

Trends and patterns of benzodiazepines prescription from 2014 to 2016: A retrospective cross-sectional study in an outpatient setting of tertiary hospital in Malaysia.

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Abstract

Background

Despite evidence of their association with adverse drug events and mortality, benzodiazepines are still among the main choice for treating many psychiatric disorders and neurological conditions. To date, there is a meager data on the prescribing trends and patterns of benzodiazepines in Malaysia.

Objective

This study aimed to investigate the trends and patterns of benzodiazepines prescribing at outpatient hospital setting.

Method

A retrospective, cross-sectional study was conducted at outpatient pharmacy of a tertiary hospital in Malaysia. Prescriptions for any of seven benzodiazepines (alprazolam, bromazepam, clobazam, clonazepam, diazepam, lorazepam and midazolam) issued from January 2014 until December 2016 were screened and included in this study. Trends and patterns of prescribed benzodiazepines were examined. Descriptive statistics and association between patient characteristics and prescribing patterns were performed using STATA® SE v.13.1 (Stata Corp LP, Texas, USA).

Results

A total of 5,728 benzodiazepines prescriptions of the seven benzodiazepines were prescribed for 1,943 patients from 2014 to 2016. BZDs were prescribed to 1,013 (52.1%) male with mean age of 46.8 ± 14.1 for the whole study population, in which 26.8% were between 45–54 years old. About 40% of benzodiazepines prescribed were classified as short-acting. About 12.6% reduction in the overall number of benzodiazepine prescriptions from 2014 ($n = 1956$) to 2016 ($n = 1709$). Alprazolam was the most frequently prescribed (43.3%) in 2014, followed by (38.9%) 2015 and (36.8%) 2016. Approximately, 69.64% ($n = 6,218$) of benzodiazepines were prescribed for a duration of 15 to 30 days, while 57.29% ($n = 5,115$) of benzodiazepines were prescribed with fixed dosing schedule.

Conclusion

Overall benzodiazepine prescription shows a decreasing trend from 2014 to 2016. Alprazolam, the short-acting benzodiazepine was the most frequently prescribed in hospital outpatient setting in Malaysia.

Introduction

Benzodiazepines are commonly prescribed for psychiatric disorder. *Mother's Little Helpers'* and *Sleepers'* are among many nick names bestowed upon this class of drugs, to describe benzodiazepines. As it possess sedative, hypnotics, anxiolytics and muscle relaxants properties; it is often medically used to treat insomnia, panic disorder, relieve stress and seizures among other [1]. BZD were widely noted as breakthrough drugs, which were believed to surpass its predecessor's effectiveness - the barbiturates.

Thus when it was marketed in the 1960, it became the most commercially successful drug at that time. They were thought to be a solution by many prescribers because they acted effectively on anxiety, mixed anxiety depression, and other nonspecific physical complaints while at the same time being comparatively safe [2, 3]. BZDs are also often used in conjunction with other psychotropic drugs. For example, the combination of BZD and antidepressant led to greater response and to less drop-out than antidepressant alone in the acute phase treatment of depression [4].

However, the joy of prescribing it in abundance has taken its toll. Albeit benzodiazepine has legitimate indication, it also has its risk and harm that should not be overseen. After society discovered BZDs are taxed with addictiveness, it remains unclear how addictive they were when compared to other related list of psychoactive drugs [2]. While short-term uses of these medications are generally safe and effective, the long term use of benzodiazepines is debatable, chiefly because of the potential of dependence, withdrawal and tolerance [5]. When use for extended period of time, they may lead to problems associated with discontinuation and withdrawal symptoms and also abuse [6, 7]. Benzodiazepine use is also associated with adverse drug events such as dementia and psychomotor impairments, which lead to premature death [8]. Known risk factors for benzodiazepine-related adverse events include lung disease, substance use, and vulnerability to fracture [9]. Although causality has not been definitively determined, strong associations between benzodiazepine prescribing and mortality have been described in younger population [8]. Benzodiazepines are drugs that should be used for very short time, at most for a few days or weeks in selected patients, carefully monitored, and stopped as soon as possible, as recommended in their summary of product characteristics and in all international recommendation [11]. The risk-benefit balance of using BZD in the long term is accordingly to be negative. BZD is commonly prescribed for short-term duration (1–4 weeks) to reduce the risk of dependence and withdrawal [11]. A WHO guideline for traumatic stress in non-specialized settings suggests that, when psychotherapy is not practical, short-term treatment with BZD may be considered [12]. Other guidelines also make similar favourable mentions [13, 14].

