Ther Adv Psychopharmacol
2021, Vol. 11: 1–14
DOI: 10.1177/20451253211011874

Trends in benzodiazepine receptor agonists use and associated factors in the Belgian general older population: analysis of the Belgian Health Interview Survey data

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Abstract

Background: Benzodiazepine receptor agonists (BZRA), which include benzodiazepines and z-drugs, are commonly prescribed for insomnia and anxiety in older adults, and used often long term. Yet, the risk–benefit ratio of BZRA use in older adults may be unfavorable and many recommendations suggest avoidance or a maximal treatment duration of 4 weeks. The aim of this study was to describe trends of BZRA use in older adults and associated factors.

Methods: Using data from the Belgian Health Interview Survey in 2004 ($n = 3594$), 2008 ($n = 2917$), and 2013 ($n = 2048$), prevalence standardized for age, sex, and region were calculated to assess trends of BZRA use in people ⩾65 years. Analysis of associated factors to BZRA use was performed using a sub-sample of 2013 data for which variables assessing sleeping disorder and anxiety disorder were not missing ($n = 1286$). Variables from seven main topics were explored using multivariate logistic regression: socio-demographic factors, geriatric factors, comorbidities, subjective health and mental health indicators, social health indicators, medication use and healthcare services use.

Results: Overall, standardized prevalence of BZRA use decreased significantly between 2004 and 2013 [22% to 18%, prevalence difference (95% confidence interval, CI): −4.0% (−6.8; −1.3)]. Factors associated with BZRA use in multivariable analysis included female gender [adjusted odds ratio (aOR) (95%CI) : 1.62 (1.14; 2.29)], poor mental health [aOR (95%CI): 1.73 (1.13–2.63)] a fall in the past 12 months [aOR (95%CI): 1.52 (1.02; 2.26), reporting a sleeping disorder [aOR (95%CI): 1.92 (1.35; 2.72)], polypharmacy [aOR (95%CI): 2.51 (1.75; 3.60)], and trazodone use [aOR (95%CI): 4.05 (1.64; 10.21)].

Conclusion: Despite an encouraging decline observed from 2004 to 2013, BZRA use remained highly prevalent in Belgian older adults. Promotion of alternatives to BZRA in treatment of sleeping problems need to be continued. Among BZRA older users, women, the oldest (⩾85 years) and high-risk subgroups should be targeted in deprescribing interventions.

Keywords: associated factors, benzodiazepine, general population, older adults

Received: 28 October 2020; revised manuscript accepted: 1 April 2021.

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Introduction

Benzodiazepine receptor agonists (BZRA) are anxiolytics and sedative drugs commonly prescribed to treat insomnia and anxiety and comprised benzodiazepines and Z-drugs. In Europe and North-America, these medications are taken frequently by older adults, often long term.[1–3] However, the risk–benefit balance of BZRA use in older adults may be non-favorable. Indeed, BZRA use in older people is associated with an increased risk of falls, especially when combined with other drugs or when prescribed to people with dementia,[4] and hip fracture,[5] leading to a greater risk of institutionalization and mortality.[6,7] Long-term BZRA use is also associated with poorer cognitive performance,[8] tolerance, and dependence.[9] In contrast, the benefits of BZRA use are limited as sleep improvement fades after 4 weeks.[10]

Therefore guidelines recommend that BZRA should be avoided or stopped after 4 weeks in older adults,[11,12] although maintenance of BZRA treatment beyond 4 weeks may be appropriate in particular cases (e.g., severe generalized anxiety disorder or alcohol withdrawal), with assessment of the risk–benefit ratio.[9,11,13]

Since 2002, the Belgian Federal Public Service of Public Health has launched several awareness campaigns aimed at patients, pharmacists, and physicians, in order to decrease sedative/hypnotic consumption in Belgium.[14] Indeed, national reports, based on the Belgian Health Interview Survey (BHIS) data, have shown that sedative or hypnotic use was frequent in the Belgian population, especially among older adults.[15] However, these reports did not focus specifically on BZRA. If previous studies estimated the BZRA use prevalence to 52–53% of the Belgian nursing home residents,[16,17] to our knowledge, no study has yet assessed BZRA use prevalence in the general older population and its evolution over time.

In the literature, several factors were found to be associated with BZRA use in older people in different countries and included female gender, depression, polypharmacy, negative health perception, insomnia, mental health diseases, and chronic diseases.[18–20] In the Belgian nursing home setting, a recent study by Evrard *et al.* showed that a history of fall in the past 3 months, chronic obstructive pulmonary disease, polypharmacy, insomnia, and antidepressant use were factors associated with BZRA use.[17] On the contrary, dementia and trazodone use were factors negatively associated with BZRA use.[17] However, no study has been conducted to identify factors associated with BZRA use in older people from the general Belgian older population.

The aim of this study was to describe national trends of BZRA use in older adults ⩾65 years using the BHIS data for 2004, 2008, and 2013 and to assess associated factors in 2013 (last data available).

