



Inappropriate prescription of benzodiazepines in acutely hospitalized older patients

C. Franchi^{a,*}, R. Rossio^b, I. Ardoino^a, P.M. Mannucci^c,
A. Nobili^a, REPOSI collaborators¹

^aDepartment of Neuroscience, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano, Italy

^bDepartment of Pathophysiology and Transplantation, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy

^cScientific Direction, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

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Abstract

Benzodiazepines (BDZs) are widely prescribed in older people. The aims of the study are to assess the prevalence of inappropriate prescription of BZDs and the associated factors in acutely hospitalized older patients. Patients aged 65 years or more hospitalized from 2010 to 2017 in more than 100 Italian internal medicine and geriatric wards in the frame of the REPOSI register were included if prescribed with BDZs at hospital admission or discharge. Appropriateness of prescription was assessed according to the 2015 Beers criteria and their modified French and German versions. Among 4681 patients discharged from hospital, 15% ($N=710$) were discharged with BDZs, and 62% of them ($N=441$, 95% CI: 58.5%-65.6%) were inappropriately prescribed, being prescribed with BDZ to be always avoided in the elderly (45%), at higher doses than recommended (31%) or with no appropriate clinical conditions (19%). From admission to discharge the prevalence of inappropriate BDZ prescription decreased by 4%, but 62% of patients inappropriately prescribed at admission were still inappropriately prescribed at discharge. Among the 179 patients first prescribed at the time of discharge, half were inappropriately prescribed. Being female (OR 1.32, 95%CI 0.95-1.85), enrolled in REPOSI during the years 2016 and 2017 (OR 1.94, 95%CI 1.10-3.39; OR 1.57, 95%CI 0.95-2.58) and living in nursing homes (OR 2.04, 95%CI 0.95-4.37) were associated with an increased risk to be inappropriately prescribed. This study

* Corresponding author at: Unit of Pharmacoepidemiological Research in Older People, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Via Mario Negri, 2, 20156 Milano, Italy.

E-mail address: carlotta.franchi@marionegri.it (C. Franchi).

¹REPOSI collaborators are listed in the online appendix.

shows a high prevalence of inappropriate use of BDZ in acutely hospitalized older patients both at hospital admission and discharge.

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1. Introduction

Benzodiazepines (BDZs) and the nonbenzodiazepine z-hypnotics (i.e. zolpidem, zopiclone, eszopiclone and zaleplon) are widely prescribed for the management of insomnia and anxiety in older people, with a prevalence ranging from 13 to 69% in hospitalized older patients (Fond et al., 2016; Pek et al., 2017) and from 8 to 38% in those community-dwelling (Maust et al., 2017; Jackson et al., 2014; Mell et al., 2017; Johnson et al., 2016; Hwang et al., 2017). Despite advice against using BDZs for anxiety and insomnia in the elderly (American Geriatrics Society 2012), their use is still high and frequently inappropriate in this population, with harms outweighing benefits (Pek et al., 2017). The major side effects include cognitive impairment, abuse and dependence, delirium, falls, respiratory failure and paradoxical reactions, such as agitation, sleep disturbance and anxiety (Airagnes et al., 2016). In general, the inappropriateness of drug prescription is an issue of major concern for its consequences on patients' health and cost of care (Moriarty et al., 2019). Inappropriate drug prescription is even more critical in older people, who are often frail, affected by multiple diseases, exposed to polypharmacy and thus at increased risk of potential drug-drug interactions and adverse events (AEs) (Franchi et al., 2016; Franchi et al., 2017; Mannucci et al., 2014; Marcucci et al., 2017). Appropriateness of medications in people aged 65 years or older can be assessed by measuring explicit (criterion-based) or implicit (judgement-based) criteria, developed in the United States by Beers and colleagues since 1991 and updated in recent versions (American Geriatrics Society 2015). These criteria indicate the drugs to be always avoided in the elderly and those to be avoided in particular clinical conditions (American Geriatrics Society 2015). In the last decades, attempts to adapt the Beers' criteria have been made in Italy, France and Germany, in order to take into account the differences in drugs marketed in Europe compared to those in Northern America (Holt et al., 2010; Laroche et al., 2007; Maio et al., 2006). To our knowledge, recent data on the inappropriate use of BZDs in older people are scanty, especially in the setting of internal medicine and geriatric hospital wards. With this background and gaps of knowledge, the aims of this study were to assess (1) the prevalence of use and inappropriate prescription of BZDs (including nonbenzodiazepine z-hypnotics) and (2) the factors associated to their inappropriate prescription, in a large cohort of older patients hospitalized in more than 100 Italian internal medicine and geriatric wards from 2010 to 2017.

