ORIGINAL ARTICLE

Prescribing Pattern of Benzodiazepine Receptor Agonists (BZRA) and Factors Associated With Duration of BZRA Use in a Malaysian Psychiatry Outpatient Clinic

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ABSTRACT

Introduction: Benzodiazepine receptor agonist (BZRA) are among the most frequently used psychotropic medications worldwide. We aim to understand the pattern of prescription of BZRA in the government healthcare facilities and identify factors affecting the likelihood of BZRA prescription and duration of use. **Method:** This is a retrospective study. Data was obtained from record of outpatient clinical notes. Medications studied were midazolam, alprazolam, lorazepam, bromazepam, clonazepam, diazepam and zolpidem. Mean duration per prescription, mean dosage per prescription and duration per patient per year were calculated for each sedative hypnotic. The likelihood of factors affecting duration of prescription were also analysed. **Results:** The prevalence of sedative hypnotic use in psychiatry outpatient clinic was 12.16%. Clonazepam was found to have the longest duration per patient per year (306.5 days). Insomnia and anxiety are the two most common reasons for sedative hypnotic prescription. Factors found to affect duration of prescription were unemployment, borderline personality disorder, alcohol and substance use disorders. **Conclusion:** Implementation of effective monitoring system on sedative hypnotic prescribing and increase use of non-pharmacological interventions for insomnia and anxiety are necessary to curb prolonged use of sedative hypnotic.
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Keywords: Prescription pattern, Benzodiazepine, Predicting factors, BZRA, Sedative hypnotics

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INTRODUCTION

Benzodiazepine receptor agonists (BZRAs) include benzodiazepines (BZD) and non-benzodiazepines such as imidazopyridines (zolpidem). BDRA are frequently used for management of anxiety and insomnia in numerous psychiatry and medical disorders including alcohol withdrawal and seizures (1–3). However, inappropriate prescription of BZRA may cause physiological and psychological dependence (3). NICE guideline recommends using the lowest effective dose for not more than of 2- 4 weeks for severe anxiety disorder (4-6).

The prescription of BZRA in elderly has been associated with substantial side effects (3, 7-8), including anterograde amnesia, physical dependence, falls, and increased risk of dementia (3,9). It was found that users of BZRA had a 3.68 times higher in the risk of mortality compared with non-users in primary care in the United Kingdom (7). Therefore, BZRA should be prescribed with careful consideration, particularly in the elderly population who often has other comorbidities and thus are at greater risk of getting side effects.

Studies showed that the use of BZRA more than 6 months is linked to development of withdrawal symptoms in approximately one third of patients (10-12). Chronic use of BZRA can cause impairment in cognition, memory, coordination, and psychomotor functions (13). A study on long term BZRA users indicated that about 50% used high doses and continued taking it for up to 1.25 years (14). The use of concomitant neurological drugs was associated with higher dosage and longer duration of BZRA use (14).

BZRA are in fact an effective treatment for anxiety disorders and insomnia. NICE guidelines recognized that BZRA is an effective short-term treatment for anxiety disorders (5). There are many studies that showed BZRA reduce sleep latency and significantly increase sleep

duration making it an effective treatment for insomnia (4, 6). Thus, the issue lies in injudicious use of BZRA without optimal treatment of comorbid or underlying condition and careful surveillance of BZRA use. Therefore, this study intended to understand the pattern of BZRA prescribing in local government healthcare facility. In addition, it also examined factors affecting duration of BZRA use.

MATERIALS AND METHODS

Study design and study population

This is a retrospective study of prescribing pattern of BZRA in a psychiatry outpatient setting of a district hospital. This is a hospital that provides secondary care and is a main referral centre for the local district in Selangor state, Malaysia. Patients who were prescribed BZRA in the year of study were identified from pharmacy dispensary record. Sampling was done via systematic random sampling. Participants eligible for the study was extracted from outpatient pharmacy dispense system in excel format. Randomization was done using excel using =RAND() formula. Systematic random sampling was done by selecting every 6th participant on the randomized list on excel. Sampling population were patients above 18 years old and attending psychiatry outpatient clinic from January to December 2019 and were prescribed BZRA. Patients who were prescribed BZRA by doctors other than psychiatry outpatient department were excluded from this study. Samples with missing data or missing record were also excluded from the study.

Data Collection

Data for the study was obtained from record of outpatient clinical notes. Data collected includes socio-demographic characteristics, diagnosis, indications, dosage of benzodiazepine prescribed, number of tablets dispensed for each prescription (dosing) and duration of sedative hypnotic prescribed for each prescription. Medications studied were midazolam, alprazolam, lorazepam, bromazepam, clonazepam, diazepam and zolpidem. Ethical approval from Ethics Committee of the National Medical Research Registry of Malaysia was obtained.