Methods

General design and population survey of the BHIS

Data from the BHIS were used.[21] BHIS is a repeated cross-sectional survey that collects sociodemographic and health data every 4 or 5 years among a representative sample of approximately 10,000 individuals in Belgium selected according to a stratified clustered multistage sampling, using the National Population Registry as sampling frame.[22] The precise design of the BHIS has been described elsewhere.[22] Briefly, the 10,000 interviews are distributed between the three regions (3500 for the Flemish Region, 3500 for the Walloon Region and 3000 for the Brussels Region).[22] The target number of interviews for each region is split into groups of 50 individuals.[22] Then, the number of groups is distributed between provinces (except for the Brussels Region where this administrative delimitation does not exist) according to their population size.[22] Within provinces, municipalities are selected following a procedure integrating probability proportional to size and systematic sampling.[22] Within municipalities, households are selected according to a systematic sampling.[22] For each household selected, a maximum of four individuals are invited to participate.[22] All Belgian residents can be selected, including individuals living in a nursing home.[22] There are no exclusion criteria of age or nationality. Selected individuals are contacted by mail with a letter explaining the survey. Participation is voluntary, in case of refusal, a matched substitute for the household is invited to participate until the planned number of interviews is reached.[22]

The data are gathered at the residency of the participant through a face-to-face interview and the auto-completion of a questionnaire for sensitive subjects.[22] In situations where participants are not able to answer (e.g., due to mental or functional limitations), a proxy is allowed to respond on their behalf, except for the auto-questionnaire.[23]

The sampling procedure was the same for each year considered for our analysis except that the older population above 75 years was oversampled in 2008 at the request of the Social Affairs Ministry and a specific recruitment of people 85 years or older was organized in 2004 and 2008.[22]

The Health Interview Survey has been approved by the Commission for the protection of private life and the Ethical Committee of Ghent University Hospital (advice EC UZG 2012/658), which guarantees that the survey procedures are in line with the privacy legislation. As our study is a secondary analysis of those data, no informed consent was required from the participants for this study but data transfer was approved by the Sectoral Committee of Social Security and Health.

Trends in BZRA use analysis

Selected population. For this part of our analysis, we used databases from years 2004, 2008, and 2013 and selected participants aged 65 years or more. That led to samples of 3594, 2917, and 2048 individuals, respectively.

BZRA use assessment. In the BHIS, information on medication use is collected during the interview by asking the participant to show the boxes of all medications used during the latest 24 h, with no distinction between their regular or "as needed" character. Medications are then converted in Anatomical Therapeutic Chemical (ATC) code up to the chemical substance level.[24]

For our analysis, BZRA drugs included ATC codes N05CD (sedative benzodiazepines), N05CF (sedative z-drugs), and N05BA (anxiolytic benzodiazepines). We analyzed trends in BZRA use up the molecule level and stratified our results according to age, gender, and number of BZRA taken. In addition, concomitant use of antidepressant (ATC code N06A) and opioids (ATC code N02A) with BZRA were assessed.

Statistical analysis. Trends in medication use over years were assessed using standardized prevalence.

The prevalence of medication use was standardized according to the age (by 5-year age groups), gender, and region by using the Belgian population on 1 January 2013 as the reference population in order to allow comparison across the years. Differences between years were assessed through the standardized prevalence differences (PD) and the standardized prevalence ratios (PR). This analysis was performed using R software 29 (version 3.5.1) and the package *dsr*, which computes directly standardized rates and their confidence interval.[25]

Factors associated with BZRA use analysis

Study population. This analysis was performed on a sub-sample of the 2013 data. In the subsample, we included only people with no missing data for the variables assessing sleeping disorder and anxiety disorders as they are the main indications for BZRA use. Consequently, on the 2048 observations available for the ⩾65 years older adults, we limited our analysis to 1286 individuals.

Main outcome. The dependent variable was BZRA use; this variable encompassed ATC codes N05CD, N05CF, and N05BA.

Explanatory variables. The BHIS collects many health data. A first selection was done on all variables available based on a previous literature review. The selected variables were grouped into seven main topics: socio-demographic factors, geriatric factors, comorbidities, subjective health and mental health indicators, social health, medication use, and healthcare services use.

Information on social-demographic and geriatric factors, on comorbidities and on healthcare services use were gathered during the interview. The interviewer asked the question and encoded the corresponding answer directly in the computer. Data on subjective, mental, and social health figured among data collected through the self-completed paper questionnaire.[23]

Socio-demographic factors included age, gender, region, civil status, educational level, country of birth, and household income.

Geriatric factors included urinary incontinence or problems controlling the bladder, falls, osteoporosis, hip fracture, Parkinson's disease, multimorbidity, low body mass index (BMI) and functional limitations. Multimorbidity was assessed through the variable "number of chronic conditions (on a total of 25 conditions)" and was defined as the presence of at least two chronic conditions. A BMI $<21\,kg/m^2$ was considered low. Functional limitations were assessed through three different variables: the severity of the handicap in mobility, severity of restrictions in performing daily activities, and severity of restrictions in performing household activities.

