Drugs & Aging
https://doi.org/10.1007/s40266-023-01029-1

ORIGINAL RESEARCH ARTICLE

Benzodiazepine Receptor Agonists Use and Cessation Among Multimorbid Older Adults with Polypharmacy: Secondary Analysis from the OPERAM Trial

François-Xavier Sibille[1,2,3] · Marie de Saint-Hubert[1,2] · Séverine Henrard[2,3] · Carole Elodie Aubert[4,5] · Namiko Anna Goto[6] · Emma Jennings[7] · Olivia Dalleur[3,8] · Nicolas Rodondi[4,5] · Wilma Knol[6] · Denis O'Mahony[7] · Matthias Schwenkglenks[9] · Anne Spinewine[3,10]

Accepted: 4 April 2023

Abstract

Background Benzodiazepine receptor agonists (BZRAs) are commonly prescribed in older adults despite an unfavorable risk–benefit ratio. Hospitalizations may provide a unique opportunity to initiate BZRA cessation, yet little is known about cessation during and after hospitalization. We aimed to measure the prevalence of BZRA use before hospitalization and the rate of cessation 6 months later, and to identify factors associated with these outcomes.

Methods We conducted a secondary analysis of a cluster randomized controlled trial (OPtimising thERapy to prevent Avoidable hospital admissions in the Multimorbid elderly [OPERAM]), comparing usual care and in-hospital pharmacotherapy optimization in adults aged 70 years or over with multimorbidity and polypharmacy in four European countries. BZRA cessation was defined as taking one or more BZRA before hospitalization and not taking any BZRA at the 6-month follow-up. Multivariable logistic regression was performed to identify factors associated with BZRA use before hospitalization and with cessation at 6 months.

Results Among 1601 participants with complete 6-month follow-up data, 378 (23.6%) were BZRA users before hospitalization. Female sex (odds ratio [OR] 1.52 [95% confidence interval 1.18–1.96]), a higher reported level of depression/anxiety (OR up to 2.45 [1.54–3.89]), a higher number of daily drugs (OR 1.08 [1.05–1.12]), use of an antidepressant (OR 1.74 [1.31–2.31]) or an antiepileptic (OR 1.46 [1.02–2.07]), and trial site were associated with BZRA use. Diabetes mellitus (OR 0.60 [0.44–0.80]) was associated with a lower probability of BZRA use. BZRA cessation occurred in 86 BZRA users (22.8%). Antidepressant use (OR 1.74 [1.06–2.86]) and a history of falling in the previous 12 months (OR 1.75 [1.10–2.78]) were associated with higher BZRA cessation, and chronic obstructive pulmonary disease (COPD) (OR 0.45 [0.20–0.91]) with lower BZRA cessation.

Conclusion BZRA prevalence was high among included multimorbid older adults, and BZRA cessation occurred in almost a quarter of them within 6 months after hospitalization. Targeted BZRA deprescribing programs could further enhance cessation. Specific attention is needed for females, central nervous system-acting co-medication, and COPD co-morbidity.

Registration ClinicalTrials.gov identifier: NCT02986425. December 8, 2016.

1 Introduction

Benzodiazepine receptor agonists (BZRA, i.e., benzodiazepines and z-drugs) have shown an unfavorable risk (e.g., falls, hip fractures, delirium)–benefit (reduced anxiety, reduced time to fall asleep) balance. This is especially remarkable in older adults, with a number needed to treat of 13 for improved sleep quality and a number needed to harm of six for all adverse events [1]. Widely used explicit criteria on potentially inappropriate medications for older adults [2, 3] recommend avoiding BZRAs, especially in those with a history of falls or for those using three or more central nervous system (CNS)-acting drugs. Moreover, although it is widely accepted that BZRA use should be limited to a maximum of 4 weeks, long-term use is often observed [4]. Despite these recommendations, the prevalence of BZRA use in EU countries remains high, as illustrated by data from the EU-PROTECT project [5] and the OECD database (25 over 1000 adults over 65 years old have prolonged use) [6], although there are significant variations between countries.

Extended author information available on the last page of the article

Published online: 23 May 2023

Key Points

Use of benzodiazepine receptor agonists (BZRAs) was high among hospitalized older adults with chronic conditions and medications.

A quarter of BZRA users had ceased their medication 6 months after admission.

Several categories of patients require specific attention because of the higher prevalence of BZRA use (female patients and people using other psychotropic medications) or a decreased likelihood of BZRA cessation (chronic obstructive pulmonary disease co-morbidity).

Even higher prevalence rates are observed in acute care settings (up to 49%) [7–9].

Deprescribing is the process of withdrawal (cessation or dose reduction) of an inappropriate medication, supervised by an appropriate healthcare professional, with the goals of managing polypharmacy and improving health outcomes [10]. Deprescribing should always be tailored to the individual patient. Evidence shows that BZRA deprescribing can reduce the risk of harms associated with chronic BZRA use, without significantly worsening sleep quality, anxiety, or depression [11]. Deprescribing interventions targeting BZRAs in older adults have achieved success rates ranging from 27 to 80%—depending on the intervention tested and the setting [12]. In their systematic review, Reeve et al. describe interventions that target the older adult, the caregiver, and/or various healthcare professionals and include pharmacological substitution, patient educational material, or psychological support [12]. Although BZRAs are considered one of the top priorities for deprescribing in older adults, we still need to identify factors associated with BZRA cessation to better frame deprescribing interventions. A recent systematic review by Evrard et al. provided useful information on barriers and enablers for BZRA deprescribing in older adults in various settings of care [13]. Many barriers remain insufficiently addressed, such as low perceived self-efficacy or older adults' and/or caregivers' reluctance for cessation [14].

