British Journal of Medicine & Medical Research
4(7): 1577-1590, 2014

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High-dose and Long-term Users of Hypnotic and Sedative Drugs among Taiwanese Outpatients: Prevalence and Correlates from a Population-based Analysis

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Authors' contributions

This work was carried out in collaboration between all authors. Authors YPW and HMT contributed to the design of the project, performed the statistical analysis, and wrote the first draft of the manuscript. Authors MJS and HCL managed the literature searches and assisted in the analyses of the study. All authors read and approved the final manuscript.

Original Research Article

Received 27th September 2013
Accepted 8th November 2013
Published 20th December 2013

ABSTRACT

Aims: This study aims to analyze the dose and length of hypnotic and sedative drug prescriptions under a free-to-visit health insurance system.
Study Design: Outpatients aged 15 years and older covered by the Taiwan National Health Insurance during 2007 (N=1,337,444) are included in this study.
Methodology: The total amount of prescriptions for each patient was described according to the WHO Defined Daily Dosage (DDD) equivalent. Participants were categorized into 4 groups by dimensions of length (90 days) and dose (3 DDD per day). Patient characteristics and prescription drug use patterns were examined using a multinomial logit regression.
Results: Although most prescription doses fell within the recommended ranges, the

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average flunitrazepam dose was substantially higher than that recommended for both long-term and high-dose users. Our results indicate that male sex, a psychiatric illness diagnosis, and receiving care at more than one institute were positively correlated with long-term use. However, these factors were negatively correlated with high-dose user. Distinct differences between the characteristics associated with long-term and high-dose use were observed, compared with normal users.
Conclusion: These findings call for clinicians and policy makers to focus their attention on potential safety and efficiency issues. The alignment of prescribing practices and guidelines is highly recommended.

Keywords: Hypnotics and sedatives; prescription drugs; population characteristics; drug utilization; health service misuse.

1. INTRODUCTION

Sedative-hypnotic drugs (SHD) are often prescribed to treat insomnia, a common clinical condition that affects significant numbers of adults [1-3]. Insomnia is associated with decreased quality of life, increased risk of other psychiatric illness, adverse health effects, accidents, higher health care utilization and increased absenteeism, resulting in a significant societal economic burden[3-5]. With the widespread increasing prevalence rates of insomnia, the prevalence and incidence of SHD use have become major concerns for many countries.

Relatively few population-based studies have been conducted on the use ofSHD prescriptions, with most studies in the literature assessing relatively small cohorts [6-11].In addition, there is no consensus on the definitions of long-term and high-dose SHD use across the previous studies. Thus, it is difficult to provide clinicians or insurers with practical knowledge to stem the increase of the SHD use.

The lack of a consensus among researchers regarding clinical criteria for long-term use may be the result of the use of retrospective questionnaires as data sources or by length of the study periods [7,12]. Long-term and high-dose SHD use is known to contribute to tolerance and addiction, and most prescription guidelines do not recommend continuous use for longer than one month [2,13]. However, the SHD use for periods exceeding 3 months is not uncommon, and continual use for as long as 10 years has been reported [9,10,14-16]. Previous studies have shown that approximately 1.6% of adult Americans have used Benzodiazepines (BZD) daily for periods over one year, and 40% to 72% of German, Italian, and Irish patients reported using BZDs for periods longer than one year [17,18]. In addition, Alexander & Perry [19] report 7.9% of Japanese patients had used BZDs longer than 3 years. The recent development of selective benzodiazepine receptor agonists (BZRAs), may reduce long-term use of SHD[4], though their claimed effectiveness over the BZDs are not without controversy [16,20].

The findings of prescription dosing have been confounded by the underestimation of the total amount prescribed. Empirical studies are often limited by data sources [21]. Seivewright and Dougal [22] define the high-dose BZD use by the unit of mg, i.e. median diazepam equivalent 140 mg/day. In accordance with the WHO's Defined Daily Dosage (DDD), Egan et al. [23] used 1 DDD in their study. WHO's DDD for BZD type descriptions range from 0.25 mg to 30 mg. In studies of prescription drug use in Taiwan, Wu [24] and Huang [25] defined high-dose use as usage in excess of 360 DDD, and 1.5 DDD per day, respectively. In addition, previous studies have focused primarily on the dose of a single compound. Such

an approach neglects the problem of poly-users, which may lead to the underestimation of the prevalence of high-dose prescription drug abuse [13,22,23].