2. Experimental procedures

2.2. Data collection and setting

Data for the present study were obtained from the register REgistro POliterate - Società Italiana Medicina Interna (REPOSI), an ongo-

ing collaboration between the Italian Society of Internal Medicine (SIMI), IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico and the Istituto di Ricerche Farmacologiche Mario Negri IRCCS. The REPOSI is a multicenter and prospective register that started in 2008 in order to collect clinical and therapeutic information on patients aged 65 or older acutely admitted to more than 100 internal medicine and geriatric wards in Italy during four index weeks during each season. Data collection were continued in 2010, 2012, 2014 and then yearly since 2016. More details are available elsewhere (Franchi et al., 2016; Franchi et al., 2017; Mannucci et al., 2014; Marcucci et al., 2017). The data set included socio-demographic factors, performance in activities of daily living (Mahoney and Barthel, 1965), the patterns of co-morbidities and their severity according to the Cumulative Illness Rating Scale (CIRS) (Miller and Towers, 1991), as well as the drugs prescribed at hospital admission and at discharge. Participation was voluntary and all patients provided signed informed consent. REPOSI was approved by the Ethics Committee of the IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico and then by the local committees of the participating centers. The study was conducted according to Good Clinical Practice and the Declaration of Helsinki. For the purposes of this analysis, we included all patients enrolled in REPOSI from 2010 to 2017 and analysed all those patients prescribed with at least one BDZ, including the nonbenzodiazepine z-hypnotic drugs (Anatomical Therapeutic Chemical classification system (ATC) codes: N05BA, N05CD, N05CF, N03AE01).

2.3. Criteria for inappropriate/appropriate prescription

Prescription appropriateness was assessed according to the American Geriatrics Society Beers Criteria (version 2015) and to the European criteria developed in France and in Germany, which specifically considered the drugs available in these countries with respect to those in the United States of America (American Geriatrics Society 2015; Holt et al., 2010; Laroche et al., 2007). Table 1 shows the criteria used for assessing the inappropriate/appropriate prescription of BDZs, both at hospital discharge and admission. For the purpose of this study, we divided BDZs in groups and considered them inappropriately prescribed because (1) they should be always avoided in older people, (2) prescribed at the higher doses than recommended, (3) prescribed without any specific and appropriate clinical conditions (i.e. anxiety, epilepsy, ethanol withdrawal), (4) co-prescribed with another BZD (ATC: N05BA and N05CD), and (5) co-prescribed with at least other two additional drugs active on the central nervous system (CNS) (i.e. antipsychotics—ATC: N05A; benzodiazepines and benzodiazepine analogs—ATC: N05B and N05C, excluding N05BA and N05CD; tricyclic antidepressants—ATC: N06AA; selective serotonin reuptake inhibitors—SSRIs, ATC: N06AB; and opioids—ATC: N02A). In the case of molecules available only in the Italian market but not included in the medication list of the Beers criteria or in those of the French and German criteria, the drug was specifically evaluated by a pharmacologist and a physician. In general, if some of the considered drugs were not listed in these criteria, we thought that BDZ of intermediate or long half-lives should be always avoided for the treatment of insomnia, agitation or delirium in the elderly, so that we considered them inappropriately prescribed (Allegri et al., 2017). Nevertheless, whenever a diagnosis of anxiety was present, the BDZ prescription was considered appropriate. When a patient was labeled as not appropriately prescribed for one

Table 1 Criteria of inappropriateness/appropriateness of benzodiazepine and nonbenzodiazepine hypnotic prescription.

(1) Always inappropriate		(2) Inappropriate at the following dosage		(3) Inappropriate if the following conditions are not present: generalized anxiety disorder (ICD-9: 300.02; 309.28), epilepsy (ICD-9: 345), ethanol withdrawal (ICD-9 291)		(4) Duplications*	(5) Co-prescription with at least other two additional central nervous system-active drugs**	(6) Always appropriate	
Sedative agent	ATC	Sedative agent	ATC	Sedative agent	ATC			Sedative agent	ATC
Alprazolam	N05BA12	Lorazepam (>2 mg/day)	N05BA06-N05BA56	Clordiazepossido	N05BA02			Ketazolam	N05BA10
Estazolam	N05CD04	Oxazepam (>60 mg/day)	N05BA04	Clonazepam	N03AE01			Clotiazepam	N05BA21
Temazepam	N05CD07	Lormetazepam (>0.5 mg/day)	N05CD06	Diazepam	N05BA01			Doxefazepam	N05CD12
Triazolam	N05CD05	Brotizolam (>0.125 mg/day)	N05CD09	Flurazepam	N05CD01			Midazolam	N05CD08
Potassium clorazepate	N05BA05	Zolpidem (>5 mg/day)	N05CF02	Quazepam	N05CD10				
Prazepam	N05BA11	Zaleplon (>5 mg/day)	N05CF0	Delorazepam	N05B49				
Clobazam	N05BA09	Zopiclone (>3.75 mg/day)	N05CF01	Pinazepam	N05BA14				
Nitrazepam	N05CD02			Etizolam	N05BA19				
Flunitrazepam	N05CD03			Bromazepam	N05BA08				
Medazepam	N05BA03								