The Committee on the Review of Medicines in the United Kingdom, for example, has issued a warning regarding the regular long-term use of benzodiazepine and expresses their concern on the high number of patients with repeat prescriptions for an unusually long period [15]. The primary basis of the worry seems to be about the risk of normal and excessive usage of benzodiazepine, the tolerance level, dependence potential and the abuse liability of benzodiazepines. Today, the dispute encircling the use of benzodiazepines is still open for debate. Benzodiazepine prescribing trends may vary in each country, but their long-term usage is usually seen and treated as the norm in many.

Quantifying benzodiazepines usage in populations helps to reaffirm the current prescribing practices and pinpoint the existence of problematic consumption that could be prophetic for primary adverse outcomes. While several developed countries have established a nationwide register of patient's data to enable them to conduct a study not only on benzodiazepines but also other medications related to current pharmacoepidemiology issues, scant information is available about the nature of benzodiazepines prescribing in Malaysia compared to other countries. Due to this limitation, the data on the trends and patterns of benzodiazepines prescriptions and its use in Malaysia are still limited. This study aimed to investigate the trends and patterns of benzodiazepines prescribing at the out-patient setting of Malaysian public hospital.

Ethics Approval

Approval to conduct this study was granted by the Medical Research Ethical Committee (MREC), Ministry of Health Malaysia (Date: 11th October 2016 / Registration no: NMRR-16-1742-28839).

Method

Study design and data source

This retrospective, cross-sectional study was conducted at the outpatient pharmacy of a public tertiary hospital in Malaysia. This study has been granted ethical approval from the Medical Research Ethical Committee (MREC), Ministry of Health Malaysia. It was carried out with the approved of the Medical Research Ethics Committee (MREC), Ministry of Health Malaysia (NMRR-16-1742-28839). The data on patient information were de-identified and only aggregate results were reported. There was no direct patients' involvement in this study that did not require informed consent from patients.

Prescriptions for seven benzodiazepines (alprazolam, bromazepam, clobazam, clonazepam, diazepam, lorazepam and midazolam) issued from January 2014 until December 2016 was identified together with these inclusion criteria; having at least one type of benzodiazepine prescribed in a prescription, the prescribed benzodiazepines must be in oral formulation only

for patient's aged 18 years old and above. Information extracted from the prescriptions includes patient age and gender, name of medication, dosage form, dose, strength, frequency, duration, the amount supplied, diagnosis, and issuing department.

Benzodiazepines were categorized according to the type, ATC code, duration of action and onset of action. Benzodiazepines were described by the ATC code as N05BA (anxiolytics: alprazolam, bromazepam, clobazam, diazepam, lorazepam), N05CD (hypnotics/sedatives: midazolam), and N03AE01 (antiepileptic: clonazepam). Based on duration of action, benzodiazepines are classified into three groups; short-acting (≤ 12 hours: alprazolam and midazolam), intermediate-acting (12–24 hours: bromazepam, clonazepam and lorazepam) and long-acting (≥ 24 hours: diazepam and clobazam). Based on the onset of action, benzodiazepines are divided into two categories; rapid action (within 15 minutes: diazepam and midazolam) and intermediate action (from 15 minutes to 30 minutes: alprazolam, bromazepam, clobazam, clonazepam and lorazepam).

Calculation for the defined daily dose (DDD)

The number of DDDs consumed is calculated according to the following formula by Truter, Wiseman, & Kotze, (1996). The calculation of DDD was done for each patient starting from the first day they received their prescription until the last day of our study frame.