In summary, past studies have shown that there are many patients reporting the long term use of SHD. While potential problems, such as drug abuse and safety issues, have been brought to the attention of clinicians and researchers, the amount of SHD used by such patients has not been adequately quantified. In particular, the prevalence of high-dose users has rarely been examined, regardless of whether they were characterized as recreational or chronic drug abusers. This gap in the knowledge base confounds efforts to assess the potential dangers posed by SHD abuse, to distinguish between the factors correlated with long-term use and those of high-dose use, and to develop useful clinical recommendations and management strategies for prevention. Moreover, the sensitivities of the current long-term and high-dose use definitions may represent shortcomings in the methodological approaches that are commonly used to study prescription drugs.

A national insurance claims data offer an opportunity to investigate the problem of high-dose and long-term SHD use on a broad scale [26]. In recent years, the Taiwan National Health Insurance (NHI) system has seen a sharp increase in SHD prescriptions. On average, claims for 1.3 billion SHD prescriptions are filed yearly in Taiwan. The total expenditures exceed 1 billion NT dollars, and are growing at an annual rate of 14% [25]. The NHI claims data is useful for identifying potential long-term and/or high-dose prescription drug users. Results derived from Taiwan data may also serve as a benchmark because patients in Taiwan are free to choose their health care facilities and physicians. This freedom to obtain prescriptions is considerably higher than many other countries.

Our study aimed to characterize the dosage and length of use of SHD prescription in Taiwan, and to identify factors correlated with these aspects of usage, with an emphasis on high-dose patients. In particular, we sought answers to the following questions: 1. What patient characteristics are associated with long-term or high-dose use of SHD prescription, and 2.what management strategies may prevent the abuse of SHD?

2. MATERIALS AND METHODS

2.1 Participants

This is a retrospective study. The data were extracted from the NHI database for the year 2007.Inpatient and ambulatory care claims, with details of orders, prescriptions, expenditures, and patient characteristics, such as registry for catastrophic illness and beneficiary types, were included. All patients, aged between 15 and 100 years, who had been prescribed oral SHD were reviewed. Patients with unknown age or sex, participants who had been admitted as an inpatient longer than 90 days, and those who had died during 2007 were excluded.

2.2 Drugs

Drugs that were included by the WHO in the Anatomical Therapeutic Chemical (ATC) Hypnotics and Sedative group, those that were coded with NHI ATC codes beginning with N05CD or N05CF, those classified as schedule III or IV controlled substances by the United States Food and Drug Administration (FDA), and those approved for clinical use as of January 2007 were considered SHD for the purpose of our study. Within the FDA

classification system, schedule III indicates a tougher control than a schedule IV designation. Based on these criteria, a total of 107 SHD were selected for sampling during the study period.

Our study defined the length of use as the period between the last prescription date and the first prescription date (both in 2007). Because our study period was only one year, we used a combined usage period of 3 months or longer for the definition of long-term use. The level of use is defined by average daily dose. The defined daily dose (DDD)is the assumed average maintenance dose per day for a drug used for its main indication in adults. Table 1 summarizes the major oral SHD recommended daily doses according to the WHO [27], government regulations [2], academic societies [28], and academic studies [29]. Except for flurazepam, nitrazepam, and flunitrazepam, the WHO DDDs are generally consistent with those suggested by the pharmaceutical manufacturers. Table 1 also showed the various SHD for which enrollees were reimbursed by the NHI during 2007. There were a total of 107 drugs, of which BZRA-type compounds (15 drugs) accounted for 53% of the total prescribed DDDs. The second most prescribed drug was the BZD-type flunitrazepam, which accounted for 18% of total DDDs.