Hospitalization in older adults may present an important opportunity for optimizing medication use during admission and after discharge, yet there are limited data on the evolution of BZRA use during and after hospital admission. A few small studies reported encouraging data showing that engaging with patients during their hospital stay may contribute to increased rates of BZRA deprescribing, but post-discharge data were reported scarce [15–17]. A scoping review from Neville et al. recently identified interventions implemented in the acute care setting, but not specifically for older adults [18]. While the effects of pharmacotherapy optimization approaches on overall rates of potentially inappropriate prescribing have been measured [19], little is known about how much these global approaches can modify BZRA use during hospitalization and after discharge. The recent MedSafer study, which evaluated the effect of electronic decision support for deprescribing in older hospitalized patients, reported significantly higher discontinuation rates at discharge in the intervention group [20]. Less evidence is available regarding the impact of a global medication review conducted during hospital stay on BZRA deprescribing at discharge and after discharge.

We aimed to perform a secondary analysis of the OPERAM (OPtimising thERapy to prevent Avoidable hospital admissions in the Multimorbid elderly) trial, a cluster randomized controlled trial conducted in four European countries, which evaluated the effect of a structured medication review process on drug-related admissions. Our first objective was to describe BZRA prevalence before admission and identify associated factors. Our second objective was to measure the rate of BZRA cessation 6 months after hospital admission and to identify factors associated with cessation.

2 Methods

2.1 OPERAM Trial

The OPERAM trial (ClinicalTrials.gov identifier: NCT02986425) was a cluster randomized controlled trial conducted in four European countries (Belgium, Ireland, the Netherlands, and Switzerland). Participants were aged 70 years or older and had multimorbidity (≥ 3 chronic medical conditions) and polypharmacy (≥ 5 chronic medications [21]). The intervention involved a structured history of medication, a medication review supported by an explicit criteria tool, followed by shared decision-making with both participant and attending physician, and a report to the primary care physician [22]. BZRA use for a period of > 4 weeks was one of the triggers of the clinical decision support system (CDSS) based on the STOPP criteria [2], but the attending physician was free to accept or reject the recommendation to discontinue the BZRA. No BZRA-specific cessation program (e.g., tapering schedule) was proposed. The control group received usual pharmaceutical care. Follow-up and outcome data were collected by blinded trained researchers through telephone interviews at 2, 6, and 12 months after randomization. Details of the protocol and intervention have been published previously [22, 23]. The intervention did not significantly affect drug-related admissions (the primary endpoint), but it caused no detriment to participants [24]. In the intervention arm, 86.1% of participants ($n = 789$) had one or more inappropriate prescription at baseline according

to the STOPP criteria version 2 [2] and 62.2% ($n=491$) had one or more recommendation successfully implemented at 2 months, predominantly discontinuation of potentially inappropriate drugs. The OPERAM trial received approval from ethics committees at each site. All methods were performed in accordance with the relevant guidelines and regulations.

2.2 Eligibility Criteria

We included all the participants from the OPERAM trial who were alive and had follow-up data available at 6 months (Fig. 1).

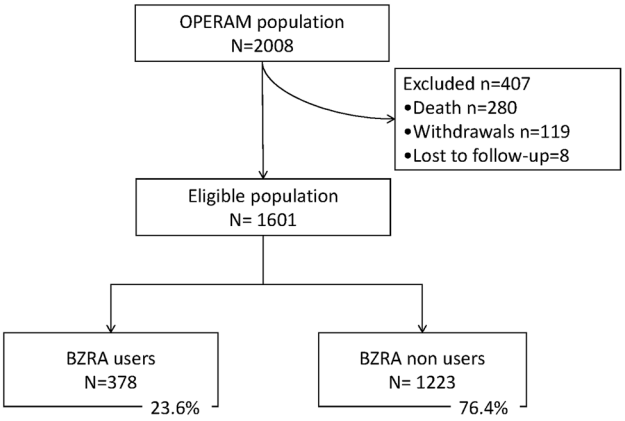
2.3 Outcomes

The first outcome of interest was BZRA prevalence at baseline, defined as the intake of at least one BZRA—taken daily and/or as needed—before admission. For descriptive purposes, we also recorded the prevalence of BZRA use at discharge. The second outcome of interest was BZRA cessation, defined as no intake of any BZRA at the 6-month follow-up in a patient taking at least one BZRA at baseline. Tapering and discontinuation could have happened during the hospital stay and/or after discharge. This time point was chosen because of the gradual dose tapering recommended, leading to withdrawal schedules lasting for several weeks [25]. The 2-month time point did not allow long tapering schedules to come to an end, and the 12-month time point was influenced more by intercurrent health condition changes. The following Anatomical Therapeutic Chemical (ATC) classes were considered as BZRAs: N03AE01, N05BA, N05CD, and N05CF. We also identified factors associated with BZRA prevalence at baseline and with BZRA cessation. Additional details are provided in the analysis section.

2.4 Statistical Analysis

Data are described as median (first and third quartiles [Q1–Q3]) for numerical variables and number (percentage) for categorical variables. Student's *t* test was used for continuous variables, and Pearson's Chi-squared test or Fisher's exact test for categorical variables.

Factors potentially associated with BZRA prevalence at baseline and with BZRA cessation were selected through literature review [26–30] and discussion among research team members. They included demographic and administrative data, comorbidities (including mental disorders or high-risk situations such as previous falls), and medication lists—with a focus on CNS-acting medications (Online Resource Supplementary Material 1 in the electronic supplementary material). Except for falls in the previous 12 months (directly available), comorbidities were identified for each patient by the International Classification of Diseases



BZRA= BenZodiazepine Receptor Agonist; OPERAM= OPtimising thERapy to prevent Avoidable hospital admissions in the Multimorbid elderly

Fig. 1 Study participant inclusion flowchart

(ICD-10 [31]) codes from discharge letters (Supplementary Material 1). The Charlson Comorbidity Index (CCI) was calculated using the ICD-10 codes [32]. Alcohol abuse was considered when consumption exceeded 7 units per week, as self-reported [33]. Functional status was assessed using the Katz index, with a lower score indicating a higher level of dependence [34]. Not living independently was defined as living in a nursing home (at least 3 months in the 6 months before the index admission) or being housebound [24]. For a quality-of-life measure, we used the item "Depression/anxiety levels" that was part of the EQ-5D Health Questionnaire [35]. We merged levels 3 (severely anxious or depressed) and 4 (extremely anxious or depressed) to avoid excessively small samples. The trial arm (intervention vs control) was also considered as a factor potentially associated with BZRA cessation because BZRA use for a period of >4 weeks was one of the triggers of the CDSS based on the STOPP criteria. Interactions between the trial arm and the other factors were tested and found to be statistically non-significant.

