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Prevalence and associated factors of hypnotics dependence among Japanese outpatients with psychiatric disorders

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ABSTRACT

This study aimed to investigate the prevalence of the dependence for benzodiazepine or their agonist (BZDs) hypnotics, as well as factors associated with this dependence among Japanese psychiatric outpatients. One thousand and forty-three patients in the psychiatric outpatient clinic of Tokyo Medical University Hospital receiving treatment with BZDs hypnotics were analyzed. The subjects answered questionnaires including demographic variables, subjective sleep difficulty assessed by the Pittsburg Sleep Quality Index (PSQI), duration of hypnotics medication, dose of diazepam equivalent BZDs hypnotics, the presence or absence of subjective side effects due to BZDs hypnotics (dizziness, fatigue, daytime sleepiness, amnesia, and headache), and dependency assessed by the Dependency 2-A (D 2-A) score. Subjects with a D 2-A score ≥ 10 were considered as having BZDs hypnotics dependence, and the variables associated with the presence of dependence were examined using logistic regression analyses. Eighty-two out of the 1043 subjects (7.9%) were determined to have BZDs hypnotics dependence. Compared with the non-dependence group, the dependence group had a significantly higher proportion of positive respondents for all the side effects. Multiple logistic regression analyses showed that the dependence was significantly associated with younger age, higher total PSQI score, and higher daily dose of BZDs hypnotics. Younger age, higher total PSQI score, and higher dose may be associated with BZDs hypnotics dependence. The finding that patients with BZDs hypnotics dependence frequently suffered from subjective side effects and had greater sleep difficulty encourages the establishment of alternative treatments for patients with insomnia symptoms refractory to BZDs hypnotics treatment.

1. Introduction

Benzodiazepine derivatives and benzodiazepine receptor agonists (benzodiazepine drugs: BZDs) hypnotics are widely used in clinical settings as the first-line treatment for insomnia (Ohayon and Caulet, 1998). BZDs are also accepted as an important treatment option for moderate to severe insomnia comorbid with psychiatric diseases (Walsh, 2004). However, the Consensus Guidelines of the U.S. National Institutes of Health (NIH) accepts only cognitive behavioral therapy (CBT) and benzodiazepine receptor agonists as appropriate treatment choices for short-term insomnia. For chronic insomnia, eszopiclone has been confirmed by randomized controlled clinical trials to be safe and effective upon relatively long-term use (Krystal et al., 2003; National Institutes of Health, 2005; Melton et al., 2005; Uchimura et al., 2012). However, the long-term use of other BZDs hypnotics has not been recommended for the treatment of chronic or short-term insomnia, because the safety of these drugs has not yet been proven by controlled studies.

The long-term use of BZDs hypnotics may lead to increased doses, which is likely to be associated with an increased frequency of adverse events, such as next morning hangover, impaired cognitive function, and impaired coordination (Ashton, 1995; Council Report CR 59 January 1997, 2002; Cuevas et al., 2003; Baker et al., 2004). Furthermore, an elevated risk for dependence and its associated withdrawal symptoms are critical problems for BZDs hypnotics use (Tyrer et al., 1983; Ashton, 1995). Moreover, of note is that withdrawal symptoms may occur under conditions of optimal use of BZDs, and this phenomenon has prohibited BZDs users from reducing the dose or discontinuing use (Vyas and Carney, 1975; Hallstrom and Lader, 1981; Ashton, 1995; O'Brien, 2005). For these reasons, BZDs hypnotics have been included in Schedule IV

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of the U.S. (DEA Drug Scheduling Reference, 1970), which is defined as drugs with a small but significant possibility of causing physical or psychological dependence that are recommended for short-term use at low doses for no longer than 4 weeks (Lader and Psych, 1999; National Institutes of Health, 2005). However, long-term continuous use and concomitant multi-drug use of hypnotics are relatively common in Japan (International Narcotics Control Board, 2011). The number of prescriptions for BZDs hypnotics has clearly decreased in the U.S. and Oceanic countries in recent years, and several European countries are experiencing a similar trend (International Narcotics Control Board, 2011). In contrast, Asian countries including Japan are experiencing a trend of increasing number of prescriptions of these drugs, particularly since 2009 (International Narcotics Control Board, 2011).

There have already been several surveys on drug dependence or abuse of legally controlled substances, and the results have shown that young people are at a high risk for these conditions (Substance Abuse and Mental Health Services Administration, 2002). However, only a limited number of studies have been conducted on the prevalence and risk factors of drug dependence for hypnotics, and systematic research addressing this issue has not been conducted in Japan. Moreover, despite the fact that a particularly high number of Japanese patients with psychiatric disorders are treated with BZDs hypnotics for long periods (Janson et al., 2001; Walsh, 2004; O'Brien, 2005), the prevalence and risk factors for BZDs hypnotics dependence in the Japanese population have not yet been investigated.