Comorbidities comprised low back disorder, osteoarthritis, diabetes, myocardial infarction, coronary heart disease (angina pectoris), and high blood pressure. In this category, we also included the level of pain assessed by the MOS 36-item Short-Form Health Survey (SF-36) bodily pain score.[26]

The EuroQol-5D-5L scale (EQ5D-5L) score was an indicator for people's subjective health.[27] The mean score of the General Health Questionnaire (GHQ-12) and the Vitality Index of the SF-36 score were used to assess mental health.[26,28] Finally, subscales of the Symptoms Checklist-90-Revised questionnaire (SCL-90-R) were used to assess depression, anxiety and sleeping problems.[29] For each of these subscales, the average scores were transformed in a binary variable with

a cut-off point set at two and more to classify the participant as reporting depression, anxiety, or sleeping problems.

Three indicators of social health were explored: the appreciation of social contacts (based on the question "How do you find your social contacts?"), the frequency of social contacts, and the perceived quality of social support. This latter indicator is based on the three questions of the Oslo Social Support Scale.[30]

Factors related to medication use encompassed opioid use (ATC code N02A), antipsychotic use (ATC code N05A), antidepressant use (ATC code N06A), selective serotonin reuptake inhibitors (SSRI) use (ATC code N06AB), tricyclic antidepressant or mirtazapine use (ATC code N06AA or N06AX11), trazodone use (ATC code N06AX05), and other antidepressant use (antidepressants except SSRI, trazodone and tricyclic antidepressant or mirtazapine). SSRI were analyzed separately as they are the recommended treatment for generalized anxiety disorders in older adults by Belgian guidelines.[31] Trazodone use was also categorized separately due to its frequent off-label use at a low dosage in the treatment of insomnia.[32] Tricyclic antidepressant use was analyzed together with mirtazapine use (because of very little mirtazapine use in our sample) as they also have sedative effects.[33] In addition, the total number of medications taken during the last 24 h, excluding BZRA, was taken to assess level of polypharmacy categorized in three levels: 0–4 medications, 5–9 medications (polypharmacy), and 10 or more medications (severe polypharmacy).

Finally, healthcare service use included having a regular GP, the number of contacts with the GP in the past 2 months, visit to a psychologist or a psychotherapist, inpatient hospitalization, and contact with emergency department in the past 12 months.

Statistical analysis. For all explanatory variables described in *Explanatory variables*, categorical variables were expressed as numbers and percentages and compared between groups using a Pearson's chi-squared test or a Fisher exact test according to the condition of validity of each test. The association between all the variables and BZRA use in 2013 was assessed using a logistic regression model. First, a univariate model was performed. All variables with a $p$value < 0.15 in the univariate model were included in a multivariable model as candidates for the final multivariable selection. Collinearity was assessed by computing the variance inflation factor (VIF). Variables obtaining a VIF above five were excluded from the model. A stepwise selection using the Akaike information criteria was the applied on the multivariable model containing all candidate variables to select the final multivariable model.

All statistical analyses were performed using R software (version 3.5.1) and the following packages: questionr, car, ResourceSelection, and ROCR.[34–38] A $p$value < 0.05 was considered statistically significant.

Results

Trends in standardized prevalence rates of BZRA use

Table 1 shows standardized prevalence of BZRA use in older adults in 2004, 2008, and 2013. Sample sizes and crude prevalence are presented in Supplemental Table S1. Between 2004 and 2013, the standardized prevalence of BZRA use in Belgian older adults decreased from 22% to 18% [PD (95% confidence interval, CI): −4.0% (−6.8%; −1.3%)]. Across the years considered, BZRA use was more prevalent in women (21.6% in 2013) and with increasing age (24.6% for the 85+ years age group in 2013) and limited mostly to the use of one BZRA. The use of a single BZRA decreased significantly from 2004 to 2013 [PD (95%CI): −3.8% (−6.5%; −1.2%)], whereas the use of two or more BZRA did not [PD (95%CI): −0.2% (−1.1%; 0.7%)].

Stratification by medication class showed that, over the years considered, benzodiazepines (N05BA and N05CD) prevalence were higher than z-drugs (N05CF) (Table 1). The prevalence of z-drugs users remained stable across the years around 3% of the older population while the prevalence of benzodiazepines users fell significantly from 19.5% in 2004 to 14.9% in 2013 [PD (95%CI): −4.6% (−7.1%; −2.0%)]. Further stratification showed that anxiolytic BZRA (N05BA) were more commonly used than sedative BZRA (N05CD and N05CF). A significant decrease was observed from 2004 to 2013 for anxiolytic BZRA [from 13.9% to 10.8%, PD (95%CI): −3.1% (−5.3%; −1.0%)] but not for sedative BZRA [from 9.6% to 8.5%, PD (95%CI): −1.1% (−3.0%; 0.8%)]. In 2004, 2008, and 2013, the

Table 1. Trends in benzodiazepines and z-drugs use in older adults (standardized prevalence[a]) in 2004, 2008, and 2013.

