CLINICAL INVESTIGATION

Benzodiazepine Use and Deprescribing in Belgian Nursing Homes: Results from the COME-ON Study

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BACKGROUND/OBJECTIVES: To describe the use and deprescribing of benzodiazepine receptor agonists (BZRAs) among nursing home residents (NHRs), to evaluate appropriateness of use and to identify factors associated with BZRA use and deprescribing.

DESIGN: Posthoc analysis of the Collaborative Approach to Optimize Medication Use for Older People in Nursing Homes (COME-ON) study, a cluster controlled trial that evaluated the impact of a complex intervention on potentially inappropriate prescriptions (PIPs) in nursing homes (NHs).

SETTING: A total of 54 NHs in Belgium.

PARTICIPANTS: A total of 797 NHRs included in the study who had complete medical, clinical, and medication information at baseline and at the end of the study (month 15).

MEASUREMENTS: Data were recorded by participating healthcare professionals. Reasons why BZRA use was considered as PIPs were assessed using the 2019 American Geriatrics Society Beers Criteria® and the Screening Tool of Older Persons' Prescriptions (STOPP) criteria, version 2. Deprescribing included complete cessation or decreased daily dose. We identified factors at the NHR, prescriber, and NH levels associated with BZRA use and BZRA deprescribing using multivariable binary and multinomial logistic regression, respectively.

RESULTS: At baseline, 418 (52.4%) NHRs were taking a BZRA. The use of BZRA for longer than 4 weeks, with two or more other central nervous system active drugs, and in patients with delirium, cognitive impairment, falls, or fractures was found in more than 67% of BZRA users. Eight NHR-related variables and two prescriber-related variables were associated with regular BZRA use. Deprescribing occurred in 28.1% of BZRA users (32.9% in the intervention group and 22.1% in the control group). In addition to four other factors, dementia (odds ratio [OR] = 2.35; 95% confidence interval [CI] = [1.45–3.83]) and intervention group (OR = 1.74; 95% CI = 1.07–2.87) were associated with deprescribing.

CONCLUSION: Use of BZRAs was highly prevalent, and reasons to consider it as PIP were frequent. Deprescribing occurred in one-fourth of NHRs, which is encouraging. Future interventions should focus on specific aspects of PIPs (ie, indication, duration, drug-drug and drug-disease interactions) as well as on nondementia patients. **J Am Geriatr Soc 00:1-10, 2020.**

Keywords: nursing homes; benzodiazepine; deprescribing; inappropriate prescribing; older adults

Benzodiazepine receptor agonists (BZRAs) encompass benzodiazepines and Z-drugs (zopiclone, eszopiclone, zolpidem, and zaleplon). These medications are widely prescribed for the management of insomnia and anxiety in older adults despite decades of evidence showing that long-term use in older adults is harmful and often not beneficial, resulting in an unfavorable benefit-risk ratio.[1-7] As a result, BZRAs are on the lists of potentially inappropriate prescription (PIP) criteria,[8,9] and deprescribing (the process of withdrawal or dose reduction of an inappropriate medication[10]) is strongly recommended in chronic BZRA users.[11,12]

Deprescribing of BZRAs is highly relevant in nursing home residents (NHRs), who are particularly at risk due to increased sensitivity and vulnerability.[13] Yet the prevalence

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DOI: 10.1111/jgs.16751

0002-8614/20/$15.00

of BZRA use in NHRs in Europe and North America remains high, with rates between 14.6% and 54.4%.[14-18] However, although the literature is replete with observational and experimental data on the use of antipsychotics in NHRs,[12,19-21] data about BZRA use and PIP in the nursing home (NH) setting remain limited.[19] Only a few studies have analyzed the evolution of BZRA use through an intervention, and most of these were conducted in a limited number of countries, had limited sample size, or lacked long-term follow-up.[17,22-24]

Identifying those factors associated with both BZRA use and BZRA deprescribing is a key step in the process of medication optimization. Female sex, older age, depression, sleeping issues, and anxiety are factors reported to be associated with BZRA use.[14,25-27] However, most of the data comes from the ambulatory setting,[25-30] and only a few studies have explored these factors in the NH setting.[14,31] Factors associated with BZRA deprescribing in NHRs remain unknown. It is likely that factors associated with BZRA prescribing and deprescribing differ between the NH setting and the ambulatory care setting, and between countries.

