Evaluation of Risk Factors Associated to Prescription of Benzodiazepines and its Patterns in a Cohort of Patients from Mental Health: A Real World Study in Spain

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ABSTRACT ~ **Purpose:** *we aimed 1) to evaluate the risk factors associated to the benzodiazepines intake; 2) to assess the impact about the use of long acting injectables antipsychotics (LAIs); 3) to assess the risk in severe and affective disorders and 4) to identify the prescription patterns of use in mental health in a cohort of patients from Spain.* **Methods:** *735 outpatients from Mental Health were included. Demographic and clinical data were collected. In order to compare the use of benzodiazepines we calculated the daily dose equivalents (mg/day) to diazepam as standard.* **Results:** *The most commonly prescribed benzodiazepine was clonazepam (33%) and the mean daily dose of diazepam equivalents was 24.9 mg. It was higher in affective disorders (40.35 ± 3.36) and lower in patients using LAIs antipsychotics (17.50 ± 1.39; p = 0.001). Multivariate analysis showed that to be women (OR = 1.559, 95% CI = 1.059–2.295, p = 0.024), the use of drugs (OR = 1.671, 95% CI = 1.127–2.477, p = 0.011) and suffering any affective disorder (OR = 1.542, 95% CI = 1.355–1.826, p = 0.040) increased the risk of benzodiazepine intake. In contrast, the use of LAIs antipsychotics significantly reduced it versus oral antipsychotics (OR = 5.226, 95% CI = 3.185–8.575, p = 0.001).* **Conclusions:** *benzodiazepines are widely prescribed, mainly clonazepam followed by lorazepam and diazepam. Most of patients used at least one benzodiazepine and the mean daily intake was 25 mg diazepam equivalents. Therefore, benzodiazepines are extensively prescribed and used at higher doses than desirable. These, findings could be useful for clinicians and their practice.* Psychopharmacology Bulletin. *2021;51(1):81–93.*

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INTRODUCTION

The first benzodiazepine was the chlordiazepoxide developed in 1955 followed by the diazepam in 1963.[1] Since then, several molecules have been developed constituting a group of drugs exerting its anxiolytic, hypnotic, anticonvulsant and muscle relaxant effects through enhancing the effect of gamma-amynobutyric acid (GABA) at its $GABA_A$ receptor.[2,3]

Despite benzodiazepines being well known for its potential dependence syndrome and their common side effects (sedation, memory loss, falls)[4] their prescription and use is widely increasing. In this regard, a 113% increased use of benzodiazepines from 2000 to 2012 has been reported in Spain.[5] In this line, a recent survey in Spanish general population showed that the prevalence of use of benzodiazepines was 20.8% sometime and 5.9% daily, always highlighting a higher consumption in women (63%).[5] Studies in general population showed that the age is the most consistent predictor of taking benzodiazepines.[6,7] Likewise, the consumption of benzodiazepines has been shown to be higher in women than in men in general population.[8–10] In contrast, only few studies evaluated the use of benzodiazepines by using a cohort from mental health services.[11–13] Unfortunately, most of them focused in particular groups of risk such as substance of abuse users,[14] depressed patients[15] or whose diagnosed with schizophrenia and panic disorders.[16]

Therefore, the aim of this study was 1) to evaluate the risk factors associated to the benzodiazepines intake; 2) to assess the impact about the use of long acting injectables antipsychotics (LAIs); 3) to assess the risk in severe and affective disorders and 4) to identify the prescription patterns of use in mental health in a cohort of patients from the Region of Murcia, Spain.

METHODS

Study Design

As previously described,[17] we designed a cross-sectional study, from 2015 to 2017, based on a representative sample of the adult and non-institutionalized population of Mental Health in the Region of Murcia. A total number of 735 patients, ≥18 years old, were included if were previously diagnosed with a mental health disorder according to the DSM-V guidelines. Exclusion criteria included institutionalized patients, use of 2 LAIs, intellectual disability or autistic spectrum disorders and patients with missing records or unable to confirm treatment continuation during 1 year. The present study was drawn up

following the 'STrengthening the Reporting of OBservational studies in Epidemiology' (STROBE) Statement ítems.[18]