Benzodiazepine prescribing patterns

Fundamentally, the patterns of benzodiazepines prescribed in the study are acquired from the information of the prescription slips. The applied patterns analysis is not corresponding to the number of patients or the number of prescriptions since one patient, or one prescription may contain more than one benzodiazepines. Moreover, each prescribing patterns are consistently following the number of dispensation, not the number of patients or prescriptions.

Data analysis

The patients and prescriptions were measured monthly and annually. Prescribing trends and patterns (ATC classification, duration of action and onset of action) for each type of benzodiazepine were also analysed and presented as number, percentage and DDD/1000/day. Descriptive statistics and association between patient characteristics and prescribing patterns were performed using STATA® SE v.13.1 (Stata Corp LP, Texas, USA).

Results

Number of benzodiazepine users

A total of 1,943 patients (52.14% male) had received 5,728 benzodiazepines prescriptions from 2014 to 2016 (Table 1). The mean age of patients received benzodiazepines was 46.8 ± 14.1 years, and it ranges from 18 to 93 years old. Out of six age ranks, patients aged 45–54 years recorded the highest percentage (26.81%), followed by 35–44 (19.3%), 25–34 (18.17%), 55–64 (15.29%), 65 and above (11.12%) and 18–24 (7.51%).

Table 1
Patients' Characteristics

Characteristicss	Patients (n = 1,943)		Prescriptions (n = 5,728)	
	n	%	n	%
Sex				
Male	1,013	52.14	2,945	51.41
Female	930	47.86	2,783	48.59
Race				
Malay	1,186	61.04	3,252	56.77
Chinese	585	30.11	2,148	37.50
Indian	146	7.51	246	4.29
Others	26	1.34	82	1.43
Age				
Mean (SD) : 46.8 (14.1)				
Range : 18–93				
Age group				
18–24	146	7.51	314	5.48
25–34	353	18.17	945	16.50
35–44	375	19.30	1,195	20.86
45–54	521	26.81	1,685	29.42
55–64	297	15.29	886	15.47
65 ≥	216	11.12	668	11.66
NA	35	1.8	35	0.61

Monthly number of benzodiazepine prescriptions

Figure 1 showed approximately 5.5% increased of prescriptions from 2014 (n = 1,956) to 2015 (n = 2,063), but later a decreasing trend of 34.3% from 2015 to 2016 (n = 1,709). A line chart with a trendline was constructed to see the trends over months of the study duration, which witnessed an increase in trend in 2014 and decreasing trends in both 2015 and 2016. In general, the study observed a drop of 12.6% number of prescriptions from 2014 to 2016.

Benzodiazepine prescribing patterns

The study discovers that from 5,728 prescriptions, there were 8,929 benzodiazepines issued throughout the three years. The analysis of prescribing patterns is described in Table 2 in regards to the number of benzodiazepines dispensation; n = 8929. In regards to the duration of supply for benzodiazepines, the study recognised there are 79 types of duration available in the data. The benzodiazepines day supply ranges as one day to a maximum of 240 days (mean 34.43 days). Those durations were then grouped into five types (1–7 days, 8–14 days, 15–30 days, 31–60 days and > 60 days), as listed in Table 2. Throughout the analysis of data, it was found that 16 types of dosing schedule involved in the study however, the dosing schedule is further categorised into two types; fixed schedule and as needed schedule (Table 2).