Binary logistic regression models were performed to assess independent variables associated with BZRA prevalence at baseline and BZRA cessation, and adjusted odds ratios (ORs) with their 95% confidence intervals (CIs) were calculated. First, a univariate analysis was performed with all variables for each outcome. Variables with a p value <0.20 in the univariate analysis were eligible for the multivariable analysis. Collinearity was assessed between quantitative variables (Pearson coefficient) and qualitative variables (Phi coefficient). The choice between two correlated variables of the one to be entered in the multivariable model was based on their respective clinical relevance. Multicollinearity was assessed using the variance inflation factor. Missing data were not imputed. All test results were two-sided, and a p value <0.05 was considered statistically significant.

All analyses were performed using R software v.4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

3 Results

A total of 2008 participants were enrolled in the OPERAM trial, of which 1601 completed the 6-month follow-up [24] and were included in the present secondary analysis (Fig. 1). Baseline characteristics are provided in Table 1. The median age [Q1–Q3] was 78 [74–83] years, 714 participants (44.6%) were female, and 777 (48.5%) were randomized into the intervention arm. The median length of stay was 6 [3–10] days. The number of participants not living independently was 276 (17.3%). A total of 999 participants (62.9%) reported not feeling anxious or depressed. At baseline, 145 participants (9.1%) had a diagnosis of depression and 101 (6.3%) had a major cognitive disorder. Six hundred and nineteen participants (38.8%) had experienced at least one fall in the previous 12 months. Severe polypharmacy (10 chronic medications or more) was present in 803 participants (50.2%), and 810 (50.6%) were taking at least one CNS-acting medication at baseline.

3.1 BZRA Prevalence at Baseline and Associated Factors

At baseline, BZRA prevalence was 23.6% (378/1601), with 70.3% of cases reporting daily use (Supplementary Material 2, see the electronic supplementary material). Most frequent BZRA molecules were zolpidem and lorazepam (Supplementary Material 3). BZRA prevalence was 22.1% in the intervention arm (172/777) and 25.0% in the control arm (206/824). In Switzerland, 121 participants (17.4%) were BZRA users at baseline, a prevalence lower than in Belgium, the Netherlands, and Ireland [respectively, 32.5%, 24.8%, and 28.0%]. Among BZRA users, 35.7% were taking three or more CNS-acting medications.

In the multivariable analysis (Table 2), the following variables were significantly associated with higher BZRA prevalence at baseline: female sex (OR [95% CI] 1.52 [1.18–1.96]), trial site (Belgium OR 2.64 [1.84–3.78], being resident in the Netherlands OR 1.90 [1.32–2.75] and Ireland OR 1.88 [1.31–2.70] as compared to Switzerland), a higher depression/anxiety level (OR up to 2.45 [1.54–3.89]), a higher number of daily medications other than BZRA (for each additional medication OR 1.08 [1.05–1.12]), the use of an antidepressant (OR 1.74 [1.31–2.31]), and the use of an antiepileptic (OR 1.46 [1.02–2.07]). Diabetes (OR 0.60 [0.44–0.80]) was significantly associated with lower BZRA prevalence at baseline

Table 1 Substudy population characteristics

	Total $N = 1601$
General information	
Median age [Q1–Q3]	78 [74–83]
Female sex, *n* (%)	714 (44.6)
Functional status	
Median Katz score [Q1–Q3]	5 [4–6]
Not living independently[a], *n* (%)	276 (17.3)
Median length of stay [Q1–Q3]	6 [3–10]
Non elective admission, *n* (%)	1208 (75.5)
Trial site, *n* (%)	
Bern (Switzerland)	696 (43.5)
Louvain (Belgium)	305 (19.1)
Utrecht (the Netherlands)	318 (19.9)
Cork (Ireland)	282 (17.6)
Trial arm, *n* (%)	
Intervention arm	777 (48.5)
Depression/anxiety level[b], *n* (%)	
No	999 (62.9)
Slight	264 (16.6)
Moderate	223 (14.1)
Severe/extreme	101 (6.4)
Comorbidities at baseline	
Median Charlson Comorbidity Index [Q1–Q3]	6 [4–7]
Depression, *n* (%)	145 (9.1)
Major cognitive disorder, *n* (%)	101 (6.3)
Bipolar or psychotic disorder, *n* (%)	15 (0.9)
Extrapyramidal syndrome, *n* (%)	125 (7.8)
Fall(s) in the previous 12 months[c], *n* (%)	619 (38.8)
Major fracture, *n* (%)	345 (21.5)
COPD, *n* (%)	304 (19.0)
Diabetes, *n* (%)	509 (31.8)
Chronic kidney disease, *n* (%)	434 (27.1)
Chronic heart disease, *n* (%)	386 (24.1)
Chronic liver disease, *n* (%)	69 (4.3)
Alcohol abuse[d], *n* (%)	208 (13.1)
Tobacco use, *n* (%)	129 (8.1)
Medications at baseline[e]	
Median total number [Q1–Q3]	10 [7–12]
BZRA use, *n* (%)	378 (23.6)
Antidepressant use, *n* (%)	376 (23.5)
Antipsychotic use, *n* (%)	77 (4.8)
Antiepileptic use, *n* (%)	216 (13.5)
Opioid use, *n* (%)	244 (15.2)

ACT Anatomical Therapeutic Chemical, *BZRA* benzodiazepine receptor agonist, *COPD* chronic obstructive pulmonary disease, *Q1–Q3* first and third quartiles

[a]three missing values

[b]Item from the EQ-5D Health Questionnaire, 14 missing values

[c]Seven missing values

[d]Nine missing values

[e]Corresponding ATC codes available in Supplementary Material 1 (see the electronic supplementary material)