Considering these issues, we aimed in this study to investigate the prevalence of BZDs hypnotics dependence among Japanese outpatients with psychiatric disorders using a dependency questionnaire developed in Japan (the Dependency 2-A: D 2-A) (Kudo and Kurihara, 1990). We also assessed the association between the side effects possibly due to BZDs hypnotics and the dependence on BZDs hypnotics. Moreover, we investigated various factors associated with the presence of this dependence, towards the establishment of a preventive method for BZDs hypnotics dependence.

2. Methods

2.1. Participants

This study was approved by the Ethics Committee of Tokyo Medical University Hospital. When conducting the survey, attending psychiatrists fully explained the main purpose of the study to eligible patients and obtained written informed consent from the participants. The participants were 1338 psychiatric patients using BZDs hypnotics, who visited the outpatient clinic of the Department of Psychiatry, Tokyo Medical University Hospital between February 1 and February 29, 2012. In this study, we included the regular use of BZDs at bed time as hypnotics. A total of 295 patients with incomplete answers were excluded from the subsequent analyses, resulting in a final sample of 1043 subjects (a valid response rate of 78%).

2.2. Assessment

The self-administered questionnaire consisted of the Japanese version of the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1988; Doi et al., 2000) to subjectively assess the participants' sleep disturbance, along with demographic background information such as age at the time of the survey, sex, height, and body weight, presence/absence of cohabiting family members, presence/absence of a shift work schedule in their daily jobs, and a college degree. The PSQI calculates a score for each of 7 different items: C1 (sleep quality), C2 (sleep latency), C3 (sleep duration), C4 (sleep efficiency), C5 (sleep disturbances), C6 (use of sleep medication), C7 (daytime dysfunction), and a total score. Duration of hypnotics use, routine timing for medication of BZDs hypnotics, the presence/absence of habitual alcohol consumption at bedtime, and the presence/absence of subjective side effects of hypnotics (dizziness, fatigue, daytime sleepiness, amnesia, and headache) (Walsh et al., 2005) were also asked. The answers "always" and "sometimes" were classified as the "yes" category, and "rarely" and "no" as the "no" category. The tendency for dependence on BZDs hypnotics was assessed using the D 2-A, which included the following questions: (1) do you feel clear-headed when taking this drug? (2) Do you feel indifferent toward persons or things you dislike when taking this drug? (3) Do you become hyperactive when taking this drug? (4) Do you become broad-minded when taking this drug? (5) Do you feel intoxicated when taking this drug? (6) Do you feel irritable or somewhat lonely when the drug effect runs out? (7) Do you want to continue taking this drug? (8) Do you think this drug is becoming less effective with repeated use? (9) Do you want to take this drug at a larger dose? (10) Do you feel nauseous or tremulous when the effect of the drug runs out? The cutoff value for the abnormal (sleep disturbance) range of the PSQI is 5.5 points (Buysse et al., 1988; Doi et al., 2000), and the cutoff value for the D 2-A is 10 points (Kudo and Kurihara, 1990). Subjects were diagnosed according to the DSM IV-TR (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition-Text Revision) and the subjects' drug prescriptions were investigated using their medical records together with confirmation from the attending physicians. The BZDs hypnotics dose taken before bedtime was expressed as the diazepam equivalent dose (Martin, 1994).

2.3. Statistical analyses

Subjects were considered to be dependent on hypnotics when their D 2-A scores exceeded the cutoff value. Based on this, the rate of subjects with hypnotics dependence was calculated. Thereafter, clinical descriptive variables (age, sex, body mass index, presence/absence of cohabiting family members, presence/absence of a shift work schedule, presence/absence of college degree, total PSQI score, duration of hypnotics use, presence/absence of habitual alcohol consumption at bedtime, presence/absence of each subjective hypnotics side effect, and diazepam equivalent dose of hypnotics) were compared between the subjects with dependence (dependence group) and those without dependence (non-dependence group). Statistical analyses of these variables were performed using the χ^2 test for categorical variables and the *t*-test for continuous variables. One-way analysis of variance (ANOVA) followed by the post hoc test was also used to compare diazepam equivalent doses of hypnotics taken before bedtime between the various categories of hypnotics medication duration (less than 1 month, 1 to less than 6 months, 6 months to less than 1 year, 1 to less than 5 years, and 5 years or longer).

In the present study, logistic regression analyses were performed to investigate factors associated with BZDs hypnotics dependence using the above-indicated descriptive parameters as independent variables. All variables were initially examined in univariate models. To control for confounding factors and to determine the main correlates, we then performed multivariate logistic regression analyses for all variables that showed a significant correlation in the univariate models. All statistical analyses were conducted using SPSS version 11.5 (SPSS Japan, Inc.), and a *P*-value less than 0.05 was considered to indicate a statistically significant difference between 2 groups.