

Benzodiazepine Prescribing Trends among Major Depressive Disorder Patients at the Outpatient Pharmacy of Hospital Bahagia Ulu Kinta

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Abstract

Introduction: Benzodiazepines should only be used as adjunct to antidepressants for the duration of less than four weeks.

Objectives: This study aimed to investigate benzodiazepine prescribing trends among the patients with major depressive disorder (MDD) in Hospital Bahagia Ulu Kinta (HBUK).

Method: This was a cross-sectional study from March 2016 to December 2016. We reviewed all prescriptions at the outpatient pharmacy with the diagnosis of MDD and sorted them per patient basis. Patient demography, drug name, dose and treatment duration were recorded in a data collection form and analysed using SPSS.

Results: A total of 908 prescriptions for 612 MDD patients were reviewed and 313 (51%) of the 612 MDD patients received one or more types of benzodiazepines. Most patients (76.7%) received benzodiazepines for more than four weeks with a median duration of 84 days (interquartile range (IQR) 35-206 days). The median dose of benzodiazepine was 3.57mg (IQR 1.78-7.14mg) of diazepam equivalents per day. Clonazepam was most prescribed, followed by zolpidem and alprazolam. Older MDD patients were prescribed benzodiazepines for a longer duration (median 126, mean rank 334.58) compared to patients of younger age (median 84, mean rank 298.50, $p=0.001$). Chinese MDD patients were also prescribed benzodiazepines for a longer duration (median 112, mean rank 168.54) compared to other ethnicities (median 56, mean rank 129.70, $p=0.0004$).

Conclusion: Notwithstanding guideline cautions, long term prescribing of benzodiazepines in depressed patients remains an occurring treatment pattern in the specialty care. Majority of the depressed patients received benzodiazepines for a period of more than four weeks albeit in low doses. However, short-acting benzodiazepines seem to be a popular choice among physicians as compared to long-acting benzodiazepines.

Keywords: benzodiazepine, depression, prescribing pattern

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Introduction

Major depressive disorder is extremely common in which community-based surveys have estimated the lifetime prevalence from 4.9% to 17% (1,2). Depression incurs substantial public health and economic costs. According to the Clinical Practice Guidelines for the Management of Major Depressive Disorder, major depression disorder (MDD) is defined as a mental health problem that disrupts a person's mood and adversely affects the psychosocial and occupational functioning, which is associated with significant morbidity and mortality (1).

Antidepressants are the recommended pharmacological treatment for depression (2). In Malaysia, antidepressants are offered as the first line measure as they are easily available and are as effective as psychological interventions (1). However, antidepressants' beneficial effects often do not occur in just several weeks, and studies have shown that the adjunctive use of benzodiazepines may confer some benefit in providing more immediate relief (1-3). Nevertheless, benzodiazepines are not free from disadvantages especially with long term use as tolerance, dependence and withdrawal effects can occur (1). Benzodiazepine withdrawal symptoms include anxiety, depression, diarrhoea, constipation, insomnia, irritability, restlessness, poor concentration and occasionally, seizures and symptoms of psychosis. These unwanted effects can be prevented by keeping the dosages minimal and courses short (4). Thus, guidelines have suggested that

benzodiazepines should be used with caution and not to be prescribed for more than two to four weeks when used as adjunct treatment with the antidepressants (1,4-6).

Daily practices in the healthcare settings, however, may not necessarily comply with these guidelines as seen in a study conducted in the United States Department of Veterans Affairs mental health settings by Valenstein and colleagues. The authors reported that depressed patients, especially the elderly patients, were particularly more likely to receive benzodiazepines for more than ninety days despite guideline cautions (2). The same was observed in Hospital Bahagia Ulu Kinta, the largest psychiatric hospital in Malaysia, which is the secondary and tertiary referral centre for the northern states in Peninsular Malaysia. Besides that, a study conducted by Woods *et al.* found that the physicians were prescribing shorter-acting benzodiazepines, which can produce a more intense withdrawal syndrome following chronic administration in preference to longer-acting benzodiazepines (7).

