

ORIGINAL ARTICLE

**BENZODIAZEPINE PRESCRIPTION PATTERNS  
AND DEPENDENCE RISK IN A GENERAL  
HOSPITAL IN SINGAPORE**

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**Abstract**

**Objective:** Benzodiazepines (BZDs) are widely used in the treatment of anxiety and depressive disorders, although one concern is its potential for tolerance and dependence compared to other classes of drugs. The study assessed BDZ prescription patterns and investigated to what extent dependency developed in the course of receiving such medications. **Methods:** From analysis of 276 randomly selected case records over a one-year period, socio-demographic and prescription-relevant data were extracted from 118 outpatients who were receiving BZD prescriptions from a general hospital in Singapore. We used three pre-determined surrogate indicators of possible dependence and made comparisons between patients with any of the surrogate indicators versus those without. **Results:** The characteristics of the BZD patients mostly followed Singaporean demographic trends. There was a higher prevalence of persons receiving BZDs in the 40-59 year age group. Less than half (about 43%) were on benzodiazepines. Although 31.4% had either one or two indicators, none had all three indicators, suggesting that any addiction potential of the BZDs had been regulated well. Dosages remained fairly constant among those receiving regular BZDs and those receiving *prn* dosing, with only approximately 10-20% changing dosages. **Conclusion:** Our study confirms the hypothesis that patients exhibit an insignificant rate of possible dependence. *ASEAN Journal of Psychiatry, Vol. 17 (1): January – June 2016: XX XX.*

**Keywords:** Benzodiazepines, Prescribing Patterns, Anxiety, Depression, Dependence

**Introduction**

Benzodiazepines (BZD) are a class of psychotropic drugs that have been in the market since 1959 when the discovery of the first compound, chlordiazepoxide, was made [1]. Since then, they have proven very useful in the management of anxiety symptoms, insomnia, and acute alcohol withdrawal, in

psychiatric emergencies, and status epilepticus as they possess sedative, hypnotic, muscle relaxant and anti-epileptic properties [2,3,4]. One of the most useful aspects of BZDs are their rapid onset of action and effective anxiolytic effects that would otherwise take antidepressants two to four weeks to do so [5]. However, with the repeated use, they are also associated with tolerance, dependence and

subsequent withdrawal symptoms, as well as other side effects, such as memory impairment, gait disturbances [6]. Other serious adverse effects, including increased problems with mobility with impairment in performing activities of daily living [7], falls [8], and a negative effect on cognitive functioning [9], impaired coordination and driving ability [10]. As such, prescribers are advised to limit the prescription of BZDs to the lowest effective dose over a short-term period [11, 12].

The primary objective of our study was to determine the outpatient BZD prescribing patterns of doctors of various grades from a department of Psychiatry in a Singapore hospital, including whether there was self-regulation to reduce the risk of iatrogenic BZD dependence in patients. The secondary objective was to investigate for possible benzodiazepine dependence among the patients. We hypothesize the rate of BZD dependence is insignificant according to pre-determined criteria.

## **Methods**

The study, approved by the hospital's Institutional Review Board, was conducted from 1<sup>st</sup> June 2013 to 31<sup>st</sup> December 2013. Data was obtained from case records of patients receiving or having received pharmacological treatment from the Department of Psychiatry of a general hospital in Singapore. The hospital is also involved in teaching undergraduate medical students and post-graduate psychiatric residents and trainees. A random sampling of one in 5 case records of patients receiving or having received treatment from 1 January 2012 - 31 December 2012 was conducted, yielding a total of 276 case records. Inclusion criteria were that patients had to suffer from insomnia, anxiety disorders or depression and receiving prescriptions for BZDs (regardless of whether they were prescribed any other medications).

Notwithstanding established diagnostic operational definitions of drug dependency (e.g. DSM-5), for the purpose of this study, we devised a simplified set of criteria as surrogate indicators of possible dependence, as follows:

1. Increase in dosage of BZDs (between first prescription and current/latest prescription)

2. Request for extra BZDs prescribed regardless of the reason.
3. Inability to decrease BZD dosages.

If any 2 of the 3 above criteria were present, a patient would be judged to be at risk for developing dependency to BZDs.