Variable	Standardized prevalence (%) (95% CI)			Comparison years 2004 and 2013		Comparison years 2008 and 2013	
	Year 2004 (*N* = 3594)	Year 2008 (*N* = 2917)	Year 2013 (*N* = 2048)	PR (95%CI) (%) 2013/2004	PD (95%CI) 2013–2004	PR (95%CI) (%) 2013/2008	PD (95%CI) 2013–2008
Total BZRA use	22.0 (20.2; 23.9)	19.6 (17.7; 21.6)	18.0 (15.9; 20.2)	0.82 (0.67; 0.96)	−4.0 (−6.8; −1.3)	0.92 (0.77; 1.07)	−1.6 (−4.4; 1.2)
Number of BZRA taken							
1	19.9 (18.2; 21.7)	17.3 (15.5; 19.2)	16.0 (14.1; 18.1)	0.81 (0.66; 0.96)	−3.8 (−6.5; −1.2)	0.93 (0.77; 1.09)	−1.2 (−3.9; 1.4)
⩾2	2.1 (1.6; 2.8)	2.3 (1.7; 3.0)	1.9 (1.3; 2.8)	0.91 (0.45; 1.36)	−0.2 (−1.1; 0.7)	0.84 (0.39; 1.30)	−0.4 (−1.3; 0.6)
Total BZRA use by age group							
65–74 years	17.1 (14.9; 19.6)	16.1 (13.4; 19.1)	14.7 (12.2; 16.7)	0.86 (0.63; 1.08)	−2.4 (−5.9; 1.1)	0.92 (0.66; 1.17)	−1.3 (−5.2; 2.5)
75–84 years	25.2 (21.7; 29.2)	21.5 (18.2; 25.1)	19.9 (16.5; 23.8)	0.79 (0.56; 1.02)	−5.3 (−10.4; −0.2)	0.93 (0.69; 1.17)	−1.5 (−6.5; 3.4)
85 or more years	31.2 (27.2; 35.5)	27.2 (24.0; 30.8)	24.6 (18.3; 32.4)	0.79 (0.49; 1.09)	−6.5 (−14.4; 1.3)	0.90 (0.60; 1.21)	−2.6 (−10.1; 5.0)
Total BZRA use by gender							
Female	26.5 (24.6–28.3)	25.0 (22.3; 28.0)	21.6 (18.6; 24.9)	0.82 (0.64; 0.99)	−4.9 (−8.9; −0.8)	0.86 (0.68; 1.04)	−3.5 (−7.7; 0.7)
Male	16.0 (13.7; 18.7)	12.2 (9.9; 14.9)	13.2 (10.7; 16.0)	0.82 (0.57; 1.07)	−2.9 (−6.5; 0.7)	1.08 (0.80; 1.36)	0.9 (−2.6; 4.5)
BZRA use by class							
Benzodiazepine use (N05BA or N05CD)	19.5 (17.8; 21.3)	17.1 (15.4; 19.0)	14.9 (13.1; 17.0)	0.77 (0.61; 0.92)	−4.6 (−7.1; −2.0)	0.87 (0.71; 1.04)	−2.2 (−4.8; 0.4)
Z-drugs use (N05CF)	3.0 (2.4; 3.8)	3.2 (2.4; 4.1)	3.2 (2.4; 4.2)	1.05 (0.70; 1.41)	0.2 (−1.0; 1.3)	1.00 (0.63; 1.37)	0.0 (−1.2; 1.2)
Sedative BZRA use (N05CD or N05CF)	9.6 (8.4; 10.9)	8.9 (7.6; 10.3)	8.5 (7.1; 10.1)	0.89 (0.68; 1.10)	−1.1 (−3.0; 0.8)	0.96 (0.74; 1.19)	−0.3 (−2.3; 1.6)
Anxiolytic BZRA use (N05BA)	13.9 (12.5 ; 15.4)	12.2 (10.7; 13.7)	10.8 (9.2; 12.5)	0.78 (0.59; 0.96)	−3.1 (−5.3; −1.0)	0.89 (0.69; 1.08)	−1.4 (−3.6; 0.8)

(Continued)

Table 1. (Continued)

Variable	Standardized prevalence (%) (95% CI)			Comparison years 2004 and 2013		Comparison years 2008 and 2013	
	Year 2004 (*N* = 3594)	Year 2008 (*N* = 2917)	Year 2013 (*N* = 2048)	PR (95%CI) (%) 2013/2004	PD (95%CI) 2013–2004	PR (95%CI) (%) 2013/2008	PD (95%CI) 2013–2008
BZRA use at molecule level							
Alprazolam	2.9 (2.3; 3.7)	3.1 (2.4; 4.0)	3.3 (2.5; 4.3)	1.13 (0.79; 1.47)	0.4 (–0.7; 1.5)	1.06 (0.71; 1.42)	0.2 (–0.9; 1.3)
Bromazepam	2.6 (2.0; 3.3)	2.8 (2.1; 3.6)	1.7 (1.1; 2.4)	0.64 (0.20; 1.09)	–0.9 (–1.8; 0.0)	0.60 (0.15; 1.06)	–1.1 (–2.1; –0.1)
Lorazepam	5.9 (5.0; 6.9)	5.2 (4.3; 6.3)	4.2 (3.3; 5.4)	0.72 (0.43; 1.00)	–1.7 (–3.1; –0.3)	0.81 (0.51; 1.11)	–1.0 (–2.4; 0.4)
Lormetazepam	4.6 (3.8; 5.5)	4.0 (3.2; 5.0)	4.3 (3.3; 5.5)	0.93 (0.62; 1.24)	–0.3 (–1.7; 1.1)	1.06 (0.73; 1.39)	0.2 (–1.1; 1.6)
Zolpidem	2.3 (1.7; 2.9)	2.4 (1.8; 3.3)	2.9 (2.1; 3.9)	1.28 (0.89; 1.68)	0.6 (–0.4; 1.7)	2.89 (0.77; 1.60)	0.5 (–0.7; 1.6)
Other	5.1 (4.3; 6.0)	4.2 (3.4; 5.1)	3.2 (2.4; 4.2)	0.63 (0.31; 0.94)	–1.9 (–3.1; –0.7)	0.76 (0.43; 1.10)	–1.0 (–2.2; 0.2)
Concomitant use of BZRA & other drugs							
Concomitant antidepressants use	5.7 (4.8; 6.6)	4.9 (4.0; 5.9)	4.8 (3.8; 6.0)	0.85 (0.57; 1.12)	–0.9 (–2.3; 0.5)	0.98 (0.69; 1.27)	–0.1 (–1.5; 1.3)
Concomitant opioid use	2.0 (1.4; 2.6)	2.5 (1.9; 3.2)	1.5 (1.0; 2.2)	0.77 (0.31; 1.23)	–0.5 (–1.2; 0.3)	0.61 (0.16; 1.05)	–1.0 (–1.8; –0.1)