Measures

From the data collected, mean duration and mean dosage per prescription was calculated for each sedative hypnotic. The mean duration of sedative hypnotic prescribed per patient was also calculated. The total duration of sedative hypnotic prescribed is defined as duration from the day when sedative hypnotic started to the day it was stopped. If the sedative hypnotic was continued in 2020, the duration was calculated from the day when it was started in 2019 to 31st December 2019. Total duration of sedative hypnotic use was categorized into < 28 days, between 29 – 90 days and > 90 days. PRN prescriptions of BZRA were identified and mean dosing and mean duration for each PRN prescription was calculated.

Statistical Analysis

Statistical analysis was done using IBM SPSS version 22 (15). Demographic characteristics of participants, PRN prescription and indications for prescription of sedative hypnotic were analysed in descriptive statistic. Mean and Standard deviations were reported for numerical or continuous variables while frequency and percentage were used for categorical variables. Patterns of sedative hypnotic use were described for the sample. Treatment duration was computed by combining duration of prescription for each prescription. The analyses were performed for prescriptions within 2019. Multinomial logistic regression were used to determine factors associated with the duration of sedative hypnotic prescribed using <28 days as reference group. Psychiatry diagnosis was controlled as a confounding factor when assessing association between demographic factors and duration of sedative hypnotic prescribed. The likelihood of a factor affecting duration of sedative hypnotic use was presented in odds ratio with corresponding 95% confidence interval and P value of ≤ 0.05 is considered significant.

Ethical Clearance

This study was permitted by Medical Research and Ethical Committee of Ministry of Health Malaysia. NMRR-20-2989-56198 (IIR); Research ID: 56198.

RESULTS

Sample description

There was a total of 233 samples and 858 prescriptions. Table I summarized the Socio demographic characteristics of study subjects. The prevalence of patients attending psychiatry outpatient clinic on BZRA was 12.16%.

Psychiatry Diagnoses

Out of 233 participants, 76 (32.6%) was diagnosed with major depressive disorders, 59 (25.2%) had schizophrenia while 52 (22.3%) had anxiety disorder. 15 (6.4%) of participants suffers from primary insomnia and 11 (4.7%) participants were benzodiazepine dependence. Other psychiatry diagnoses found in participants were substance use disorder (N= 22, 9.4%), bipolar disorder (N=18, 7.7%), adjustment disorder (N=10, 4.3%), dementia (N=8, 3.4%), borderline personality (N=8, 3.4%), intellectual disability (N=7, 3.0%), post-traumatic stress disorder (N=3, 1.3%) and antisocial personality (N=1, 0.4%). 52 (22.3%) of the participants has more than one psychiatry diagnoses.

BZRA use

Lorazepam was the most common sedative hypnotic prescribed (N=95, 40.7%). There were 9 participants on two BZRA and 1 participant on 3 BZRA at any

Table 1: Socio-demographic characteristics of study subjects

Items	N	%
Age		
18-59 years old	180	77.3
> 60 years old	53	22.7
Gender		
Male	101	43.3
Female	132	56.7
Employment Status		
Unemployed	62	26.6
Employed	102	4.38
Retired / Student / Housewife	69	29.6
Marital status		
Single	103	44.2
Married	95	40.8
Widow / Widower	16	6.9
Separated / Divorced	19	8.2
Education		
No Formal Education	9	3.9
Primary	49	21.0
Secondary	102	43.8
Tertiary	82	35.2
Alcohol Use		
Actively using	17	7.3
History of alcohol use	17	7.3
No alcohol use	199	85.4
Smoking		
Smoker	50	21.5
Non-smoker	183	78.5
Co-morbid medical disorder (excluding Liver or Renal Disease)		
Yes	86	36.9
No	147	63.1
Liver Disease		
Yes	3	1.3
No	230	230
Renal Disease		
Yes	2	0.9
No	231	99.1

one time. The indications for BZRA prescribed for each prescription is summarized in table II. The mean duration per prescription and duration per patient per year is summarized in table III. The pattern of PRN prescribing is summarized in table IV. Factors associated with duration of sedative hypnotic prescribing is shown in table V and table VI. It was found that participants between 18 to 59 years old, unemployed or with personality disorders were more likely to be on BZRA > 3 months. Participants with alcohol or illicit substance use disorder were more likely to be prescribed BZRA for 1 to 3 months.