Legend: ATC=Anatomical Therapeutic Chemical Classification System, ICD-9=International Classification of Diseases, 9th revision, CNS= central nervous system.

* Duplication is a co-prescription of two different benzodiazepines/hypnotics (ATC: N05BA and N05CD).

** Antipsychotics (ATC: N05A), benzodiazepines and benzodiazepine analogs (ATC: N05B and N05C, excluding N05BA and N05CD), tricyclic antidepressants (ATC: N06AA), selective serotonin reuptake inhibitors (SSRIs) (ATC: N06AB) and opioids (ATC: N02A).

criterion, assessment on prescription appropriateness was stopped and the actual patient was included in the correspondingly inappropriately prescribed group. Ultimately, appropriately prescribed patients were all those who had overcome the 5 inappropriateness criteria defined above, plus those prescribed with ketazolam, clonazepam, doxepin, midazolam, because of their short half-lives (group 6 in Table 1). Patients with missing data on drug doses or indication of use were considered not assessable. Furthermore, for the first 4 mostly prescribed BZDs we also assessed the three most frequent combinations with other drugs, in order to evaluate whether or not potential drug-drug interactions occurred. Diagnoses were coded according to the International Classification of Diseases, 9th Revision (ICD-9) system.

2.4. Statistical analysis

Data were summarized as frequencies (%), means and standard deviations or medians and interquartile ranges as appropriate. Confidence intervals for proportions were calculated according to the Wilson score formula. Univariate and multivariable logistic regression models were used to determine, among BZD users, factors associated with inappropriate prescription at hospital discharge. Risk factors considered were sex, age, year of the REPOSI, geographical area and living arrangement.

3. Results

Among 7005 patients enrolled in the REPOSI Register, 5442 were hospitalized from 2010 to 2017 in Italian internal medicine and geriatric wards, among them 4681 being discharged alive.

3.1. Hospital discharge

At hospital discharge, 710 (15.2%, 95% CI: 14.2%–16.2%) patients were prescribed BZDs, 34 taking two different drugs. Table 2 reports the main patients' characteristics at hospital discharge according to being BZD users. These are mostly females (61.7%), aged 75 years or more (46.3%), living in Northern Italy (68.7%), living with family members (57.2%), taking several concomitant drugs (76.1%), affected by COPD (20.8%), chronic kidney disease (18.5%), delirium (18.3%), anxiety disorders (16.6%) and previous falls (14.5%). The number of BZD users did not show any trend over time, their use being almost constant and varying from 14.5% in 2010 to 16.5% in 2017. The most prescribed sedative/hypnotic drugs was lorazepam ($N=244$, 32.8%), followed by alprazolam ($N=132$, 17.7%), bromazepam ($N=78$, 10.5%) and zolpidem ($N=69$, 9.3%). Table 3 shows the profiles of inappropriateness/appropriateness of prescription in BZD users. All in all, 441 (62.1%, 95% CI: 58.5%–65.6%) patients were inappropriately prescribed, mainly because prescribed with sedatives/hypnotics that are always inappropriate in the elderly ($N=201$; 45.6%). Then those prescribed at the high doses ($N=136$; 30.8%) and those prescribed with no proper indication ($N=84$; 19.0%). In addition, 35 patients received duplications of BZDs and 35 patients a combination of BZD with at least other two CNS drugs. No potential drug-drug interactions were found between lorazepam, alprazolam, bromazepam

or zolpidem and the first three drugs co-prescribed (i.e. furosemide, acetylsalicylic acid, bisoprolol).

3.2. Factors associated with prescription inappropriateness

In the adjusted logistic regression model including sex, age, year of the REPOSI, geographical area, and living arrangement, being enrolled in the REPOSI 2016 (OR 1.94, 95%CI 1.10-3.39) and 2017 (OR 1.57, 95%CI 0.95-2.58) and living in nursing home (OR 2.04, 95%CI 0.95-4.37) were slightly associated with BZD inappropriateness prescription (Table 4). On the contrary, being older (OR 0.97, 95%CI 0.95-0.99) was inversely associated with prescription inappropriateness (Table 4).