Study Measures

Data collected included demographical information such as age, sex, civil status, tobacco and other drugs use as well as clinical data such as the disorder, its evolution (years), the benzodiazepines dosage as well as concomitant psychiatric medications, including the use of both, oral and long-acting injectable (LAIs) antipsychotics, antidepressants, mood stabilizers and biperiden. In order to compare the use of benzodiazepines we calculated the daily dose equivalents of benzodiazepines (mg/day) by diazepam as standard to compare the corresponding doses as previously published.[19]

Statistical Analysis and Confounding Factors

All analyses were performed using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA). We expressed quantitative variables as means [± standard error media (SEM)] and categorical variables as numbers (percentage). We assessed normality of distributions using histograms and the Shapiro–Wilk test. Sample basal characteristics were analyzed by univariate analysis. Variables associated in the univariate analysis and variables with statistical trend ($p < 0.1$) were entered as factors in a bivariate logistic regression model to identify the variables independently associated to benzodiazepine intake. Student's t-test was used to assess differences in diazepam equivalents within groups by sex, use of LAIs or affective disorder. Differences with a p value <0.05 were considered significant.

RESULTS

Sample basal characteristics are shown in Table 1. Patients taking benzodiazepines were more frequently women (70% versus 66% in men; $p = 0.006$), with shorter disease duration (10.9 ± 0.4 versus 13.0 ± 0.7 in no-users; $p = 0.035$) and used more frequently drugs (38% versus 22% in non-users; $p = 0.001$). The 87% and the 67% of patients diagnosed with a general or severe psychiatric disorder, respectively, were prescribed with benzodiazepines. Furthermore, the 81% of patients diagnosed with an affective disorder were prescribed with benzodiazepines while the 64% of patients diagnosed with no-affective disorders took benzodiazepines. Among LAIs users, the rate of benzodiazepines prescription was lower compared to no-LAIs users (62% vs. 86%, respectively).

TABLE 1

UNIVARIATE ANAYSIS BETWEEN USERS AND NON-USERS OF BENZODIAZEPINES

	TOTAL N = 735	NO BDZ N = 234	BDZ N = 501	P-VALUE
Sex (%)				0.006
Women	325 (44)	96 (41)	229 (49)	
Men	410 (56)	138 (58)	272 (51)	
Age (y ± SEM)	41.6 ± 0.5	41.7 ± 0.9	41.5 ± 0.5	0.305
Disorder duration (y ± SEM)	11.5 ± 0.4	13.0 ± 0.7	10.9 ± 0.4	0.035
Legal status (%)				0.140
Single/Divorced/Widow	563 (77)	158 (78)	405 (76)	
Coupled/Married	172 (23)	44 (22)	128 (24)	
Tobacco & Drugs (%)				
Tobacco	325 (44)	87 (43)	238 (45)	0.461
Other drugs	247 (33)	44 (22)	203 (38)	0.001
Mental Disorder				0.091
General Disorders	203 (28)	27 (13)	176 (33)	
Severe Disorders	532 (72)	175 (87)	357 (67)	
Affective Disorders				0.005
No	349 (47)	127 (63)	222 (42)	
Yes	386 (53)	75 (37)	311 (58)	
Use of LAI-antipsychotic				0.001
No	323 (44)	46 (23)	277 (52)	
Yes	412 (56)	156 (77)	256 (48)	

Affective disorders included depressive, anxiety-depressive, anxiety, schizoaffective, bipolar and personality disorders. Non-affective disorders included schizophrenia, psychosis, delusional disorders. BDZ = bendozdiazepines, LAI = long acting injectables antipsychotics, SEM = standard error mean.

We performed a logistic bivariate regression analysis to truly establish the factors independently associated with the intake of benzodiazepines. As shown in Table 2, bivariate logistic regression model showed that women had higher risk of benzodiazepine intake compared to men (OR = 1.559, 95% CI = 1.059–2.295, p = 0.024). Furthermore, the use of drugs (OR = 1.671, 95% CI = 1.127–2.477, p = 0.011) and suffering any affective disorder (OR = 1.542, 95% CI = 1.355–1.826, p = 0.040) increased the risk of benzodiazepines intake. In contrast, the use of LAIs antipsychotics significantly reduced the risk of benzodiazepines intake versus oral antipsychotics (OR = 5.226, 95% CI = 3.185–8.575, p = 0.001).