Concomitant psychotropic medications

89.7% of participants were prescribed concomitant psychotropics medications. 50% of participants were on antidepressants in addition to BZRA while 50.1% had concomitant antipsychotics. Antidepressants that the participants were on include fluvoxamine (N=28, 12.0%), fluoxetine (N=7, 3.0%), escitalopram (N=57, 24.4%), sertraline (N=12, 5.1%), mirtazapine (N=5, 2.1%), amitriptyline (N= 3, 1.3%), dothiapine (N=2, 0.9%) agomelatine (N=1, 0.4%) and duloxetine (N=1, 0.4%). The most common antipsychotic use was risperidone (N=45, 19.2%), followed by olanzapine (N=21, 9.0%). Other antipsychotics used includes haloperidol, perphenazine, sulpiride, quetiapine, clozapine, aripripazole, fluophenazine and flupentizol decoanate. 12.4% of participants were on mood stabilizers which includes lithium, lamotrigine, carbamazepine and sodium valproate. 19.3% of participants are on a combination of 2 medications of either antidepressant, antipsychotic or mood stabilizer in addition to BZRA. 5.3% of participants were on antidepressants, antipsychotics and mood stabilizers in addition to BZRA.

DISCUSSION

The prevalence of patients attending psychiatry outpatient clinics who were on benzodiazepine in this study was 12.16%. This finding is similar to other studies on prevalence of BZRA use in France (16), Denmark (17), Pakistan (18), Lleida (19), and Lebanon (20), US (21). However, the studies done in France and Pakistan

Table II: Indications for each prescription of BZRA

Indications	N (%) of prescription according to types of benzodiazepine							
	Lorazepam	**Clonazepam**	**Alprazolam**	**Diazepam**	**Bromazepam**	**Midazolam**	**Zolpidem**	**Total**
Anxiety	16 (7.0)	5 (3.0)	130 (84.4)	0	1 (9.1)	0	7 (3.2)	159 (18.5)
Insomnia	173 (75.9)	87 (51.5)	2 (1.3)	22 (59.5)	8 (72.7)	3 (23.1)	181 (82.6)	476 (55.5)
Akathisia (Side effects)	1 (0.4)	0	0	2 (5.4)	0	0	0	3 (0.35)
Aggression / irritability	15 (6.6)	12 (7.1)	0	0	1 (9.1)	0	0	28 (3.26)
Restless (symptoms of Psychiatry disorder)	4 (1.8)	0	0	0	0	0	0	4 (0.47)
Episodic dysphoria	0	1 (0.6)	0	1 (2.7)	0	0	1 (0.5)	2 (0.23)
Alcohol withdrawal	0	0	0	5 (13.5)	0	0	0	5 (0.58)
Medication was continued same	14 (6.4)	8 (4.7)	1 (0.6)	0	0	0	5 (2.3)	56 (6.53)
Behavioural problem	1 (0.4)	7 (4.1)	0	0	1 (9.1)	0	0	9 (1.05)
Benzodiazepine Dependence	4 (1.8)	49 (29.0)	21 (13.6)	7 (18.9)	0	10 (76.9)	25 (11.4)	116 (13.52)
Total number of prescriptions	228	169	154	37	11	13	219	858

Table III: Pattern of BZRA prescribing

Types	N	%	Mean Duration / Prescription Days (SD)	Duration Per Patient Per Year (Days)	Mean Dosage Prescribed mg (SD)	Mean Diazepam equivalent Dose mg
Lorazepam	95	40.7	40.9 (43.29)	98.3	0.94 (0.49)	9.4
Clonazepam	37	15.9	67.1 (51.86)	306.5	1.6 (0.9)	32
Alprazolam	43	18.4	44.5 (38.49)	159.2	0.4 (0.58)	8
Diazepam	9	3.9	43.8 (44.64)	180.0	8.4 (3.28)	8.4
Bromazepam	5	2.1	33.5 (18.93)	73.6	2.6 (0.70)	5.2
Zolpidem	52	22.3	63.9 (50.75)	269.1	7.1 (4.50)	3.6
Midazolam	2	0.9	33.8 (15.14)	219.5	13.3 (3.29)	17.7
All	233	100	52.9 (47.33)	188.6		12.0

SD: Standard Deviation

Table IV: Pattern of PRN Prescriptions for all BZRA

Types	PRN Prescription (PS)		
	Rates (%)	**Mean Dosing / PS** Dosing (SD)	**Mean Duration** Days (SD)
Lorazepam	72.4	16.4 (24.03)	46.8 (45.37)
Clonazepam	29.6	31.8 (29.96)	66.4 (51.43)
Alprazolam	74.0	12.6 (9.34)	40.6 (31.7)
Diazepam	45.9	23.1 (14.29)	62.7 (45.22)
Bromazepam	90.9	8.9 (5.15)	35.8 (18.20)
Zolpidem	67.1	17.8 (15.86)	59.5 (44.96)
Midazolam	15.4	14.0 (0.00)	28 (0.00)
All	60.8	17.6 (20.06)	51.27 (43.54)

Dosing – number of times of a prescribed dose of benzodiazepine (E.g. T. Lorazepam 1 mg PRN (5 doses) i.e. dosing is 5)
SD: Standard Deviation
PS: Prescription

involved participants from community-based cohort while the other studies were done in outpatient setting.