The sum of all prescription doses was calculated for each participant, and converted into the DDD equivalent according to the WHO ATC Hypnotics and Sedative Group criteria. We used 3 DDD/d for the definition of high-dose use. The cut-off points that we used for high-dose and long-term use were similar to those used in previous studies and guidelines.

Participants were categorized into 4 groups by prescription dose and length of use. A length of use over 90 days was considered to indicate a *long-term user*. A length of use over 90 days and an average daily dose higher than 3 DDDs was considered to indicate a *long-term, high-dose user*. A length of use less than 90 days with a average daily dose greater than 3 DDDs was considered to indicate a *high-dose user*. A length of use less than 90 days and an average daily dose less than 3 DDDs was considered to indicate a *normal user*.

These definitions differed from previous studies [21-25] in that we considered the length of use and the amount used separately to define user types and identify factors associated with long-term and/or high-dose users. Our more inclusive definition of the length of use may contribute to overestimations of the data in cases of discontinuous use, but does allow the identification of repetitive episodes of high dose use within the study period. We realized that our one year study period required a strict limit on the length of use. We considered our definition to represent a compromise between accuracy in estimations of the number of days of use and the ability to identify high-dose use, which has not been well described in the current literature.

2.3 Statistical Analysis

The data regarding health, demographic, and prescription records were categorized to facilitate correlation analysis. Participants with mental disorders were identified by ICD 9 diagnosis codes between 209 and 319. Circulatory diseases were identified by diagnosis codes between 390 and 459. A catastrophic illness status was categorized as either *mental catastrophic illness* or *other catastrophic illness*. The present study used enrollee category (EC) as a proxy measure of socioeconomic status to classify participants into 6 subgroups: EC1 (employees and their dependents), EC2 (e.g. union or foreign crew members), EC3 (e.g. members of the farmers, fishers, and irrigation associations), EC4 (e.g. military

Table 1. Suggested daily dose of sedative and hypnotic medicine, by source and component

ATC component		Recommended daily dose				2007 NHI statistics		
		Bureau of National Health Insurance [2]. Instructions of Pharmaceutical Co.	Tariq and Shailaja [29]	Taiwan Society of Sleep Medicine [28]	WHO [27] Defined Daily Dosage	No. of drugs covered by NHI	Total No. of DDD (1,000s)	% of total DDD prescribed
BZD	Flurazepam	15~30mg up to 60mg	10-60mg	15-30mg	30mg	11	4,152	2
	Nitrazepam	5mg up to 10-20mg	5-10 mg	5-10mg	5mg	28	2,523	1
	Flunitrazepam	1-2mg	0.5-6 mg	0.5-1mg	1mg	16	39,569	18
	Estazolam	1~2mg	2-4 mg	1-2mg	3mg	8	27,694	13
	Triazolam	0.25-0.5mg	0.25-0.5 mg	0.125-0.25mg	0.25mg	13	5,862	3
	Lormetazepam	1mg-2mg	0.5-1 mg	--	1mg	2	38	0
	Midazolam	7.5-15mg	7.5-15 mg	7.5-15mg	15 mg	2	2,705	1
	Brotizolam	0.25 mg	0.25 mg	0.25-0.5mg	0.25mg	1	2,925	1
	Nimetazepam	5 mg	3-5 mg	5mg	5mg	4	471	0
BZRA	Zopiclone	7.5mg	5-10 mg	3.75-7.5mg	7.5mg	7	15,677	7
	Zolpidem	10mg	5-20 mg	5-10 mg	10mg	15	115,989	53
Total						107	217,607	100

conscripts, military school students, and widows of deceased military personnel), EC5 (e.g. low-income households), and EC6 (e.g. veterans and individuals who registered through local government agencies). Because NHI enrollment is compulsory, an interruption in enrollment was considered to indicate probable job loss, incarceration, loss of citizenship, or missing-person status over 6 months. Patient prescription variables included any schedule III controlled drug and the collection of prescriptions at different hospitals, clinics, or pharmacies.