Table 2
Patterns of Benzodiazepines Prescribed Based on Prescription

Patterns (n = 8929)	2014 (n)	2015 (n)	2016 (n)	Frequency (n)	Percentage (%)
Types of Benzodiazepines					
Alprazolam	1272	1255	1015	3,542	39.67
Bromazepam	20	24	24	68	0.76
Clobazam	3	6	0	9	0.1
Clonazepam	415	604	511	1,530	17.14
Diazepam	543	662	646	1,851	20.73
Lorazepam	672	657	551	1,880	21.05
Midazolam	16	21	12	49	0.55
Class of Benzodiazepines by ATC Code					
Antiepileptic (N03AE)	415	604	511	1,530	17.14
Anxiolytic (N05BA)	2510	2604	2236	7,350	82.32
Hypnotic / Sedative (N05CD)	16	21	12	49	0.55
Class of Benzodiazepines by Duration of Action					
Short-Acting (< 12 hr)	1288	1276	1027	3,591	40.22
Intermediate-Acting (12–24 hr)	1107	1285	1086	3,478	38.95
Long-Acting (≥ 24 hr)	546	668	646	1,860	20.83
Class of Benzodiazepines by Onset of Action					
Rapid action (within 15 minutes)	1231	1340	1209	3,780	42.33
Intermediate action (15–30 minutes)	1710	1889	1550	5,149	57.67
Dosing Schedule					
Fixed Dosing	1661	1866	1588	5,115	57.29
As Needed Dosing	1280	1363	1171	3,814	42.71
Duration of Supply					
1–7 days	340	376	300	1,016	11.38
8–14 days	365	289	339	993	11.12
15–30 days	2056	2274	1888	6,218	69.64
31–60 days	159	252	222	633	7.09
> 60 days	21	38	10	69	0.77
Concurrent Medications (n = 17,106)					
Antidepressant	1287	1169	1013	3,469	20.28
Antipsychotic	757	857	809	2,423	14.16

Patterns (n = 8929)	2014 (n)	2015 (n)	2016 (n)	Frequency (n)	Percentage (%)
Antiparkinson	293	361	291	945	5.52
Antiepilepsy	219	283	279	781	4.57
Analgesic	6	15	8	29	0.17
Others	162	194	174	530	3.1
Diagnosis					
Psychiatric Disorder	2664	2889	2528	8,081	90.5
Non-Psychiatric Disorder	277	340	231	848	9.5
Issuing department					
Psychiatry Department	2466	2586	2228	7,280	81.53
Non-Psychiatry Department	475	643	531	1,649	18.47

Out of seven types of benzodiazepines included in the study, alprazolam has the most significant percentage (39.67%), with 3,542 dispensations, followed by lorazepam (21.05%), diazepam (20.73%), clonazepam (17.14%), bromazepam (0.76%), midazolam (0.55%) and lastly clobazam (0.1%). Alprazolam remained the highest benzodiazepines prescribed from the outpatient pharmacy throughout the study duration. Based on the ATC classification, benzodiazepines that fall under anxiolytics are the highest prescribed by the prescribers since 2014. The result also revealed that short-acting benzodiazepines are the leading choice (n = 3591, 40.22%) in terms of frequency (n) and percentages (%) for three years; compared to long-acting (n = 1,860, 20.83%) and intermediate-acting benzodiazepines (n = 3,478, 38.95%). However, the pattern of prescribing changed from short-acting benzodiazepines in 2014, towards intermediate-acting in recent years (2015 and 2016).

The analysis also indicates that in view on the onset of action, prescribers frequently prescribed intermediate-action benzodiazepines (57.67%) rather than rapid-action (42.33%) benzodiazepines. This pattern continues from 2014 till 2016. Throughout the study period, there were no changes in the patterns of dosing schedule, duration of supply, concurrent medications, diagnosis and issuing department. All three years saw fixed dosing as the most frequent dosing schedule, 15–30 days was the most common duration of supply, antidepressant as the most common type of medication concurrently prescribed with benzodiazepines, a psychiatric disorder was the highest diagnosis written for benzodiazepines patient and psychiatry department mainly prescribed BZD in the study.

Prescribing Trends of Benzodiazepines Based on Defined Daily Dose (DDD)

Table 3 presents the trends of benzodiazepines in milligrams and DDD for year 2014, 2015 and 2016. In 2014, 117,942.5mg of benzodiazepines was dispensed, and the number increased 20% to 141,588.5mg in 2015. However, a 10% reduction was seen in 2016 (126,676.75mg), making a total of 386,208mg of benzodiazepines dispensed throughout the study period. There was a surge of 6% in yearly defined daily dose (DDD/1000 patients/year) from 2014 to 2015 before it came down 15% in the subsequent year. Meanwhile, a decreasing trend was noticed in regards to the DDD/1000 patients/day in which 1.9% and 7.25% decrease was observed in 2015 and 2016, respectively.