3.3. Hospital admission

At hospital admission, 668 patients (14.3%, 95% CI: 13.2%–15.3%) were prescribed with BZDs. Lorazepam ($N=212$, 29.9%) was the most frequently prescribed, followed by alprazolam ($N=141$, 19.9%) and bromazepam ($N=77$, 11.1%). Overall, 443 (66.3%, 95% CI: 62.6%–69.8%) patients were inappropriately prescribed (Table 3). At hospital discharge the pattern of inappropriateness was similar: the majority of patients ($N=209$, 47.2%) were inappropriately prescribed with drugs that should be always avoided in the elderly, followed by 29.3% ($N=130$) prescribed at the wrong doses and by 19.6% ($N=87$) prescribed with no proper indication. Finally, 43 patients were on duplications of BZDs and 28 patients were on combination of BZDs with at least other two CNS drugs.

3.4. Changes from hospital admission to discharge

Among 668 patients prescribed BZDs at hospital admission, 137 (20.5%) stopped them at discharge, while among 3971 patients not prescribed at admission, 179 patients (4.5%, 95%CI: 3.9%–5.2%) were first prescribed at discharge. Of the latter, 91 (50.8%) were inappropriately prescribed (37 with drugs always to avoid, 26 at high dosage, 21 with no proper indication, 3 had duplications, 4 had CNS drug combinations). Among 531 patients prescribed at both times admission and discharge, 329 (62.0%, 95%CI: 57.8%–66.0%) continued to be inappropriately prescribed from admission to discharge, only 149 (28.0%, 95% CI: 24.4%–32.0%) continued to be appropriately prescribed.

4. Discussion

Among older patients acutely hospitalized in internal medicine and geriatric wards from 2010 to 2017, 15% were discharged with BZDs or related z-hypnotic drugs. Overtime, there was no improvement in the prescription, but rather an increase risk to be inappropriately prescribed in the last two register years (REPOSI 2016: OR 1.94, 95%CI 1.10-3.39;

Table 2 Demographic and clinical characteristics of 710 patients prescribed benzodiazepines at hospital discharge.

Variables	Benzodiazepine users N (%)	Missing N
<i>Overall</i>	710	
<i>Sex</i>		
Male	272 (38.3)	
Female	438 (61.7)	
<i>Age (years) - mean (SD)</i>	79.4 (7.3)	
65-74	196 (27.6)	
75-84	329 (46.3)	
≥85	185 (26.1)	
<i>Study years</i>		
2010	171 (24.1)	
2012	179 (25.2)	
2014	135 (19.0)	
2016	96 (13.5)	
2017	129 (18.7)	
<i>Geographical area</i>		
North	488 (68.7)	
Centre	117 (16.5)	
South	105 (14.8)	
<i>Living arrangement</i>		23
Alone	202 (29.4)	
With family members	393 (57.2)	
Nursing home	40 (5.8)	
Other	52 (7.6)	
<i>Body mass index - mean (SD)</i>	25.5 (4.6)	75
<i>Barthel index</i>		21
Total dependence	77 (11.2)	
Severe dependence	75 (10.9)	
Moderate dependence	99 (14.4)	
Mild dependence	118 (17.1)	
No dependence	320 (46.4)	
<i>Short blessed test</i>		42
Normal	249 (37.3)	
Possible cognitive impairment	38 (20.7)	
Moderate cognitive impairment	210 (31.4)	
Severe cognitive impairment	71 (10.6)	
<i>Drinking</i>		17
Never	366 (52.8)	
Ex drinker	35 (5.0)	
Drinker	121 (17.5)	
Social drinker	171 (24.7)	
Polypharmacy (≥ 5 drugs other than benzodiazepines)	539 (76.1)	
<i>Specific drugs classes</i>		
Antidepressants (tricyclic and SSRI)	139 (19.6)	
Antipsychotics	57 (8.0)	
Opioids	63 (8.9)	
Barbiturates	7 (1.0)	
<i>Diagnosis</i>		
Number - median (IQR)	4 (6 - 8)	
Chronic kidney disease	131 (18.5)	
Cirrhosis	12 (1.7)	
Epilepsy	11 (1.5)	
Depression	105 (14.8)	
Dementia	53 (7.5)	
Delirium	130 (18.3)	

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Table 2 (continued)