Table 2 Factors associated with BZRA use at baseline

	Univariate		Multivariable	
	OR [95% CI]	*P* value	OR [95% CI]	*P* value
General information				
Age	1.01 [0.99–1.03]	0.422		
Female sex	1.64 [1.30–2.08]	< 0.001*	1.52 [1.18–1.96]	0.001*
Not living independently	1.74 [1.30–2.31]	< 0.001*	1.10 [0.80–1.51]	0.565
Non elective admission	1.16 [0.89–1.54]	0.284		
Trial site				
Bern (Switzerland)	1		1	
Louvain (Belgium)	1.96 [1.44–2.67]	< 0.001*	2.64 [1.84–3.78]	< 0.001*
Utrecht (the Netherlands)	1.30 [0.94–1.78]	0.115	1.90 [1.32–2.75]	0.001*
Cork (Ireland)	1.46 [1.05–2.03]	0.023*	1.88 [1.31–2.70]	0.001*
Depression/anxiety level[a]				
No	1		1	
Slight	1.33 [0.95–1.84]	0.077	0.98 [0.68–1.38]	0.893
Moderate	2.43 [1.76–3.33]	< 0.001*	1.54 [1.08–2.18]	< 0.001*
Severe/extreme	3.86 [2.52–5.88]	< 0.001*	2.45 [1.54–3.89]	< 0.001*
Comorbidities at baseline				
Charlson Comorbidity Index	0.97 [0.92–1.03]	0.327		
Depression	2.92 [2.05–4.14]	< 0.001*		
Dementia	1.90 [1.23–2.89]	0.003*		
Bipolar or psychotic disorder	3.81 [1.36–10.93]	0.010*		
Extrapyramidal syndrome	1.36 [0.90–2.03]	0.136	1.25 [0.79–1.93]	0.331
Fall(s) in the previous 12 months	1.12 [0.88–1.41]	0.360		
Major fracture	1.05 [0.79–1.38]	0.730		
COPD	1.35 [1.02–1.79]	0.036*	0.86 [0.61–1.20]	0.367
Diabetes mellitus	0.77 [0.59–0.99]	0.044*	0.60 [0.44–0.80]	< 0.001*
Chronic kidney disease	0.83 [0.63–0.99]	0.168	0.82 [0.60–1.12]	0.218
Chronic heart disease	0.82 [0.62–1.08]	0.161		
Chronic liver disease	1.17 [0.66–1.98]	0.585		
Alcohol abuse	0.93 [0.65–1.31]	0.697		
Tobacco use	1.47 [0.98–2.17]	0.056	1.26 [0.79–1.97]	0.317
Medications at baseline				
Total number without BZRA	1.04 [1.01–1.06]	0.006*	1.08 [1.05–1.12]	< 0.001*
Antidepressant use	2.26 [1.75–2.90]	< 0.001*	1.74 [1.31–2.31]	< 0.001*
Antipsychotic use	2.35 [1.53–3.57]	< 0.001*	1.55 [0.91–2.62]	0.104
Antiepileptic use	1.36 [0.99–1.85]	0.053	1.46 [1.02–2.07]	0.035*
Opioid use	1.87 [1.53–2.48]	< 0.001*	1.18 [0.83–1.65]	0.348*

BZRA benzodiazepine receptor agonist, *CI* confidence interval, *COPD* chronic, *OR* odds ratio obstructive pulmonary disease

*Statistically significant

[a]Item from the EQ-5D Health Questionnaire

3.2 BZRA Cessation and Associated Factors

At the 6-month follow-up, BZRA cessation had occurred in 86 participants (22.8% of BZRA users at baseline). Among these 86 participants, 42 (48.8%) had their BZRA already discontinued at discharge. Among the 67 older adults who had their BZRA discontinued at discharge, 42 (62.7%) were still BZRA-free at 6 months (Fig. 2). Regarding the trial arm, 37 participants (18.0%) from the control arm and 49 (28.5%) from the intervention arm had ceased their BZRA at the 6-month follow-up.

In the multivariable analysis (Table 3), any antidepressant use at baseline (OR [95% CI] 1.74 [1.06–2.86]) and a history of falling in the previous 12 months (OR [95% CI] 1.75

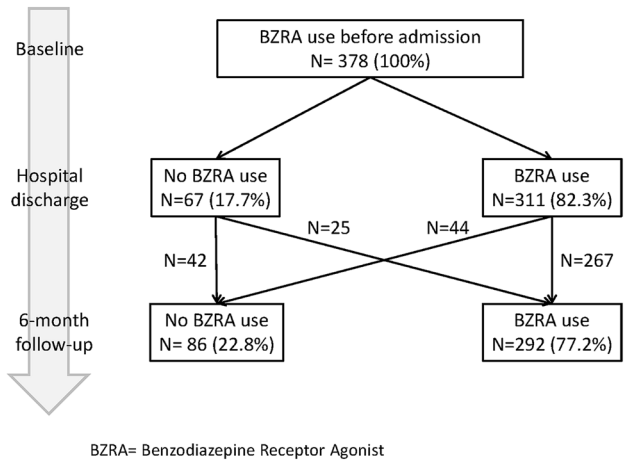


Figure 2 Benzodiazepine receptor agonist (BZRA) use at discharge and 6-month follow-up

[1.10–2.78]) were associated with higher BZRA cessation rates. Also, being in the intervention arm showed a similar but not statistically significant association with BZRA cessation (OR [95% CI] 1.47 [0.95–2.30]). Chronic obstructive pulmonary disease (COPD) was associated with a lower BZRA cessation rate (OR [95% CI] 0.45 [0.20–0.91]).

4 Discussion

In this substudy including older adults with multimorbidity and polypharmacy, the prevalence of BZRA use at baseline was 23.6%. Approximately one quarter of BZRA users at baseline had discontinued their BZRA 6 months after their hospitalization, and discontinuation occurred more frequently in patients with concurrent antidepressant medication.

The observation that approximately a quarter of older adults were taking a BZRA at baseline aligns with the prevalence reported in the recent MedSafer trial involving older adults with polypharmacy hospitalized in Canada [36]. However, the prevalence of BZRA use in OPERAM significantly differed across sites. Despite the limited generalizability because data were collected from only one trial site per country, variations across countries have been previously reported [6]. Although there is no clear basis for this variation, the explanation is probably multifactorial and may include factors at the level of the healthcare system. For instance, Belgium, the country with the highest prevalence of BZRA use in OPERAM, has no specific regulation for BZRA prescription such as there is in France, where zolpidem is treated as a restricted drug [37]. More research is needed to understand the influence of patients, healthcare professionals, and system-level factors on BZRA use.