Table 3
Trends of Benzodiazepines in Milligrams and Defined Daily Dose

Amount/Year	2014	2015	2016	Total
Amount of benzodiazepines dispensed (mg)	117,942.5	141,588.5	126,676.75	386,208
DDD/1000 patients/day (DDD)	0.23405	0.22956	0.21291	0.67652
DDD/1000 patients/year (DDD)	86.664	92.226	77.648	256.538

The Association between Gender, Age Group and Type of Benzodiazepines

Table 4 concludes the association of benzodiazepines types and patient's age group. It was noted that patient aged 45–54 years are the most common to received benzodiazepines, especially alprazolam (n = 1,149, 12.87%). In addition, it also found that those who were prescribed with alprazolam were significantly more likely to be male (P < 0.001), 21.63%. The P-value showed result lower than 0.001, which indicates a strong association between patient's age group and the selection of benzodiazepines' type.

Table 4
Association Between Gender, Age Group and Types of Benzodiazepines

Types of Benzodiazepines n (%)								
Age Group	Alprazolam	Bromazepam	Clobazam	Clonazepam	Diazepam	Lorazepam	Midazolam	Total
18–24	137	-	-	86	100	109	4	436
	(1.53)	-	-	(0.96)	(1.12)	(1.22)	(0.04)	(4.88)
25–34	451	-	-	130	407	251	12	1,251
	(5.05)	-	-	(1.46)	(4.56)	(2.81)	(0.13)	(14.01)
35–44	640	-	1	277	407	374	12	1,711
	(7.17)	-	(0.01)	(3.1)	(4.56)	(4.19)	(0.13)	(19.16)
45–54	1,149	24	8	430	526	505	9	2,651
	(12.87)	(0.27)	(0.09)	(4.82)	(5.89)	(5.66)	(0.1)	(29.69)
55–64	669	19	-	369	286	292	7	1,642
	(7.49)	(0.21)	-	(4.13)	(3.2)	(3.27)	(0.08)	(18.39)
≥ 65	467	25	-	233	123	336	5	1,189
	(5.23)	(0.28)	-	(2.61)	(1.38)	(3.76)	(0.06)	(13.32)
Missing	29	-	-	5	2	13	-	49
	(0.32)	-	-	(0.06)	(0.02)	(0.15)	-	(0.55)
Total	3,542	68	9	1,530	1,851	1,880	49	8,929
	(39.67)	(0.76)	(0.1)	(17.14)	(20.73)	(21.05)	(0.55)	(100)
Pearson chi-square				399.4975				
P-value	p < 0.001							
Gender	1,611	12	8	690	834	1,134	38	4,327
Female	(18.04)	(0.13)	(0.09)	(7.73)	(9.34)	(12.7)	(0.43)	(48.46)
	1,931	56	1	840	1,017	746	11	4,602
Male	(21.63)	(0.63)	(0.01)	(9.41)	(11.39)	(8.35)	(0.12)	(51.54)
	3,542	68	9	1,530	1,851	1,880	49	8,929
Total	(39.67)	(0.76)	(0.1)	(17.14)	(20.73)	(21.05)	(0.55)	(100)
Pearson chi-square	182.281							
P-value	p < 0.001							

The Association between Gender, Age Group and Duration of action of Benzodiazepines

Short-acting benzodiazepines are the most commonly prescribed benzodiazepines among male patients (n = 1,942, 21.75%) and among patient aged 45–54 years old (n = 1,158, 12.97%) (Table 5). Pearson chi-square analysis shows a significant relationship (P < 0.001) between gender, age group and the duration of action of benzodiazepines.