Variables	Benzodiazepine users N (%)	Missing N
Insomnia	39 (5.5)	
Generalized anxiety disorders	118 (16.6)	
COPD	148 (20.8)	
Falls/ fractures/osteoporosis/prosthesis	103 (14.5)	

Legend: COPD = chronic obstructive pulmonary disease; SD = standard deviation; IQR = interquartile range.
 ICD-9 codes for diagnosis: chronic kidney disease (585), cirrhosis (571.2, 571.5), epilepsy (345), depression (296.2-296.3, 300.4, 311), dementia (290, 294, 331), delirium (295-298), insomnia (327.0, 780.52), generalized anxiety disorders (300.0), BPCO (491.2), falls/ fractures/osteoporosis/prosthesis (V1588, V436, 800-829, 733).

Table 3 Benzodiazepine and hypnotic appropriateness of prescription at hospital discharge and admission.

	Hospital discharge		Hospital admission	
	Benzodiazepine/hypnotic users	N (%)	Benzodiazepine/hypnotic users	N (%)
<i>Not appropriate</i>		441 (62.1)		443 (66.3)
Always		200 (45.4)		209 (47.2)
Alprazolam	132		141	
Triazolam	57		55	
Prazepam	7		8	
Estazolam	3		4	
Clobazam	1		1	
At particular doses		137 (31.1)		130 (29.3)
Lorazepam	62		55	
Zolpidem	42		35	
Lormetazepam	22		26	
Brotizolam	9		10	
Zopiclone	2		4	
With no proper indication		83 (18.8)		87 (19.6)
Clonazepam	29		20	
Bromazepam	22		32	
Delorazepam	13		13	
Diazepam	14		11	
Flurazepam	4		7	
Etizolam	1		3	
Clotiazepam	-		1	
Duplicates	8	8 (1.8)	7	7 (1.6)
Co-prescription with ≥ 2 CNS drugs	13	13 (2.9)	10	10 (2.3)
<i>Appropriate</i>		260 (36.6)		213 (31.9)
Lorazepam	151		128	
Zolpidem	16		8	
Lormetazepam	1		3	
Brotizolam	1		2	
Oxazepam	5		5	
Clonazepam	10		7	
Bromazepam	46		37	
Delorazepam	14		11	
Diazepam	11		8	
Flurazepam	1		-	
Etizolam	3		3	
Ketazolam	1		1	
<i>Not assessable</i>	9	9 (1.3)	12	12 (1.8)

Legend: CNS= Central nervous system.

Table 4 Associated factors to inappropriate prescription or non prescription of benzodiazepines/hypnotics.

	Odds ratio	95% confidence interval	
Sex (female vs male)	1.32	0.95	1.85
Age (1 year)	0.97	0.95	0.99
2012 versus 2010	0.99	0.64	1.55
2014 versus 2010	1.12	0.69	1.81
2016 versus 2010	1.94	1.10	3.39
2017 versus 2010	1.57	0.95	2.58
Living with family versus alone	1.20	0.83	1.72
Living in nursing home versus alone	2.04	0.95	4.37
Living with a caregiver versus alone	1.53	0.79	2.96

REPOSI 2017: OR 1.57, 95%CI 0.95-2.58). At hospital discharge the majority of BDZ users (62%) were inappropriately prescribed, especially because prescribed with BZDs to be always avoided in the elderly (45%), but also because prescribed at high dosage (31%) or in particular clinical conditions (19%). From hospital admission to discharge there was only a slight decrease (4%) in the prevalence of inappropriate prescription, but more than half of the patients (62%) inappropriately prescribed at admission, were still inappropriately prescribed at discharge. Furthermore, among those patients first prescribed at hospital discharge, about half were inappropriately prescribed. BZD users were mostly females, who are also at increased risk to be inappropriately prescribed. Also living in nursing home was a risk factor to be inappropriately prescribed.

To our knowledge no studies have been yet conducted in internal medicine and geriatric wards assessing the prevalence of use and prescription appropriateness of BDZs in hospitalized older people, most of the available results reflecting outpatients or dealing with older psychiatric inpatients (Fond et al., 2016; Hwang et al., 2017; Windle et al., 2007; Lagnaoui et al., 2004). Compared with a recent study on the use of benzodiazepines in the older general population, the prevalence of BZD use in our study is lower (Hwang et al., 2017). On the contrary we are in line with the prevalence of use reported by other studies conducted in older outpatients in France and Australia (Windle et al., 2007; Lagnaoui et al., 2004). As shown by others in different settings (Fond et al., 2016; Pek et al., 2017; Hwang et al., 2017; Airagnes et al., 2016), we found a high rate (62%) of inappropriate prescription at hospital discharge. The use of BDZs that should be always avoided in the elderly was the main cause of inappropriateness, followed by BDZs that are prescribed at high doses and by those not prescribed in specific clinical conditions. Even if from hospital admission to discharge there is a slight improvement in the appropriateness of BDZ prescription, physicians seemed to fail to review this therapy in acutely hospitalized older patients, as shown by the fact that most of those inappropriately prescribed at admission remained inappropriately prescribed at discharge. Furthermore, among those newly prescribed at discharge, most were inappropriately prescribed, especially with BDZs to be always avoided, prescribed at high dosages or with no proper indication. In addition, it was surprising that there is still a proportion of patients with duplications of BDZs or combinations with other drugs active central nervous system-active, with a possi-