The Collaborative Approach to Optimize Medication Use for Older People in Nursing Homes (COME-ON) study was a cluster controlled trial performed in 54 Belgian NHs over a period of 15 months (April 2015–June 2016) to evaluate the effect of a complex intervention on the appropriateness of medicines prescribed for NHRs.[32] Overall, the intervention had a positive impact on the appropriateness of prescribing.[33] The COME-ON database offers a unique opportunity to explore further the appropriateness of use and deprescribing of BZRAs in NHRs.

The aim of the present study was to perform a post hoc analysis of the COME-ON study to (1) describe baseline BZRA use among Belgian NHRs, in terms of prevalence, medication use, dosage, regimen, duration, indications, and appropriateness and its associated factors, and (2) describe the BZRA deprescribing rate at the end of the follow-up among the Belgian NHRs and its associated factors.

METHODS

The COME-ON Study

This work is a post hoc analysis of data from the COME-ON study, a cluster controlled trial aimed at evaluating the impact of a complex intervention on PIPs in Belgian NHs. The protocol was described elsewhere.[32] In total, 54 NHs that applied to the study project and were eligible for randomization participated. Eligible NHRs were those aged 65 or older treated by a participating general practitioner (GP). Randomization was performed at the NH level. Allocation to study arms was stratified according to province, experience in case conferencing, and type of pharmacy (hospital or community pharmacy). Each GP only had patients either in the intervention or in the control group. A total of 1,804 residents were included. Participating healthcare professionals (HCPs) recorded data online at three study points: baseline, month 8, and month 15 (end of study). Medication data were recorded by pharmacists, administrative, and clinical data by nurses and comorbidities were recorded by the GP. For the present work, we analyzed data collected at baseline and at the end of the study (month 15).

