

Prescription patterns of benzodiazepines in the Lebanese adult population: a cross-sectional study

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Abstract: This study assessed the profile of benzodiazepine (BDZ) users in Lebanon. Adult patients visiting the pharmacies with prescriptions of BDZs were included in the study. Seven hundred and eighty-six current BDZ users were included, of whom 54.2% were females. Twenty-three percent reported being alcohol consumers and were mostly males. The two most commonly used BDZs were alprazolam (34.6%) and bromazepam (33.6%). The indication for use was mainly anxiety (44.4%), insomnia (22.5%), and depression (15.9%). The prescribing physicians were primarily psychiatrists (43.2%), followed by general practitioners (29.7%). Forty percent had been taking the drug for more than a year. Among those using BDZs for at least 1 month, 35.5% increased the dose with time. Thirty-three percent reported having experienced side effects. Eighteen patients (2.3%) reported taking more than one BDZ concomitantly, while 18.3% were taking drugs that should not be prescribed along with BDZs. In conclusion, the use of BDZs is highest among females, especially for the treatment of anxiety. Moreover, continuous use of the drugs for more than a year as well as significant potential drug interactions was identified.

Keywords: benzodiazepines, prescribing patterns, controlled substances

Introduction

Nonmedical use of prescription medications is a growing global concern.¹ The use of prescription drugs seems to be increasing at a faster rate than that of illicit substances.² In Lebanon, ~20% of the young adult population is taking psychoactive substances in nonmedical aspects that differ from the prescription recommendations.^{3,4} This practice puts the Lebanese population at increased risk for dangerous physical and psychological side effects.³ In addition to health implications, this practice has major economic consequences. While there is a lack of data on the economic impact of nonmedical use of prescription drugs in Lebanon, studies conducted in the US clearly highlighted its associated financial burden on society.⁵

Benzodiazepines (BDZs) are among the most widely and frequently used psychoactive substances in the world. They have an important role in clinical medicine and are used in numerous clinical conditions like anxiety and sleep disorders, alcohol withdrawal, the augmentation of antidepressants and antipsychotics, mania, muscle relaxation, seizures, as well as in many non-approved indications.^{6,7} Their clinical use, however, should be monitored closely due to their adverse effects and potential for misuse and abuse. Several adverse reactions have been associated with the use of BDZs including motor disturbances, cognitive decline, unwanted sedation, and reduced coordination.⁷

Across countries, studies have shown a relatively high prevalence of BDZ use in the general population with a somewhat different pattern of use ranging from as low as 6.2%

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in developed countries up to 36% in developing ones.^{8–21} In the US, a recent report revealed that a 12-month prevalence of BDZ use as tranquilizers was 8.6%.²² A prevalence estimate of 9.2% BDZ usage was reported from a combined population of six European countries.²³ The prevalence of BDZ use in an elderly population of a Canadian province exceeds 10%.²⁴

Most developed countries have routinely collected data on BDZs prescription and consumption; however, limited data exist on the rates and patterns of use in Lebanon. The main objective of this study is to assess the patterns of BDZs use, profile of users in Lebanon regarding their demographic characteristics, the clinical indication for use, duration of use, perceived side effects, and potential drug–drug interactions.

Materials and methods

This is an observational study that was conducted at 27 community pharmacies in Lebanon over a period of 2 years, from June 2012 till May 2014. The targeted population were ambulating Lebanese patients aged ≥ 18 years, recruited in various community pharmacies across different regions of Lebanon. To ensure a representative sample of adults, the pharmacies were randomly selected across the six Lebanese governorates: North of Lebanon, Mount Lebanon, Beirut, South of Lebanon, Beqaa, and Nabatieh. Patients visiting the pharmacies with prescriptions of BDZs were asked if they were willing to participate in the study. Family members of patients who came to the pharmacies to get the BDZs were asked to provide the telephone number of the patients and about the possibility to call them. Phone interviews were done when patients consented to participate in the study. An interview questionnaire was used to collect the data. The study was approved by the LAU University Institutional Review Board, and a waiver of consent was obtained to fill out the questionnaire.

The questionnaire gathered data on sociodemographic characteristics including age, sex, place of residence, pregnancy, breastfeeding, and alcohol intake. Data on patterns of BDZ use included indication(s) for use, specialty of prescribing physician, duration of therapy, perceived side effects, concomitant medications used, and increase in BDZ dose with time.