ble increased risk of falls and cognitive impairment. In this study we chose not to assess underprescription of BDZs, because their use in the elderly people is always discouraged, so that the use of alternative nonpharmacological therapies should be instead recommended.

As in our previous studies (Franchi et al., 2018; Ardoino et al., 2017), hospitalization failed once more to improve the quality of drug prescription in this at high risk and frail population. Indeed, all our results conducted in the internal medicine and geriatric wards suggest that many hospital physicians ignore suggestions and recommendations made by guidelines and drug labels. The prescription and use of long-acting BDZs is concerning in the elderly population and the Beers criteria strongly suggest avoiding them, except for some specific indications such as seizures disorders, ethanol withdrawal and severe generalized anxiety disorders (American Geriatrics Society 2012, American Geriatrics Society 2015). As recently as in 2012 Beers and colleagues suggested to avoid the use of BDZs in older people for the management of insomnia and agitation (American Geriatrics Society 2012). The French and German criteria herein adopted are a touch more flexible than Beers criteria on the evaluation of inappropriateness of these drugs and provide a cut-off of dosage for the appropriate use of specific BDZs and z-hypnotics in the elderly (American Geriatrics Society 2015; Holt et al., 2010; Laroche et al., 2007). Notwithstanding, we found that the prescription of BDZs at high dosages is the second cause of inappropriate prescription of these drugs. Negative consequences of the inappropriate use of BDZs are much more likely to occur in older people with a history of falls and with clinical conditions such as chronic kidney disease, COPD, delirium and dementia, that were indeed prevalent diseases in the cohort of patients enrolled in this study (American Geriatrics Society 2015; Vozoris and Stephenson, 2015; Markota et al., 2016). Living in nursing homes, being female, being younger and enrolled in the last two yearly runs of the REPOSI register were associated with a slight increased risk to be inappropriately prescribed. In agreement with other studies, patients who live in nursing home and old women have a higher prevalence of inappropriate prescription of BDZ (Airagnes et al., 2016; Piccoro et al., 2000), probably due to the fact that nursing home residents received on average more prescriptions than those community-dwelling (Piccoro et al., 2000) and that older women are more likely be widow and lonely (Canham, 2015). Even if REPOSI register has previously shown among the continuously participating centres a general improve-

ment over time on the issue of the reduction of the number of drugs in the hospitalized older people (Franchi et al., 2017), this was not true pertaining to drug prescription appropriateness. Indeed, in this study we found that in the last two years 2016-2017 of the register, the BZD users are more likely to be inappropriately prescribed.

4.1. Limitations and strengths

This study has some limitations. Firstly, in the frame of the REPOSI register there is no information on the duration of the therapy prescribed, making for us impossible to assess if BDZs were inappropriate because prescribed for long-term use. Furthermore, any information on the characteristics of the prescribing physicians was not recorded in the REPOSI database, thus making impossible to identify physician-related factors possibly associated with prescription inappropriateness. The main strength of the study is that the large number of internal medicine and geriatric wards throughout Italy participating to the REPOSI register provide a representative and unselected sample of older inpatients, thus reflecting the overall prescribing habits for these drugs in these wards in the country.

4.2. Conclusion

In conclusion, this study shows a high prevalence of inappropriate use of BDZs and related z-hypnotics in acutely hospitalized older people in internal medicine and geriatric wards assessed from 2010 to 2017. Paradoxically, even if there was a small decrease in the inappropriateness of BZD use from hospital admission to discharge, most patients inappropriately prescribed at admission are still inappropriate at discharge. Because the hospital setting should be an important opportunity to improve the quality of drug prescription for frail multimorbid and polytreated older patients, more educational efforts are needed to increase clinicians' knowledge on the appropriate use of BZDs, in order to decrease the risk of avoidable and harmful adverse events for older patients and unnecessary direct and indirect costs for healthcare systems.