All data were analyzed with SAS computer software (Cary,NC,USA). The data of individuals' characteristics and SHD prescription patterns were first summarized and compared by frequency or percentage. Next, multinomial-logit regression models were performed to estimate the strength of association estimates across the user groups.

3. RESULTS

The final number of participants included in our study cohort was 1,337,774.Among 1.34 million SHD users, the long-term, high-dose users account for 1.9% of the cohort (n = 25,361). The high-dose users accounted for 0.7% (n = 9305). The long-term users accounted for 41.1% (n = 550,484), and 56.3% (n = 752,624) were normal users.

Table 2 summarizes the characteristics of SHD users. All categories of users were greater than 50% female. The high-dose group had the lowest rate of female gender. We observed distinct differences between user groups with regard to their demographic characteristics, their health, and the prescriptions that they received. The long-term, high-dose users were significantly different than the other groups in many ways. The majority of the long-term, high-dose users were between ages 40 and 64 years. They comprised the largest proportion of participants in enrollee category 5 and 6, indicating their job types and incomes were significantly different from those of the other groups. Perhaps as a consequence of their job types, the long-term, high-dose users had a 9.2% insurance interruption rate, which was higher than that of the long-term and normal user groups. In addition, 91.9% of the long-term, high-dose users had received a psychiatric diagnosis, among which 33.8% of them had been diagnosed with a major psychiatric illness. The long-term user group displayed the highest rate of circulatory disease (31.2%).

Over 50% of all the groups had been prescribed zolpidem, with the exception of the high-dose users. Flunitrazepam and schedule III controlled drugs were most often used by the long-term, high-dose users and high-dose users. Approximately 56% of the long-term, high-dose users and 12.6% of the high-dose users had obtained SHD prescriptions at multiple institutions. However, high-dose users were distinct in regard to 73.3% of them receiving prescriptions from clinics alone, rather than from hospitals.

SHD expenditures in 2007 was approximately 1.43 billion NTD, of which the long-term users contributed to 77.7%. The average drug expenditure for the long-term, high-dose users was 7051 NTD, which was significantly higher than that of all the other user groups. However, their average DDD was slightly lower than that of the long-term users. The average dose for both the long-term, high-dose users and the long-term users exceeded 4.7 DDD/d.

Table 2. Descriptive statistics by types of usage

	User Types				Total
	Long-term high-dose	**High-dose only**	**Long-term only**	**others**	
N	**25,361**	**9,305**	**550,484**	**752,624**	**1,337,774**
Patient characteristics					
female**	53.2%	50.5%	57.7%	62.6%	60.3%
age* （SD）	47.8 (13.8)	46.3（16.3）	57.9（16.3）	50.67（16.9）	53.56（17.0）
Age category**					
15-19 yrs	0.2%	1.0%	0.3%	1.3%	0.9%
20-39 yrs	31.2%	38.2%	14.3%	26.5%	21.7%
40-64yrs	56.3%	43.8%	47.7%	49.2%	48.7%
65 and over	12.3%	16.9%	37.7%	22.9%	28.8%
Insurance Coverage					
Type 5 enrollee**	7.6%	1.7%	2.6%	1.1%	1.8%
Type 6 enrollee	39.3%	29.2%	28.5%	19.8%	23.8%
Coverage abruption	9.2%	11.1%	5.5%	7.7%	6.9%
History					
Psychiatric disease**	91.9%	42.9%	49.3%	28.5%	38.4%
Psychosis **	33.8%	4.1%	10.8%	2.0%	6.3%
Circulatory disease **	10.7%	1.1%	31.2%	12.4%	20.0%
Other major illness**	6.0%	3.5%	9.5%	6.1%	7.5%
Prescription					
3rd level controlled Drugs **	83.8%	79.6%	16.2%	13.5%	16.4%
Zolpidem**	55.8%	29.2%	69.9%	69.6%	69.2%
Flunitrazepam**	77.9%	65.0%	8.5%	2.3%	6.7%
Institute crossing**	56.2%	12.6%	32.8%	10.9%	20.8%
Branch crossing**	10.3%	1.8%	4.7%	1.3%	2.9%
Clinic prescription**	45.8%	73.3%	39.5%	54.8%	48.5%
Total drug claims ($1,000)	178,820	3,260	1,113,850	138,270	1,434,190
drug claims (%)	12.50%	0.20%	77.70%	9.60%	100.%
Average drug claims ($)**	7,051（7,854）	350（469）	2,023（1,425）	184（207）	1,072（1,878）
Total DDD (thousands)	38,910	1,070	158,710	18,950	217,630
DDD (%)	17.90%	0.50%	72.90%	8.70%	100.00%