Table 5
Association Between Gender, Age Group and Benzodiazepines Duration of Action

Age Group	Duration of Action n (%)		
	Short-Acting (< 12 hr)	Intermediate-Acting (12–24 hr)	Long-Acting (≥ 24 hr)
18–24	141 (1.58)	195 (2.18)	100 (1.12)
25–34	463 (5.19)	381 (4.27)	407 (4.56)
35–44	652 (7.3)	651 (7.29)	408 (4.57)
45–54	1,158 (12.97)	959 (10.74)	534 (5.98)
55–64	676 (7.57)	680 (7.62)	286 (3.2)
≥ 65	472 (5.29)	594 (6.65)	123 (1.38)
Missing	29 (0.32)	18 (0.2)	2 (0.02)
Total	3,591 (40.22)	3,478 (38.95)	1,860 (20.83)
Pearson chi-square	266.4689		
P-value	p < 0.001		
Gender			
Female	1,649 (18.47)	1,836 (21)	842 (9.43)
Male	1,942 (21.75)	1,642 (18.39)	1,018 (11.4)
Total	3,591 (40.22)	3,478 (38.95)	49 (0.55)
Pearson chi-square	42.9528		
P-value	p < 0.001		

Discussion

The National Health and Morbidity Survey (NHMS) 2015 reported that there is an increasing trend in the prevalence of mental health problems among adults. The prevalence of approximately escalates threefold from 10.7% in 1996 to 29.2% in 2015 [17]. Naturally, in keeping with the increasing cases, we would expect a similar increase in the prescribing trends of psychotropic drugs, especially benzodiazepines. However, the Malaysian Statistics on Medicines (MSOM) 2015 reported a drop of 22% in the overall usage of benzodiazepines; from 1.313 DDD/1000 patients/day in 2011 to 1.024 DDD/1000 patients/day in 2014 [18]. In summary, our study showed similar decreasing trends on the number of patients receiving benzodiazepines, the number of benzodiazepines prescriptions and also the DDD of benzodiazepines in comparison to the MSOM 2015. However, the prescribing trends of this study are comparatively low in contrast to other research outside Malaysia that was done during the same study period. Prior research in Australia also showed decreasing trends in benzodiazepines utilisation, though the overall benzodiazepines consumption remained relatively high. There were a total of 27.7, and 20.8 DDD/1000 patients/day of benzodiazepines dispensed in 1992 and 2011, while 14.2 DDD/1000 people/day were dispensed between 2013 to 2016, respectively [19, 20]. Furthermore, the yearly study in Finland also documented a declining trend from 15.7, 14.69 and 13.6 DDD/1000 people/day in 2014, 2015 and 2016, respectively [21].

The overall reduction trends in the number of prescriptions and the benzodiazepines defined daily dose is likely due to strict governmental enforcement and establishment of levels of authority in relation to prescriber's category that prevented the widespread usage and over-prescribing of benzodiazepines in government healthcare facilities. The law and regulations covering the benzodiazepines have also prevented 'doctor shopping' and self-prescribes by patients via community pharmacies or illegal online stores since a prescription is compulsory for the purchasing of benzodiazepines. Moreover, there are also public educations of benzodiazepines potential adverse effects in this country. The reduction of trends can also be attributed to the changes in the price of benzodiazepines in the market throughout the year of study. However, since the study did not include the estimation of sales and procurement data, we cannot confidently associate to this factor.

Consequently, the prescribing trends of benzodiazepines can be seen as a result of multimodal influence including from patient, prescriber and local prescribing practice [22–25]. Verily, the use of benzodiazepines in each region varies greatly, depending on the nation, legislature and local practice. Benzodiazepine was not uncommon in Japan and was found in up to 11.9% of annual prescriptions in a tertiary care hospital [26]. In Hong Kong and Beijing, benzodiazepine prescription was found in up to 29.9% of prescriptions to 505 outpatients [25, 27]. In North India, half of the psychotic and bipolar patients and two-third of depressive patients of the study group received benzodiazepines [28].

On the other hand, Kaufmann et al., (2016), Tu, Mamdani, Hux, & Tu, (2001) and Cunningham, Hanley, & Morgan (2010) reported that the elderly (aged 65 and above) to be the majority in using BZDs [29–31]. Benzodiazepines are more dominant in female, and its use is increased steadily with age, which indicates the elderly are usually the highest receiver [18, 30, 32–37].

Nevertheless, there is a significant similarity in view to the age group of benzodiazepines patient of this study compared with other established studies. Most of the patient that received benzodiazepines falls under the age of 45 years old and above. The lower rates of benzodiazepines prescribing to the elderly patients (65 years old and above) receiving benzodiazepines compared to other age groups in this study can be contributed to the practice guidelines which strongly recommended initiation of non-pharmacologic approaches and then the use of antidepressant over benzodiazepines as first-line treatment for insomnia and anxiety among the elderly [38]. Conversely, this finding provides evidence of the prescriber's adherence to the guidelines.