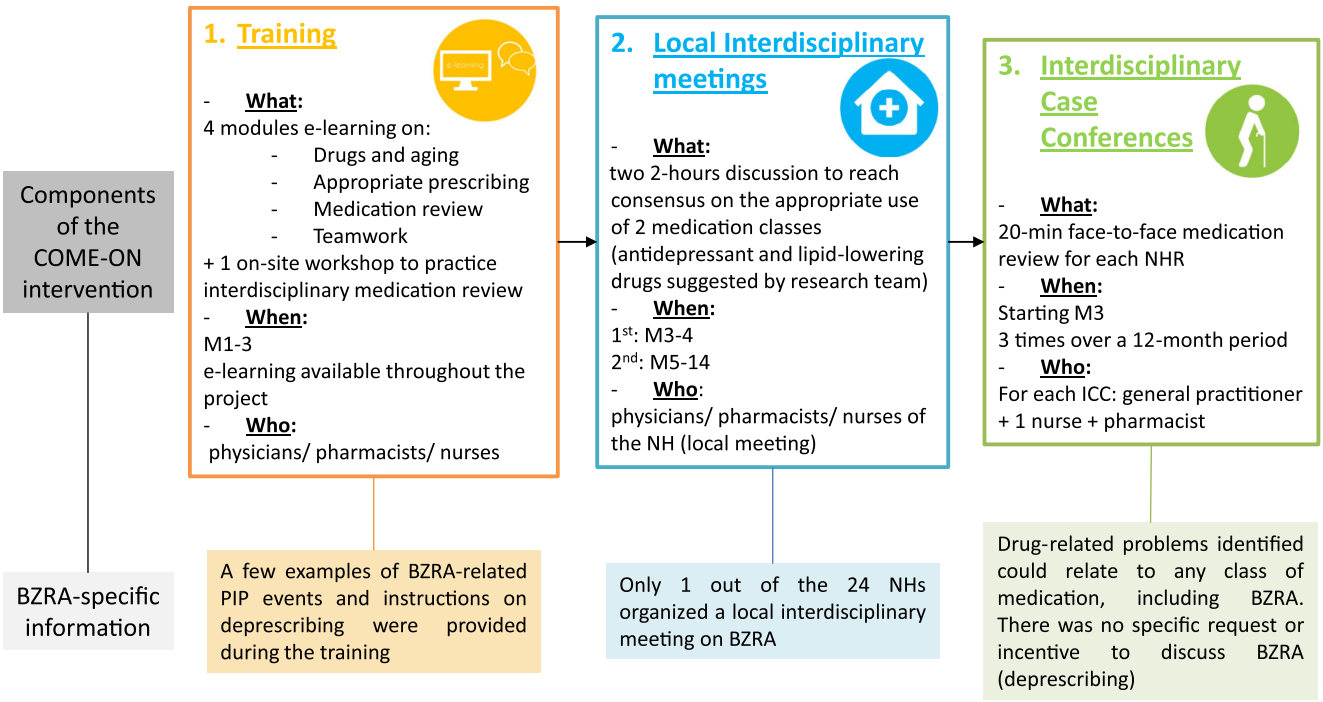

Figure 1. COME-ON intervention components and timeline, adapted from Anrys et al.[32] BZRA, benzodiazepine receptor agonists (benzodiazepines and related Z-drugs); ICC, interdisciplinary case conference; M, month; NH, nursing home; NHR, nursing home resident; PIP, potentially inappropriate prescriptions.

Table 1. Study Population Characteristics and BZRA Prescribing Patterns (N = 797)

Population characteristics	
Age, y[a]	
Median (IQR)	87 (81.75–91)
Sex, n (%)	
Male	215 (27.0)
Female	582 (73.0)
No. of medicines taken	
Median (IQR)	9 (6–12)
No. of CNS-active medicines taken	
Median (IQR)	3 (1–4)
Comorbidities (as reported by the GP), n (%)	
Insomnia	204 (25.6)
Anxiety (past or current)	235 (29.5)
History of falls in previous 3 mo	107 (13.4)
Dementia	183 (23.0)
Delirium, current	22 (2.8)
Depression, past or current	148 (18.6)
History of fragility fracture	101 (12.7)
BZRA prescribing patterns	
BZRA users, n (%)	418 (52.4)
BZRA multiple users, n (%)	76 (9.5)
Most prescribed BZRA, n (%)	
Lorazepam	123 (15.4)
Lormetazepam	108 (13.6)
Alprazolam	87 (10.9)
Zolpidem	71 (9.8)
Half-life of prescribed BZRA, n (%)	
Short- and intermediate-acting BZRA	392 (49.2)
Long-acting BZRA	49 (6.1)
Regimen, n (%)	
Regular use	380 (47.7)
If needed use[b]	37 (4.6)
Duration of use, n (%)	
≤4 wk	7 (.88)
>4 wk and ≤6 mo	41 (5.1)
>6 mo and ≤1 y	63 (7.9)
>1 y	323 (40.5)
Daily chronic BZRA dose among BZRA users (lorazepam equivalent in milligrams)	
Median (IQR)	1 (1–2)
(min; max)	(.25; 10.5)
Presumed indication,[c] n (%)	
BZRA user with documented insomnia	159 (19.9)
BZRA user with documented anxiety	154 (19.3)
BZRA user without documented insomnia or anxiety	175 (22.0)

Note: Short- and intermediate-acting BZRAs: triazolam, midazolam, zolpidem, alprazolam, bromazepam, oxazepam, lorazepam, lormetazepam, brotizolam, loprazolam, zopiclone, and clotiazepam. Long-acting BZRAs: diazepam, clorazepate, prazepam, flurazepam, nitrazepam, and flunitrazepam.

Abbreviations: BZRA, benzodiazepines receptors agonists (Anatomical Therapeutic Chemical classes N05BA, N05CD, and N05CF); CNS, central nervous system; GP, general practitioner; IQR, interquartile range.

[a]Five missing data (.63%).

[b]A resident was considered as an "if needed" user of BZRA when receiving an if needed BZRA without any chronic BZRA.

[c]According to comorbidities/health problems recorded by the GP.