	User Types				Total
	Long-term high-dose	High-dose only	Long-term only	others	
Per person DDD**	1,534（976）	115（120）	288（192）	25（27）	163（294）
Per person per dayDDD**	4.72（2.39）	5.19（2.61）	1.08（0.49）	0.91（0.36）	1.08（0.84）
Length of prescription**	319（81）	25（25.6）	259（96）	28（25）	128（133）
Times of prescription**	23.37（22.9）	3.07（3.56）	11.33（6.10）	2.08（1.86）	6.30（7.30）

** P<0.001; standard deviation in parentheses

Table 3. Average daily dosage (unit=DDD) by patient types

ATC component		Patient types								
		Long-term high-dose		High-dose		Long-term		Normal		Total
		Average daily dose (SD)	% of total dose	Average daily dose (SD)	% of total dose	Average daily dose (SD)	% of total dose	Average daily dose (SD)	% of total dose	
BZD										
Flurazepam	4	1.63(0.68)	1%	1.65(1.25)	1%	1.21(0.55)	2%	1.02(0.45)	1%	1.23(0.58)
Nitrazepam	3	2.19(1.72)	1%	5.19(3.42)	5%	1.25(0.73)	1%	0.98(0.53)	3%	1.18(0.92)
Flunitrazepam	3	3.74(1.40)	57%	5.00(1.99)	72%	1.88(0.85)	10%	1.83(0.91)	5%	2.67(1.50)
Estazolam	4	1.10(0.45)	3%	2.07(2.27)	2%	0.76(0.31)	15%	0.69(0.29)	11%	0.76(0.33)
Triazolam	3	2.05(1.41)	2%	6.10(3.97)	6%	1.25(0.70)	3%	1.14(0.69)	2%	1.37(1.08)
Lormetazepam	4	1.75(1.01)	0%	4.09(5.7)	0%	1.13(0.46)	0%	1.03(0.49)	0%	1.31(0.82)
Midazolam	4	0.87(0.24)	1%	0.91(0.37)	0%	0.60(0.26)	1%	0.51(0.18)	1%	0.60(0.26)
Brotizolam	3	1.89(0.74)	1%	2.39(1.37)	0%	1.18(0.47)	2%	1.01(0.42)	1%	1.21(0.53)
Nimetazepam	3	2.14(0.90)	0%	2.50(1.93)	0%	1.49(0.70)	0%	1.09(0.54)	0%	1.50(0.74)
BZRA										
Zopiclone	4	1.76(0.71)	3%	3.05(3.76)	1%	1.11(0.48)	8%	0.97(0.42)	6%	1.12(0.53)
Zolpidem	4	1.64(1.08)	31%	3.99(4.95)	13%	1.05(0.49)	57%	0.95(0.41)	68%	1.07(0.60)

A further examination of the distribution of prescriptions revealed that trends were present in the types of drugs prescribed. However, the particular drug that was most often used differed across the user groups. Table 3 shows that 72% and 57% of the total doses during the study period were flunitrazepam among the long-term, high-dose users and the high-dose users, respectively. In contrast, 68% and 57% of the total doses were zolpidem among the normal users and long-term users, respectively.

The average daily dose per drug type varied by approximately 1 DDD, as shown in the last column of Table 3.Flunitrazepam was used at an average of 2.67 DDD/d. In addition, although flunitrazepam accounted for only 18% of the total SHD prescribed, it accounted for approximately 72% of the high-dose users' prescriptions. Furthermore, the average zolpidem dose was 3.99 DDD/d among the high-dose users, and the average doses of Nitrazepam and Triazolam among the high-dose users were both over 5 DDD/d.