Alprazolam remained as the most frequent benzodiazepines prescribed to the study cohort throughout the study period. In Malaysia, alprazolam is available in three strength of tablet (0.25mg, 0.5mg and 1mg) while other benzodiazepines only have one strength of tablet. This could be one of the reasons that appointed them as the golden choice for prescribers. Variable options in tablet strength ensure convenience in dose tapering and high suitability for patient compliance. Alprazolam was observed in our study as the most prescribed benzodiazepines in which it is consistent with the findings in the previous works of literature [37, 39–40]. Though the choice of prescribing alprazolam seems to have its legitimacy, it is essential to note that, while alprazolam has a short duration of action, it has higher toxicity in overdose, and has been reported to be associated with fatality in relative to other benzodiazepines [40].

The choice of benzodiazepines frequently prescribed in the current study differs from other studies, which have been published previously. For instance, Sundaran et al., (2019), Grover et al. (2012) and Tor et al. (2011) found that the most commonly prescribed benzodiazepines were lorazepam and clonazepam [23, 28, 36]. A 20 years (1992–2011) study on benzodiazepines trends in Australia found that surprisingly, temazepam is the most dispensed benzodiazepines in the country, accounting to 35% of the whole prescriptions studied. Meanwhile, previous studies had reported diazepam as the most frequently prescribed [20, 41–43]. Although clonazepam and diazepam both are listed as prescriber category B (ie. a prescription item) by the Ministry of Health Malaysia, they are not as frequently prescribed compared to other benzodiazepines. This gives rise to a question of whether the prescriber who prescribed alprazolam correctly fulfill the authorisation level provided. Therefore, we found that the differences in the choice of benzodiazepines in each country are assumed to be due to availability factors and differences in clinical practice.

Short-acting benzodiazepines such as alprazolam and midazolam are an excellent choice for acute relief of anxiety, panic attack, and stabilising mood. This is because they are rapidly absorbed, thus takes effect more quickly, and their therapeutic effect did not last too long to affect daily life routine. A recent study mentioned that short-acting benzodiazepines are recommended over long-acting benzodiazepines to alleviate the risk of dependency [44]. Furthermore, previous studies also recorded the long-acting formulations of benzodiazepines such as diazepam and lorazepam are the dominant choices among the prescribers [35–36, 42]. Both the usage of short and long-acting benzodiazepines is recommended in many guidelines for different medical conditions. Due to the insufficient data to support the reason behind the selection of short or long-acting formulation, the study could not justify such preference.

In the present study, findings showed that the male patient is more likely to be prescribed with anxiolytics, short-acting benzodiazepines and alprazolam. Additionally, looking into the duration of supply patterns, male patients are more likely to be dispensed with duration of 15 to 30 days, and the benzodiazepines were ordered with a fixed dosing schedule. The significantly higher odds of male prescribed with benzodiazepines can be seen in another study as well [45]. There is a statistically significant association seen between the tested variables and majority of patients aged 45–54 years old are very likely to receive anxiolytics, short-acting benzodiazepines, the duration of supply and the dosing schedule. Referring to Jessell et al., (2020) and Bushnell et al., (2017), they had described that patient aged 40 years and above and diagnosed with psychiatric disorders are more likely to be dispensed with benzodiazepines, especially if the prescribers are from the psychiatric department, compared with if other departments manage the patient [44–45]. The high occurrence of benzodiazepines prescriptions in older patients may reflect an association between age, the prevalence of psychiatric illness and longer benzodiazepine prescriptions. The combination of the above may contribute to adverse clinical outcomes that frequently associated with benzodiazepines in the elderly, such as the risk of fall, dose-dependency and mortality.