Generally, it is a known fact that many depressed patients are taking benzodiazepines longer than the recommended period but no solid evidence is available. It is also a worrying issue that many depressive patients who come to the pharmacy to collect their supply of medications are more interested in their benzodiazepines instead of their antidepressants. Some patients have even requested the pharmacists to provide extra tablets of benzodiazepine. Thus, this study aimed to identify the benzodiazepine prescribing trends among MDD patients at the outpatient pharmacy of Hospital Bahagia Ulu Kinta (HBUK), Perak. It was hoped that the findings will be able to create awareness not only among the healthcare professionals but also the public, on the trends of benzodiazepine usage among depressed patients in Malaysia.

Method

This was a cross-sectional study on the benzodiazepine prescribing trends among the MDD patients at the outpatient pharmacy of HBUK that was conducted from March to December 2016. In this study, the term 'benzodiazepine' applied to all benzodiazepines available in HBUK which were alprazolam, lorazepam, clonazepam, midazolam, bromazepam and diazepam, as well as zolpidem which is a non-benzodiazepine hypnotics. Zolpidem was included in this study as zolpidem also causes habit forming on prolonged use and is frequently prescribed in HBUK as an alternative to benzodiazepines.

Using the sample size calculator for prevalence study developed by Naing *et al.* 2006, setting the precision level at 5% and confidence level at 95%, the minimum sample size required was 369. During the study period, all prescriptions available at the outpatient pharmacy of HBUK with MDD written as the diagnosis, with and without comorbidities, were included for data collection. The diagnosis of MDD was based on the criteria in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders V (DSM-5) (1). Prescriptions with benzodiazepines but without any diagnosis written were excluded from the study. All pharmacists involved in the data collection were briefed on how to screen and sort the prescriptions based on the patient selection criteria and then the prescriptions were sorted out per patient basis. A data collection template was designed via Microsoft Excel and data was keyed in directly into the template. Patient demography, drug name, dose and treatment duration were recorded in the data collection form and analysed via SPSS.

Ethical approval from the Medical Research and Ethics Committee (MREC) of Ministry of Health Malaysia (MOH) was obtained and the study was registered in the National Medical Research Register (NMRR). All data collected were kept confidential, and no unique identifiers were collected. The data presented did not identify any individuals and the data used for publication would not review any identity of the subjects. The hard copies of study data were kept locked in a specified cabinet, and the soft copies of the study data were password encrypted to ensure that all information was only accessible by the two investigators and the supervisor for pharmacy research and development in HBUK. Study data will be stored for duration of three years and will be destroyed thereafter.

Patients' demographic characteristics and benzodiazepine prescribing trends were tabulated in a table. Continuous variables were represented as count (n) with percentage and median with interquartile range (IQR) in view of data was not normally distributed while the categorical variables were presented as n with percentage. The mean prescribed dose was calculated by adding up the diazepam-equivalent milligrams dispensed and dividing it by the duration of benzodiazepine prescribed (number of days). The non-parametric Chi-square test was used to determine if differences existed between benzodiazepine usages with each independent variable.

The non-parametric Mann Whitney U test was also used to determine if differences existed between the daily doses and duration of benzodiazepines of each independent variable as the data were not normally distributed. Results were considered statistically significant if the p value is less than or equal to 0.05.

Results

Patients characteristics

A total of 908 prescriptions for 612 MDD patients were identified. Of that, a number of 313 patients (51.1%) received a prescription containing benzodiazepine(s) for at least once during the period of data collection. All MDD patients who were prescribed with benzodiazepine(s) were also on antidepressants. The demographic characteristics of the patients and information about benzodiazepine use were presented in Table 1.

In line with the HBUK's MDD population, 64.9% (n=397) of the MDD patients included in this study were female. The median age of MDD patients was 52 years (IQR 41-63 years) with 79.2% of them were in the range of less than 65 years. Only 21.6% (n=132) of the depressed patients had a comorbid psychiatric diagnosis in which 11.1% (n=68) had psychosis and 8.2% (n=50) had an anxiety disorder. Other comorbid psychiatric diagnoses were obsessive-compulsive disorder, substance disorder, sleep disorder, borderline personality disorder and adjustment disorder which only made up of 2.3% (n=14) of the overall sample.