Two factors associated with BZRA use at baseline deserve specific attention. First, one third of BZRA users at baseline were using three or more CNS-acting medications and participants with a higher number of other medications were more likely to use a BZRA at baseline. More precisely, for each additional drug, there was an 8% greater risk of BZRA use. This is particularly concerning considering that both CNS-acting co-medication in particular and polypharmacy in general are associated with an increased risk of falls and fractures [38]. As falls are associated with high morbidity and mortality [39], clinicians should consider these situations as high risk and prioritize deprescribing conversations with patients. Second, consistent with published data, women were more likely to be BZRA users than men [5]. Previous evidence highlighted higher rates of depression (symptoms) and anxiety in (older) women [40], and differences in sleep behavior and sleep disorders [41]. These differences may not be driven only by biological factors but by gender differences in the way women and men report symptoms, in socioeconomic status, or in history of (gender-based) violence [42]. Further research on sex and gender differences is needed and could contribute to better address discontinuation from a gender perspective.

Discontinuation at 6 months occurred in almost one in four BZRA users. First, antidepressant co-medication was significantly associated with higher discontinuation rates. This is consistent with a recent study investigating BZRA deprescribing at discharge from Belgian specialist geriatric wards [9] and could be explained by potentially positive effects of some antidepressants on benzodiazepine withdrawal symptoms and on symptoms of anxiety after BZRA deprescribing [43]. Second, a history of falling in the previous 12 months was also associated with BZRA cessation, which could be the result of deprescribing in response to an adverse event of BZRAs, since they may cause ataxia and impaired sensorium predisposing to additional falls [3]. This so-called reactive deprescribing is indeed the most common deprescribing activity in the acute context [44]. Third, in our study, COPD was associated with a lower BZRA cessation rate, but not with a different BZRA prevalence at baseline. Although data suggest that patients with COPD are more likely to experience a higher level of anxiety or depression [45], this association is difficult to explain and should be considered with caution given the large CI.

Interestingly, we did not find differences between trial sites regarding BZRA cessation. In other words, and with the limitation of small subpopulations, BZRA cessation was similar and limited across countries, whatever the baseline prevalence was. This is an interesting finding highlighting the need for a comprehensive, multifaceted, patient-centered strategy to facilitate BZRA deprescribing.

Table 3 Factors associated with BZRA cessation at 6-month follow-up

	Univariate analysis		Multivariable analysis	
	OR [95% CI]	*P* value	OR [95% CI]	*P* value
General information				
Age	1.02 [0.99–1.06]	0.197	1.00 [0.97–1.04]	0.807
Female sex	1.54 [0.99–2.38]	0.055	1.15 [0.71–1.85]	0.557
Not living independently	1.70 [1.01–2.77]	0.038*	1.36 [0.77–2.33]	0.270
Length of stay	1.01 [0.98–1.04]	0.337		
Non elective admission	1.01 [0.62–1.71]	0.977		
Trial site				
Bern (Switzerland)	1			
Louvain (Belgium)	0.99 [0.53–1.77]	0.964		
Utrecht (the Netherlands)	0.94 [0.50–1.69]	0.850		
Cork (Ireland)	1.14 [0.62–2.03]	0.659		
Trial arm				
Intervention arm	1.43 [0.93–2.23]	0.109	1.45 [0.93–2.29]	0.106
Depression/anxiety level[a]				
No	1		1	
Slight	0.83 [0.42–1.53]	0.577	0.70 [0.34–1.30]	0.280
Moderate	0.82 [0.39–1.57]	0.577	0.67 [0.31–1.31]	0.267
Severe/extreme	1.71 [0.77–3.42]	0.153	1.08 [0.46–2.28]	0.844
Comorbidities at baseline				
Charlson Comorbidity Index	0.97 [0.87–1.07]	0.545		
Depression	2.05 [1.09–3.64]	0.019*		
Dementia	2.89 [1.48–5.25]	0.001*		
Bipolar or psychotic disorder	1.26 [0.07–6.39]	0.824		
Extrapyramidal syndrome	1.60 [0.76–3.04]	0.178	1.06 [0.48–2.11]	0.872
Fall(s) in the previous 12 months	1.97 [1.28–3.07]	0.002*	1.75 [1.10–2.78]	0.018*
Major fracture	1.44 [0.87–2.31]	0.142	1.09 [0.63–1.82]	0.755
COPD	0.42 [0.19–0.83]	0.022*	0.45 [0.20–0.91]	0.040*
Diabetes mellitus	0.64 [0.37–1.04]	0.083	0.62 [0.37–1.05]	0.088
Chronic kidney disease	0.86 [0.51–1.40]	0.564		
Chronic heart disease	0.60 [0.32–1.04]	0.084	0.66 [0.35–1.17]	0.178
Chronic liver disease	0.25 [0.01–1.15]	0.172	0.27 [0.02–1.27]	0.199
Alcohol abuse	0.58 [0.24–1.18]	0.169	0.71 [0.29–1.51]	0.414
Tobacco use	0.69 [0.24–1.58]	0.434		
Medications at baseline				
Total number without BZRA	1.00 [0.95–1.05]	0.952		
Antidepressant use	2.13 [1.34–3.32]	0.001*	1.74 [1.06–2.86]	0.026*
Antipsychotic use	0.96 [0.29–2.40]	0.944		
Antiepileptic use	1.76 [1.00–2.96]	0.040*	1.46 [0.78–2.59]	0.217
Opioid use	1.75 [1.01–2.89]	0.036*	1.26 [0.69–2.20]	0.439

BZRA benzodiazepine receptor agonist, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *OR* odds ratio