[a]Standardized prevalence: prevalence standardized for age, gender and region.
CI, confidence interval; BZRA, benzodiazepine receptor agonists; PD, standardized prevalence difference; PR, standardized prevalence ratio.

most frequently used BZRA were alprazolam, bromazepam, lorazepam, lormetazepam, and zolpidem. All other BZRA, grouped together, were used in at most 5.1% (in 2004) of older adults. Stratification up to the molecule level showed that only lorazepam and the group of other BZRA declined significantly between 2004 and 2013.

In 2013, 4.8% of the older adults used concomitantly a BZRA and an antidepressant, which represented, if considering only the BZRA users, more than a quarter of them (Table 1). The concomitant use of a BZRA and an opioid concerned 1.5% of the older population in 2013, 10% of BZRA users. No significant reductions in this concomitant use with BZRA were observed between 2004 and 2013, or between 2008 and 2013. In parallel, antidepressants and opioids use showed no significant trend between 2004 and 2013 (data not shown). Antidepressant use remained stable around 10% of the older adults, and opioids use around 4%. Trazodone use increased slightly from 2% to 2.7%, but this increase was not significant.

Factors associated with BZRA use in 2013

As previously explained, a subsample of 2013 data (1286 observations out of the 2048 available) was used for this analysis. The main characteristics of included participants are described in Table 2. Slightly more than half of them were women (53.1%) and 56.9% were aged <75 years; 53% reported suffering from two or more chronic conditions (Table 2). Of the 1286 included participants, 217 (16.9%) were BZRA users (Table 2). Regarding potential indication for a BZRA use, nearly half of the BZRA users reported a sleeping disorder and 15.7% reported an anxiety disorder against 26.7% and 7.2%, respectively, of the non-users (Table 2).

Table 3 presents factors associated with BZRA use in older adults in 2013 in univariate and multivariable logistic regression. Detailed results of the univariate analysis can be found in Supplemental Table S2. In total, 46 potential associated variables were explored in the univariate analysis of which a large majority was significant and thus candidate for the multivariable analysis (all candidate variables for the multivariable analysis are listed in Supplemental Table S3).

Among all sociodemographic factors included, only female gender was significantly associated

Table 2. Main characteristics of the included participants for the analysis of associated factors.

Variable	Total (*N* = 1286)	BZRA use (*N* = 217)	No BZRA use (*N* = 1069)	*p* value[a]
	n (%)	*n* (%)	*n* (%)	
Age				0.004
65–74 years	732 (56.9)	102 (47.0)	630 (58.9)	
75–84 years	439 (34.1)	89 (41.0)	350 (32.7)	
85 years or more	115 (8.9)	26 (12.0)	89 (8.3)	
Gender				<0.001
Female	683 (53.1)	138 (63.6)	545 (51.0)	
Household income				<0.001
Quintile 1 (lowest quintile)	192 (14.9)	28 (12.9)	164 (15.3)	
Quintile 2	307 (23.9)	61 (28.1)	246 (23.0)	
Quintile 3	248 (19.3)	55 (25.3)	193 (18.1)	
Quintile 4	203 (15.8)	30 (13.8)	173 (16.2)	
Quintile 5 (highest quintile)	195 (15.2)	21 (9.7)	174 (16.3)	
Missing data	141 (11.0)	22 (10.1)	119 (11.1)	
Reporting an anxiety disorder				<0.001
Yes	111 (8.6)	34 (15.7)	77 (7.2)	
Reporting a sleeping disorder				<0.001
Yes	390 (30.3)	105 (48.4)	285 (26.7)	
Mean score of positive mental health				<0.001
⩾50	862 (67.0)	107 (49.3)	755 (70.6)	
<50	261 (19.6)	82 (36.9)	179 (16.1)	
Missing	163 (12.7)	28 (12.9)	135 (12.6)	
EQ-5D-5L score, median (P_{25}; P_{75})[b]	0.76 [0.64; 1.00]	0.66 [0.49; 0.76]	0.77 [0.68; 1.00]	<0.001
Mean number of chronic conditions[c]				<0.001
0–1	590 (45.9)	66 (30.4)	524 (49.0)	
2–5	614 (47.7)	125 (57.6)	489 (45.7)	
6 or more	77 (6.0)	25 (11.5)	52 (4.8)	
Fall in the past 12 months				<0.001
Yes	226 (17.6)	66 (30.4)	160 (15.0)	