CRedit authorship contribution statement

C. Franchi: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Writing - original draft. **R. Rossio:** Data curation. **I. Ardoino:** Formal analysis. **P.M. Mannucci:** Writing - review & editing. **A. Nobili:** Writing - review & editing.

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Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.euroneuro.2019.05.004](https://doi.org/10.1016/j.euroneuro.2019.05.004).

References

- Airagnes, G., Pelissolo, A., Lavallée, M., Flament, M., Limosin, F., 2016. Benzodiazepine misuse in the elderly: risk factors, consequences, and management. *Curr. Psychiatry Rep.* 18 (10), 89. doi:[10.1007/s11920-016-0727-9](https://doi.org/10.1007/s11920-016-0727-9), Review.
- Allegri, N., Rossi, F., Del Signore, F., Bertazzoni, P., Bellazzi, R., Sandrini, G., Vecchi, T., Liccione, D., Pascale, A., Govoni, S., 2017. Drug prescription appropriateness in the elderly: an Italian study. *Clin. Interv. Aging* 12, 325-333. doi:[10.2147/CIA.S109125](https://doi.org/10.2147/CIA.S109125).
- American Geriatrics Society 2012 Beers Criteria Update Expert Panel, 2012. American Geriatrics Society updated beers criteria for potentially inappropriate medication use in older adults. *J. Am. Geriatr. Soc.* 60 (4), 616-631. doi:[10.1111/j.1532-5415.2012.03923.x](https://doi.org/10.1111/j.1532-5415.2012.03923.x).
- American Geriatrics Society 2015 Beers Criteria Update Expert Panel, 2015. American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. *J. Am. Geriatr. Soc.* 63 (11), 2227-2246. doi:[10.1111/jgs.13702](https://doi.org/10.1111/jgs.13702).
- Ardoino, I., Rossio, R., Di Blanca, D., Nobili, A., Pasina, L., Mannucci, P.M., Peyvandi, F., Franchi, C.R.E.P.O.S.I. Investigators, 2017. Appropriateness of antiplatelet therapy for primary and secondary cardio- and cerebrovascular prevention in acutely hospitalized older people. *Br. J. Clin. Pharmacol.* 83 (11), 2528-2540. doi:[10.1111/bcp.13355](https://doi.org/10.1111/bcp.13355).
- Canham, S.L., 2015. What's loneliness got to do with it? Older women who use benzodiazepines. *Australas J. Ageing* 34 (1), E7-E12. doi:[10.1111/ajag.12133](https://doi.org/10.1111/ajag.12133).
- Fond, G., Fajula, C., Dassa, D., Brunel, L., Lançon, C., Boyer, L., 2016. Potentially inappropriate psychotropic prescription at discharge is associated with lower functioning in the elderly psychiatric inpatients. A cross-sectional study. *Psychopharmacology (Berl.)* 233 (13), 2549-2558. doi:[10.1007/s00213-016-4312-z](https://doi.org/10.1007/s00213-016-4312-z).
- Franchi, C., Antoniazzi, S., Proietti, M., Nobili, A., Mannucci, P.M., Collaborators, S.I.M.-A.F., 2018. Appropriateness of oral anticoagulant therapy prescription and its associated factors in hospitalized older people with atrial fibrillation. *Br. J. Clin. Pharmacol.* 84 (9), 2010-2019. doi:[10.1111/bcp.13631](https://doi.org/10.1111/bcp.13631).
- Franchi, C., Ardoino, I., Nobili, A., Pasina, L., Mannucci, P.M., Marengoni, A., Perticone, F., 2017. REPOSI investigators. Pattern of in-hospital changes in drug use in the older patient from 2010 to 2016. *Pharmacoepidemiol. Drug Saf.* 26 (12), 1534-1539.
- Franchi, C., Marcucci, M., Mannucci, P.M., Tettamanti, M., Pasina, L., Fortino, I., Bortolotti, A., Merlino, L., Nobili, A., 2016. Changes in clinical outcomes for community-dwelling older people exposed to incident chronic polypharmacy: a comparison between 2001 and 2009. *Pharmacoepidemiol. Drug Saf.* 25 (2), 204-211.
- Holt, S., Schmiedl, S., Thürmann, P.A., 2010. Potentially inappropriate medications in the elderly: the PRISCUS list. *Dtsch Arztebl. Int.* 107 (31-32), 543-551.
- Hwang, S.H., Han, S., Choi, H., Park, C., Kim, S.M., Kim, T.H., 2017.