As seen in Table 1, older patients were more likely to be prescribed with benzodiazepines as compared to younger patients. Nevertheless, the difference was not statistically significant (p=0.109). Among the three main races in Malaysia (Malays, Chinese and Indians), the Chinese were most likely to receive benzodiazepines. A Chi-square test of independence was performed to examine the relation between race (Chinese and non-Chinese) and benzodiazepine usage. The relation between these variables was not statistically significant (p=0.243). Among the depressed patients receiving benzodiazepines, only 24.2% (n=76) had psychiatric comorbidities. Although depressed patients with concomitant psychiatric comorbidities were more likely to receive benzodiazepines, the differences showed no significance.

Table 1: Benzodiazepine use among patients with MDD by patient characteristics (n=612)

Variable	Patients with MDD (n=612), n (%)	MDD Patients Prescribed with Benzodiazepines (n=313), n (%)	X ² statistics ^a	P-value ^a
Age group			2.575	0.109
<65	485 (79.2)	240 (49.5)		
≥65	127 (20.8)	73 (57.5)		
Ethnicity			1.364 ^b	0.243 ^b
Malay	118 (19.3)	54 (45.8)		
Chinese	417 (68.1)	220 (52.8)		
Indian	61 (10.0)	30 (49.2)		
Others	16 (2.6)	9 (56.3)		
Gender			0.031	0.860
Female	397 (64.9)	202 (50.9)		
Male	215 (35.1)	111 (51.6)		
Psychiatric comorbidity			2.786	0.095
Present	132 (21.6)	76 (57.6)		
Absent	480 (78.4)	237 (49.4)		

^a Chi-square test of independence; ^b Chinese versus other ethnicities

Trends of Benzodiazepine Prescribing

A large portion of users, 94.9% (n=297) received only one benzodiazepine for each prescription they received throughout the period of data collection while only 3.8% (n=12) received two benzodiazepines in each single prescription throughout the period of data collection. One patient was receiving two benzodiazepines concomitantly which was then increased to three benzodiazepines for a period of 6 months and then reduced back to two benzodiazepines. Three patients received prescriptions with a mixture of one and two benzodiazepines throughout the period of data collection.

The median dose of benzodiazepines prescribed was 3.57mg/day (IQR 1.78-7.14mg/day) of diazepam equivalents. A total of 76.7% (n=240) of the patients received benzodiazepines for more than four weeks and the median duration of benzodiazepines prescribed was 84 days (IQR 35-206 days). The doses and durations of benzodiazepine prescribed were presented in Table 2.

No statistically significant difference was observed between the doses of benzodiazepines prescribed and the characteristics of the patients. Older patients received longer duration of benzodiazepines (median 126 days, mean rank 334.58) as compared to the younger patients (median 84 days, mean rank 298.50). The difference was found to be statistically significant (p=0.001). Besides that, Chinese patients received statistically significant longer duration of benzodiazepines (median 112 days, mean rank 168.54) as compared to other ethnicities (median 56 days, mean rank 129.70) (p=0.0004).

Majority of benzodiazepine users received prescription(s) for benzodiazepines for as needed (p.r.n.), which accounted for 60.7% (n=190) of all depressed patients on benzodiazepines. A total of 30.0% (n=94) had regular doses of benzodiazepine prescribed to them while only 9.3% (n=29) of benzodiazepine users were given both as needed (p.r.n.) and regular doses. Clonazepam was the most frequently prescribed benzodiazepine, followed by alprazolam and zolpidem, which can be seen in Table 3.