Table 4 indicates that patients of different groups displayed different preferences with regard to where they obtained their prescriptions. Clinic pharmacies were the most common institution where participants had obtained their prescriptions, rather than hospitals. However, there were distinct differences across the user groups regarding the proportion of their prescriptions that were obtained at clinics. The high-dose users obtained 75% of their prescriptions at clinics, while the long-term users obtained 21% of their prescriptions at medical centers. The long-term, high-dose users obtained their prescriptions at an average of 2.83 institutions.

The estimated coefficients of the logit regressions, using the normal user as the reference group, are reported in Table 5.The value of the coefficient indicates the effect ofbeing in a particular group, compared with being in the normal user group. Controlling for potentially confounding factors, the characteristics that were positively and significantly correlated with the probability of being a long-term or high-dose user were distinctively different, compared with those of the normal user group. An older age, a psychiatric illness, a non-psychiatric major illness, a circulatory disease, the interruption of insurance coverage, the use of zolpidem, and filling prescriptions at institutions other than clinics were positively and significantly correlated with the probability being a long-term, high-dose user, and were negatively and significantly correlated with being a high-dose user.

Table 4. Prescriptions by institute types

	Patient types				**Total**
	Long-term high-dose	**High-dose**	**Long-term**	**normal**	
Medical centers	14%	5%	21%	12%	19%
Regional hospitals	27%	12%	26%	17%	25%
District hospitals	18%	8%	17%	15%	17%
Clinics	37%	75%	30%	55%	35%
Pharmacy	4%	0.3%	5%	1%	4%
No. of insurance branches **	1.11(0.36)	1.02(0.14)	1.05(0.22)	1.02(0.12)	1.03(0.18)
No. of institutes **	2.83(3.83)	1.17(0.6)	1.48(0.85)	1.13(0.39)	1.30(0.86)

***P<0.001*

Table 5. Logit regression coefficients

	Long-term high-dose		High-dose		Long-term	
	(1)		(2)		(3)	
Intercept	-7.684	**	-5.711	**	-2.451	**
Socioeconomic characteristics						
female	-.147	**	-.257	**	-.140	**
age	.010	**	-.002	**	.025	**
Type 5 enrollee **	1.051	**	.255	*	.545	**
Type 6 enrollee	.582	**	.278	**	.264	**
Coverage abruption	-.171	**	.136	**	-.202	**
History						
Psychiatric disease	2.425	**	-.034		1.060	**
Major Psychiatric illness	1.726	**	.094		1.332	**
Other major illness	.623	**	-.444	**	.536	**
Circulatory disease	1.007	**	-2.055	**	1.236	**
Prescription characteristics						
3rd level controlled Drugs **	1.155	**	1.153	**	-.152	**
Zolpidem**	.197	**	-.419	**	.057	**
Flunitrazepam**	3.273	**	3.394	**	1.152	**
Service Providers						
Institute crossing**	1.666	**	-.441	**	1.327	**
Branch crossing**	.224	**	.117		.152	**
Clinic prescription**	-.684	**	.918	**	-.722	**

a. the reference group is the normal usage group characterized by non-long-term and non-high-dose use b. Seudo R2 : Cox and Snell =0.312、Nagelkerke=0.391、McFadden=0.234
*** P< 0.001*

4. DISCUSSION

We investigated the use of SHD prescription in Taiwan through a study of the prescription data stored during 2007 in the NHI database. The results indicate that after controlling other potentially confounding variables, the characteristics correlated with being a long-term or high-dose user were significantly different from those of the other user groups.

The high-dose users had very high average daily DDDs for several drugs, and exhibited distinct behaviors with regard to illness patterns and interruptions of insurance coverage, indicating their health, prescription drug use, and economic security may have been quite different from that of the other groups. The use of the schedule III controlled drug flunitrazepam, also known as the date-rape drug [13], was concentrated among the high-dose participants, and a much higher average dose was used, indicating potential abuse problems among these types of users. These findings are consistent with those of previous studies [25,30]. New evidence emerged from our study in that most of the high-dose users obtained their prescriptions at the same clinic. These data may indicate potential problems of safety and abuse, and call for clinical attention to further utilization analyses.