This study found that, like other studies, the most common indication for BZRA use is insomnia (1, 22). The most common prescribed BZRA for insomnia in this study is zolpidem, followed by, lorazepam and clonazepam. Existing local and international guidelines limits the use of pharmacological treatment for short-term insomnia of 2-4 weeks and is not recommended as the mainstay of treatment for chronic insomnia (23 - 27). Cognitive behavioural therapy for insomnia (CBT-I) is the recommended gold standard treatment for chronic insomnia in adults of any age (28). Pharmacological treatment can be initiated if CBT-I cannot be provided or when it is not sufficiently effective in improving insomnia (28). Pharmacological treatment of insomnia

Table V: Association of demographic factors and duration of BZRA use adjusted for confounding factor

Factors	29 – 90 days			> 90 days		
	OR	CI	P	OR	CI	P
Age						
18 – 59	1.28	0.29 – 5.61	0.74	**0.29**	**0.10 – 0.88**	**0.03***
> 60 (reference group)	1			**1**		
Gender						
Male	0.73	0.28 – 1.87	0.51	1.17	0.54 – 2.54	0.70
Female (reference group)	1					
Education						
No Formal Education	1.28	0.07 – 25.15	0.87	0.66	0.05 –8.60	0.75
Primary	0.33	0.03 – 3.28	0.34	0.79	0.15 – 4.20	0.78
Secondary	1			1		
Tertiary (Reference group)						
Marital status						
Single	4.45	0.44 – 45.00	0.21	0.43	0.12 – 1.56	0.20
Married	3.75	0.35 – 39.98	0.28	0.95	0.25 – 3.59	0.94
Widow / widower	2.41	0.14 – 42.23	0.55	0.39	0.06 – 2.62	0.33
Separate / Divorced (Reference group)	1			1		
Employment status						
Employed	0.99	0.11 – 8.88	0.99	5.74	0.45 – 73.36	0.18
Unemployed	1.54	0.15 – 16.22	0.72	**16.12**	**1.15 – 225.77**	**0.04***
Retired / Student / Housewife (Reference group)	1			1		
Smoking						
Yes	1.32	0.28 – 6.17	0.72	1.45	0.38 – 5.47	0.59
No (Reference Group)	1			1		

Reference group is < 28 days OR: Odds Ratio CI: Confidence Interval P: p value *p ≤ 0.05

Table VI: Psychiatry Disorders associated with duration of BZRA prescription

Factors	29 – 90 days			> 90 days		
	OR	CI	P	OR	CI	P
Anxiety	1.59	0.42 – 6.00	0.49	1.77	0.58 – 5.41	0.32
Depression	0.59	0.25 – 1.40	0.23	0.53	0.26 – 1.10	0.07
Schizophrenia	0.88	0.20 – 3.74	0.86	1.27	0.38 – 5.07	0.71
Bipolar disorder	0.57	0.09 – 3.74	0.55	0.95	0.22 – 4.18	0.95
Adjustment Disorder	1.46	0.00	1.00	0.69	0.09 – 5.07	0.71
Primary Insomnia	0.71	0.07 – 7.25	0.77	1.89	0.30 – 11.90	0.50
Dementia	1.54	0.11 – 21.88	0.75	1.86	0.18 – 18.92	0.61
Intellectual Disability	15666554.85	0.00	1.00	43672174.73	0.00	1.00
Personality Disorder	0.67	0.00	1.00	**1.60**	**2.87 – 8.93**	**< 0.001***
Alcohol Use Disorder	**9.15**	**9.15-9.151**	**<0.001***	0.62	0.18 – 2.15	0.45
Substance Use Disorder	**1.56**	**1.56 -1.561**	**<0.001***	0.38	0.08 – 1.80	0.22
Number of psychiatry diagnosis						
> Three	0.88	0.18-4.37	0.88	0.39	0.05 – 3.25	0.39
Two	1.45	0.61-3.45	0.41	1.43	0.62 – 3.30	0.41
One (reference group)						

Reference group is < 28 days OR: Odds Ratio CI: Confidence Interval P: p value *p ≤ 0.05

recommended by American guidelines involves the use of BZRA, melatonin receptor antagonist or histamine receptor antagonist (29). However, European guideline does not recommend the use of antihistamine, melatonin or antipsychotics for treatment of insomnia (28). There are studies that concluded that zolpidem is effective and safe for long term use ranging from 3-6months (30).

