

## ORIGINAL ARTICLE

# Benzodiazepines Refusal During Dispensing Process Among Patients Diagnosed With Depression or Schizophrenia in Malaysia

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## ABSTRACT

**Introduction:** Benzodiazepines (BZDs) are commonly prescribed to psychiatric patients. However, there have been few studies evaluating BZD refusal among patients with psychiatric disorders during the dispensing process. Thus, this study aimed to determine 1) the factors associated with BZD refusal during the dispensing process and to determine 2) the association between BZD refusal and psychiatric medication adherence among patients diagnosed with depression or schizophrenia. **Method:** This study was conducted at the Specialist Clinic Pharmacy, Jerantut Hospital, Malaysia, from May 2018 to June 2018. BZD refusal status was determined after the dispensing process, and general information on BZD was determined using a questionnaire developed by the researchers. Medication adherence was assessed using the Malaysian Medication Adherence Scale (MALMAS). **Results:** Overall, 75 patients with psychiatric disorders participate in the study. Participants had been on BZD treatment for a mean of  $32.8 \pm 21.6$  months. The BZD refusal rate was 38.7%. BZD refusal was significantly associated with several factors. A one-year increase in age resulted in increased odds of BZD refusal by 1.16 times (95% CI 1.05-1.27). Other factors were male gender (OR, 9.14; 95% CI, 1.17-71.27), being single (OR, 15.07; 95% CI, 1.12-184.28), the diagnosis of schizophrenia (OR, 13.45; 95% CI, 1.75-10.33) and not having history of illicit drug use (OR, 20.63; 95% CI, 2.49-171.0). Medication adherence was not associated with BZD refusal. **Conclusion:** BZD refusal was significantly associated with demographic factors such as increased age, male gender and being single and diagnosis factors namely schizophrenia diagnosis and not having history of illicit substance use. Thus, the need for BZD in these groups of patients should be reviewed regularly.

**Keywords:** Benzodiazepines, Adherence, MALMAS, Psychiatric

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## INTRODUCTION

Characteristic manifestations in schizophrenia and depression differ in several aspects. Disorganization in reward processing and cognitive function was observed in schizophrenia in contrast to deficits in anticipatory pleasure, development of reward associations and integration of information from past experience (1). However, they share several similarities such as marked depressive symptoms that were followed by negative symptoms and functional impairment at the onset of these conditions (1,2).

Treatments for schizophrenia and depression involve various pharmacological modalities including benzodiazepines (BZDs). In the short term, BZDs might

be useful for sedation and calming agitated patients with schizophrenia (3). The use of BZDs for up to four weeks among patients diagnosed with depression was also found to be effective at improving antidepressant adherence (4,5,6,7). This is very beneficial considering that medication non-adherence is a common problem in psychiatric patient populations (4,8,9,10) which may cause adverse outcomes, such as increased hospital admissions (11).

However, there are several issues related to BZD treatments, such as overprescribing by physicians (12), prolonged use (exceeding four weeks) in 40% of patients receiving antidepressants (6), dependence in about 47.6% to 60% of patients (13, 14), and misuse (15). Long term BZD use was also shown not to improve antidepressant medication adherence among older patients diagnosed with depression (16). Thus, regular assessment of BZD use is vital. Usually, BZD use can be assessed using patient surveys (14), pharmacy databases (17), prescription bottle examinations, and

'patient reported use duration' (18). These activities, namely medication adherence and BZD use assessment by pharmacists during the dispensing process, are beneficial in reducing medication waste and identifying medication-related problems (19). In addition, research has shown that pharmacist involvement in the care of psychiatric patients has led to a reduction in unnecessary prescribing in patients with schizophrenia (20) and improved medication adherence (10).

In the current setting, we observed that some of the psychiatric patients diagnosed with depression or schizophrenia on BZD treatment exceeding four weeks tended to refuse BZDs during the dispensing process. BZD refusal among these patients also seemed to relate with better adherence to antidepressant or antipsychotic medications. Since currently available studies are mainly focused on factors associated with prolonged BZD use and BZD dependence alone, we thus aimed to determine 1) the factors associated with BZD refusal and 2) the association between BZD refusal and adherence to antidepressant or antipsychotic medication in patients receiving BZDs for a period exceeding four weeks.