Study Limitations

Our study has several limitations. We focused only on the prescription data, and this necessarily does not reflect the exact clinical situation. Moreover, our study was limited to one tertiary care, which may or may not reflect the national trends. Furthermore, the prescription data may not include the indication for initiating treatments since the principal diagnosis written on the prescription does not necessarily refer to the primary indication of each benzodiazepine. Due to compliance problems, some of the prescribed drugs may not have been consumed according to what has been ordered in the prescription. Hence, we can only get the total number of benzodiazepine prescribed to the patient, but not the total number of benzodiazepine consumed.

Besides, there is insufficient data to support the status of the patient; whether they are naïve or chronic benzodiazepine user. The study is unable to determine that the first appearance of the patient in the data collected during the study period is the first dispensation of benzodiazepine to the patient or the first time the patient takes the medication. The patient may have defaulted follow up for a few weeks or months before the start of the study. A comprehensive comparison with a longer duration of retrospective years was limited due to lack of data availability.

Conclusions

The overall benzodiazepines prescribing trends in Malaysia was low throughout the three retrospective years compared to the increasing psychiatric problems in the country. As a whole, it is believed that this study provides sufficient data that could be a jump start for future work. The trends and patterns described in the study allow for an estimation of the prevalence of the medical condition, providing the basis of risk assessment and pharmacovigilance and also set a standard for future reference of trends and patterns of benzodiazepines in Malaysia. A comprehensive analysis as the current study on the prescribing trends and patterns of benzodiazepines and their association with patient's demographic characteristics may offer valuable information on future policy and planning of the public health measures concerning benzodiazepines.

Declarations

Statements and Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

NSAR and CSZ contributed to the study conception and design. Material preparation, data collection and analysis were performed by FAP and NSAR. The first draft of the manuscript was written by FAP and was revised and refined by NSAR. All authors commented on the revised versions of the manuscript. All authors read and approved the final manuscript.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Consent to participate

This study did not involve direct communication or participation with subjects or patients. Research only involved data of patients and medications retrieved from prescriptions and record books. Thus, patients consent is not require in this study.

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Figures

Amount of drug dispensed in 1 year (mg)

$$\text{DDD (mg) x 365 (days) x No. of patients} \quad \times 1000$$

Figure 1

The Defined Daily Dose Per 1000 Patients Per Day (16).

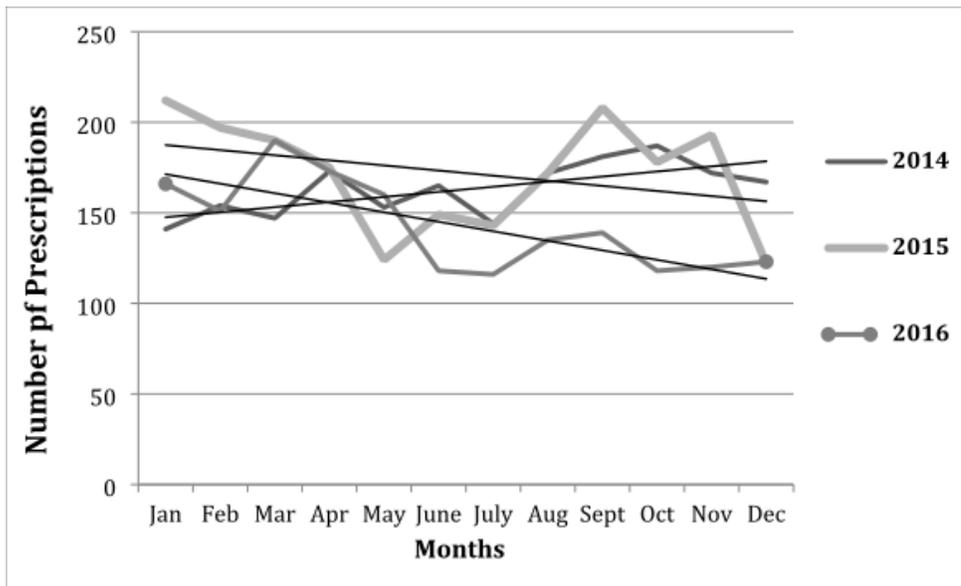


Figure 2

The Prescribing Trends of Benzodiazepines Based on Number of Prescriptions