Association between benzodiazepine prescriptions and potential risk factors of adverse drug reactions among elderly and very elderly: findings from Friuli Venezia Giulia region, Italy

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ABSTRACT

Background: benzodiazepines (BDZs) highly increase the risk of adverse drug reactions (ADRs), especially in the elderly with certain medical conditions.
Methods: point-prevalence study in December 2017; 2,456 patients ≥65 years were included from 14 regional public and private hospitals, 24 long-term chronic care facilities (LTCCFs) and 20 nursing homes (NHs). Data regarded BDZ prescriptions and comorbidities, co-prescriptions, or concurrent diseases, which could increase the risk of ADRs in BDZ users. Univariate and multivariate logistic regression analyses were used to assess associations between ADRs in BDZ users vs. non-users, as well as within users.
Results: 671 patients were prescribed BDZ, whose half were in NHs. Being prescribed 10 or more drugs was twice more common among BDZ users compared to non-users. BDZs were prescribed for long-term to 80% of patients in NHs, while proportions were halved in hospitals and LTCCFs. In the analyses within BDZ users, patients in NHs and LTCCFs were at higher risk of dementia and concurrent use of opioid analgesic and antipsychotics compared to hospitalized patients.
Conclusions: the use of BDZs in older patients is common in FVG. A great extent of comorbidities and concurrent medications at higher risk of ADRs was found. Analyses in different healthcare settings can allow to drive evidence-based interventions in order to discourage the use of BDZs and monitor the raise of ADRs.

Key words: benzodiazepine, elderly, adverse drug reaction, polypharmacy, Italy

INTRODUCTION

Benzodiazepines (BDZs) have been well established as one of the most prescribed drug classes worldwide [1-7], although available data on the use of BDZ in the "real-world" showed a high variation, mainly due to different methods to assess BDZ use [8]. Findings based on national registers of prescriptions indicated a prevalence of BDZ varying from 4-5% [6,4], to 12-14% [9,1]. Further, BDZ use has been observed to increase with age [1,10,8,3,4,11,6,9]. Nonetheless, BDZs have been indicated to highly increase the risk of several adverse drug reactions (ADRs), if used in patients with certain medical conditions, such as disorders increasing the risk of respiratory insufficiency and the risk of falls and fractures, liver diseases, dementia and myasthenia gravis [1,12-15]. Concurrent use of certain medications, such as opioid analgesic, barbiturates, drugs depressing the central nervous system (CNS) or active on CNS further increases ADRs risk [1]. The elderly using BDZs were observed to be at the highest risk of developing ADRs, given those comorbidities and concurrent drug use [1,10,13,16,7,2]. According to Beers criteria [17], strong recommendation to totally avoid BDZs and hypnotics in the elderly has been given, particularly in case of delirium, dementia and history of falls and fractures. Minimizing the use of CNS drugs and avoid the concurrent use of three or more drugs active on CNS has been also strongly recommended [17]. Furthermore, long-term use of BDZs has been indicated to be particularly harmful in older patients, albeit it has been found to be more common in the elderly than in other ages [10,18,4,5,7]. Despite these warnings, however, few research assessed the extent of potential ADRs in older users of BDZs [1].

However, the amount of data with regard to inappropriate BDZ prescriptions is scarce [8]. Italy is sharing with many countries this issue, since BDZ are not included in the medications reimbursed by the National Health System (NHS), and, thus, are not recorded in national registers of prescriptions [19,20]. To our knowledge, further, no studies assessed the use of BDZs comparing different healthcare settings. This seems striking instead, since a detailed analysis of prescriptions' pattern at different healthcare levels can be a first step for facing inappropriate prescriptions of BDZs and the potential onset of ADRs. A previous study based on a survey administered in Friuli Venezia Giulia (FVG) region, in fact, demonstrated that BDZs were ranking among the ten most frequently prescribed drugs and accounted for the majority of potential inappropriate prescriptions in regional hospitals, long-term chronic care facilities (LTCCFs) and primary care [21]. Elderly from the region were also likely to polypharmacy and potentially inappropriate prescriptions, in particular in hospitals and LTCCFs compared to community setting [21]. Another study from FVG found that BDZs were prescribed to 95% of older patients by a sample of General Practitioners (GPs) [19]. This study also observed that indications for BDZ prescriptions were in two-third of cases for psychiatric disorders, mainly for depressive and anxiety disorders [19].