The intervention encompassed (1) education and training of HCPs, (2) local interdisciplinary meetings (LIMs), and (3) repeated interdisciplinary case conferences (Figure 1). The intervention was global and not focused on BZRAs or psychotropic drugs. However, a few examples of BZRA-related PIPs and instructions on BZRA deprescribing were provided during the training. During case conferences, drug-related problems discussed could relate to any class of medication, including BZRAs, but there was no specific incentive to discuss BZRA deprescribing. The intervention was implemented in 24 NHs over a 15-month period. The 30 control NHs operated as usual.

Selection of Residents

For the present study, residents with medical, clinical, and medication data available at both baseline and end of study were included. Residents for whom BZRA deprescribing was not appropriate (ie, residents entering palliative care, residents with ongoing alcohol withdrawal) and residents with ongoing BZRA withdrawal documented at baseline were excluded.

Assessments

BZRA Use

For descriptive purposes, we extracted data at baseline and end of study relative to drug name, dosage, dosage regimen, time and duration of use, and presumed indications, based on comorbidities recorded by the GP (ie, insomnia and/or anxiety). These Anatomical Therapeutic Chemical classes were considered: N05BA, N05CD, and N05CF. To enable dosage comparisons, every BZRA dosage was converted into a lorazepam-equivalent dose, using a national conversion table.[34]

Factors Associated with BZRA Use at Baseline

The selection of factors for which the association with either chronic or as-needed BZRA use was to be tested was based on literature data[14,25-31] as well as on relevance as judged by the research team. These included factors at the level of the NHR (n = 29), the GP (n = 6), and the NH (n = 6) (detailed list of factors in Supplementary Table S1).

Reasons to Consider BZRAs as PIPs

We evaluated BZRA appropriateness at baseline and end of study in control and intervention groups, based on the 2019 American Geriatrics Society (AGS) Beers Criteria® (use of any BZRA; use of BZRA in a patient with delirium, dementia, or cognitive impairment, history of falls or fractures; simultaneous use of BZRA and opioid; simultaneous use of three or more central nervous system [CNS] active drugs),[9] and on the Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) criteria, version 2 (use of BZRA for >4 weeks; use of BZRA without "valid indication").[8] For the latter criterion, insomnia and anxiety were considered the only valid indications for BZRA use, based on Belgian recommendations[12] and from the Canadian Deprescribing Network.[11]

Deprescribing and Associated Factors

Deprescribing was defined as the achievement of any of these three situations: (1) complete cessation of BZRA, (2) decrease in overall chronic daily BZRA dose, and (3) cessation of an "if needed" BZRA prescription, in addition to an unchanged chronic dose. Data collection on deprescribing was performed by the main researcher (P.E.) who was blinded to intervention status at the time of data collection.

Factors potentially associated with BZRA deprescribing were selected through literature review[14,25-31] and discussion among research team members. These included factors at the level of the NHR (n = 31), the GP (n = 6), the NH (n = 6), and the study group (intervention or control) (detailed list of factors in Supplementary Table S2).

Statistical Analysis

Continuous variables are presented as medians (P_{25}; P_{75}). Categorical variables are presented as number and proportions.

Variables associated with the type of BZRA use ("regular" or "if needed") at baseline were assessed using a multinomial logistic regression. Variables associated with BZRA deprescribing were assessed using a logistic regression in people having a BZRA at baseline (N = 418). All variables associated with the outcome in univariate analysis with $P < .15$ were candidates for the multivariable model. A stepwise selection based on the Akaike information criterion was then applied to select the final multivariable model.

All analyses were performed using R software v.3.3.1. (R Foundation for Statistical Computing, Vienna, Austria); $P <. 05$ was considered statistically significant.