Diazepam Equivalents

The mean daily doses of benzodiazepines are shown in Figure 1 as diazepam equivalents. Mean daily dose of diazepam equivalents in our cohort was 24.9 mg (24.90 ± 1.42). As shown in A) student's t-test showed no

TABLE 2

**Risk Factors Associated to Benzodiazepine Intake by Bivariate Logistic Regression Model**

	OR	95% CI	P-VALUE
Sex			0.024
Women	1.559	1.059–2.295	
Men	1		
Disorder duration	0.999	0.980–1.018	0.894
Drugs use			0.011
No	1		
Yes	1.671	1.127–2.477	
Mental Disorder			0.175
General	1.433	0.852–2.411	
Severe	1		
Affective Disorder			0.040
No	1		
Yes	1.542	1.355–1.826	
Use of LAIs			0.001
No	5.226	3.185–8.575	
Yes	1		

LAIs = long acting injectable antipsychotics.

statistical differences between the daily dose of women and men (27.41 $\pm$ 2.04 and 23.29 $\pm$ 1.79, respectively). Nonetheless, as shown in B) and C), statistical differences were found between affective (40.35 $\pm$ 3.36) or no-affective disorders (21.98 $\pm$ 1.37, $\chi^2_{[df = 1,734]}$ = 6.06; p = 0.001) as

FIGURE 1

Diazepam Equivalents by (A) Sex, (B) Affective vs No-Affective Disorders and (C) Long-Acting Injectable Use (LAIs)
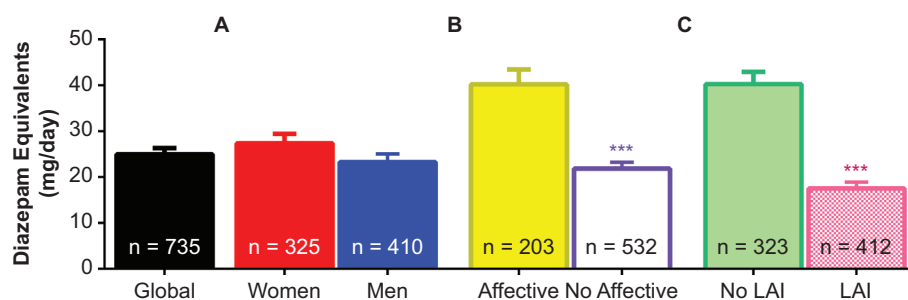
Global column represents the mean data from the whole cohort of patients. Data are expressed as the mean $\pm$ SEM. Student's t-test revealed statistical differences between affective and no-affective disorders (***p = 0.001) as well as when comparing the use of oral versus LAIs (***p = 0.001) Abv: LAIs = long acting-injectables antipsychotics.

well as when comparing the use of oral (40.25 ± 2.99) versus LAI anti-psychotics (17.50 ± 1.39, $\chi^2_{[df = 1,734]}$ = 7.89; p = 0.001).

Use of Benzodiazepines by Sex and Mental Disorder

As shown in Table 3, the most commonly prescribed benzodiazepine in both sexes was clonazepam in 33 and 32% of cases, followed by lorazepam (32% in women and 24% in men) and Diazepam (21% in women and 22% in men). Likewise, as shown in Table 4, patients diagnosed with a depressive-anxiety disorder were the more frequently prescribed with benzodiazepines (92%) followed by patients suffering from depression (88%) and schizoaffective disorder (79%). In contrast, a lower rate of patients with bipolar disorder took benzodiazepines (57%). Among psychotic disorders, 65% of patients with schizophrenia took benzodiazepines while only the 48% and 36% of patients with psychosis and Deliroid disorder, respectively. It worth to point out that about 75% of patients diagnosed with a personality disorder were prescribed with benzodiazepines. Most of patients used only one type of benzodiazepine (48%) and the 19% used 2 types. Nonetheless, the 44% and the 24% of patients diagnosed with anxiety-depressive and personality disorders, respectively, used two different benzodiazepines. Once again, clonazepam was the most used in the different disorders (mean 22%, range 4–30) excepting in deliroid, anxiety-depressive and depression disorders which more frequently were prescribed with lorazepam.