The aim of this study was, thus, to assess the occurrence of BDZ prescriptions and their association with potential risk factors inducing ADRs among the elderly and very elderly patients in three different healthcare settings of Region Friuli Venezia Giulia (FVG).

METHODS

Study design and population

This is a point-prevalence study of BDZs and other drug prescriptions, carried out in three health-care settings in the FVG region from 11th December 2017 to 24th December 2017: all 14 regional public and private hospitals, 24 LTCCFs and 20 nursing homes (NHs).

The eligible study sample were the elderly (aged from 65 to 79 years) and the very elderly (aged more than 79 years) who were taking at least one medication at the time of the survey, according to selection criteria listed below. Among them, we selected a sub-sample of BDZ users, who were dispensed at least one BDZ.

Selection criteria were differently defined according to the health care setting. Regarding the hospital setting, patients were surveyed at the time of discharge from hospital. It involved all patients who were discharged during fourteen consecutive working days from the wards of internal medicine, geriatrics, cardiology, and neurology, patients that died during the hospitalization were excluded. Regarding LTCCFs, 50% of the residents were involved in the survey and they were randomly selected among the 24 out of 90 regional LTCCFs which joined the study. Regarding NH, 10% of the residents were involved in the survey and they were randomly selected among the 20 out of 90 regional NH which joined the study.

Recruitment of patients started simultaneously in the three settings. Nonetheless, we prevented the chance of being double-included in case of transfer from hospital to LTCCFs or NH carrying out the survey in these setting considering only residents that were present in the first day of survey.

Data on diagnoses and drug prescriptions were retrieved from discharge letters among hospitalized patients, whereas medical records were used regarding LTCCFs and NH. All data were centralized and then analysed at the FVG Regional 'Safety Care' Group, based in Udine, Italy.

All data were managed confidentiality, patient identifiers were anonymous at the level of database and analysis; the surveys were included in the yearly goals for hospital chief executive officers (CEOs) as a part of the RHS program for the 'safe-care network' regional team.

Diagnoses

Several selected patients' diseases available at the time of the survey were registered. Diseases were classified according to International Classification of Diseases, tenth revision (ICD-10).

Diagnoses which could increase the risk of ADRs in BDZ users were then selected (Table 1) [1,17].

Drug prescriptions

All prescriptions available at the time of the survey were reported. Medications were classified according to the Anatomical Therapeutic Chemical classification [22]. Topical medications, homeopathic, over-the counter, and/or natural remedies were considered outside of the scope of the study and were excluded from this analysis. Likewise, antineoplastic drugs were excluded from the analysis, as it is likely that these drugs are usually prescribed by oncologists in different specific wards.

Prescription attitude was defined as normal when <5 drugs were co-prescribed, as polypharmacy when 5 to 9 drugs were co-prescribed, and as hyper-polypharmacy when 10 or more drugs were co-prescribed.

Individuals having received at least one BDZ were then selected. Different BDZ medications were classified in two groups, according to the duration of action [17], as follows:

- Short and intermediate acting: oxazepam (N05BA04), alprazolam (N05BA12), etizolam (N05BA19), lorazepam (N05BA06), bromazepam (N05BA08), brotizolam (N05CD09), lormetazepam (N05CD06), estazolam (N05CD04), triazolam (N05CD05);
- Long acting: diazepam (N05BA01), ketazolam

TABLE 1. Comorbidities and concurrent drug treatment which can increase the risk of adverse drug reactions (ADRs) in benzodiazepine users

