and that the regulations to reduce the supply of NPS were effective, at least to some extent.

The switch group contained a higher proportion of women. It also contained a greater proportion of people with a history of being taken into custody, arrested, or confined in a correctional facility for non-drug-related crimes, and a high percentage of individuals with lifetime experience of methamphetamine use. Most people’s first drug experience was not with NPS. Although there was no statistically significant difference, a higher percentage of subjects in the switch group had used cannabis. NPS had been the first drug used by most people in the NPS group, while most of those in the switch group had started with cannabis use.

These results suggest that many of those in the switch group had used illegal drugs such as cannabis and methamphetamine before taking NPS, and that their resistance to using illegal drugs was low. Many of them may therefore have switched to a different drug of abuse and started to use illegal drugs, such as methamphetamine, after regulations were tightened and sale outlets closed down.

Taken together, we suggest that there may be two patterns for people who originally abused NPS, and were drug-dependent, and who continued to use drugs after regulations were tightened. The first pattern is to search for a different addictive drug instead of NPS, and return to using illegal drugs such as methamphetamine, which they had abused in the past. The second pattern is to switch to hypnotics and anxiolytics as drug of abuse while worrying about judicial consequences such as being arrested. Interrupting the supply of addictive drugs may therefore result in conversion to other drugs, rather than preventing drug abuse altogether. If particular drugs are not available, those who suffer from drug addiction will search for and use alternatives. There is supporting evidence that may substantiate this hypothesis. For example, the number of patients who were dependent on NPS, based on their ICD-10 subclass, significantly increased from 2012 to 2014, while the number dependent on methamphetamine did not change. This may suggest that the demand for addictive drugs among patients with NPS-related disorders might have increased despite regulatory changes. It is possible that regulatory tightening as an antidrug measures in Japan has even resulted in new categories of drug abuse such as in the switch group.

Making the abuse of drugs illegal through tightened regulations causes another important issue. When the use of drugs becomes illegal, fewer abusers may seek medical care because of fear that the police will be informed. This might be one reason why the number of patients with NPS-related disorders drastically decreased after regulatory changes. Poorer access to medical care means that people with drug dependence do not receive treatment, and as a result, it is not possible to reduce the demand for drugs. In recent years, many European countries have responded quickly to NPS by classifying certain substances as medicines. Although products defined as medicines require more rigorous testing and face more regulatory controls on the marketing of any physiological corrective benefits, classifying an NPS as a medicine would avoid criminalizing its use. Several NPS have successfully been removed from markets in a handful of European countries. Legal frameworks such as consumer safety and medicine laws appear to be useful in protecting public health without the need for new drug laws with heavy criminal penalties. A blanket ban is likely to minimize, but not eliminate, NPS abuse but increase the prevalence of other substance abuse.

This study had several limitations. First, its targets were patients with substance-related disorders who were treated at psychiatric care facilities as an inpatient or outpatient. These patients therefore do not necessarily reflect the characteristics of drug abusers in the community. The second limitation is that the number of subjects was very small so future studies should try to involve more people. The third limitation is that the information used in this study was collected by the attending physician for individuals with substance-related disorders at each trial site. It is possible that the evaluation criteria used by each physician varied, and that in therapeutic settings, patient declarations were biased. The fourth limitation is that to set up an appropriate multivariate analysis model, the target variables used for the analysis were reduced to the requisite minimum. The analysis therefore did not include variables, for example, for comorbid disorders or family background, which might have affected results.

5 | CONCLUSION

From the mid-2000s, NPS have been a serious social problem in Japan. As a result of regulatory changes, however, the number of patients with disorders relating to these drugs in psychiatric care sharply decreased. This study showed that a proportion of subjects who had mainly abused NPS in the past had switched to other drugs of abuse, and that about half of these people switched to methamphetamine or cannabis. Compared with individuals who continued to abuse NPS after regulatory changes, many patients who switched from NPS to other drugs had experience of previous use of methamphetamine and had used other drugs before starting to use NPS. This suggests that these patients might have switched from NPS to illegal drugs such as methamphetamine, or to legal drugs such as prescription drugs, when NPS became less available.

It is important to control access to dangerous drugs by law. This study, however, shows that when particular drugs are made unavailable, people who suffer from drug addiction will search for and use other drugs instead. Limiting access to one particular type of drug therefore does not solve the problem of drug dependence. Antidrug measures in Japan traditionally interrupted the supply of drugs, but this does not seem to be sufficient. It is also important to ensure that the demand for drugs is reduced, by providing treatment and support systems to prevent drug abuse.
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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA REPOSITORY

We offered Supporting Information.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

The conduct of this investigative study was approved by the ethics committee of the National Center of Neurology and Psychiatry (Approval No. A2016-002).

INFORMED CONSENT

This Nationwide Mental Hospital Survey on Drug-related Psychiatric Disorders used the same method as in previous years. All target sites were notified in writing about the aim and method of the survey and were asked to cooperate with the survey and inform their patients about it. Patients were only interviewed if they had given verbal consent. A survey request letter, survey information leaflet, and survey form were sent by mail to each target site.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

n/a.

ANIMAL STUDIES

n/a.

AUTHOR CONTRIBUTIONS

Y.T. wrote the manuscript, T.M. collected data, conducted statistical analyses, and supervised Y.T.'s completion of the final manuscript, and T.S. planned the survey and obtained the grant for the work. All authors read and approved the final manuscript.

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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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