*Statistically significant

[a]Item from the EQ-5D Health Questionnaire

The pharmacotherapy optimization intervention of OPERAM was not aimed specifically at reducing BZRA use, but BZRA use for a period of > 4 weeks was one of the triggers of the CDSS, generating a signal recommending deprescribing BZRA that the attending physician was free to accept or not. Data from two OPERAM secondary analyses

show that this STOPP criterion was triggered in 181 of 826 participants (21.9%) in the intervention arm, and that the pharmacotherapy team accepted 64.1% of these STOPP signals, resulting in a recommendation to the attending hospital physician [46]. In addition, 55.1% of BZRA cessation recommendations were agreed with by both patient and attending physician. When disagreement occurred, the main reason was patients' reluctance to discontinue the medication [47]. Previous publications have shown efficacy of in-hospital interventions in decreasing potentially inappropriate medication exposure [24, 48]. We could not show that the OPERAM intervention was associated with significantly higher BZRA cessation in comparison with usual care, probably in part because our sample was insufficiently powered for this purpose. In MedSafer, deprescribing (defined as discontinuation or dose decrease 30 days after discharge) occurred significantly more often in the intervention group compared to the control group (adjusted difference 22.7% [95% CI 12.0–33.5]). The MedSafer intervention included one additional component as compared to OPERAM: participants or their caregivers received an educational pamphlet on deprescribing, as well as a patient-oriented sedative-hypnotic deprescribing pamphlet from the Canadian Deprescribing Network [36]. Wilson et al. used the same sedative-hypnotic deprescribing pamphlet, with a substantial increase of BZRA deprescribing [17]. Another way of supporting deprescribing in the hospital setting would be to target practitioners' behavior by measuring, reporting, and sharing deprescribing activity [49]. A recent scoping review on interventions implemented in the acute care setting, but not specific to older adults, reported that multifaceted interventions aimed at patients and healthcare providers that include a combination of education, sleep protocols, and deprescribing may support reductions in benzodiazepine or other sedative/hypnotic drug use [18].

Almost two thirds of older adults who had their BZRA discontinued at discharge were still BZRA-free at 6 months, which is encouraging and could have been supported by the discharge report sent to the general practitioner—a key component for sustained deprescribing [50]. Conversely, less than half of older adults with BZRA cessation at the 6-month follow-up had already ceased at discharge. This could be explained by the required slow dose tapering exceeding the length of hospital stay or the preference of the participants to either discuss discontinuation with their general practitioners and/or to initiate the process outside the acute setting.

This study has several strengths. First, it examines data from a large sample of older adults with multimorbidity and polypharmacy recruited prospectively in several countries. Second, the 6-month follow-up is a period long enough to allow for a full deprescribing scheme based on participants' needs and preferences. This study has some limitations also. First, we did not consider specific details of dose reduction of BZRAs. This would have provided a clearer picture of BZRA deprescribing and enabled more direct comparisons with other studies. Second, we have no detailed data about possible failed attempts at BZRA cessation, although two published secondary analyses provide some highlights on the acceptance of and reasons for rejecting recommendations to discontinue medications in the OPERAM trial [46, 47]. Third, due to the broader scope of the OPERAM trial, no specific data were collected regarding the indication for BZRA use (anxiety and/or sleep disorder, other). Finally, we did not collect specific patient-reported outcomes, such as withdrawal symptoms and sleep patterns, which would have been interesting to better capture the participant experience. This information was not available since the OPERAM intervention did not focus on BZRA cessation.

5 Conclusion

BZRA use was observed in almost one quarter of hospitalized older adults with multimorbidity and polypharmacy, and BZRA cessation occurred in almost one quarter of BZRA users. To increase BZRA cessation or dose reduction, a more targeted deprescribing program is most probably needed, with components addressing barriers at patient, healthcare professional, and organization levels. Future studies also need to pay specific attention to older adults taking CNS-acting medications, females, and COPD co-morbidity.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40266-023-01029-1.

Acknowledgements The first author would like to thank Alain Guillet (Support en méthodologie et calculs statistiques, Université Catholique de Louvain) for his support in the data management and statistical analysis. We thank all participants of the OPERAM trial that provided the data for this secondary analysis.

Declarations

Funding This work is part of the project "OPERAM: OPtimising thERapy to prevent Avoidable hospital admissions in the Multimorbid elderly" supported by the European Union's Horizon 2020 research and innovation program under the grant agreement No. 634238, and by the Swiss State Secretariat for Education, Research and Innovation (SERI) under contract number 15.0137. The OPERAM project was also partially funded by the Swiss National Scientific Foundation (SNSF 320030_188549 and 325130_204361). François-Xavier Sibille is a Clinical Master Specialist Applicant for a Ph.D. of the Fonds de la Recherche Scientifique—FNRS. The opinions expressed herein are those of the authors and do not necessarily reflect the official views of the funders. The funders had no role in the study design; data collection, analysis, and interpretation; or writing of the report. Open access funding was provided by UCLouvain and CHU UCL Namur.

Conflict of Interest François-Xavier Sibille is a Clinical Master Specialist Applicant for a Ph.D. of the Fonds de la Recherche Scientifique—FNRS. The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All other authors declare that they have no conflict of interest.

Data Availability The datasets analyzed during the current study will be made available on reasonable request. Data will be made available for scientific purposes for researchers whose proposed use of the data has been approved by the OPERAM publication committee.

Ethics Approval The OPERAM trial was approved by the independent research ethics committees at each participating site (lead ethics committee: Cantonal Ethics Committee Bern, Switzerland, ID 2016-01200; Medical Research Ethics Committee Utrecht, the Netherlands, ID 15-522/D; Comité d'Ethique Hospitalo-Facultaire Saint-Luc-UCL: 2016/20JUL/347–Belgian registration No: B403201629175; Cork University Teaching Hospitals Clinical Ethics Committee, Cork, Republic of Ireland; ID ECM 4 [o] 07/02/17), and Swissmedic as the responsible regulatory authority. The authors certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to Participate Written informed consent was obtained from the participants or their legal representatives before enrollment in the OPERAM trial.

Consent for Publication Not applicable.

Code Availability The codes used during the current study will be made available on reasonable request.