Data were processed and analyzed through the application of the Statistical Package for Social Sciences (version 22; IBM Corporation, Armonk, NY, USA). The association of BDZ use by sociodemographic variables and indication, duration of use, and perceived side effects was assessed by applying the chi-square statistical test using a significance level of 5%.

Results

Sociodemographic characteristics

Table 1 describes the sociodemographic characteristics of the 786 sampled BDZ current users, of whom 45.8% were males and 54.2% were females, and three were pregnant or breastfeeding. The proportion of BDZ users who agreed to participate in the study approached 86%. Twenty-three percent reported being alcohol consumers, with a significant differential by age and sex of study participants. Males reported a significantly higher proportion of alcohol consumption (33.5%) compared to female users (14.9%), even after adjusting for age. There were 24 (3.1%) and 21 individuals (2.7%) who reported suffering from liver and renal diseases, respectively.

BDZ use characteristics

The two most commonly used BDZs were alprazolam (34.6%) and bromazepam (33.6%), followed by clonazepam (12.1%) and lorazepam (10%), and the least commonly used were diazepam (5.3%), midazolam (3%), and temazepam (1.3%). There was a significant differential of type of medication used by sex specifically among the younger age group of users (20–50 years); the proportion of females using bromazepam was significantly higher (34.3%) compared to males (24.6%). Males were more frequent users of

Table 1 Distribution of sociodemographic characteristics of a sample BDZ current user

	Frequency N (%)
Sex	
Male	352 (45.8)
Female	416 (54.2)
Age (years)	
20–29	48 (6.3)
30–39	116 (15.1)
40–49	184 (24.0)
50–59	192 (25.0)
60–69	144 (18.8)
70+	84 (10.9)
Geographical distribution	
Beirut	172 (22.4)
Beirut suburbs	119 (15.5)
Byblos	67 (8.7)
Jounieh	199 (25.9)
Tripoli	152 (19.8)
Saida	59 (7.7)
Total	768 (100.0)
Proportion of alcohol consumption	
Male	(33.5)
Female	(14.9)
BDZ consumers with comorbidities	
Renal disease	(2.7)
Liver disease	(3.1)

Abbreviation: BDZ, benzodiazepine.

diazepam (11.2%) and clonazepam (19.0%) compared to females (3% and 11.8%, respectively) (Table 2).

The indication for BDZ use was mainly anxiety (44.4%), insomnia (22.5%), depression (15.9%), epilepsy (5.7%), minor surgery/procedures (5.6%), schizophrenia (1.2%), pain (1.0%), muscle spasm (0.4%), and multiple sclerosis (0.3%). Reports of anxiety, insomnia, and depression were more frequently reported among females than males, while epilepsy, pain relief, and surgery seemed to be reported more frequently by males compared to females. When sex was stratified by age group, the sex differential was significant only among the younger age group, that is, those aged 20–50 years old (Table 3).

Table 4 shows that the distribution of type of BDZ medication differs significantly by reported indication for BDZ use. The most common drugs prescribed for anxiety, insomnia, depression, and pain relief were bromazepam and alprazolam; however, clonazepam was the drug of choice for epilepsy.

Prescriber of the BDZ and duration of use

The BDZ was usually prescribed by a medical doctor except for one case by a pharmacist for insomnia and three cases by a dentist for minor surgery. The prescribing physician was primarily a psychiatrist (43.2%), a general practitioner (29.7%), or a surgeon (2.3%). There were nine cases where the BDZ was prescribed by a pediatrician, four for anxiety, four for insomnia, and one for pain relief.

The medical indication for prescribing BDZ varied significantly by the prescribing physician specialty. Psychiatrists prescribed BDZs mainly for anxiety and depression (65%), followed by general practitioners (56%), cardiologists (53%), and other specialists (49%).

Approximately 15% of the patients were taking BDZ on an “as-needed” basis, and 40% had been taking the drug for more than a year. The duration of BDZ use for >1 year did differ significantly by the specialty of the prescribing physician; it was reported as 52% among cardiologists and 43% by psychiatrists compared to 34% by general practitioners and other specialists. Table 5 shows the distribution of duration of therapy by physician specialty.