Malaysia has yet to have clinical practice guideline for insomnia. Expert in CBT-I is also not widely available in local practice. Up to date, management of insomnia as part of a symptom of a psychiatry disorder is largely based on clinical practice guidelines of respective disorders such as clinical practice guideline for major depressive disorder and schizophrenia. Often in current local clinical practice, BZRA is continued if insomnia persists.

The mean duration per patient per year for all BZRA in this study is around 6 months with clonazepam having the longest duration per patient per year (306.5 days). Hypnotic benzodiazepine such as Flurazepam, temazepam, quazepam, estazolam, and triazolam which are among the recommended BZRA for insomnia in international guidelines are not included in the Ministry of Health Medicine Formulary, thus making clonazepam, lorazepam and zolpidem among the most commonly prescribed BZRA in local setting (31). Long acting BZRAs such as clonazepam are favoured over short acting BZRA in patients who requires long term BZRA due to risk of dependence and tolerance with short-acting BZRA. Lack of availability of non-pharmacological interventions in local setting especially for insomnia may be one of the reason leading to need of long term prescription of BZRA. In addition, lack of implementation of prescribing monitoring and continuity of care are also speculated as reasons which contributed to about 6.53% of use of BZRA in this study. The lack of continuity of care as patient is seen by different doctor each visit may also contributed to the prolonged use of BZRA. Other reason for prolonged use of BZRA could be due to suboptimal treatment of primary disorder resulting in residual symptoms of insomnia and anxiety. It was noted in this study that all participants were prescribed with at least one concomitant psychotropic medications. However, further study is needed to examine whether these medications were sufficiently optimized for the treatment of the underlying disorder.

Bromazepam was the least use BZRA in this study because it was in the process of being removed from hospital prescribing formulary during the period of study. No specific agent within BZRAs group is recommended as superior to the others. The selection of BZRAs is based on factors such as symptom presentation, previous response to treatment, cost, and patient preference (27, 29). Compared with benzodiazepine, non-benzodiazepine (zolpidem) appears to have greater selectivity for certain GABA-A subunit subtypes, which explains its anxiolytic effect and lesser range of side effects (32).

Adults aged 18 – 59 were found to be more likely to have BZRA prescription of more than 90 days compared to elderly aged above 60 in this study. This is contrary to findings in other studies where elderly were more likely to continue with long term use of BZRA (33, 34-35). This is most likely because there is a lot of caution taken in prescribing BZRA in elderly for long duration due to the possible side effects which include greater risk of

falls and fractures and overall mortality (36-39). Several studies revealed that chronic use of benzodiazepine in elderly is significantly associated with dementia (40-42) BZRA prescription more than 90 days was found to be associated with unemployment and presence of personality disorders. The odds of being on BZRA > 90 days were 16 times higher in unemployed group compared to retiree, student, or housewife. This finding is parallel with studies which reported longer duration of BZRA usage in people who were unemployed and receiving social welfare (16, 43). Longer duration of BZRA use in unemployment may be due to increased psychological distress due to financial difficulties and loss of social status (44). Patients with personality disorders is associated with inability to stop benzodiazepine use due to tendency of having recurrent episodes of psychological distress associate with the natural course of the disorder (45). BZRA prescription of < 90 days was found to be associated with substance and alcohol use disorder. This is in line with detox program which in involves the use of BZRA for duration of about 3 months (46).

This is a retrospective study looking at data from clinical records. Retrospective study is generally limited by incomplete data. There were about 13.7% participants were excluded due incomplete data. Therefore, this study was subject to limitations because of missing data due to poor documentations in clinical records remains. Another limitation of the study is the use of secondary data. In this study, data was collected from patient's medical record. While the use of secondary data may be time-saving, the data collected may be out of date, inaccurate or insufficient in details.

The study involved psychiatry patients attending outpatient setting in district hospital in Malaysia and thus the study findings are not generalizable to other population.

One of the strengths of this study is that it provides a comprehensive overview of pattern of BZRA prescription in an outpatient setting. Although the findings are not generalizable, this study highlights the importance of surveillance measures in the use of BZRA for clinicians and local policy makers. Findings on factors associated with duration of BZRA prescription provides insight for further studies in this area.