Answers to the following questions were sought.

1. Name of Benzodiazepine?
2. Dosage of Benzodiazepine?
3. Regular use or taken when necessary (*prn*)?
  - a. if regular intake did the dosage increase (between initial and current/ latest prescription)?
  - b. if *prn* dosing, did the dosage increase?
  - c. if *prn* dosing, did the dosage decrease?
4. Is the patient still on BZD (at time of recording)?
5. Was there any attempt (by the doctor) to decrease the dosage?
6. Any request for extra medication before the appointment date?

All analyses were performed using IBM SPSS 20.0. Chi-square test was used to compare the differences in demographic variables, and between the subjects with partial fulfilment of the dependence criteria and those who did not fulfil the criteria, with significance set at  $p < 0.05$ .

## **Results**

Of 276 case records, 118 were found to have received prescriptions for BZD. The mean age of the patients was 49.4 years. There were 136 patients (49.3%) with depressive disorders, 72 (26.1%) with anxiety disorders, 44 (16.0 %) with mixed anxiety depressive disorder, 12 (4.3%) with adjustment disorder and another 12 (4.3%) whose diagnosis was unknown. Table 1 shows the socio-demographic characteristics of the patients. The majority (almost 72%) received at least secondary school education. There were 15 patients whose educational status was not identified, and these were not included in the analyses. More than half (58.5%) were females (female to male ratio 1.4:1) Approximately 87% of the patients were Chinese, 4.2 % Malays, 5% Indians, and 4% from other races, consistent with the ethnic distribution of the Singapore population.

**Table 1. Socio-demographic Characteristics**

Age ( years)	^N ( %)	Population of Singapore*	P- value
20-39	32 (27.1)		
40-59	53 (44.9)		
60 and above	33 (28.0)		
<b>Ethnicity</b>			0.007
Chinese	103 (87.3)	74.2	
Malay	5 (4.2)	13.3	
Indian	6 (5.1)	9.2	
Others	4 (3.4)	3.3	
<b>Educational Level</b>			0.001
Nil to Primary	22 (18.4)	33.4	
Secondary and Tertiary	96 (81.6)	66.6	
Unknown	15		

^N = size number; \* Singapore Demographic Profile 2014[16]

In Table 2 we present cross tabulation analysis between gender and other socio-demographic characteristics. This revealed a higher prevalence of females in the 40-59 year age group with a lower prevalence of females in

the 60 and above group. Slightly more females seemed to have attained secondary and tertiary education compared to males. However these were trends, not attaining statistical significance.

**Table 2. Socio-demographic data by gender**

Age ( years)	Male (%)	Female (%)	p value
20-39	13 (26.0)	19 (27.9)	
40-59	19 (38.0)	34 (50.0)	
60 and above	18 (36.0)	15 (22.1)	0.227
<b>Ethnicity</b>			
Chinese	44 (89.8)	59 (85.5)	
Malay	2 (4.1)	3 (4.3)	
Indian	2 (4.1)	4 (5.8)	
Others	1 (2.0)	3 (4.3)	0.878
<b>Educational Level</b>			
Nil to Primary	10 (23.3)	9 (15.0)	
Secondary and Tertiary	33 (76.7)	51 (85.0)	0.287

In Table 3, we described the different BZD dosing arrangements, for example, 40% were receiving regular BZD doses, nearly a quarter (23.4%) were receiving regular doses but required increase in doses, about 10% were receiving irregular doses and required dose

increase, and about a third (33.6%) were still receiving BZD at the time of the study. In nearly 18% patients there were attempts by the doctor to decrease the BZD dose, and in a minority 6.8% patients there were requests for extra BZDs.