## MATERIALS AND METHODS

This cross-sectional study was conducted at the Specialist Clinic Pharmacy of Jerantut Hospital, Malaysia, from May 2018 to June 2018, using convenience sampling among patients with depression or schizophrenia attending the psychiatric clinic. It was approved by the Medical Research and Ethics Committee (MREC) (registration number: NMRR-18-536-40594).

Medication dispensing for potential research participants was done in a counselling room instead of a pharmacy counter at the Specialist Clinic Pharmacy to ensure patient comfort and confidentiality. Medication dispensing and data collection were performed in Malay language by the same researchers, who were all pharmacists at the current facility. The dispensing process used by the researchers followed the standard operating procedure at the current facility. Participants were provided with information related to their respective psychiatric medications, including BZDs. This information includes medication's dosing, indication, administration time, missed dose management and possible side effects. The researchers also provided counselling on medication use, adherence, the role of BZDs in psychiatric disorders, and the risk of BZD treatment, such as misuse and dependence (21) and medication storage. The content of the medication counselling was discussed between the researchers prior to the data collection and the checklist for medication counselling was prepared by the researchers in order to standardise the information provided. After the dispensing process was completed, patients were informed regarding the study. Written consent was obtained for those who agreed to participate after the content of the consent form was read to them.

After that, participants were asked if they needed the BZDs and other medications previously dispensed. BZD refusal or acceptance status referred to the patient's act of declining or accepting the BZDs prescribed for them during the medication dispensing process.

This survey was conducted using face-to-face interview whereby the questions were read to the participants by the researchers. This technique was used in order to minimise cognitive burden and recall bias while increasing the survey completions of the participants (22). The questions were developed based on the common advice given during BZD tapering down counselling (21). It contained questions such as 'availability of BZD balance at home', 'patient's ability to sleep without using BZD', 'concern of dependence to BZD', 'concern of daytime drowsiness due to BZD consumption' and 'history of illicit drug use' (21).

The assessment of antidepressant or antipsychotic adherence was done using the Malay version of Malaysian Medication Adherence Scale (MALMAS) (23). This scale contained one domain with eight items. The first item of the MALMAS consisted of five responses: [1] All the time, [2] Often (>15 but less than 30 times), [3] Sometimes (6–15 times), [4] Rarely (1–5 times), and [5] Never. Items two to eight were dichotomous with an answer of either 'Yes' or 'No'. A total score of less than 6 indicated a low adherence, 6–8 indicated a medium adherence, and above 8 indicated a high adherence (23). MALMAS has a good internal consistency with Cronbach's alpha value of 0.565 (23). Overall, researchers allocate between 30 to 45 minutes for conducting the medication counselling, medication dispensing and data collection for the survey.

The inclusion criteria of the study included psychiatric patients diagnosed with depression or schizophrenia whom had been prescribed BZDs for longer than four weeks, patients receiving treatment with antidepressants or antipsychotics from the specialist psychiatric clinic at Jerantut Hospital and adults who were over 18 years of age at the time of the study and collected medications by themselves. Those with an overlapping diagnosis, who refused to participate, who had communication problems such as a language barrier (difficulty conversing or understanding Malay language) or hearing issues, who had been taking BZDs for less than four weeks and those who were intellectually challenged were excluded.

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 18.0. Categorical variables were described as frequencies and percentages (%) while continuous variables were reported as mean and standard deviation (SD). Binary logistic regression was used to determine possible independent variables associated with BZD refusal. Independent variables with a p-value of less than 0.2 were selected for inclusion in the multivariate analysis

using forward and backward linear regression steps. Independent variables that remained significant in both forward and backward linear regression steps were included for final multivariate analysis. Factors associated with BZD refusal in patients diagnosed with schizophrenia or depression was analysed separately using independent T-test and Chi-square test and a p-value of less than 0.05 was considered statistically significant.