TABLE 3

Use of Benzodiazepines by Sex

	TOTAL N = 735	WOMEN N = 325	MEN N = 410
BDZs' users (%)	n = 501	n = 229	n = 272
1	353 (48)	159 (69)	194 (71)
2	127 (17)	60 (26)	67 (25)
3	21 (3)	10 (5)	11 (4)
BDZs (%)			
Alprazolam	27 (5)	12 (5)	15 (6)
Bromazepam	14 (3)	8 (3)	6 (2)
Clonazepam	164 (33)	76 (33)	88 (32)
Clorazepate	18 (4)	8 (3)	10 (4)
Diazepam	108 (22)	48 (21)	60 (22)
Flurazepam	96 (19)	40 (17)	56 (21)
Ketazolam	10 (2)	7 (3)	3 (1)
Lorazepam	139 (28)	74 (32)	65 (24)
Lormetazepam	94 (19)	48 (21)	46 (17)

BDZs = benzodiazepines.

TABLE 4

Use of Benzodiazepines by Mental Disorder

	TOTAL N = 735	SCH N = 277	PSY N = 44	DELD N = 28	SCHAFF N = 90	BPD N = 93	PDS N = 112	DEPD N = 42	ADD N = 39	OTHERS N = 10
N benzodiazepines (%)	**501 (68)**	**181 (65)**	**21 (48)**	**10 (36)**	**71 (79)**	**53 (57)**	**83 (74)**	**37 (88)**	**36 (92)**	**9 (90)**
1	353 (48)	128 (46)	18 (41)	8 (29)	51 (57)	38 (38)	52 (45)	27 (64)	22 (56)	9 (90)
2	127 (19)	44 (16)	3 (9)	2 (7)	16 (18)	14 (19)	25 (24)	9 (21)	14 (44)	–
3	21 (3)	9 (3)	–	–	4 (4)	1 (1)	6 (5)	1 (3)	–	–
BDZs (%)										
Alprazolam	27 (4)	13 (5)	1 (2)	1 (4)	–	1(1)	7 (6)	2 (5)	1 (3)	1 (10)
Bromazepam	14 (2)	5 (2)	1 (2)	–	2 (2)	2 (2)	2 (2)	2 (5)	–	–
Clonazepam	164 (22)	59 (21)	7 (16)	1 (4)	27 (30)	22 (24)	27 (24)	10 (24)	10 (26)	1 (10)
Clorazepate	18 (2)	7 (3)	–	1 (4)	6 (7)	1 (1)	2 (2)	1 (2)	–	–
Diazepam	108 (15)	38 (14)	2 (5)	1 (4)	17 (19)	5 (5)	24 (21)	8 (19)	12 (31)	1 (10)
Flurazepam	96 (13)	39 (14)	4 (9)	2 (7)	12 (13)	10 (11)	18 (16)	3 (7)	8 (21)	–
Ketazolam	10 (1)	3 (1)	–	–	2 (2)	3 (3)	2 (2)	–	–	–
Lorazepam	139 (19)	43 (16)	7 (16)	5 (18)	17 (19)	13 (14)	23 (21)	13 (31)	13 (33)	5 (50)
Lormetazepam	94 (13)	36 (13)	2 (5)	1 (4)	12 (13)	12 (13)	15 (13)	9 (21)	6 (15)	1 (10)

Sch = schizophrenia, Psy = psychosis disorder, DelD = delusional disorder, SchAff = schizoaffective disorder, BPD = bipolar disorder, PDs = personality disorder, DepD = depresive disorders, ADD = anxiety–depresive disorder.

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Concomitant Treatments

Full treatments are shown as supplementary material (Table 5). Interestingly, antipsychotics are widely used not only in schizophrenia and psychosis (100% and 95%, respectively) but also in personality (66%), bipolar (61%) and schizoaffective (67%) disorders. In this regard, most of patients with schizophrenia were treated with at least 2 different antipsychotics (>67%). Furthermore, antidepressants were extensively used in depression (100%) and anxiety-depressive disorders (64%) but also in personality (49%). Finally, mood stabilizers were often used in bipolar and schizoaffective disorders (74% and 48% respectively).