**Table 3. Type of Benzodiazepine (BDZ) dosing**

<b>BDZ prescription</b>	<b>Yes (%)</b>	<b>No (%)</b>
Prescribed on regular basis	47 (39.8)	71 (60.2)
Regular use dose increase	28 (23.4)	90 (76.6)
Irregular use dose increase	12 (9.9)	106 (90.1)
Continued use	40 (33.6)	78 (66.4)
Attempt to decrease	21 (17.8)	97 (82.2)
Request for extra	8 (6.8)	110 (93.2)

The four most commonly prescribed BZDs were Lorazepam (35.6%), Diazepam (33.9%), Alprazolam (16.9%) and Clonazepam (8.6%). About a third (32.2%) of patients were prescribed more than one BZD during the course of their treatment. The reasons were that the initial BZD was found to be ineffective or not well tolerated. The four most common alternative BZDs after switching from the initial BZDs were Alprazolam (26.3%), Diazepam (21.1%), Lorazepam (18.4%) and Clonazepam (15.8%).

No patient satisfied all three items of the criteria for possible dependence. A sub-group of 37(31.4%) patients with partial fulfilment of the criteria ( i.e. “potentially dependent subgroup”) were identified as follows: 12 (10.2%) fulfilled 2 of 3 criteria, and 14

(11.8%) had only one of 3 criteria, including 11 (9.3%) who required an increase in BZD dosing from the initial prescription without fulfilling the other 2 criteria.

Mean age of the 37 patients was 50.2 years, with females outnumbering males in a 2 to 1 ratio. For this subgroup, Table 4 describes their characteristics. There were no significant differences between males and females in this subgroup ( $p>0.05$ ). Table 5 compares the characteristics of the potentially dependent subgroup with the non-dependent subgroup. Once again, no significant differences were found ( $p>0.05$ ). Conversely, more than two thirds (68.6%) exhibited none of the three items of the criteria for potential BZD dependence.

**Table 4. Demographic characteristics of potentially dependent sub- group**

<b>Characteristic</b>	<b>Male (%) (%)</b>	<b>Female (%)</b>	<b>p- value</b>
<b>Age ( years)</b>			
20-39	1 (7.1)	9 (39.1)	0.103
40-59	8 (57.1)	9 (39.1)	
60 and above	5 (35.8)	5 (21.8)	
<b>Ethnicity</b>			
Chinese	14 (100)	18 (78.3)	0.3180
Malay	0 (0.0)	1 (4.3)	
Indian	0 (0.0)	2 (8.7)	
Others	0 (0.0)	2 (8.7)	
<b>Educational Level</b>			
Nil to Primary	5 (35.8)	5 (21.8)	0.935
Secondary and Tertiary	9 (64.2)	18 (78.2)	

**Table 5. Demographic characteristics of potentially dependent subgroup vs non-dependent group**

	Potentially dependent	Non-dependent	p value
<b>Gender</b>			
Male	14 (37.8)	36 (44.4)	0.551
Female	23 (62.2)	45 (66.6)	
<b>Age</b>			0.985
20-39	10 (27.0)	22 (27.2)	
40-59	17 (46.0)	36 (44.4)	
60 and above	10 (27.0)	23 (28.4)	
<b>Ethnicity</b>			0.811
Chinese	32 (86.5)	71 (87.7)	
Malay	1 (2.7)	4 (4.9)	
Indian	2 (5.4)	4 (4.9)	
Others	2 (5.4)	2 (2.5)	
<b>Educational Level</b>			0.115
Nil to Primary	10 (27.0)	9 (13.6)	
Secondary and Tertiary	27 (73.0)	57 (86.4)	

## Discussion

Previous study examining benzodiazepine dependence in this country offered a different profile of BZD abusers compared to our present study sample [13]. Their mean age was 39.4 years (SD = 9.7), 88% were Chinese, 58% males, 46% married, 48% had received secondary school education, and 48% were unemployed. The authors deduced that BZD abuse might be partly attributed to doctor-shopping behaviour and doctors' prescribing practices.