- Trends in the prescription of benzodiazepines for the elderly in Korea. *BMC Psychiatry* 17 (1), 303.
- Jackson, G., Gerard, C., Minko, N., Parsotam, N., 2014. Variation in benzodiazepine and antipsychotic use in people aged 65 years and over in New Zealand. *N. Z. Med. J* 127 (1396), 67-78.
- Johnson C.F., Frei C., Downes N., McTaggart S.A., Akram G. Benzodiazepine and z-hypnotic prescribing for older people in primary care: a cross-sectional population-based study. *Br. J. Gen. Pract.* 2016;66(647):e410-5. doi: 10.3399/bjgp16X685213.
- Lagnaoui, R., Depont, F., Fourrier, A., Abouelfath, A., Bégau, B., Verdoux, H., Moore, N., 2004. Patterns and correlates of benzodiazepine use in the French general population. *Eur. J. Clin. Pharmacol.* 60 (7), 523-529.
- Laroche, M.L., Charmes, J.P., Merle, L., 2007. Potentially inappropriate medications in the elderly: a French consensus panel list. *Eur. J. Clin. Pharmacol.* 63, 725-731.
- Mahoney, F.I., Barthel, D.W., 1965. Functional evaluation: the BARTHEL index. *Md. State Med. J.* 14, 61-65.
- Maior, V., Yuen, E.J., Novielli, K., Smith, K.D., Louis, D.Z., 2006. Potentially inappropriate medication prescribing for elderly outpatients in Emilia Romagna, Italy A population-based cohort study. *Drugs Aging* 23 (11), 915-924.
- Mannucci, P.M., Nobili, A. REPOSI Investigators, 2014. Multimorbidity and polypharmacy in the elderly: lessons from REPOSI. *Intern. Emerg. Med.* 9 (7), 723-734. doi:10.1007/s11739-014-1124-1, Epub 2014 Aug 28. Review.
- Marcucci, M., Franchi, C., Nobili, A., Mannucci, P.M., Ardoino, I. REPOSI Investigators, 2017. Defining aging phenotypes and related outcomes: clues to recognize frailty in hospitalized older patients. *J. Gerontol. Biol. Sci. Med. Sci.* 72 (3), 395-402.
- Markota, M., Rummans, T.A., Bostwick, J.M., Lapid, M.I., 2016. Benzodiazepine use in older adults: dangers, management, and alternative therapies. *Mayo Clin. Proc.* 91 (11), 1632-1639. doi:10.1016/j.mayocp.2016.07.024.
- Maust, D.T., Blow, F.C., Wiechers, I.R., Kales, H.C., Marcus, S.C., 2017. National trends in antidepressant, benzodiazepine, and other sedative-hypnotic treatment of older adults in psychiatric and primary care. *J. Clin. Psychiatry* 78 (4), e363-e371. doi:10.4088/JCP.16m10713.
- Mell, T., Jacob, L., Fuhr, I., Dick, S., Rapp, M.A., Kostev, K., 2017. Patterns of benzodiazepine prescribing by neuropsychiatrists and general practitioners for elderly patients in Germany in 2014. *Int. J. Clin. Pharmacol. Ther.* 55 (6), 466-471. doi:10.5414/CP202904.
- Miller, M.D., Towers, A., 1991. *Manual of Guidelines for Scoring the Cumulative Illness Rating Scale for Geriatrics (CIRS-G)* // Pittsburgh, Pa: University of Pittsburgh.
- Moriarty, F., Cahir, C., Bennett, K., Fahey, T., 2019. Economic impact of potentially inappropriate prescribing and related adverse events in older people: a cost-utility analysis using Markov models. *BMJ Open* 9 (1), e021832.
- Pek, E.A., Remfry, A., Pendrith, C., Fan-Lun, C., Bhatia, R.S., Soong, S., 2017. High prevalence of inappropriate benzodiazepine and sedative hypnotic prescriptions among hospitalized older adults. *J. Hosp. Med.* 12 (5), 310-316. doi:10.12788/jhm.2739.
- Piccoro, L.T., Browning, S.R., Prince, T.S., Ranz, T.T., Scutchfield, F.D., 2000. A database analysis of potentially inappropriate drug use in an elderly medicare population. *Pharmacotherapy* 20 (2), 221-228.
- Vozoris, N.T., Stephenson, A.L., 2015. Benzodiazepine drug use and adverse respiratory outcomes among older adults with COPD. *Eur. Respir. J.* 45 (2), 566-567.
- Windle, A., Elliot, E., Duszynski, K., Moore, V., 2007. Benzodiazepine prescribing in elderly Australian general practice patients. *Aust. N. Z. J. Public Health* 31 (4), 379-381.