Despite these limitations, findings from this study have important implications for clinicians and local policy makers. Results indicated that mean duration of sedative hypnotic prescription were > 90 days for all types of sedative hypnotic except bromazepam. There was also indication that sedative hypnotic was continued during follow up without clear indications in some patients. Chronic use of BZRA is a worldwide issue and was found in many countries including France (16), Australia (47), Columbia (14), and Europe (33). Chronic use of BZRA leads to tolerance of the sedative effects and is significant by 2–3 weeks (48). Any abrupt ceasation of benzodiazepine in patients who have taken more than 4 weeks may develop withdrawal symptoms.(19, 48). Prolonged use of BZRA may be needed in patients with residual symptoms especially those who were treatment resistant or with multiple psychiatric co-morbidities. However, in this study, over prescribing of BZRA was noted in some cases where clear indication for continuation of BZRA was not stated. This may be due to lack of awareness of risk of dependence of sedative hypnotic and lack of continuity of patient care. Therefore, the development of clear prescription guidelines with effective monitoring of sedative hypnotic use is needed to improve these issues. One suggestion is to include monitoring of sedative hypnotic prescribing in regular local psychiatry audit to ensure appropriate indication for sedative hypnotic prescribing and to avoid unnecessary prolonged use.

Insomnia was found to be the main indications for sedative hypnotic prescription in this study. In this context, implementations of psychological interventions such as Cognitive Behavioural Therapy for Insomnia (CBT-I) should be taken into consideration. CBT-I is recommended as the gold standard for treatment of insomnia. (24, 49-50). Anxiety was found to be the second most common reason for the use of sedative hypnotic in this study. Thus, other psychological interventions should also be implemented to aid symptom relief in anxiety. Treatment regime should also focus on treating the underlying problem via psychological interventions instead of focusing on symptom relief.

CONCLUSION

We found evidence that mean duration of sedative hypnotic prescription is high in this population. Factors affecting duration of prescription include unemployment, borderline personality disorder, alcohol and substance use disorders. Further effort is needed to implement proper guidelines and monitoring system to ensure appropriate prescribing and prevent over-prescribing. Implementation of non-pharmacological interventions may also curb problems with over-prescribing.

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REFERENCES

1. Ramadan WH, El Khoury GM, Deeb ME, Sheikh-Taha M. Prescription patterns of benzodiazepines in the Lebanese adult population: a cross-sectional study. Neuropsychiatr Dis Treat [Internet]. 2016;12:2299–305. doi:10.2147/NDT.S113078