RESULTS

BZRA Use at Baseline and Associated Factors

From the 1,804 NHRs included in the COME-ON study, 511 left the study before the end (mainly because of death), 392 did not have complete data at baseline and/or end, and 104 were not eligible for BZRA deprescribing. In total, 797 NHRs were included in this analysis (Supplementary Figure S1). Comparison of included and excluded residents is available in Supplementary Table S3. The median age of the included NHRs was 87 years; 73.0% were women

Table 2. Factors Associated with Type of Use of BZRA at Baseline in Final Multivariable Multinomial Logistic Regression (N = 754)

	Multivariable model			
	BZRA regular vs no use		BZRA if needed vs no use	
Variable	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Patient's baseline characteristics				
Male	.83 (.57–1.21)	.335	2.50 (1.14–5.49)	.023[a]
Clinical characteristics at baseline				
Fall history in the past 3 mo	1.59 (1.07–2.38)	.022[a]	.80 (.31–2.11)	.658
Comorbidities at baseline				
Dementia	.66 (.44–.99)	.047[a]	.67 (.26–1.78)	.427
BPSD	1.05 (.69–1.61)	.805	3.95 (1.47–10.56)	.006[a]
Anxiety	1.60 (1.09–2.36)	.017[a]	.75 (.31–1.83)	.525
Insomnia	3.19 (2.10–4.84)	<.001[a]	4.15 (1.76–9.79)	.001[a]
COPD	1.73 (1.02–2.95)	.042[a]	.92 (.24–3.57)	.900
Medications at baseline				
No. of medications without BZRA				
0–4	1.00		1.00	
5–9	2.90 (1.70–4.96)	<.001[a]	1.06 (.31–3.58)	.926
10–13	2.79 (1.57–4.95)	<.001[a]	.90 (.23–3.50)	.876
≥14	4.00 (1.89–8.47)	<.001[a]	1.66 (.36–7.66)	.517
Antidepressant	2.74 (1.59–4.71)	<.001[a]	1.74 (.49–6.13)	.390
Trazodone	.46 (.26–.82)	.008[a]	2.55 (.91–7.17)	.076
SSRI	.65 (.37–1.12)	.118	1.53 (.55–4.21)	.414
NH characteristics				
Ratio of NHRs per nurse	.95 (.90–1.01)	.092	.87 (.72–1.06)	.180
GP characteristics				
Age, per 10 additional y	1.19 (1.01–1.40)	.036[a]	.85 (.61–1.18)	.324
Residents for which the GP is the CP	.69 (.48–.99)	.042[a]	.22 (.07–.68)	.009[a]

Abbreviations: BZRA, benzodiazepines receptors agonists (Anatomical Therapeutic Chemical classes N05BA, N05CD, and N05CF); BPSD, behavioral and psychological symptoms of dementia; CI, confidence Interval; COPD, chronic obstructive pulmonary disease; CP, coordinating physician; GP, general practitioner; NH, nursing home; NHR, nursing home resident; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor.
[a]Significant: $P < .05$.

Table 3. Evolution of BZRA-Related PIPs Prevalence between Baseline and Endpoint of the COME-ON Study

	Intervention group						Control group					
	Baseline			End			Baseline			End		
PIP criteria	n	% Total NHRs (N = 453)	% BZRA users (N = 237)	n	% Total NHRs (N = 453)	% BZRA users (N = 214)	n	% Total NHRs (N = 344)	% BZRA users (N = 181)	n	% Total NHRs (N = 344)	% BZRA users (N = 173)
Use of any BZRA	237	52.3	100.0	214	47.2	100.0	181	52.6	100.0	173	50.3	100.0
Duration of use												
Use of BZRA for >4 wk (STOPP D5)	235	51.9	99.2	211	46.6	98.6	176	51.2	97.2	168	48.8	97.1
Lack of indication reported by GP												
Use of BZRA without insomnia or anxiety (STOPP A1)	100	22.1	42.2	81	17.9	37.9	75	21.8	41.4	68	19.8	39.3
Drug-disease interaction												
Use of BZRA in patient with delirium, dementia, or cognitive impairment or history of falls or fractures (AGS Beers Criteria® 2019)	167	36.9	70.5	154	34.0	72.0	114	33.1	63.0	114	33.1	65.9
Drug-drug interaction												
Simultaneous use of BZRA and opioid (AGS Beers Criteria® 2019)	55	12.1	23.2	49	10.8	22.9	33	9.6	18.2	38	11.0	22.0
Simultaneous use of BZRA and two or more other CNS-active drugs (AGS Beers Criteria® 2019)	170	37.5	71.7	156	34.4	72.9	111	32.3	61.3	119	34.6	68.8

Abbreviations: AGS, American Geriatrics Society; BZRA, benzodiazepine receptor agonists (Anatomical Therapeutic Chemical classes N05BA, N05CD and N05CF); CNS, central nervous system; GP, general practitioner; NHRs, nursing home residents; PIPs, potentially inappropriate prescriptions; STOPP, Screening Tool of Older Persons' Prescriptions.