(Continued)

Table 2. (Continued)

Variable	Total (*N* = 1286)	BZRA use (*N* = 217)	No BZRA use (*N* = 1069)	*p* value[a]
	n (%)	*n* (%)	*n* (%)	
Number of medications excluding BZRA				<0.001
0–4	942 (73.3)	109 (50.2)	833 (77.9)	
5–9	302 (23.5)	90 (41.5)	212 (19.8)	
10 or more	42 (3.3)	18 (4.6)	24 (2.2)	
Number of contacts with GP in the past 12 months				<0.001
0	449 (34.9)	36 (16.6)	413 (38.6)	
1	527 (41.0)	91 (41.9)	436 (40.8)	
⩾2	310 (24.1)	90 (41.5)	220 (18.7)	

[a]Comparison BZRA use *versus* No BZRA use: Pearson's chi-squared test, Fisher's exact test or Mann–Whitney test.
[b]52 missing values (*n* = 52/1286, 4%).
[c]5 missing values (*n* = 5/1286; 0.4%).
BZRA, benzodiazepine receptor agonists (ATC N05BA, N05CD, and N05CF); EQ-5D-5L, EuroQol 5 dimensions, 5 levels.

with BZRA use in older adults in the final multivariable model [adjusted odd ratio (aOR) (95%CI): 1.62 (1.14; 2.29), $p = 0.007$] (Table 3). Age was not retained in the final model and neither was multimorbidity nor any specific comorbidities. Regarding geriatric factors, a low BMI was significantly associated with BZRA intake [aOR (95% CI): 2.02 (1.13–3.50), $p = 0.015$] as well as reporting a fall in the past 12 months [aOR (95% CI): 1.52 (1.02; 2.26), $p = 0.037$]. Two mental health indicators were associated with BZRA use in older adults: a mean score of positive mental health (of the MOS SF-36 vitality scale) below 50 [aOR (95% CI): 1.73 (1.13; 2.63), $p = 0.011$] and reporting having a sleeping disorder [aOR (95% CI): 1.92 (1.35; 2.72), $p < 0.001$]. Reporting having anxiety or depressive disorder were not retained in the multivariate analysis. BZRA use was also associated with polypharmacy [aOR: 2.51 (1.75; 3.60), $p < 0.001$] and excessive polypharmacy [aOR: 2.82 (1.30; 6.04), $p = 0.008$], trazodone use and other antidepressant use (antidepressants excluding SSRIs, trazodone, and tricyclic antidepressants or mirtazapine). Of the variables assessing healthcare services use, only the number of contacts with the GP in the past 2 months was associated with BZRA use. The higher the number of visits, the higher the aOR.

Discussion

BZRA use remained highly prevalent in Belgian older adults even if it declined significantly from 22% in 2004 to 18% in 2013. This latter percentage was comparable with other European studies among older adults, with 20% reported in a Swiss study using data from 2017 and between 15% and 20% in a German study using data gathered from 2010 to 2014.[1,39] Consistent with other studies, BZRA use was found to be more prevalent with increasing age and in women.[1,39,40]

A similar trend toward a reduction in BZRA use by older adults was observed in other countries. In Canada, a population-based study among Ontarian residents aged 65 years or more showed that benzodiazepine use decreased from 23% to 15% between 1998 and 2013.[40] In Europe, a Danish study also reported a reduction of benzodiazepine use from 1998 to 2008 in the older groups of the population: from 26% to 19% for the 65–74 years, 36% to 26% for the 75–84 years and 42% to 30% for the 85 or more years.[41] This trend toward a decline in benzodiazepine use might indicate a change in prescribing culture supported by local policies in these countries.[40,41] Similarly, the reduction in BZRA use in Belgium might be the result of several national campaigns targeting physicians, pharmacists, and patients to

Table 3. Factors associated with benzodiazepine and z-drugs use in older adults in 2013 in univariate and multivariable logistic regression.[a]