Table 2: Doses and durations of benzodiazepine among patients with MDD by patient characteristics (n=313)

Variable	Dose of Benzodiazepine, mg/day of diazepam equivalents, median (IQR)	U statistics ^a	P-value ^a	Duration of benzodiazepine, days, median (IQR)	U statistics ^a	P-value ^a
Age group		8037	0.756		6.024	0.001
<65	3.57 (1.78-7.28)			84 (33.5-173.5)		
≥65	4.72 (1.88-6.73)			126 (42-231)		
Ethnicity		6341 ^b	0.690 ^b		7.944 ^c	0.0004 ^c
Malay	4.34 (2.16-7.47)			56 (28-84)		
Chinese	3.72 (1.78-7.14)			112 (42-236)		
Indian	3.57 (1.78-6.87)			97 (43.5-199.5)		
Others	2.50 (1.33-10.22)			49 (28-175)		
Gender		1.056	0.730		9.802	0.176
Female	3.57 (1.85-6.71)			98 (35-224)		
Male	4.04 (1.78-9.59)			84 (35-169)		
Psychiatric comorbidity		8032	0.155		7.756	0.067
Present	4.16 (2.43-7.51)			84 (28-215)		
Absent	3.57 (1.78-7.14)			84 (35-196)		

^a Mann Whitney U test; ^b Malay versus other ethnicities; ^c Chinese versus other ethnicities

Table 3: Types of benzodiazepine prescribed (n=313)

Types of Benzodiazepine	Prescribed Frequency, n (%)
Clonazepam	145 (38.6)
Alprazolam	75 (19.9)
Zolpidem	73 (19.4)
Lorazepam	62 (16.5)
Diazepam	12 (3.2)
Bromazepam	9 (2.4)

Discussion

This study, which examined the usage of benzodiazepines among depressed patients treated in a tertiary psychiatric referral centre, showed high levels of benzodiazepine use and for longer duration than recommended in the guidelines. In this study, benzodiazepine use was more prevalent in the older patients as compared to the younger age group. This finding was similar to a population-level retrospective study of benzodiazepine usage conducted in the United States by Ofelson *et al.* where they found that the percentage that used benzodiazepines increased with age (8). This finding was also similar to other studies where they found that benzodiazepine use was more common among the older patients, which is quite unexpected given that the risks of benzodiazepine increase with age (2,9,10). Valenstein *et al.* reported that this finding was possibly due to the fact that higher portion of older patients had exposure to benzodiazepine(s) and thus were more likely to request these medication(s) from their physicians. Besides that, older patients may also have more difficulty in discontinuing benzodiazepine(s) once they have started. This explains the similar findings with the study by Valenstein *et al.* that older patients received benzodiazepines for a longer duration as compared to the younger patients (2). It is worrying that the median dose received by our older depressed patients was higher as compared to the younger patients although the difference was not statistically significant. This finding was different from the findings by Valenstein *et al.* whereby they reported that even though older patients were more likely to use benzodiazepines than younger patients, they received lower benzodiazepine doses (2). Healthcare professionals may want to address this matter in view of the risks and adverse events related with benzodiazepine use in older patients such as increased risk of vehicular accidents, falls and hip fractures that increased with age, cognitive and psychomotor adverse events or deaths.

Clonazepam was shown to be the most prescribed benzodiazepine among our depressed patients. However, it should be taken into consideration that when this study was conducted, there was insufficient stock of lorazepam due to the review of the import permit of its raw material by the regulatory agency. Therefore, to counter this problem, many patients who were receiving lorazepam in HBUK were converted to clonazepam instead. Taking this into account, the prescribing pattern of benzodiazepines in HBUK leaned more towards the short-acting benzodiazepines. This finding was interesting as in a study carried out in six Asian countries by Tor *et al.*, lorazepam and clonazepam were found to be the top most prescribed benzodiazepines, taking note that lorazepam is a short-acting while clonazepam is a long-acting benzodiazepine (11,12). In another study carried out in Lebanon by Ramadan *et al.*, alprazolam and bromazepam were the most commonly prescribed benzodiazepines, both of which belong to the short-acting group (12,13). Maniam *et al.* reported lorazepam to be the most prescribed benzodiazepine in a study conducted in a university hospital in Kuala Lumpur (14). In addition, according to the Malaysian Statistics on Medicines 2010, the top three benzodiazepines prescribed in Malaysia were alprazolam, zolpidem and lorazepam, which reflect closely to the findings in HBUK (15). It can be seen that Asian countries in general were more in favour of short-acting benzodiazepines as compared to western countries where long-acting benzodiazepines were preferred. Two studies conducted in the United States by Valenstein *et al.* and Gray *et al.* reported that the most prescribed benzodiazepines were diazepam, clonazepam and lorazepam where else in Canada, a cross-sectional study conducted in depressed patients by Rizvi *et al.* showed that clonazepam and lorazepam were the most common benzodiazepines prescribed (2,16,17).