Interval for BDZ dosage increase and perceived side effects

All the patients who had used the BDZ medication for at least 1 month were asked to report on the timing of the increase in the BDZ dose and its side effect. The proportion of the sample who had not started their BDZ medication yet was 6.1%. Among those who had used their medication for at least

Table 2 Distribution of BDZ medication type by sex and age

Drug type	Age (years)						Total					
	20–50		50–60		60+		Male N (%)	Female N (%)				
	Male N (%)	Female N (%)	Total N (%)	Male N (%)	Female N (%)	Total N (%)						
Bromazepam	44 (24.6)	58 (34.3)	100 (29.3)	32 (47.1)	43 (34.7)	75 (39.1)	33 (31.4)	48 (39.0)	81 (35.5)	109 (31.0)	149 (35.8)	258 (33.6)
Lorazepam	16 (8.9)	14 (8.3)	30 (8.6)	5 (7.4)	14 (11.3)	19 (9.9)	15 (14.3)	13 (10.6)	28 (12.3)	36 (10.2)	41 (9.9)	77 (10.0)
Diazepam	20 (11.2)	5 (3.0)	25 (7.2)	2 (2.9)	3 (2.4)	5 (2.6)	6 (5.7)	5 (4.1)	11 (4.8)	28 (8.0)	13 (3.1)	41 (5.3)
Alprazolam	61 (34.1)	65 (38.5)	126 (36.2)	18 (26.5)	42 (33.9)	60 (31.3)	35 (33.3)	45 (36.6)	80 (35.1)	114 (32.4)	152 (36.5)	266 (34.6)
Midazolam/temazepam	4 (2.2)	7 (4.1)	11 (3.2)	4 (5.9)	7 (5.6)	11 (5.7)	5 (4.8)	6 (4.9)	11 (4.8)	13 (3.7)	20 (4.8)	33 (4.3)
Clonazepam	34 (19.0)	20 (11.8)	54 (15.5)	7 (10.3)	15 (12.1)	22 (11.5)	11 (10.5)	6 (4.9)	17 (7.5)	52 (14.8)	41 (9.9)	93 (12.1)
Total	179 (100)	169 (100)	348 (100)	68 (100)	124 (100)	192 (100)	105 (100)	123 (100)	228 (100)	352 (100)	416 (100)	768 (100)
P-value	0.009		0.645		0.489		0.01					

Abbreviation: BDZ, benzodiazepine.

Table 3 Distribution of type of indication for prescribing BDZ by respondent's sex and age

BDZ indication	Age (years)						Total		
	20–50		50–60		60+		Male N (%)	Female N (%)	
	Male N (%)	Female N (%)	Total N (%)	Male N (%)	Female N (%)	Total N (%)			
Anxiety	57 (31.8)	71 (42.0)	128 (36.8)	37 (54.4)	59 (47.6)	96 (50.0)	53 (50.5)	64 (52.0)	117 (51.3)
Insomnia	38 (21.2)	42 (24.9)	80 (23.0)	10 (14.7)	26 (21.0)	36 (18.8)	26 (24.8)	31 (25.2)	57 (25.0)
Depression	32 (17.9)	33 (19.5)	65 (18.7)	11 (16.2)	24 (19.4)	35 (18.2)	9 (8.6)	13 (10.6)	22 (9.6)
Epilepsy/MS/SCZ	28 (15.6)	8 (4.7)	36 (10.3)	5 (7.4)	5 (4.0)	10 (5.2)	5 (4.8)	7 (5.7)	12 (5.3)
Pain/minor surgery/intoxication	24 (13.4)	15 (8.9)	39 (11.2)	5 (7.4)	10 (8.1)	15 (7.8)	12 (11.4)	8 (6.5)	20 (8.8)
Total	179 (100)	169 (100)	348 (100)	68 (100)	124 (100)	192 (100)	105 (100)	123 (100)	228 (100)
P-value	0.005		0.639		0.75		0.007		0.007

Abbreviations: BDZ, benzodiazepine; MS, multiple sclerosis; SCZ, schizophrenia.

1 month, 64.5% did not increase the dose, while 7.6% did after 1 month, 3.6% after 2 months, 8.9% after 3 months, and 9.4% after 6 months. There was no differential in the reported BDZ dosage increase by participant sex controlling for BDZ user age interval in years. Only 1.2% of all BDZ users reported having to take a higher dose than recommended by the manufacturers.

Thirty-three percent (237 cases) of the surveyed users reported having experienced side effects due to the intake of BDZ. The reported side effects were restlessness (38%), display of aggressive behavior (15.6%), headache (11.4%), delusions (10.5%), inappropriate behavior (10.1%), nightmares (9.7%), and stomach upset (4.6%). The reported perceived side effects did not vary significantly by sex and age of the study participants. However, there was a significant variation in prevalence of side effects by type of medication prescribed. Perception of side effects was reported most frequently among those taking bromazepam and the least among those on diazepam.