Variables	Univariate model (*N* = 1286)		Multivariable model (*N* = 1225)	
	OR (95%CI)	*p* value	aOR (95%CI)	*p* value
Socio-demographic factors				
Female	1.68 (1.25; 2.28)	<0.001	1.62 (1.14; 2.29)	0.007
Geriatric factors				
Low BMI (<21 kg/m²)	1.64 (0.98; 2.64)	0.051	2.02 (1.13; 3.50)	0.015
Fall in the past 12 months	2.48 (1.77; 3.46)	<0.001	1.52 (1.02; 2.26)	0.037
(Mental) health indicators				
Reporting sleeping disorder[b]	2.58 (1.91; 3.48)	<0.001	1.92 (1.35; 2.72)	<0.001
Mean score of positive mental health (SF-36 Vitality Index)				
⩾50	1.00		1.00	
<50	3.23 (2.32; 4.50)	<0.001	1.73 (1.13; 2.63)	0.011
Missing data (*n* = 163)	1.46 (0.91; 2.28)	0.101	1.18 (0.68; 1.98)	0.552
EQ-5D-5L score[c]	0.05 (0.02; 0.09)	<0.001	0.35 (0.14; 0.84)	0.019
Medication use				
Number of medications BZRA excluded				
0–4	1.00		1.00	
5–9 (polypharmacy)	3.24 (2.36; 4.46)	<0.001	2.51 (1.75; 3.60)	<0.001
⩾10 (severe polypharmacy)	5.73 (2.98; 10.86)	<0.001	2.82 (1.30; 6.04)	0.008
Trazodone use	7.01 (3.28; 15.37)	<0.001	4.05 (1.64; 10.21)	0.003
Other antidepressants use (antidepressants except trazodone, SSRI and tricyclic antidepressant or mirtazapine)	4.80 (2.20; 10.42)	<0.001	2.91 (1.16; 7.39)	0.022
Healthcare services use				
Number of contacts with GP in the past 2 months				
0	1.00		1.00	
1	2.39 (1.60; 3.64)	<0.001	1.89 (1.22; 3.02)	0.004
⩾2	4.69 (3.11; 7.22)	<0.001	2.15 (1.33; 3.51)	0.002

[a]The complete univariate analysis is available in Supplemental Table S2. All variables that were candidate for the final model are listed in Supplemental Table S3.
[b]2 missing values (*n* = 2/1286; 0.2%).
[c]52 missing values (*n* = 52/1286; 4.0%).
CI, confidence interval; aOR, adjusted odds ratio; BMI, body mass index; BZRA, benzodiazepines receptors agonists (ATC N05BA, N05CD, and N05CF); EQ-5D-5L, EuroQol 5 dimensions, 5 levels; GP, general practitioner; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor.

promote a rational use of BZRA and encourage non-pharmacological alternatives to anxiety and sleep problems.[14] However, these campaigns did not target specifically older adults, whereas previous research has shown that the vast majority of older adults are unworried about BZRA long-term side effects and unaware of the potential harmful consequences.[42] Greater reduction in BZRA use might be achieved with awareness campaigns targeted to older adults.

If encouraging, the decline in BZRA use in Belgium was not homogenous. Indeed, while benzodiazepine use declined, z-drugs use remained stable across the considered years. This was also observed in Denmark and Canada, where z-drugs use even rose concurrently to benzodiazepine use reduction.[41,43] Previous literature has shown that doctors perceived z-drugs to be safer in general than benzodiazepines.[44,45] this might be one factor explaining the absence of decrease observed in our country. Since 2017, French regulations for zolpidem prescription impose the use of secure prescription booklets, a thorough specification of dosage and quantity, and maximal 4 weeks treatment duration.[46] An evaluation of these measures has demonstrated efficacy, with a drastic decrease of zolpidem use in the general population.[46] This might be an interesting lead for future health policies in our country.

In 2013, 27% of BZRA users also took an antidepressant and 10% took an opioid. These results are consistent with those of Maust *et al.*, who studied older adult's visits to ambulatory care services.[47] They found that 25% of visits that implied a BZRA prescription also included prescription of an antidepressant, and that concurrent prescription of a BZRA and an opioid concerned 10% of visits. Antidepressant use in older adults has been associated with a higher risk of falls and opioid use with a higher risk of fractures.[48,49] These risks may increase those potentially induced by BZRA intake. Moreover, the updated Beers Criteria published in 2019 strongly recommend avoidance of opioid use with a BZRA due to increased risk of overdose.[11] The fact that no significant decrease between 2004 and 2013 was found in concomitant users of BZRA and antidepressant or opioid in our study is thus of concern as it also concerns a sizeable proportion of older BZRA users. A similar preoccupation is for older adults taking $\geqslant 2$ BZRA (10% of BZRA users in 2013). Indeed, the concomitant use of several psychotropic medications was associated with a greater risk of fall injuries, hospitalization, and death.[50]

Our analysis of associated factors showed that female gender was associated with BZRA use, which is consistent with previous research.[39,47] Also similar to previous research conducted among older adults,[18,20,51] our results showed that polypharmacy (taking 5–9 medications) and excessive polypharmacy (taking 10 or more medication) were associated with BZRA use. These subgroups particularly would benefit from deprescribing, which is "the planned and supervised process of dose reduction or stopping medication that may be causing harm or are no longer providing benefits".[52] A recent systematic review has shown that successful BZRA deprescribing in older adult could be achieved using various interventions, ranging from pharmacological substitution to patient education.[53]

Falls were found to be associated with BZRA use, consistent with the result of a meta-analysis in 2018.[54] In contrast, neither multimorbidity nor specific comorbidities were associated significantly with BZRA, contrary to previous literature showing that BZRA users were more likely to suffer from chronic diseases.[47] However, the number of general practitioner (GP) contacts was associated with BZRA use, which, with polypharmacy, indirectly suggests poor health in BZRA users. The fact that BZRA users are more likely to see their GP could be an opportunity to design deprescribing interventions by involving GPs in the process. In Canada, the D-PRESCRIBE trial, involved both a community pharmacist and a GP, yielded 43% of discontinuation rate in BZRA use in older adults *versus* 9% in the control group,[55] showing the efficacy of a partnership with the GP.