## RESULTS

As of June 2018, 75 patients with psychiatric disorders at Jerantut Hospital who received BZD treatment and fit the inclusion criteria agreed to participate in the study during the dispensing process. The majority of the participants were male (64%, n=48), Malay race (72%, n=54), had education lower than secondary school (60%, n=45) and unemployed (74.7%, n=56). In terms of diagnosis, 58.7% of the participants (n=44) were diagnosed with schizophrenia and 20% (n=15) had reported history of illicit drug use.

Frequently prescribed BZDs were lorazepam and diazepam, with 37.3% (n=28) and 32% (n=24), respectively. Participants had been on BZD treatment for a mean of 32.8± 21.6 months. Second generation antipsychotics (SGAs) and selective serotonin reuptake inhibitors (SSRIs) were the most commonly prescribed drugs in the current setting (60.7% [n=37] and 87.1% [n=27], respectively). Around 54.8% (n=17) from 31 patients diagnosed with depression received treatment augmentation with antipsychotics. Around 38.7% (n=29) of the participants refused their BZDs. Half of the participants claimed to have a balance of BZDs at home and 72.0% (n=54) claimed to be able to sleep without using BZDs. Around 48% of the participants had a concern of becoming dependant on BZDs and 34.7% (n=26) showed concern of daytime sleepiness. Data are shown in Table I.

### Factors associated with benzodiazepine refusal in the univariate analysis

#### Demographics

Several demographic factors were associated with BZD refusal namely number of households (OR,0.59; 95% CI, 0.43-0.81), gender (OR,4.40; 95% CI, 1.43-13.53), marital status (OR,4.98; 95% CI, 1.71-14.54), education level (OR,6.05; 95% CI, 2.18-16.81) and employment (OR,7.91; 95% CI, 1.67-37.51).

#### Diagnosis and treatment aspects

Patients' diagnosis (OR,13.48; 95% CI, 3.55-51.17), not having history of illicit drug use (OR,5.32; 95% CI, 1.10-25.64), ability to sleep without taking BZDs (OR,21.54; 95% CI, 2.69-172.08) and concerned of becoming dependant on BZDs (OR,4.17; 95% CI, 1.54-11.25) were significantly associated with BZD refusal.

**Table I: Participants' demographic and medications details**

Characteristics	n (%)
Age (years old)†	48.0 (13.1)
Gender	
Male	48 (64.0)
Female	27 (36.0)
Marital Status	
Married	32 (42.7)
Single	43 (57.3)
Race	
Malay	54 (72.0)
Others	21 (28.0)
Education	
Lower than secondary school	45 (60.0)
College or university	30 (40.0)
Employment	
Employed	19 (25.3)
Unemployed	56 (74.7)
Diagnosis	
Schizophrenia	44 (58.7)
Depression	31 (41.3)
History of illicit drug use	
Yes	15 (20.0)
No	60 (80.0)
Type of BZD Prescribed	
Diazepam	24 (32.0)
Alprazolam	11 (14.7)
Lorazepam	28 (37.3)
Clonazepam	12 (16.0)
Duration on BZD+ (months)	32.8 (21.6)
Antipsychotic prescription	
Yes	61 (81.3)
No	14 (18.7)
Antipsychotic type	
First generations	24 (39.3)
Second generations	37 (60.7)
Antidepressant medications	
Selective Serotonin Reuptake Inhibitors (SSRIs)	27(87.1)
Mirtazapine	4 (12.9)
Depression treatment	
Antidepressant alone	14 (45.2)
Antidepressant with antipsychotic	17 (54.8)
BZD Refusal Status	
Refused	29 (38.7)
Accept	46 (61.3)
Balance of BZD available at Home	
Yes	38 (50.7)
No	37 (49.3)
Able to Sleep Without BZD	
Yes	54 (72.0)
No	21 (28.0)
Concern of becoming dependent on BZD	
Yes	36 (48.0)
No	39 (52.0)
Concern of daytime drowsiness	
Yes	26 (34.7)
No	49 (65.3)

†Data expressed as mean ±SD  
SD: Standard deviation

### Antidepressant or antipsychotic medication adherence

BZD refusal was not significantly associated with high and medium adherence, (OR,4.06; 95% CI, 0.95-17.29) and (OR,0.45; 95% CI, 0.08-2.68) respectively. Data are shown in table II.