DISCUSSION

Anxiolytics and hypnotics have been one of the most prescribed drugs in Western countries. The 68% of patients in our cohort from mental health took benzodiazepines. The prevalence of benzodiazepine use in general population varies from 13.8% in France,[20] between 10 and 25% in the Netherlands,[21] and 26.1%in the United Kingdom.[22] First, our results demonstrated that the prescription of benzodiazepines was associated to women and to patients who use drugs of abuse. These results are in line with previous findings[23,24] suggesting that women could suffer more frequently affective health disorders or symptoms such as insomnia or anxiety. In addition, patients who use drugs may be not aware about the risks of benzodiazepines use. Second, while affective disorders are more likely prescribed with benzodiazepines, the use of LAIs are associated to a lower benzodiazepines intake and lower pharmacy costs.[17,25] Although several studies have already examined the influence of these factors either in the context of general population, primary care settings or in some particular mental disorders, the present study is, to the best of our knowledge, the first that investigates this issue using a cohort from mental health.

Diazepam Equivalents

Although our results demonstrated that to be woman is a risk factor to become prescribed with benzodiazepines, our data showed no differences in the dose of diazepam equivalents used by both women and men. This finding is consistent with previous reports using a cohort from mental health.[17] In this line, no differences between sexes were found in a cohort of patients diagnosed with schizophrenia.[26] In contrast, patients diagnosed with an affective disorder doubled the used dose of diazepam equivalents. Interestingly, patients treated with a LAI used

lower diazepam equivalents. This finding was also found in patients diagnosed with psychotic disorders when oral versus LAIs antipsychotic treatments were compared.[26,27]

Use of Benzodiazepines by Sex and Mental Disorder

In both sexes, clonazepam and lorazepam were the more frequently prescribed benzodiazepines. Similarly, clonazepam and lorazepam were the most frequently prescribed in the different mental disorders. It worth to point out that clonazepam was more prevalent within non-affective disorders while lorazepam was more used in affective disorders. In this regard, clonazepam and lorazepam were also the most used benzodiazepines in several studies.[28,29] In contrast, other studies reported diazepam[30,31] or bromazepam[32] as the most used benzodiazepine. It is important to note that these divergences may occur due to the different groups studied and/or the several drugs that are available in different countries.

Overall, the present study demonstrated that the long-term (1-year) use of benzodiazepines is higher than desirable (>48%). In contrast, scientific evidence recommends the use of benzodiazepine as an adjuvant in treating anxiety, insomnia or depression only during the first four weeks of the treatment. As previously pointed out Smith and Tett,[33] clinical guidelines and restriction campaigns contribute to raise awareness of inappropriate use of benzodiazepines. Nonetheless, in Western countries, patients are not treated according to clinical guidelines based on scientific evidence.[23] It has been shown that long term use of benzodiazepines (>1 year) increased the risk of abstinence syndrome, accidents, suicide attempt (especially in depressed individuals), reduction of the work capability and increase in the costs of hospitalization.[20–22] Therefore, physicians should try to withdrawal benzodiazepines since the first prescription and try to avoid their use in the long-term management of the disease.

Limits

Given our inclusion/exclusion criteria were not restrictive; our cohort provides a high external validity to the western countries, in particular to Spain. Nonetheless, our study may hide some biases. For example, some clinical data, such as tobacco and drugs, are often unrecorded. Moreover, psychotropic medication could be also used in organic diseases such as neuropathic pain, migraine or others. Due to the lack about this information we could have overestimated the use of benzodiazepines in our cohort. In addition, Compliance with the LAIs was guaranteed given the treatment was administered by trained healthcare staff and it could impact

in the need of concomitant treatments. Furthermore, considering that the severity of each patient's condition was not available from hospital records, it is not possible to elucidate whether patients of LAI groups had a worse prognosis versus patients treated with oral antipsychotics. Therefore, more studies including anxiety, anger, depression scales and prescriber habits are needed to truly establish the underlying reasons and risk factors involved in the prescription of benzodiazepines in mental health.