Perception of reported side effects was significantly associated with the medication duration of use being more frequent among those who use it on an as-needed basis and among those who have been using it for >2 months.

Duplication of BDZ drug therapy

In order to check for possible BDZ drug duplication therapy, the names of the different BDZs were cross-checked and analyzed. The duplication of therapy was noted among 18 patients (2.3%) only.

Use of other medications

Patients were asked whether they were taking other medication with BDZ, and 56.1% reported taking other medications. Among those who reported taking other medication, 18.3% of the cases were taking drugs that should not be prescribed along with BDZs. The type of potential drug–drug interaction was analyzed, and the results are shown in Table 6.

Discussion

The discovery of BDZs in the late 50s was met with a lot of excitement by physicians leading to an alarming rise of their use around the world.¹ This study assessed the profile of BDZ users in Lebanon. Among Lebanese BDZ users, there was a slight preponderance of females, a finding consistent with previously published trials.^{8,15,16,20,25} Facts that might explain this finding are the higher prevalence of anxiety among females, as well as the higher life expectancy and higher compliance described in females.^{13,26}

Table 4 Distribution of type of BDZ medication by indication of use

BDZ type	BDZ drug indication					Total N (%)	P-value
	Anxiety	Insomnia	Depression	Epilepsy/MS/SCZ	Pain/intoxication		
	N (%)	N (%)	N (%)	N (%)	N (%)		
Bromazepam	125 (36.7)	54 (31.2)	45 (36.9)	9 (15.5)	25 (33.8)	258 (33.6)	0.000
Lorazepam	29 (8.5)	24 (13.9)	13 (10.7)	5 (8.6)	6 (8.1)	77 (10.0)	
Diazepam	14 (4.1)	4 (2.3)	6 (4.9)	7 (12.1)	10 (13.5)	41 (5.3)	
Alprazolam	140 (41.1)	54 (31.2)	42 (34.4)	12 (20.7)	18 (24.3)	266 (34.6)	
Midazolam/temazepam	4 (1.2)	23 (13.3)	2 (1.6)	0 (0.0)	4 (5.4)	33 (4.3)	
Clonazepam	29 (8.5)	14 (8.1)	14 (11.5)	25 (43.1)	11 (14.9)	93 (12.1)	
Total	341 (100)	173 (100)	122 (100)	58 (100)	74 (100)	768 (100)	

Abbreviations: BDZ, benzodiazepine; MS, multiple sclerosis; SCZ, schizophrenia.

Most BDZs are considered to have similar efficacy; therefore, selection is based on pharmacokinetic considerations and the US Food and Drug Administration (FDA)-labeled indication. The two most common types of BDZs used were alprazolam and bromazepam, both of which are intermediate acting with a relatively rapid onset of action as compared to other BDZs.²⁷ Bromazepam and alprazolam were also found to be mostly used in Pakistan.^{16,18} Clonazepam was mainly used for seizure disorders as it is one of the few BDZs approved by the FDA for this indication. One of the least-used agents was diazepam characterized by its much longer half-life and increased tolerance.²⁷

According to the World Health Organization, anxiety is the most prevalent mental disorder.²⁸ In addition, ~30% of a variety of adult samples drawn from different countries report having insomnia.²⁹ Among the Lebanese BDZ users, 44.4% were taking the BDZ for anxiety and 22.5% for insomnia followed by 16% for depression. Studies suggest that BDZ can be an effective option for patients with anxiety with minimal roles for other indications as depression, muscle relaxation, and schizophrenia. Furthermore, the better safety profile

of the newer non-BDZ hypnotics (ie, zolpidem, zaleplon, eszopiclone, and ramelteon) makes them better first-line pharmacological choices for the management of insomnia. Despite that, numerous studies have shown that BDZs are overprescribed for extended periods in many countries.^{30–32} The findings of this study indicated that a proportion of patients were inappropriately using BDZs for indications like pain management and continued use after minor surgeries.