**Table II: Univariate analysis for factors associated with BZD refusal**

Factors	Reference	OR	95% CI	p-value
Age		1.03	0.99-1.07	0.152
Number of households		0.59	0.43-0.81	0.001
Gender	Female	4.40	1.43-13.53	0.010
Marital status	Married	4.98	1.71-14.54	0.003
Education	Secondary or lower	6.05	2.18-16.81	0.001
Employment	Employed	7.91	1.67-37.51	0.009
Diagnosis	depression	13.48	3.55-51.17	<0.05
History of illicit drug use	Yes	5.32	1.10-25.64	0.037
Balance of BZD available at home	No balance	2.33	0.89-6.03	0.082
Able to sleep without using BZD	Unable to sleep without BZD	21.54	2.69-172.08	0.004
Concern of becoming dependent on BZD	Not Concern of becoming addicted	4.17	1.54-11.25	0.005
Concern of daytime drowsiness	Not Concern of drowsiness	1.61	0.61-4.26	0.334
Antipsychotic	FGA vs None	2.00	0.34-11.62	0.440
	SGA vs None	7.88	1.54-40.28	0.013
Medication adherence	Medium vs high	0.17	0.20-1.46	0.106
	Low vs high	0.20	0.02-2.19	0.189
Total number of meds		0.794	0.510-1.236	0.307
Total number of pills		1.053	0.876-1.265	0.586
Duration on BZD		1.009	0.987-1.030	0.440

BZD: Benzodiazepines

FGA: First generation antipsychotics

SGA: Second generation antipsychotics

OR= Odd ratio

95% CI= 95% confidence interval

### ***BZD refusal in the subgroups of patients with schizophrenia and depression***

Several factors were found to be significantly associated between those who accepted or refused BZDs in subgroups of patients with schizophrenia or depression. Those patients with schizophrenia who refused BZDs were significantly older, had lower number of household and had been on BZDs treatment for longer duration compared to those who accepted. They also differed significantly in terms of education, employment, history of illicit drug use, medication adherence, availability of BZDs balance at home and concern of becoming dependant on BZDs.

There are no significant differences between those who accepted or refused BZDs in subgroup of patients diagnosed with depression in terms of demographic, diagnosis, treatment aspects or medication adherence. Data are shown in table III.

### **Factors associated with benzodiazepine refusal in the multivariate analysis**

#### ***Demographics***

A one-year increase in age resulted in increased odds of BZD refusal by 1.16 times (95% CI 1.05-1.27). Male gender (OR,9.14; 95% CI, 1.17-71.27) and being single (OR,15.07; 95% CI, 1.12-184.28), were also significantly

associated with BZD refusal.

#### ***Diagnosis and treatment aspects***

The only diagnosis aspects associated with BZDs refusal were schizophrenia diagnosis (OR,13.45; 95% CI, 1.75-10.33) and not having history of illicit drug use (OR,20.63; 95% CI, 2.49-171.0). Data are shown in table IV.

### **DISCUSSION**

Jerantut Hospital is a district hospital without a psychiatric ward. It only provides psychiatric treatment on an outpatient basis for stable patients. During psychiatric clinic day, a visiting psychiatric specialist from a major hospital in Temerloh will come to review those with mental disorder.

One of the most frequently prescribed medications for patients with psychiatric disorder are BZDs drugs. In current setting, BZDs were prescribed for more than two years, and it was reported that prolonged BZD use was common in patients under psychiatrist treatment (6). In Brazil, more than 50% of the patients reported using BZDs for more than one year (14). However, a high BZD refusal rate of 38.7% in the current study indicates that BZDs prescribed might not always be needed by some of these patients.