Conclusions

In summary, this is the first study showing the patterns of prescription of benzodiazepines in a cohort from mental health and comparing its dosage in diazepam equivalents. Despite the limitations of our study, we demonstrated that benzodiazepines are widely prescribed, mainly clonazepam followed by lorazepam and diazepam. Most of patients used at least one benzodiazepines and the daily mean intake of benzodiazepines corresponds to 25 mg of diazepam equivalents. Therefore, benzodiazepines are extensively prescribed and used at higher doses than desirable. Further research is needed to clarify the risk factors and reasons to benzodiazepine prescriptions; however, our findings could be useful for clinicians and their practice. ✤

Conflict of Interests

None of the authors have conflict of interest.

Ethics Approval

Ethics and methodology issues approval for the study were granted by both the Research Ethic Committee of the Murcia Health Service and by the Ethic Committee of the San Antonio Catholic University of Murcia (UCAM) (CE031914). No identifiable information was retained or is presented in this manuscript.

Key points

1. Benzodiazepines are widely prescribed, mainly clonazepam followed by lorazepam and diazepam

2. To be women and affective disorders are the main risk factors for the prescription of benzodiazepines while the long acting-injectables antipsychotics lower the risk.

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Benzodiazepines in Mental Health

SUPPLEMENTRY MATERIAL

FULL TREATMENTS BY MENTAL DISORDER

	TOTAL N = 735	SCH N = 277	PSY N = 44	DELD N = 28	SCHAFF N = 90	BPD N = 93	PDS N = 112	DEPD N = 42	ADD N = 39	OTHERS N = 10
N benzodiazepines (%)	501 (68)	181 (65)	21 (48)	7 (25)	71 (79)	53 (57)	83 (74)	37 (88)	39 (100)	9 (90)
1	338 (46)	126 (46)	17 (39)	5 (18)	48 (53)	34 (35)	50 (45)	27 (64)	22 (56)	9 (90)
2	141 (19)	46 (17)	4 (9)	2 (7)	18 (20)	18 (19)	27 (24)	9 (21)	17 (44)	–
3	21 (3)	9 (3)	–	–	4 (4)	1 (1)	6 (5)	1 (3)	–	–
N antipsychotics (%)	535 (73)	277 (100)	42 (95)	14 (50)	61 (67)	57 (61)	74 (66)	5 (12)	2 (5)	3 (30)
1	169 (23)	45 (16)	18 (41)	9 (32)	13 (14)	28 (30)	46 (41)	5 (12)	2 (5)	3 (30)
2	284 (39)	185 (67)	20 (45)	4 (14)	34 (38)	17 (18)	24 (21)	–	–	–
3	69 (9)	39 (14)	4 (9)	1 (4)	12 (13)	9 (9)	4 (3)	–	–	–
4	13 (2)	8 (3)	–	–	2 (2)	3 (3)	–	–	–	–
Biperiden (%)	105 (14)	67 (24)	6 (14)	6 (21)	14 (16)	5 (5)	7 (6)	–	–	–
N antidepressants (%)	250 (34)	64 (24)	10 (22)	7 (25)	22 (24)	21 (22)	55 (49)	42 (100)	25 (64)	4 (40)
1	204 (28)	53 (19)	10 (22)	6 (21)	18 (20)	18 (19)	46 (41)	29 (69)	20 (51)	4 (40)
2	46 (6)	11 (4)	–	1 (4)	4 (4)	3 (3)	9 (8)	13 (31)	5 (13)	–
Mood stabilizer (%)	200 (27)	39 (14)	5 (11)	4 (14)	43 (48)	69 (74)	27 (24)	8 (19)	4 (10)	1 (10)
1	178 (24)	37 (13)	5 (11)	4 (14)	36 (40)	56 (60)	27 (24)	8 (19)	4 (10)	1 (10)
2	19 (3)	2 (1)	–	–	7 (8)	10 (11)	–	–	–	–
3	3 (0.4)	–	–	–	–	3 (3)	–	–	–	–

Sch = schizophrenia, Psy = psychosis disorder, DelD = delusional disorder, SchAff = schizoaffective disorder, BPD = bipolar disorder, PDs = personality disorder, DepD=depresive disorders, ADD = anxiety-depresive disorder.

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