	ICD-10 Codes	ATC Codes
Comorbidities increasing the risk of ADRs in benzodiazepine user		
Comorbidities at risk for adverse respiratory effects		
COPD	J41-J44	R03
Asthma	J45-J46	
Comorbidities that contraindicate benzodiazepine use		
Myasthenia gravis		N07AA
Liver disease	K70-K77	A05
Dementia	F00-F03	N06D
Comorbidities that increase the risk of falls and fracture		
Osteoporosis and other disorders of bone density		M05BA, M05BB
Gait and balance disorders		
Parkinson disease	G20	N04
Rheumatoid arthritis	M05-M06	
Concurrent treatments increasing the risk of ADRs in benzodiazepine users (Beers criteria 2015)		
Respiratory depressant		
Opioid analgesics		N02A
Barbiturates		N03AA
CNS-depressants		
Antipsychotics		N05A (N05AN excluded)
Centrally acting antihypertensives		C02A
Non-benzodiazepine anxiolytics (idrossiazine)		N05BB
Sedative antidepressants (agomelatine, amitriptyline, doxepin, mianserin, mirtazapine, trimipramine, trazodone)		N06AX21, N06AA09, N06AA12, N06AX03, N06AX11, N06AA05, N06AX05
Other CNS active		
Muscle relaxants, centrally acting agents		M03B

(N05BA10), prazepam (N05BA11), flurazepam (N05CD01), clonazepam (N03AE01), chlordesmethyldiazepam;

Midazolam (N05CD08) was excluded, as mainly used as anesthetics.

Individuals using hypnotics (zolpidem; N05CF02) were included, as a separate group.

Long-term use of BDZ was assessed if they were used for more than four weeks, as reported at the time of the survey in each healthcare setting, with regard to the last prescription assessed.

Assessment of increased risk of adverse drug reaction

Comorbidities, co-prescriptions, or concurrent diseases and prescriptions, which can be considered to increase risk of adverse drug reactions (ADRs) in BDZ users, are summarized in Table 1. ADRs may regard different symptoms mainly related to depressant effect on CNS, such as respiratory depression, drowsiness, muscle weakness, sedation [1]. According to Beers criteria [17] and international literature [1], they regarded co-morbidities with diseases and drugs at higher risk of adverse respiratory effects, falls and fractures, general contraindication to BDZ (liver disorders, dementia and myasthenia gravis), concurrent use of drugs with depressant effect on respiratory system and CNS, as well as other drugs active on CNS.

Statistical analysis

All variables were dichotomous or categorical and were tabulated into contingency tables and the chi-square statistic (χ^2) for categorical data was used to test the differences between observed and expected frequencies.

Univariate and multivariate logistic regression analyses were used to assess the associations between outcomes (use of BDZ vs. non-use of BDZ) and predictors (gender, age groups, number of prescribed drugs, setting and comorbidities and concurrent drug treatment which can increase the risk of adverse drug reactions (ADRs) associated to BDZ use). Multivariate logistic regression analyses were also applied within BDZ users to assess the association between outcomes (gender, age groups and setting) and predictors (comorbidities and concurrent drug treatment).

Crude and adjusted odds ratios (OR) and 95% confidence intervals (95% CI) were estimated from the logistic regression coefficients and their respective standard errors. A P-value (P) < 0.05 was set as the threshold for statistical significance.

Descriptive and inferential analyses were performed using the statistical software Stata/SE (version 15.1).

RESULTS

Characteristics of patients prescribed and not prescribed benzodiazepines

TABLE 2. Patient's characteristics

	Individuals not prescribed BDZ				Individuals prescribed at least one BDZ			
	H (n =1142) N (%)	LTCCF (n =260) N (%)	NH (n =383) N (%)	P	H (n =178) N (%)	LTCCF (n =179) N (%)	NH (n =314) N (%)	P
Gender								
Males	575 (50.4)	103 (39.6)	91 (23.8)		64 (36.0)	56 (31.3)	82 (26.1)	0.170
Females	561 (49.1)	154 (59.2)	290 (75.7)	0.000	114 (64.0)	123 (68.7)	231 (73.6)	
Missing	6 (0.5)	3 (1.2)	2 (0.5)		0	0	1 (0.3)	
Age (years)								
Elderly (65-79)	454 (39.8)	79 (30.4)	78 (20.4)		75 (42.1)	85 (47.5)	80 (25.5)	
Very elderly (≥80)	688 (60.2)	181 (69.6)	305 (79.6)	0.000	103 (57.9)	94 (52.5)	234 (74.5)	0.000
N of prescribed drugs								
1-4	306 (26.8)	55 (21.2)	80 (20.9)		26 (14.6)	15 (8.3)	26 (8.2)	
5-9	679 (59.5)	155 (59.6)	236 (61.6)	0.022	103 (57.9)	105 (58.7)	163 (51.9)	0.021
≥10	157 (13.7)	50 (19.2)	67 (17.5)		49 (27.5)	59 (33.0)	125 (39.8)	