2. Rickels K, Lucki I, Schweizer E, Garcна-Espaca F, Case WG. Psychomotor performance of long-term benzodiazepine users before, during, and after benzodiazepine discontinuation. J Clin Psychopharmacol [Internet]. 1999;19(2):107–13. doi:10.1097/00004714-199904000-00003
3. Uzun S, Kozumplik O, Jakovljević M, Sedić B. Side effects of treatment with benzodiazepines. Psychiatr Danub 2010;22:90–3
4. Kennedy KM, O'Riordan J. Prescribing benzodiazepines in general practice. Br J Gen Pract [Internet]. 2019;69(680):152–3. doi:10.3399/bjgp19X701753
5. Ford C, Law F. Guidance for the use and reduction of misuse of benzodiazepines and other hypnotics and anxiolytics in general practice 2014
6. Holbrook A, Crowther R, Lotter A, Endeshaw Y. The role of benzodiazepines in the treatment of insomnia: meta-analysis of benzodiazepine use in the treatment of insomnia. J Am Geriatr Soc [Internet]. 2001;49(6):824–6. doi:10.1046/j.1532-5415.2001.49161.x
7. Weich S, Pearce HL, Croft P, Singh S, Crome I, Bashford J, et al. Effect of anxiolytic and hypnotic drug prescriptions on mortality hazards: retrospective cohort study. BMJ [Internet]. 2014;348(mar19 5):g1996. doi:10.1136/bmj.g1996
8. Beracochea D. Anterograde and retrograde effects of benzodiazepines on memory. ScientificWorldJournal [Internet]. 2006;6:1460–5. Available from: http://dx.doi.org/10.1100/tsw.2006.243
9. Gomm W, von Holt K, Thomй F, Broich K, Maier W, Weckbecker K, et al. Regular benzodiazepine and Z-substance use and risk of dementia: An analysis of German claims data. J Alzheimers Dis [Internet]. 2016;54(2):801–8. Adoi:10.3233/JAD-151006
10. Willems IAT, Gorgels WJMJ, Oude Voshaar RC, Mulder J, Lucassen PLBJ. Tolerance to benzodiazepines among long-term users in primary care. Fam Pract [Internet]. 2013;30(4):404–10. doi:10.1093/fampra/cmt010
11. Lader M. Benzodiazepine harm: how can it be reduced?: Benzodiazepine harm: how can it be reduced? Br J Clin Pharmacol [Internet]. 2014;77(2):295–301. Available from: http://dx.doi.org/10.1111/j.1365-2125.2012.04418.x
12. Pottie K, Thompson W, Davies S, Grenier J, Sadowski CA, Welch V, et al. Deprescribing benzodiazepine receptor agonists: Evidence-based clinical practice guideline. Can Fam Physician. 2018;64(5):339–51.
13. Dell'osso B, Lader M. Do benzodiazepines still deserve a major role in the treatment of psychiatric disorders? A critical reappraisal. Eur Psychiatry [Internet]. 2013;28(1):7–20. Adoi:10.1016/j.eurpsy.2011.11.003
14. Moreno-Gutнerrez PA, Gaviria-Mendoza A, Ochoa-Orozco SA, Yepes-Echeverri MC, Machado-Alba JE. Long-term users of benzodiazepines in Colombia: Patterns of use and cessation of treatment. Drug Alcohol Depend [Internet]. 2020;210(107962):107962. doi:10.1016/j.drugalcdep.2020.107962
15. IBM. IBM SPSS for Windows Version 20. 2011
16. Airagnes G, Lemogne C, Renuy A, Goldberg M, Hoertel N, Roquelaure Y, et al. Prevalence of prescribed benzodiazepine long-term use in the French general population according to sociodemographic and clinical factors: findings from the CONSTANCES cohort. BMC Public Health [Internet]. 2019;19(1). Adoi:10.1186/s12889-019-6933-8
17. Tjagvad C, Clausen T, Handal M, Skurtveit S. Benzodiazepine prescription for patients in treatment for drug use disorders: a nationwide cohort study in Denmark, 2000–2010. BMC Psychiatry [Internet]. 2016;16(1). doi:10.1186/s12888-016-0881-y
18. Iqbal SP, Ahmer S, Farooq S, Parpio Y, Tharani A, Khan RAM, et al. Benzodiazepine use among adults residing in the urban settlements of Karachi, Pakistan: a cross sectional study. Subst Abuse Treat Prev Policy [Internet]. 2011;6(1):19. doi:10.1186/1747-597X-6-19
19. Torres-Bondia F, de Batlle J, Galvбn L, Buti M, Barbй F, Picol-Ripoll G. Trends in the consumption rates of benzodiazepines and benzodiazepine-related drugs in the health region of Lleida from 2002 to 2015. BMC Public Health [Internet]. 2020;20(1):818. doi:10.1186/s12889-020-08984-z
20. Ghandour LA, El Sayed DS, Martins SS. Alcohol and illegal drug use behaviors and prescription opioids use: how do nonmedical and medical users compare, and does motive to use really matter? Eur Addict Res [Internet]. 2013;19(4):202–10. doi:10.1159/000345445.
21. Maust DT, Lin LA, Blow FC. Benzodiazepine use and misuse among adults in the United States. Psychiatr Serv [Internet]. 2019;70(2):97–106. doi:10.1176/appi.ps.201800321
22. Mell T, Jacob L, Fuhr I, Dick S, Rapp MA, Kostev K. Patterns of benzodiazepine prescribing by neuropsychiatrists and general practitioners for elderly patients in Germany in 2014. Int J Clin Pharmacol Ther [Internet]. 2017;55(6):466–71. doi:10.5414/CP202904
23. Gupta R, Das S, Gujar K, Mishra KK, Gaur N, Majid A. Clinical practice guidelines for sleep disorders. Indian J Psychiatry [Internet]. 2017;59(Suppl 1):S116–38. doi:10.4103/0019-5545.196978.
24. Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med. 2008;4(5):487–504..