A little less than half of the patients reported continuous use of BDZs for more than a year. Among prescribers, cardiologists and psychiatrists tend to prescribe BDZs for a longer period of time which might be explained by the chronic diseases they usually treat. Doses used were increased by ~35% after the first month that could be due to tolerance to the agents but remained therapeutic. BDZs are associated with troublesome sedation and cognitive impairment as well as tolerance and dependence with prolonged use.³³ Recommendations for the duration of treatment with BDZ especially in elderly are usually no more than 2–4 weeks of continuous use.³⁴ In resistant or critical severe cases, BDZs should not be used for >8–12 weeks,

Table 5 Distribution of duration of therapy by physician specialty

Duration of therapy	Physician specialty				Total Frequency (%)
	Psychiatry/ neurology Frequency (%)	Cardiology Frequency (%)	General practice Frequency (%)	Other specialty Frequency (%)	
As needed	52 (15.7)	14 (13.0)	37 (16.2)	15 (15.0)	118 (15.4)
2 weeks–2 months	33 (9.9)	8 (7.4)	38 (16.7)	14 (14.0)	93 (12.1)
2–6 months	50 (15.1)	11 (10.2)	30 (13.2)	20 (20.0)	111 (14.5)
6–12 months	54 (16.3)	19 (17.6)	47 (20.6)	17 (17.0)	137 (17.8)
>1 year	143 (43.1)	56 (51.9)	76 (33.3)	34 (34.0)	309 (40.2)
Total	332 (100.0)	108 (100.0)	228 (100.0)	100 (100.0)	768 (100.0)

Table 6 Distribution of BDZ drug users who reported taking other medication by type of expected drug interaction

Type of drug interaction	Frequency	Percentage	Interacting drugs
Inhibition of BDZ metabolism/ increase serum level or effect	20	30	Antifungals, SSRIs, oral contraceptives
Additive CNS depression	45	66	Hypnotics, antipsychotics, TCAs, antiepileptics, opiates
Induction of BDZ metabolism/ decrease serum level or effect	3	4	Carbamazepine
Total	68	100	

Abbreviations: BDZ, benzodiazepine; SSRIs, selective serotonin reuptake inhibitors; CNS, central nervous system; TCAs, tricyclic antidepressants.

as tolerance and physical and psychological dependence can occur. The findings of this study highlight the scale of the need for interventions to reinforce the adherence to guidelines by having clinicians use the lowest therapeutic doses for the briefest duration of time.

The study participants were prescribed BZDs by qualified health care providers except for cases where BDZs were prescribed by community pharmacists not entitled to dispense controlled substances. Nine adults were prescribed BDZs by pediatricians which raises the question about the justification of those prescriptions. Previously published evidence showed the easy access to prescription medications in Lebanon and documented a lack of awareness on the dangers of prescription misuse. The role of the Lebanese pharmacists in dispensing prescription drugs without medical prescriptions has been identified as a major contributor, while the role of the Lebanese government in controlling the drug supply system was described as insufficient.^{3,4}

It was found that 23% of BDZ users reported being alcohol consumers and were more likely to be males. The higher percentage of males being alcohol consumers as compared to females is consistent with older studies as females may carry a lower genetic risk for alcohol use disorders while males have fewer perceived social sanctions for drinking.^{35,36} Alcohol has a documented potentiation effect on gamma-aminobutyric acid receptors. In addition to alcohol intake, a significant proportion of the study participants reported taking other medications that interacted significantly with BDZ either by affecting its metabolism (antifungals, oral contraceptives, selective serotonin reuptake inhibitors) or by potentiating its central nervous system depression effects. These important drug–drug interactions are associated with drug-induced death, drug overdoses, and traffic accidents or fatalities and require adequate patient education and awareness by prescribers and pharmacists.²⁸

One of the limitations of this study is its observational nature. Not all Lebanese pharmacies were included in the sample; however, the big number of patients recruited from

different geographical areas as well as the long duration of the study diluted this limitation and made the sample representative. Additionally, patients' self-reporting of side effects to BDZ could have been subjective and confounded by patient's disease states and/or concomitant medications. Also, it would be possible that more patients were taking higher doses than recommended by the manufacturer than being reported and were reluctant to admit the misuse of their medications.

Despite the mentioned limitations, the major strength of this study resides in the fact that it was the first one to report on BDZ use across a large number of individuals from across the country.

Conclusion

Understanding the patterns of BDZ use in the Lebanese community is an essential first step toward the implementation of interventions to reduce its misuse and abuse. To our knowledge, the present study is the first to report patterns of BDZ in the Lebanese adult ambulatory population. Results showed that the use of this class of medication is highest among females especially for the treatment of anxiety. Moreover, continuous use of the drugs for more than a year as well as significant potential drug interactions was identified. A collaborative effort of governmental bodies and health care providers is recommended to educate, regulate, and promote the appropriate and safe use of BDZ.

Disclosure

The authors report no conflicts of interest in this work.

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