**Table III: BZD refusal in the subgroups of patients with schizophrenia and depression**

	Schizophrenia			Depression		
	Accept (n=18)	Refused (n=26)	p-value	Accept (n=28)	Refused (n=3)	p-value
Age†	41.4 (8.5)	50.2 (10.6)	0.006	49.4 (15.8)	55.7 (20.6)	0.527
Household†	4 (1)	2 (2)	0.012	4 (2)	4 (2)	0.676
Education (n, %)						
Lower than secondary school	13 (61.9)	8 (38.1)	0.007	22 (91.7)	2 (8.3)	0.639
College or university	5 (21.7)	18 (78.3)		6 (85.7)	1 (14.3)	
Employment (n, %)						
Employed	8 (100.0)	0 (0.0)	<0.05	9 (81.8)	2 (18.2)	0.281
Unemployed	10 (27.8)	26 (72.2)		19 (95.0)	1 (5.0)	
History of illicit drug use (n, %)						
Yes	8 (80.0)	2 (20.0)	0.004	5 (100.0)	0 (0)	0.424
No	10 (29.4)	24 (70.6)		23 (88.5)	3 (9.7)	
Medication adherence						
High	7 (25.0)	21 (75.0)	0.016	10 (83.3)	2 (16.7)	0.345
Medium	8 (72.7)	3 (27.3)		12 (100.0)	0 (0.0)	
Low	3 (60.0)	2 (40.0)		6 (85.7)	1 (14.3)	
Balance of BZD available at Home						
Yes	12 (57.1)	9 (42.9)	0.036	15 (88.2)	2 (11.8)	1.000
No	6 (26.1)	17 (73.9)		13 (92.9)	1 (7.1)	
Concern of becoming dependent on BZD						
Yes	6 (24.0)	19 (76.0)	0.009	10 (90.9)	1 (9.1)	1.000
No	12 (63.2)	7 (36.8)		18 (90.0)	2 (10.0)	
Duration on BZD†	25.2 (11.9)	36.9 (20.1)	0.032	35.2 (27.3)	20.3 (7.2)	0.362

BZD: Benzodiazepines

Data are analysed using Chi-Square except where indicated

†Data are expressed as mean(SD)

**Table IV: Summary of multivariate analysis for factors significantly associated with BZD refusal**

Factors	Reference	OR	95% CI	p-value
Age		1.16	1.04-1.27	0.005
Gender	Female	9.14	1.17-71.27	0.043
Marital status	Married	15.07	1.123-184.28	0.034
Diagnosis	Depression	13.45	1.75-103.33	0.012
History of illicit drug use	Yes	20.63	2.49-171.00	0.005
Able to sleep without using BZD	Unable to sleep without BZD	8.23	0.54-127.59	0.129

BZD: Benzodiazepines

OR= Odd ratio

95% CI= 95% confidence interval

## Factors associated with BZD refusal

### Demographic factors

A study in Spain has shown that consumptions of BZDs have increased with age (24). In contrast, our finding indicates that refusal of BZDs increased significantly with age. Several factors could have contributed to this observation. Firstly, previous studies analysed use of BZDs in a variety of health complications ranging from psychiatric issues, to diabetes, to cardiovascular disorders which were noted mostly with those aged older than 45 years (74%) (24). Instead, our finding was quite similar to that of a study involving several regions in Asia which reported that combined use of BZDs with antidepressants was common in the younger patients (25). Use of BZDs might be less favourable in the elderly due to BZD side effects such as fatigue, weakness and sedation (26). Previous study has also

reported that younger patients had a higher medication knowledge score (27) and hence willingness to take the medication. Other explanation for BZD preference in the elderly can be viewed from medication belief perspective. In Malaysia, more than half of patients diagnosed with depression have negative beliefs regarding antidepressant treatment and nonadherence to medication was also common (28). In older Egyptian patients, negative beliefs such as medicines causing harm, being overprescribed and causing side-effects has also resulted in decreased antidepressant adherence (29). Thus it is possible that those aforementioned factors could have also contributed toward low BZDs acceptance among older Malaysian patients.