The median dose of benzodiazepines received by our MDD patients was 3.57mg diazepam equivalent per day. According to the Canadian Agency for Drugs and Technologies in Health, high dose of benzodiazepine(s) is defined as doses of more than 10mg diazepam equivalents (18). Janhsen *et al.*, who studied the problems of long-term treatment with benzodiazepines and related substances in Germany, defined high dose of benzodiazepine as 20mg or more of diazepam equivalents (19). Benzodiazepine therapy can give rise to physiologic and psychologic dependence depending on the drug's dosage, duration and potency. Therefore, dependence will develop sooner in a patient receiving a high dosage of benzodiazepine as compared to a patient receiving a low dosage of benzodiazepine (20). Even though this study showed high levels of benzodiazepine use among outpatient depressed patients in HBUK, the dose received by the patients were considered low, and majority received a p.r.n. dose instead of a regular dose, which was less worrying. This finding differed from the findings in the REAP study which was a cross-sectional study conducted across nine Asian countries from 2001 to 2008. In the REAP study, the mean benzodiazepine daily dose prescribed in

Malaysia was 18.7mg (SD 14.1mg) of diazepam equivalents, which was much higher than the median dose prescribed in HBUK (11).

More than one half of the depressed patients received benzodiazepine(s) for more than four weeks with a median duration of 84 days (12 weeks) which was similar to other studies. Factors such as the desire to prevent a distorted physician-patient relationship, lack of time dealing with patients and failure to reassess patients' needs for benzodiazepines could have contributed to this finding. Valenstein *et al.* described that many physicians responded to their patients' requests for continuation of benzodiazepine(s) due to the worries that a good physician-patient relationship will be distorted if they decline the patients' requests (2). Two other studies also found that physicians continue to prescribe benzodiazepine(s) because of insufficient time in dealing with their patients (21,22). Physicians may also began benzodiazepine treatment as an adjunct to the antidepressants in the early stage of treatment and then failed to reassess the patients' need for the medication or may be hesitant to discontinue the medication as their patient is doing better (2). The EMPOWER trial showed that direct-to-consumer education could effectively elicit shared decision making around the overuse of medications that increase the risk of harm in older adults (23). Therefore, counselling about the risk of benzodiazepine dependence to newly diagnosed MDD patients may help to improve the awareness and reduce patients' dependence to the drugs.

To date, there was no published article on benzodiazepine prescribing pattern and usage among the MDD patients in Malaysia. Hence, this study provided important findings to create awareness among the healthcare professionals and public on the extent of benzodiazepine usage among MDD patients in the local setting. Since all prescriptions retained in the pharmacy for the treatment of MDD over the ten months period (March –December 2016) has been accounted for, the findings were highly reliable. There are limitations of this study, however, that should be taken into consideration. All prescriptions received from March 2016 to December 2016 that fit into the study criteria were included to study the benzodiazepines prescribing trend. However, some prescriptions were endorsed without diagnosis being written. Hence, some prescriptions in which patients were diagnosed with MDD could have been missed out in this study. Moreover, there could be a possibility that the patients did purchase benzodiazepines from the private general practitioners or community pharmacies without the hospital's knowledge.

Conclusion

Notwithstanding guideline cautions, long term prescribing of benzodiazepines in MDD patients remains an occurring treatment pattern in the mental health specialty care. Majority of the depressed patients receive benzodiazepines for a period of more than four weeks albeit only in low doses. Short-acting benzodiazepines were popular choices among the physicians of HBUK compared to long-acting benzodiazepines. Further studies are needed to clarify physicians' reasons for long-term treatment with benzodiazepines, the preference of short-acting benzodiazepines and the effectiveness of this practice. Other than that, it will be interesting to explore whether thorough counselling regarding the risk of benzodiazepine dependence with chronic use of benzodiazepines to newly diagnosed MDD patients will help to improve the awareness and reduce patients' dependence on the drugs in Malaysia.

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Conflict of Interest Statement

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