The findings of our study deviate from those of earlier studies in several ways. First, the schedule IV controlled drug zolpidem was shown to have replaced flunitrazepam in 2007 as the most commonly used SHD [16,24,31]. Second, after separating the high-dose users from the long-term, high-dose users, both groups exhibited very high average DDDs of flunitrazepam with different patterns. To prevent potential abuse of the long-term, high-dose users, physicians will need better information support system, such as a smart card that reveals recent prescriptions obtained by a patient, because they visited an average of 2.83 facilities to obtained prescriptions. An integrated circuit card is currently used by the NHI, but it provides limited information which is rarely examined carefully. On the other hand, for the high-dose users, they visited an average of 1.17 facilities, which indicates that improving physician prescribing practice may help to prevent potential abuse.

Griffiths and Johnson [32] classified 19 SHD by intoxication level and probability to be abused. Although there were no significant differences in the intoxication levels among the insurance-approved drugs, there was moderate variation between the probabilities of abuse. Among the 19 drugs ranked, flunitrazepam was ranked fourth and zolpidem was ranked 13th. The abusers of flunitrazepam tended to be 18 to 25 years of age, which is similar to the high-dose users in our study cohort.

Compared with previous studies, our operational definition of long-term is relatively short at 90 days. It is, however, consistent with clinical guidelines. The proportion of overall long-term users comprising 43% of the entire cohort is also consistent with previous studies of oral SHD use. Although the exclusion criteria prevented the analyses of extremely ill and young patients, the sample allowed us to focus on general prescription patterns over a wide range of age groups. To evaluate the robustness of the results, we used 60 and 90 days as alternate definitions of long-term use, and a high-dose use of 2 to 3 times the average DDD/d separately. The coefficients were stable, except that the probability of being a high-dose user was inversed, and became positively related with a psychiatric illness diagnosis. Overall the results were consistent, regardless of the operational definitions.

Our study found that flunitrazepam prescriptions in general tended to exceed the recommended dosage. Among the high-dose users and the long term, high-dose users, the average DDDs exceeded the suggested DDD by greater than 2.74-fold. Among the long term and normal user groups, the average DDD was at 1.8 times the suggested DDD. This finding implies that prescriptions for flunitra zepam in general have deviated from the clinical guidelines for prescribing the drug [33]. It is difficult to ascertain whether this deviation can be attributed to the patients or the physicians. However, it calls for clinical attention to the practices of both [16,34].

5. CONCLUSION

Utilizing the population-based study design, our study highlighted two key points. First, the average dose of flunitrazepam prescriptions was substantially higher than that recommended, ranged from 1.8 times for both long-term and normal users to 2.74 times for the high-dose and/or long-term users. Second, with respect to characteristics of different user groups, factors in domains of individual socioeconomics (i.e. an older age and interruption of insurance coverage), pharmacological agents (i.e. the use of zolpidem), disease history (i.e. being diagnosed with a psychiatry illness or a circulatory disease), and service providers (i.e. filling prescriptions at institutions other than clinics) are all shown to exert significant relation in the incidence of a long-term and high dose use. Although SHD have useful clinical applications, they are subject to abuse and safety concerns if prescribing

practices and patient compliance are not in accordance with clinical guidelines. Moreover, for health care systems in which patients are free to select health care providers and pharmacies of their own preference, our findings are consistent with those of other investigators that indicate the importance of monitoring prescriptions across different institutes to prevent high-dose use and the associated potential safety problems.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

ACKNOWLEDGEMENTS

This paper is in part supported by the National Science Council of Taiwan (NSC 101-2410-H-182-016-MY2; NSC 101-2410-H-182-025) and Chang Gung University UARPD390021in the writing and publication of the manuscript.

COMPETING INTERESTS

Authors have declared that No competing interests exist.

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