H hospital; LTCCF long-term chronic care facilities; NH nursing home; N numbers

P-value was obtained by chi-square test and was used to assess whether proportions of individuals not prescribed BDZ or prescribed BDZ, respectively, were differently distributed in the three settings in relation to genders, age groups and number of drugs prescribed

Overall, 2,456 patients were included, whose 671 (27.3%) were prescribed at least one BDZ. In all settings, beside BDZ prescription, patients were more likely to be females, aged over 80 years old and being prescribed five to nine drugs (Table 2). Interestingly, hyper-polypharmacy was almost twice more common among BDZ users compared to non-users in all different settings, with almost 40% of BDZ users in NHs being prescribed 10 or more drugs.

Nearly half of BDZ users were in NHs, (Table 2). The majority (64.0%) of subjects who were not dispensed BDZs were hospitalized, whilst BDZ users were only 26%. Patients in LTCCFs were more likely to be not prescribed BDZs (59.2%), than prescribed (40.8%).

When BDZ users were compared with non-BDZ users in the multivariate regression analysis (Table 3), BDZ users were 1.5 times more likely to be females and 4 times more likely of being in outpatient services (LTCCF and NH) than in hospital. BDZ users were also at higher risk of being prescribed from 5 to 10 and more drugs, compared to patients being prescribed up to 4 drugs

Information on benzodiazepine use

As summarized in Table 4, short-intermediate acting BDZs were the most used (N = 431; 64.2%), and they significantly differed between settings, albeit almost 70% of patients in NHs and in hospital were prescribed these drugs. Among different BDZ active principles, chlordesmethyldiazepam and lorazepam were the most used, representing almost half of total prescriptions in all settings. Interestingly, almost 80% of patients in NHs were prescribed BDZs for more than 4 weeks, while proportions were 37% in hospitals and 24.5% in LTCCFs.

Almost 10% of patients (N = 62) were dispensed two BDZs simultaneously, while 4 patients were dispensed three.

Adverse drug reactions in benzodiazepine users

In the multivariate regression analysis, being prescribed BDZs was significantly associated only to Parkinson disease, whilst the use of antipsychotics was negatively associated to BDZ use (Table 3).

When the analyses were restricted to BDZ users (Table 5), women and subjects aged 80 years and more were at higher risk of dementia and osteoporosis compared to men and younger than 80 years, respectively. Patients in NHs were at higher risk of dementia, while they were at lower risk of COPD compared to hospital patients. On the other hand, patients in LTCCFs were at lower risk of liver diseases and concurrent use of sedative antidepressants. Patients in LTCCFs and in NHs were more likely to concurrent use antipsychotics compared to hospitalized patients.

DISCUSSION

The use of benzodiazepines

Our study highlighted that more than 60% of BDZs in older patients were prescribed to women and subjects with 80 years and more, consistent with international literature [1,8,11,6,13,9,23,16]. Old women were at 1.5 higher risk of being prescribed BDZs, as observed in a previous Swedish study [16]. Among patients not prescribed BDZs, however, the majority were also women and very elderly, indicating a frequently observed drugs' dispensation pattern [24,20,21]. Moreover, BDZ users were more exposed to polypharmacy than non-BDZ users. This can be related with a poorer health status among BDZ users [25], which can be associated with a higher use of medical care [12] and consequent increase in drugs' prescription.