Reporting a sleeping disorder was associated significantly with BZRA use but not to reporting an anxiety disorder or a depressive disorder. This was similar to the study of Gerlach *et al.*,[56] conducted among American low-income older adults between 2008 and 2016 even though participants to the BHIS are from all socio-economic backgrounds. In contrast, a study among older Taiwanese outpatients found that BZRA prescription was associated with anxiety and depression as well as insomnia.[19] An explanation for this difference might be that our study was based on self-reported answers to validated scales that have no medical diagnosis value. Another explanation might be related to the importance of sleeping

problems in a patient's life. A recent qualitative meta-synthesis, including nine publications from 2000 to 2015 in Western countries, explored patient's perceptions of BZRA use and factors that influenced BZRA continuation in older adults.[57] The authors explained that patients perceive insomnia as highly disruptive to the quality of life and report anxiety and depression as consequences or causes of a lack of sleep.[57] This could explain why, in contrast to reporting anxiety disorder or depressive disorders, reporting a sleeping disorder was strongly associated with BZRA use in our study. It might also indicate that anxiety and depression may hide behind the report of a sleeping problem. This might also explain why antidepressant use was significantly associated with BZRA use while reporting depression was not.

Whereas previous studies among older adults have shown that BZRA use was associated with age,[51,58] this result was not found in our multivariable analysis. An explanation might be the inclusion in our analysis of variables assessing health-related quality of life, mental health status, and pain, which may better explain BZRA use than age itself. Contrasting with a systematic review that showed significant results concerning association between income and BZRA use,[2] we found no association with income in the multivariable analysis, despite the non-reimbursement of BZRA in our country. This could mean that perceived benefits of BZRA use may outweigh the costs even for older adults with low socio-economic status.

Finally, while many variables were statistically significant in the univariate analysis, only a few were retained and significant in the final multivariable model. It suggests that older adult's profile is more likely to predict BZRA use than isolated characteristics.

Our study has several limitations. Firstly, information on medication use was obtained by asking the participants to show all the boxes of all medication taken in the last 24 h. Although this produces more reliable data than self-reported information, it also excludes some medications taken at an "as needed" frequency. BZRA use prevalence might thus be underestimated. No information on the duration of the BZRA use was available in the study. Our study is thus not able to estimate the extent of potentially inappropriate BZRA use based on the guideline of a maximum duration of 4 weeks. Moreover, our study was not able to assess if the observed decrease was due to less BZRA initiation or to BZRA deprescribing. No information on the place of living of the participant was available, so that no distinction between older adults living at home or in a nursing home was possible. Secondly, observed trends need to be confirmed with more recent data. Indeed 2013 was the last data available for our analysis, though BZRA deprescribing has gained attention in the scientific literature in recent years.[59–61]

Finally, missing data are a frequent problem in using databases for surveys because of incomplete cases. A quite large fraction (37%) of the original sample had to be excluded from the analysis due to missing data present in the indications for BZRA use, that is, reporting anxiety or sleeping disorder, that were expected to be associated with BZRA use. These two variables are comprised in the Mental Health section of the BHIS. As a sensitive subject, the questionnaire regarded this section as self-administered.[23] Moreover, the proxy is not allowed to answer the self-administered questionnaire on behalf of the participant.[23] This could explain the presence of the large number of missing values in our data. Significant sociodemographic differences existed between included and excluded observations and are presented in Supplemental Table S4. Our results, even if in line with previous literature, have thus to be taken with caution.

However, to our knowledge, this is the first study to assess BZRA use prevalence rates in the older Belgian general population. As they are not reimbursed in Belgium, no data about BZRA use is collected systematically, making monitoring of their consumption difficult. Using Health Interview Survey data allowed to work on representative data of the Belgian older population and to perform an in-depth analysis of BZRA use associated factors by including a large panel of explanatory variables.

Conclusion

Despite a significant and encouraging decrease in BZRA use in the general older population in Belgium between 2004 and 2013, it still extended to 18% of them in 2013. Efforts to reduce BZRA use in older adults should be enhanced by specifically targeting them in awareness campaigns, as the risk-benefit balance of BZRA use may not be positive in

this population. Promotion of alternatives to BZRA in treatment of sleeping problems needs to be continued. Deprescribing interventions in older BZRA users should target women and the oldest (⩾85 years) among whom BZRA use remain particularly prevalent as well as multiple BZRA users, concomitant users of antidepressants or opioids and older adults under polypharmacy, high-risk subgroups for whom medication safety would be greatly improved.

Author contributions

CP was involved in the conception of the work, performed the statistical analysis under the supervision of SH, drafted the first version of the manuscript, and approved the final version.
AS was involved in the interpretation and discussion of the results, revised the manuscript critically for important intellectual content and approved the final version.
SH was involved in the conception of the work, supervised data analysis, was involved in the interpretation of the results, revised the manuscript critically for important intellectual content and approved the final version.

Conflict of interest statement

The author declares that there is no conflict of interest.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

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Supplemental material

Supplemental material for this article is available online.

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