Author Contributions Authorship eligibility is based on the International Committee of Medical Journal Editors (ICMJE) authorship criteria. The authors certify that they have participated in the following aspects: conception and design (all authors); acquisition and interpretation of data (FXS, MdSH, SH, AS); drafting the article (FXS, MdSH, AS) and revising it critically for important intellectual content (all authors). All authors have approved the final article, and agree to be accountable for the work.

References

1. Glass J, Lanctôt KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. BMJ (Clin Res Ed). 2005;331(7526):1169.
2. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing. 2015;44(2):213–8.
3. 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2019;67:674–94.
4. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. JAMA Psychiat. 2015;72(2):136–42.
5. Huerta C, Abbing-Karahagopian V, Requena G, Oliva B, Alvarez Y, Gardarsdottir H, et al. Exposure to benzodiazepines (anxiolytics, hypnotics and related drugs) in seven European electronic healthcare databases: a cross-national descriptive study from the PROTECT-EU Project. Pharmacoepidemiol Drug Saf. 2016;25(Suppl 1):56–65.
6. OCDE. Panorama de la santé 2017: Les indicateurs de l'OCDE. Éditions OCDE; 2017.
7. Pek EA, Remfry A, Pendrith C, Fan-Lun C, Bhatia RS, Soong C. High prevalence of inappropriate benzodiazepine and sedative hypnotic prescriptions among hospitalized older adults. J Hosp Med. 2017;12(5):310–6.
8. Beuscart JB, Ficheur G, Miqueu M, Luyckx M, Perichon R, Puisieux F, et al. Co-prescriptions of psychotropic drugs to older patients in a general hospital. Eur Geriatr Med. 2017;8(1):84–9.
9. Sibille F-X, Spinewine A, Zerah L, Maljean L, Schoevaerdts D, de Saint-Hubert M. Current practice in benzodiazepine receptor agonists deprescribing on acute geriatric wards: a cohort study. BMC Geriatr. 2022;22(1):88.
10. Reeve E, Gnjidic D, Long J, Hilmer S. A systematic review of the emerging definition of "deprescribing" with network analysis: implications for future research and clinical practice. Br J Clin Pharmacol. 2015;80(6):1254–68.
11. Ng BJ, Le Couteur DG, Hilmer SN. Deprescribing benzodiazepines in older patients: impact of interventions targeting physicians, pharmacists, and patients. Drugs Aging. 2018;35(6):493–521.
12. Reeve E, Ong M, Wu A, Jansen J, Petrovic M, Gnjidic D. A systematic review of interventions to deprescribe benzodiazepines and other hypnotics among older people. Eur J Clin Pharmacol. 2017;73(8):927–35.
13. Evrard P, Pétein C, Beuscart J-B, Spinewine A. Barriers and enablers for deprescribing benzodiazepine receptor agonists in older adults: a systematic review of qualitative and quantitative studies using the theoretical domains framework. Implement Sci. 2022;17(1):41.
14. Choi J, Vordenberg SE. Older adults' perceptions of deprescribing chronic benzodiazepines. J Am Pharm Assoc. 2021;61(5):533-538.e3.
15. Carr F, Tian P, Chow J, Guzak J, Triscott J, Mathura P, et al. Deprescribing benzodiazepines among hospitalised older adults: quality improvement initiative. BMJ Open Qual. 2019;8(3):e000539.
16. Gnjidic D, Ong HMM, Leung C, Jansen J, Reeve E. The impact of in hospital patient-education intervention on older people's attitudes and intention to have their benzodiazepines deprescribed: a feasibility study. Ther Adv Drug Saf. 2019;10:2042098618816562.
17. Wilson MG, Lee TC, Hass A, Tannenbaum C, McDonald EG. EMPOWERing hospitalized older adults to deprescribe sedative hypnotics: a pilot study. J Am Geriatr Soc. 2018;66(6):1186–9.
18. Neville HL, Granter C, Adibi P, Belliveau J, Isenor JE, Bowles SK. Interventions to reduce benzodiazepine and sedative-hypnotic drug use in acute care hospitals: a scoping review. Res Soc Admin Pharm RSAP. 2022;18(5):2874–86.
19. Graabæk T, Kjeldsen LJ. Medication reviews by clinical pharmacists at hospitals lead to improved patient outcomes: a systematic review. Basic Clin Pharmacol Toxicol. 2013;112(6):359–73.