One of main findings of the present study was that BDZs were four times more likely to be prescribed in outpatient healthcare settings compared to hospital. Almost half of patients in NHs, for instance, had been prescribed at least one BDZ, which was much greater than a study from United States, where BDZs were dispensed to only 1.7% of NH residents [26]. Conversely, our findings of BDZ prescription to 13% of inpatients is somewhat in line with other hospital studies, which indicated that new BDZs were dispensed in 2.2% to 24% of admissions [8]. Most of patients in all settings were dispensed short-intermediate acting BDZs, consistent with other studies [10,6,13,19]. However, we observed that almost 80% of patients in NHs were long-term BDZ users, compared to more than half lower proportions in LTCCFs and hospitals. Although long-term use of BDZ is very common [8], particularly in the elderly [10,18,4,5], whether this was so prominent in NHs might be related to different factors. In FVG, most of prescriptions at the primary care level, including NHs, are filled by GPs [27], and GPs had been previously observed to dispense BDZ for long time to older patients [19]. On the other hand, BDZs are usually prescribed to inpatients by specialized doctors, who are less prone to dispensing these drugs [28]. Similarly, specialized doctors are also the main prescribers at LTCCFs. Other reasons for the greatest long-term use of BDZs in NHs might be related to higher competitive demands on doctor time to other medical needs, or minor access to other therapeutic alternatives [6].

To date, a strength of our study is that provided a comparison on BDZs prescriptions' patterns in three different settings, which is crucial for guiding policies aimed to enhance safer drug use and patients' safety [20]. In contrast, research on BDZ is usually based on a specific healthcare setting [7]. Our findings indicate that interventions should be addressed primarily to NHs and secondly to LTCCFs and hospital, according to the extent of BDZ prescriptions. Several studies had explored effective interventions to reduce the use

TABLE 3. Comparison between non use of BDZ and use of BDZ according to patient's characteristics, comorbidities and concurrent drug treatment which can increase the risk of adverse drug reactions (ADRs) at univariate and multivariate logistic regression. . Significant Odds ratio and 95% Confidence Intervals were highlighted in bold.

	No BDZ a (n = 1785)	BDZ (n = 671)	Univariate			Multivariate		
Variables	**N (%)**	**N (%)**	**P**	**OR**	**95% CI**	**P**	**OR**	**95% CI**
Gender [b]								
Males	769 (43.1)	202 (30.1)		1.0	-		1.0	-
Females	1005 (56.3)	468 (69.7)	**0.000**	**1.773**	**1.466-2.143**	**0.000**	**1.504**	**1.213-1.866**
Age (years)								
Elderly (65-79)	611 (34.2)	240 (35.8)		1.0	-		-	-
Very elderly (≥80)	1174 (65.8)	431 (64.2)	0.475	0.935	0.776-1.125		-	-
N of prescribed drugs								
1-4	441 (24.7%)	67 (10.0%)		1.0	-		1.0	-
5-9	1070 (59.9%)	371 (55.3%)	**0.000**	**2.282**	**1.720-3.028**	**0.000**	**2.059**	**1.530-2.771**
≥10	274 (15.4%)	233 (34.%)	**0.000**	**5.597**	**4.102-7.637**	**0.000**	**4.535**	**3.236-6.356**
Setting								
Hospital	1142 (64.0)	178 (26.5)		1.0	-		1.0	-
LTCCF	260 (14.6)	179 (26.7)	**0.000**	**4.417**	**3.449-5.656**	**0.000**	**4.072**	**3.142-5.278**
NH	383 (21.4)	314 (46.8)	**0.000**	**5.260**	**4.233-6.536**	**0.000**	**4.498**	**3.531-5.729**
Comorbidities								
COPD	341 (19.1)	111 (16.5)	0.145	0.839	0.663-1.062		-	-
Asthma	14 (0.8)	4 (0.6)	0.627	0.759	0.249-2.313		-	-
Myasthenia gravis	2 (0.1)	1 (0.1)	0.816	1.331	0.120-14.698		-	-
Liver disease	161 (9.0)	70 (10.4)	0.286	1.175	0.874-1.579		-	-
Dementia	411 (23.0)	163 (24.3)	0.509	1.073	0.871-1.321		-	-
Osteoporosis	387 (21.7)	192 (28.6)	**0.000**	**1.448**	**1.183-1.772**	**0.928**	**1.011**	**0.804-1.270**
Parkinson disease	91 (5.1)	66 (9.8)	**0.000**	**2.031**	**1.460-2.825**	**0.000**	**1.938**	**1.339-2.806**
Rheumatoid arthritis	76 (4.3)	20 (3.0)	0.148	0.691	0.419-1.140		-	-
Concurrent medications								
Opioid analgesics	214 (12.0)	144 (21.5)	**0.000**	**2.006**	**1.589-2.533**	**0.112**	**1.239**	**0.951-1.612**
Barbiturates	37 (2.1)	16 (2.4)	0.636	1.154	0.638-2.089		-	-
Antipsychotics	432 (24.2)	218 (32.5)	**0.000**	**1.507**	**1.241-1.831**	**0.037**	**0.786**	**0.627-0.986**
CA antihypertensives	22 (1.2)	7 (1.0)	0.699	0.845	0.359-1.987		-	-
Idrossiazine	6 (0.3)	3 (0.4)	0.686	1.332	0.332-5.339		-	-
Sedative AD [c]	107 (6.0)	69 (10.3)	**0.000**	**1.797**	**1.310-2.467**	**0.621**	**1.092**	**0.769-1.551**
CA Muscle relaxants	10 (0.6)	10 (1.5)	**0.028**	**2.685**	**1.113-6.481**	**0.232**	**1.795**	**0.687-4.691**