25. National Collaborating Centre for Mental Health. Depression: The NICE guideline on the treatment and management of depression in adults. Leicester ;London: British Psychological Society (BPS) ;Royal College of Psychiatrists (RCP); 2010
26. Ministry of Health Malaysia. Management of Major Depression Disorder (2nd Edition). 2019
27. Joint Formulary Committee. BNF 76 (British National Formulary) 76th ed. London, England: Pharmaceutical Press; 2018
28. Riemann D, Baglioni C, Bassetti C, Bjorvatn B, Dolenc Groselj L, Ellis JG, et al. European guideline for the diagnosis and treatment of insomnia. J Sleep Res [Internet]. 2017;26(6):675–700. doi:10.1111/jsr.12594.
29. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: An American academy of sleep medicine clinical practice guideline. J Clin Sleep Med [Internet]. 2017;13(02):307–49. doi: 10.5664/jcsm.6470
30. Buysse DJ. Insomnia. JAMA 2013;309:706–16. doi: 10.1001/jama.2013.193.
31. Ministry of Health Medicines Formulary (MOHMF). GovMy n.d. https://www.pharmacy.gov.my/v2/en/documents/ministry-health-medicines-formulary-mohmf.html (accessed September 28, 2021).
32. Rudolph U, Mμhler H. GABAA receptor subtypes: Therapeutic potential in Down syndrome, affective disorders, schizophrenia, and autism. Annu Rev Pharmacol Toxicol [Internet]. 2014;54(1):483–507. doi:10.1146/annurev-pharmtox-011613-135947
33. Kurko TAT, Saastamoinen LK, TΔhkΔpΔΔ S, Tuulio-Henriksson A, Taiminen T, Tiihonen J, et al. Long-term use of benzodiazepines: Definitions, prevalence and usage patterns - a systematic review of register-based studies. Eur Psychiatry [Internet]. 2015;30(8):1037–47. doi:10.1016/j.eurpsy.2015.09.003
34. Taipale H, SΔrkilΔ H, Tanskanen A, Kurko T, Taiminen T, Tiihonen J, et al. Incidence of and characteristics associated with long-term benzodiazepine use in Finland. JAMA Netw Open [Internet]. 2020;3(10):e2019029. doi:10.1001/jamanetworkopen.2020.19029
35. Hata T, Kanazawa T, Hamada T, Nishihara M, Bush AI, Yoneda H, et al. What can predict and prevent the long-term use of benzodiazepines? J Psychiatr Res [Internet]. 2018;97:94–100. doi:10.1016/j.jpsychires.2017.11.012
36. de Jong MR, Van der Elst M, Hartholt KA. Drug-related falls in older patients: implicated drugs, consequences, and possible prevention strategies. Ther Adv Drug Saf [Internet]. 2013;4(4):147–54. doi:10.1177/2042098613486829
37. Pétein C, Spinewine A, Henrard S. Trends in benzodiazepine receptor agonists use and associated factors in the Belgian general older population: analysis of the Belgian health interview survey data. Ther Adv Psychopharmacol [Internet]. 2021;11:20451253211011870. doi:10.1177/20451253211011874
38. Donnelly K, Bracchi R, Hewitt J, Routledge PA, Carter B. Benzodiazepines, Z-drugs and the risk of hip fracture: A systematic review and meta-analysis. PLoS One [Internet]. 2017;12(4):e0174730. doi:10.1371/journal.pone.0174730.
39. Patorno E, Glynn RJ, Levin R, Lee MP, Huybrechts KF. Benzodiazepines and risk of all cause mortality in adults: cohort study. BMJ [Internet]. 2017;j2941. doi:10.1136/bmj.j2941
40. Islam MM, Iqbal U, Walther B, Atique S, Dubey NK, Nguyen P-A, et al. Benzodiazepine use and risk of dementia in the elderly population: A systematic review and meta-analysis. Neuroepidemiology [Internet]. 2016;47(3–4):181–91. doi:10.1159/000454881.
41. Penninkilampi R, Eslick GD. A systematic review and meta-analysis of the risk of dementia associated with benzodiazepine use, after controlling for protopathic bias. CNS Drugs [Internet]. 2018;32(6):485–97. doi:10.1007/s40263-018-0535-3
42. Ettcheto M, Olloquequi J, S6nchez-Lypez E, Busquets O, Cano A, Manzine PR, et al. Benzodiazepines and related drugs as a risk factor in Alzheimer's disease dementia. Front Aging Neurosci [Internet]. 2019;11:344. doi:10.3389/fnagi.2019.00344
43. Ekedahl A, Lidbeck J, Lithman T, Noreen D, Melander A. Benzodiazepine prescribing patterns in a high-prescribing Scandinavian community. Eur J Clin Pharmacol [Internet]. 1993;44(2):141–6. doi:10.1007/bf00315471
44. Nagelhout GE, Hummel K, de Goeij MCM, de Vries H, Kaner E, Lemmens P. How economic recessions and unemployment affect illegal drug use: A systematic realist literature review. Int J Drug Policy [Internet]. 2017;44:69–83. doi:10.1016/j.drugpo.2017.03.013.
45. Ross HE. Benzodiazepine use and anxiolytic abuse and dependence in treated alcoholics. Addiction [Internet]. 1993;88(2):209–18. doi:10.1111/j.1360-0443.1993.tb00804.x.
46. NICE Guidelines for Drug misuse: opiate detoxification for drug misuse. 2007
47. Brett J, Murnion B. Management of benzodiazepine misuse and dependence. Aust Prescr [Internet]. 2015;38(5):152–5. doi:10.18773/austprescr.2015.055.
48. Who Regional Office for the Western Pacific. Clinical guidelines for withdrawal management and treatment of drug dependence in closed settings. Manila, Philippines: WHO Regional Office for the Western Pacific; 2009
49. Mellor A, Hamill K, Jenkins MM, Baucom DH, Norton PJ, Drummond SPA. Partner-assisted

cognitive behavioural therapy for insomnia versus cognitive behavioural therapy for insomnia: a randomised controlled trial. Trials [Internet]. 2019;20(1):262. doi:10.1186/s13063-019-3334-3

50. Tan HJR. Sleep well: A guide on cognitive behavioural therapy for insomnia. Partridge Publishing; 2020.