Apparently, male patients were 9.14 times more likely to refuse BZDs in the current setting compared to female patients. Thus, the need for BZDs in male patients

should be assessed regularly since it was reported that males did not use their medicines frequently and were associated with preventable medication waste (19). On the other hand, female gender was commonly associated with long-term BZD use (6,12,14,30,31) due to factors such as more stress (14) and dependence to BZDs (32). However, females also tend to have more confidence in the pharmacological treatment hence frequent use of the healthcare system (6,31). It was also reported that different coping mechanisms between genders might have resulted in different observations toward medication adherence. For instance, it was reported that males might resort to alcohol to deal with stress while females might prefer medication to cope with psychological issues (31).

Higher BZD refusal among single patients in current study is similar to that of questionnaire surveys in developing countries such as Brazil (14) and Pakistan (33). Those studies (14,33) found that the use of BZDs was more common in married patients. On the contrary, database studies in developed countries such as Sweden (34) and France (31) have indicated that being single is a factor for BZD use. In general, relationships between marital status and BZD use varied across different studies globally due to the different socioeconomic status and cultures of the patients (14,33) and assessment techniques used (14,31,33,34). In addition, bias between self-reported interviews and database information is a common challenge (35). In our opinion, database assessments contain information on prescriptions written for patients from the prescribers and the medication collection histories at the pharmacies, yet there is no certainty that patients take those medications at home.

### ***Diagnosis and treatment factors***

In term of diagnosis, those with schizophrenia were more likely to refuse BZDs compared to those diagnosed with depression. In fact, previous study has reported that depressive state was a predictor for BZD dependence (31). Research has also found that as many as 52% of patients with depression developed BZD dependence (36) compared to 0–20% in patients diagnosed with schizophrenia (15). Dependence to BZDs among patients with depression could be due to problematic BZD use and lack of compliance with the physician's recommendations coupled with personality disorders (36). On the other hand, refusal to take BZDs in patients with schizophrenia in current study might have stemmed from awareness on the risk of BZD dependence associated with long term BZD therapy. This awareness might have developed as a result of frequent promotion on BZD dependency given by the pharmacists at our setting during dispensing process.

Current study showed that those without a history of illicit drug use were more likely to refuse BZDs compared to their counterparts. Apparently, illicit drug use is common in those with psychotic symptoms

including schizophrenia (37) and it might be co-abused with BZDs as well (26). It is quite concerning because BZDs might trigger compulsive drug-seeking behaviour among patients with prior history of illicit drug abuse (37). Furthermore, 89% of these patients with history of illicit drug use tend to re-use these illicit substances at certain points of their antipsychotic treatment (37). Even though patients might want to taper down or stop taking BZDs, it might be a challenging process (38) and a cycle of illicit drug abuse coupled with BZD abuse might occur (26). Thus, monitoring for any signs of BZD dependence or abuse in those with a history of illicit drug use is needed.

### ***Antidepressant or antipsychotic medication adherence***

Similar to previous study (16), the benefits of the long-term treatment with BZDs in current study was also questionable since there was no significant association between antidepressants or antipsychotic medication adherence and BZD refusal.

This study has several limitations. Firstly, this study is limited by its small sample size. Secondly, 'yes-saying' and social desirability bias could occur in face-to-face interview resulting in inaccurate reflection of BZD refusal factors. Thirdly, this study did not involve the prescribers thus there might be conflict regarding the role of advising the BZDs needs between the researchers and prescribing doctors. However, to avoid any risk to the participants, they were informed to finish their remaining BZDs at home first or to walk in to our outpatient pharmacy at any time in case they did not have sufficient BZDs at home. Due to these limitations, the generalisability of the findings might be limited to the current setting alone.

### **CONCLUSION**

In summary, the need of BZDs should be regularly reviewed by the prescribers since they are frequently refused during the dispensing processing especially in older, male, single patients and those diagnosed with schizophrenia. This is vital in order to avoid BZD overprescribing and also to ensure success of the medication therapy and maintain patients' safety. Ideally, long-term BZDs should be avoided since they do not provide any benefits in improving antidepressant or antipsychotic medication adherence in patients diagnosed with depression or schizophrenia. Assessment regarding awareness on BZDs dependence must also be conveyed to psychiatric patients receiving BZDs especially those with the history of illicit substance use in order to prevent issues such as misuse.

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