N numbers; BDZ benzodiazepine; OR odds ratio; CI confidence interval; COPD Chronic obstructive pulmonary disease; CA central acting; AD antidepressants

[a] *Individuals who were not prescribed BDZ were used as reference category (OR =1)*

[b] *Gender is missing in 12 patients*

[c] *Agomelatine, amitriptyline, doxepin, mianserin, mirtazapine, trimipramine, trazodone*

of BDZs in older people [29,7,30]. They regarded reduction of BDZs using combined patient-centered care [7], clinical education and medication review [29], as well as minimal strategies, such as clinical reassessment of benefits and harms [30]. Recently, FVG healthcare system adopted a deprescribing algorithm for BDZ and hypnotics, based on Pottie and al. guidelines [31].

TABLE 4. Distribution of benzodiazepines (BDZ) prescriptions in different settings. Percentages of BDZ used for more than four weeks were calculated on the number of individuals prescribed with each type of BDZ.

	H (n =178)[a]		LTCCF (n =179)[a]		NH (n =314)[a]		
Benzodiazepines	**N (%)**	**% >4 w [b]**	**N (%)**	**% >4 w [b]**	**N (%)**	**% >4 w [b]**	**P**
Short-intermediate acting	**120 (67.4)**	**44.2**	**100 (55.9)**	**23.0**	**211 (67.2)**	**75.4**	**0.24**
alprazolam	25 (14.0)	44.0	17 (9.5)	5.9	21 (6.7)	71.4	0.027
bromazepam	21 (11.8)	23.8	26 (14.5)	30.8	35 (11.1)	77.1	0.53
lorazepam	38 (21.3)	55.3	28 (15.6)	25.0	85 (27.1)	78.8	0.01
lormetazepam	10 (5.6)	60.0	18 (10.1)	33.3	39 (12.4)	64.1	0.05
triazolam	24 (13.5)	41.7	12 (6.7)	16.7	42 (13.4)	80.9	0.06
other [c]	5 (2.8)	40.0	3 (1.7)	-	7 (2.2)	85.7	0.77
Long acting	**50 (28.1)**	**30.0**	**65 (36.3)**	**26.1**	**101 (32.2)**	**85.1**	**n.s.**
diazepam	9 (5.1)	22.2	8 (4.5)	25.0	18 (5.7)	77.8	0.25
chlordesmethyldiazepam	34 (19.1)	32.3	54 (30.2)	27.8	71 (22.6)	88.7	0.04
other [d]	7 (3.9)	28.6	4 (2.2)	-	23 (7.3)	78.3	0.03
Hypnotics (zolpidem)	**13 (7.3)**	**7.7**	**22 (12.3)**	**4.5**	**22 (7.0)**	**40.9**	**0.10**