20. McDonald EG, Wu PE, Rashidi B, Forster AJ, Huang A, Pilote L, et al. The MedSafer study: a controlled trial of an electronic decision support tool for deprescribing in acute care. J Am Geriatr Soc. 2019;67(9):1843–50.
21. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017;17(1):230.
22. Crowley EK, Sallevelt B, Huibers CJA, Murphy KD, Spruit M, Shen Z, et al. Intervention protocol: OPtimising thERapy to prevent avoidable hospital Admission in the Multi-morbid elderly (OPERAM): a structured medication review with support of a computerised decision support system. BMC Health Serv Res. 2020;20(1):220.
23. Adam L, Moutzouri E, Baumgartner C, Loewe AL, Feller M, M'Rabet-Bensalah K, et al. Rationale and design of OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people (OPERAM): a cluster randomised controlled trial. BMJ Open. 2019;9(6): e026769.
24. Blum MR, Sallevelt B, Spinewine A, O'Mahony D, Moutzouri E, Feller M, et al. Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults (OPERAM): cluster randomised controlled trial. BMJ. 2021;13(374): n1585.
25. Pottie K, Thompson W, Davies S, Grenier J, Sadowski CA, Welch V, et al. Deprescribing benzodiazepine receptor agonists: evidence-based clinical practice guideline. Can Fam Physician. 2018;64(5):339–51.
26. Joester J, Vogler CM, Chang K, Hilmer SN. Hypnosedative use and predictors of successful withdrawal in new patients attending a falls clinic: a retrospective, cohort study. Drugs Aging. 2010;27(11):915–24.
27. Aoki T, Yamamoto Y, Ikenoue T, Fukuhara S. Factors associated with patient preferences towards deprescribing: a survey of adult patients on prescribed medications. Int J Clin Pharm. 2019;41(2):531–7.
28. Alvarenga JM, Loyola Filho AI, Firmo JO, Lima-Costa MF, Uchoa E. A population based study on health conditions associated with the use of benzodiazepines among older adults (The Bambuí Health and Aging Study). Cad Saude Publica. 2009;25(3):605–12.
29. Allary A, Proulx-Tremblay V, Bélanger C, Hudon C, Marchand A, O'Connor K, et al. Psychological predictors of benzodiazepine discontinuation among older adults: results from the PASSE 60. Addict Behav. 2020;102: 106195.
30. Couderc AL, Bailly-Agaledes C, Camalet J, Capriz-Ribière F, Gary A, Robert P, et al. Adaptations of psychotropic drugs in patients aged 75 years and older in a departement of geriatric internal medecine: report of 100 cases. Geriatr Psychol Neuropsychiatr Vieil. 2011;9(2):163–70.
31. (WHO) WHO. ICD-10 Version:2016; 2021.
32. Bannay A, Chaignot C, Blotière PO, Basson M, Weill A, Ricordeau P, et al. The best use of the Charlson comorbidity index with electronic health care database to predict mortality. Med Care. 2016;54(2):188–94.
33. Saitz R. Clinical practice. Unhealthy alcohol use. N Engl J Med. 2005;352(6):596–607.
34. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychosocial function. JAMA. 1963;185:914–9.
35. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997;35(11):1095–108.
36. McDonald EG, Wu PE, Rashidi B, Wilson MG, Bortolussi-Courval É, Atique A, et al. The MedSafer study-electronic decision support for deprescribing in hospitalized older adults: a cluster randomized clinical trial. JAMA Intern Med. 2022;182(3):265–73.
37. Chambost E, Chappuy M. Impact de la nouvelle réglementation du zolpidem—enquête dans la circonscription départementale du Rhône. Le Pharmacien Hospitalier et Clinicien. 2018;53(4):288–300.
38. Seppala LJ, Wermelink A, de Vries M, Ploegmakers KJ, van de Glind EMM, Daams JG, et al. Fall-risk-increasing drugs: a systematic review and meta-analysis: II. Psychotropics. J Am Med Dir Assoc. 2018;19(4):371.e11-371.e17.
39. Ganz DA, Latham NK. Prevention of falls in community-dwelling older adults. N Engl J Med. 2020;382(8):734–43.
40. Riecher-Rössler A. Sex and gender differences in mental disorders. Lancet Psychiatry. 2017;4(1):8–9.
41. Mallampalli MP, Carter CL. Exploring sex and gender differences in sleep health: a Society for Women's Health Research Report. J Womens Health (Larchmt). 2014;23(7):553–62.
42. Kiely KM, Brady B, Byles J. Gender, mental health and ageing. Maturitas. 2019;129:76–84.
43. Baandrup L, Ebdrup BH, Rasmussen J, Lindschou J, Gluud C, Glenthøj BY. Pharmacological interventions for benzodiazepine discontinuation in chronic benzodiazepine users. Cochrane Database Syst Rev. 2018;3(3): CD011481.
44. Scott S, Clark A, Farrow C, May H, Patel M, Twigg MJ, et al. Deprescribing admission medication at a UK teaching hospital; a report on quantity and nature of activity. Int J Clin Pharm. 2018;40(5):991–6.
45. Halvorsen T, Martinussen PE. Benzodiazepine use in COPD: empirical evidence from Norway. Int J Chron Obstruct Pulmon Dis. 2015;10:1695–702.
46. Sallevelt B, Huibers CJA, Heij J, Egberts TCG, van Puijenbroek EP, Shen Z, et al. Frequency and acceptance of clinical decision support system-generated STOPP/START signals for hospitalised older patients with polypharmacy and multimorbidity. Drugs Aging. 2022;39(1):59–73.
47. Huibers CJA, Sallevelt BTGM, Heij JMJ, O'Mahony D, Rodondi N, Dalleur O, et al. Hospital physicians' and older patients' agreement with individualised STOPP/START-based medication optimisation recommendations in a clinical trial setting. Eur Geriatr Med. 2022;13:541–52.
48. Xuan Vu T, Bui Thi Huong Q. The effect of the pharmacist's intervention on potentially inappropriate medication use in older adults using the 2015 Beers criteria. Pharm Sci Asia. 2019;46(1):54–61.
49. Scott S, May H, Patel M, Wright DJ, Bhattacharya D. A practitioner behaviour change intervention for deprescribing in the hospital setting. Age Ageing. 2020;50(2):581–6.
50. Nguyen AD, Baysari MT, Duong M, Zheng WY, Ng B, Lo S, et al. Communicating deprescribing decisions made in hospital with general practitioners in the community. Intern Med J. 2021;51(9):1473–8.

Authors and Affiliations

François-Xavier Sibille[1,2,3] · Marie de Saint-Hubert[1,2] · Séverine Henrard[2,3] · Carole Elodie Aubert[4,5] · Namiko Anna Goto[6] · Emma Jennings[7] · Olivia Dalleur[3,8] · Nicolas Rodondi[4,5] · Wilma Knol[6] · Denis O'Mahony[7] · Matthias Schwenkglenks[9] · Anne Spinewine[3,10]

✉ François-Xavier Sibille
francois-xavier.sibille@chuuclnamur.uclouvain.be

1 Department of Geriatric Medicine, CHU UCL Namur, Avenue Dr Gaston Therasse, 1, 5530 Yvoir, Belgium

2 Institute of Health and Society, Université Catholique de Louvain, Brussels, Belgium

3 Clinical Pharmacy Research Group, Louvain Drug Research Institute, Université Catholique de Louvain, Brussels, Belgium

4 Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland

5 Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

6 Department of Geriatric Medicine, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

7 Department of Medicine, School of Medicine, University College Cork, Cork, Republic of Ireland

8 Department of Pharmacy, Cliniques Universitaires Saint-Luc, Brussels, Belgium

9 Institute of Pharmaceutical Medicine (ECPM), University of Basel, Basel, Switzerland

10 Department of Pharmacy, CHU UCL Namur, Yvoir, Belgium