In our present study, there was a greater number of females in the 20-59 year old age group which is to be expected given that many psychiatric conditions requiring BZD prescriptions (such as anxiety and depressive disorders) are more prevalent in females than males. Notably, our patients were older, in that about 45% of the samples were between ages 40 - 59, which may suggest an over-representation of patients in this age group. It is uncertain whether this over-representation arose from a higher preponderance of patients attending our outpatient clinics from this age group, or whether it was unique to patients receiving BZD prescriptions.

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The characteristics of patients who fulfilled any of the three criteria of possible dependence are worth noting. Some 27 (73%) of them were 60 years and below – as compared to 10 (23%) who were 60 and above, which might suggest that relatively younger patients were more susceptible to dependency issues. In regard to ethnicity, there was a trend not amounting to statistical significance, for an over-representation of Chinese patients. This may reflect the ethnic distribution of the patients treated by the Department of Psychiatry in this hospital. In terms of educational attainment, our sample of patients achieved higher levels, i.e. secondary to tertiary education compared with the

national average. In our sample where female to the male ratio was found to be 1.4:1, this would probably reflect prescription patterns in this hospital, whereby males were more likely to receive BZD prescriptions than females, or conversely, that females were less likely to require BZD prescriptions than males.

The study revealed that nearly half (43%) of 276 patients were receiving BZD prescriptions. BZDs with a shorter half-life are known to be at a higher risk of causing dependence, such as Lorazepam and Alprazolam, which formed the majority of BZDs prescribed in this study. However, none of the patients fulfilled all of our pre-determined criteria for dependence among those receiving these two BZDs. That only a minority of patients achieved dose reductions, regardless of whether they were on prn dosing or not, demonstrates the possible dependency potential of BZDs. Not surprisingly, of the 47 (39.8%) patients initially prescribed BZDs on a regular basis, 40 (33.6 %) continued to ingest regularly, which suggests that only about 6% managed to reduce their intake.

There have been concerns that long term ingestion may result in the development of tolerance characterised by loss of efficacy or dose escalation [13]. The fact that the majority of BZD users did not seem to require escalating doses suggests that, although they seemed to rely on the BZD presumably for its anxiolytic property, such reliance is not to be equated with dependence. Moreover, there was evidence to suggest that sustained use was not associated with an increase in dosages [14].

The findings confirm the hypothesis that the rate of BZD dependence among our patients is insignificant. While dependency potential remains, careful prescription and monitoring ensured that no patient in the study had been conclusively found to develop BZD dependence based on our pre-determined criteria. In Singapore, the Ministry of Health has issued a guideline which requires doctors to prescribe no more than two to four weeks of BZDs per appointment, to prevent abuse [15]. These guidelines, and the influence of prudent prescribing habits by senior clinicians fostering a healthy concern over dependence potential, might have shaped prescribing habits of doctors.

There are strengths and limitations of our study. To the best of our knowledge, this is the first study which attempts to document the state of BZD outpatient prescriptions in a Singapore hospital. As all prescriptions are digitally recorded, medication identity and dosages can be easily read and recorded. However, a retrospective case record study has several limitations, including illegible entries in the case of some socio-demographic data, and missing or incomplete information that is not otherwise rectifiable without patient contact. It is uncertain whether patients who were on regular dosing were obtaining their BZD prescriptions surreptitiously from clinics outside of the hospital. Moreover, it is impossible to verify this with any degree of certainty. None of the prescribers was involved in the data collection or analysis. Despite the MOH guidelines, the prescribers were not under any inducement to reduce their patients' BZD dosages.

### **Conclusion**

The study was limited to a single large hospital in Singapore, hence conclusions drawn may not be representative of the status of BZD prescriptions in the country. As most junior doctors in our department are undergoing training in Psychiatry, they are probably cognizant of the dependency potential of BZDs. It is noteworthy that no patients have been found to show obvious signs of benzodiazepine dependence in this study although a fair percentage was on regular BZD use.

As junior doctors rotate through different general hospitals during their training, it is hoped that sensible prescribing habits would remain with the doctor regardless of whichever hospital they are deployed to work in, thus propagating a good trend nationwide. Concomitantly, it would be the duty of teachers of psychiatry to continue to train their junior colleagues on the use and possible abuses of BZDs.

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