H hospital; LTCCF long-term chronic care facilities; NH nursing home; N numbers; w weeks; on d. on demand;
P-value was obtained by chi-square test and was used to assess whether proportions of BDZ type were differently distributed in the three settings
[a] Numbers are lower than the sum of patients in different benzodiazepine and hypnotic drugs, due to co-prescriptions
[b] Percentages were calculated on the number of individuals prescribed with each type of BDZ
[c] Brotizolam, etizolam, estazolam, oxazepam
[d] Clonazepam, flurazepam, prazepam, ketazolam

The extent of factors which can induce adverse drug reactions

Potential factors inducing ADRs were analysed using two parameters: first, we compare BDZ users and non-users with regard to these factors; second, we assess the extent of potential ADRs among BDZ users in different healthcare settings. This is a strength of the present study, although previous research had clearly identified the risk of developing ADRs under certain comorbidities and concurrent drug use [1,15,12-14].

In contrast with other studies [12,11], which demonstrated a higher degree of medical comorbidities among BDZ users, in our study BDZs were positively associated only to Parkinson disorder when compared to non-users. This might be related to the high association of anxiety disorders to Parkinson and the paucity of effective treatments [32], which may lead to the choice of BDZs, since they can be used also on demand [33]. Conversely, antipsychotics were negatively associated to BDZ use in the multivariate analysis. This can indicate a competitive treatment choice between antipsychotics and BDZs in the elderly [18], when taken into account several comorbidities and concurrent drug use. Nonetheless, proportions of comorbidities and concurrent medications at increased risk of ARDs among BDZ users were in general higher than those observed in other studies [1,9]. Our findings, however, are based on healthcare settings, while the other two studies [1,9] were population-based, with the consequence of a possible drop in comorbid disorders and concurrent medications. In any case, our study observed that one-quarter of BDZ users were patients with dementia, which was almost three times higher than previous finding from Israel [9]. Further, BDZ users in NHs were at almost three times increased risk of dementia compared to hospital. Since a recent study demonstrated a strong association between long-term exposure to BDZs and risk of Alzheimer disease [15], this seems of particular concern.

Moreover, it was noteworthy that antipsychotics, which could increase the risk of ADRs in BDZ users, were significantly associated to NH patients. This confirms the need of addressing interventions to discourage the use of BDZs and monitoring the potential onset of ADRs, primarily among patients in NHs.

Limitations

Several limitations should be acknowledged for the correct interpretation of our results. Firstly, the voluntary basis of the adherence to the study by NHs and LTCCFs may represent a bias. Secondly, only patients who were taking at least one drug during the two-weeks study's recruitment were included. This may have biased our results, since patients included had probably more severe health conditions. Nonetheless, the study was carried out not to analyse the prevalence of citizens that took medications but to identify the major concerns about drugs

TABLE 5. Multivariate logistic regression for comorbidities and concurrent drug treatment which can increase the risk of adverse drug reactions (ADRs) in benzodiazepine users, according to gender, age groups and settings. Mutually adjusted odds ratios (OR) and 95% confidence intervals (95% CI) are estimated by means of logistic regression analysis. Significant ORs are highlighted in bold.

	Gender [a]		Age [b]		Setting [c]			
	Female		Very elderly (≥80)		LTCCF		NH	
Variables	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Comorbidities								
COPD	0.80	0.52-1.29	**1.06**	**0.66-1.65**	**0.60**	**0.35-1.03**	**0.9**	**0.30-0.78**
Asthma	-	-	**0.83**	**0.08-8.41**	-	-	1.52	0.15-15.28
Myasthenia gravis	-	-	**-**	**-**	-	-	-	-
Liver disease	0.75	0.42-1.37	**0.36**	**0.20-0.65**	**0.45**	**0.21-0.98**	0.71	0.38-1.36
Dementia	**1.81**	**1.16-2.83**	**1.74**	**1.14-2.66**	1.15	0.64-2.03	**2.60**	**1.60-4.14**
Osteoporosis	**3.12**	**1.96-4.96**	**1.58**	**1.06-2.35**	1.62	0.99-2.67	1.35	0.86-2.12
Gait and balance disorders [d]	1.18	0.70-1.99	**0.24**	**0.14-0.40**	0.54	0.27-1.08	1.30	0.74-2.29
Concurrent medications								
Opioid analgesics	1.47	0.78-2.77	0.66	0.370-1.216	1.51	0.68-3.34	1.91	0.93-3.91
Barbiturates	0.84	0.29-2.39	**0.22**	**0.07-0.64**	0.30	0.03-2.89	3.39	0.93-12.33
Antipsychotics	0.79	0.52-1.11	**0.58**	**0.40-0.84**	**2.00**	**1.17-3.40**	**4.93**	**3.06-7.93**
CA antihypertensives	1.12	0.21-6.17	0.68	0.14-3.40	1.92	0.18-21.59	2.41	0.26-22.16
Idrossiazine	0.21	0.13-3.62	-	-	-	-	-	-
Sedative AD [e]	0.83	0.47-1.48	0.81	0.46-1.43	**0.34**	**0.14-0.80**	1.00	0.55-1.77
CA Muscle relaxants	0.34	0.07-1.71	0.40	0.07-1.93	0.22	0.02-1.90	-	-

N numbers; LTCCF long-term chronic care facilities; NH nursing home; OR odds ratio; CI confidence interval; COPD Chronic obstructive pulmonary disease; CA central acting; AD antidepressants

[a] *Males were used as reference category (OR =1)*

[b] *Elderly (65-79 years) was used as reference category (OR =1)*

[c] *Hospital was used as reference category (OR =1)*

[d] *Parkinson disease and Rheumatoid Arthritis*

[e] *Agomelatine, amitriptyline, doxepin, mianserin, mirtazapine, trimipramine, trazodone*

management. [21]. Thirdly, the territorial area where the study was performed was limited, with the consequence of a low number of patients in certain subgroups, which hindered more detailed analyzes and the generalizability of the conclusions. Fourthly, no information on the volume, the dosage and the number of prescriptions of BDZs were available. Fifthly the reason for prescribing BDZs was missing. However, indication is often not well documented in other research [6,9], and BDZs are often prescribed "off-label" [8], which can increase the lack of reliable data on indications. Moreover, diagnoses derived from both medical records and discharge letters which may have been differently filled. They were also clinical and not validated, as acknowledged in other register studies from the Region [34,35]. Sixthly, long-term use was assessed when BDZs were dispensed for more than four weeks, according to international recommendations [5]. However, we had no information on the exact length of each BDZ dispensation, albeit it is likely that most of long-term prescriptions were much longer than one month, particularly in NHs where people are resident and data about drugs therapy can be available for a long period of time. A recent study, in fact, suggested to define long-term BDZ use when BDZs are prescribed continuously for six months and more during one year, in order to obtain data closer to real-world use [5]. Finally, the extent of factors inducing ADRs in BDZ users is not complete and consequent risk estimation may had been conservative, as previously highlighted in other studies [1,13]. A possible underestimation of ADRs in BDZ users, for instance, would have happened in case of concurrent use of alcohol or illicit drugs [1,13].

CONCLUSIONS

The present study highlighted that BDZs were broadly used in older patients in different healthcare

settings in FVG, particularly among women and very elderly. Our findings are consistent with population-based studies [1,8,11,6,13,9,23,16], although international recommendations claim to avoid BDZ use among the elderly [17]. Moreover, we found that some comorbidities and concurrent medications, which can highly increase the risk of ARDs, were more likely among BDZ users, when comparing different settings. In certain conditions such as dementia, where BDZs are strongly contraindicated, this is a reason of concern[15,17]. Since no previous studies compared the use of BDZs among different healthcare settings, an original finding was the greatest degree of prescriptions among outpatients in NHs compared to hospital. This is of major interest to drive focused policies to enhance safer drug use and patients' safety [20]. Notwithstanding the limitations, our findings indicate that evidence-based interventions [29,7,30,31] should be addressed to discourage the use of BDZs and monitor the raise of ADRs. Future research would benefit from the monitoring of BDZ prescription trends using longitudinal data at the individual level in different settings.

Competing Interest Statement

none declared

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