(Table 1). The number of medicines per NHR ranged from 0 to 25 with a median of 9.

Overall, 418 (52.4%) NHRs were prescribed a BZRA. Most users had been taking a BZRA for more than a year (n = 323 [77.3%]) and on a regular schedule (n = 380 [90.9%]). Of the 160 and 204 NHRs with reported anxiety and insomnia, respectively, 117 (73.1%) and 159 (77.9%) were taking a BZRA. Among BZRA users, 175 (41.9%) had no documentation of insomnia or anxiety by the GP. Baseline data are presented in Table 1.

In multivariable analysis, eight NHR characteristics and two GP characteristics but no NH characteristics were associated with regular BZRA use versus no BZRA use (Table 2). History of a fall in the past 3 months, anxiety, insomnia, chronic obstructive pulmonary disease, number of medicines without counting BZRA, use of antidepressant, and age of GP were associated with regular BZRA use. Conversely, dementia, use of trazodone, and being cared by the NH coordinating physician were associated with lower odds of regular BZRA use (Table 2 lists odds ratios [ORs] and 95% confidence intervals [CIs]). In the same model, three NHR characteristics and one GP characteristic but no NH characteristic were associated with *if needed* BZRA use versus no BZRA use (Table 2). Residents with insomnia, behavioral, and psychological symptoms of dementia and male residents were more likely to receive if needed BZRA than no BZRA. Anxiety was not associated with if needed prescriptions. Residents receiving care from the coordinating physician were less likely to receive if needed BZRA compared with no BZRA (Table 2 lists the ORs and 95% CIs, and Supplementary Table S4 describes the univariate model).

Potentially Inappropriate Prescriptions

All 418 BZRA users flagged the AGS Beers Criteria® "use of any BZRA" for potentially inappropriate medication. The STOPP criterion "duration of use over 4 weeks" was flagged for 98.3% of users. Many of these users had additional reasons for PIP: lack of indication (41.9% of users),

Table 4. Factors Associated with BZRA Deprescribing at the End of the Study in Univariate and Multivariate Logistic Regression[a]

	Univariate model		Multivariable model	
Variable	**OR (95%CI)**	***P* value**	**OR (95%CI)**	***P* value**
Study arm				
Intervention vs control	1.73 (1.12–2.71)	.016[b]	1.74 (1.07–2.87)	.029[b]
Clinical characteristics at baseline				
Katz score	1.06 (1.01–1.11)	.018[b]		
Dependency				
O	1.00			
A	3.47 (1.19–12.66)	.034[b]		
B	5.23 (1.94–18.28)	.003[b]		
C	5.03 (1.69–18.64)	.007[b]		
C dementia	7.61 (2.84–26.56)	<.001[b]		
D	15.31 (3.02–90.08)	.001[b]		
Hospitalization in the past 3 mo	1.79 (.95–3.32)	.066	2.01 (1.02–3.91)	.039[b]
Incontinence	1.70 (1.09–2.68)	.022[b]	1.52 (.92–2.52)	.103
Comorbidities at baseline				
Parkinson/Extrapyramidal syndrome	2.03 (1.12–3.63)	.018[b]	2.26 (1.19–4.25)	.011[b]
Dementia	2.31 (1.50–3.61)	<.001[b]	2.35 (1.45–3.83)	.001[b]
BPSD	2.14 (1.39–3,316)	.001[b]		
Delirium	2.22 (1.23–3.96)	.007[b]		
NH characteristics				
Ownership status				
Private nonprofit	1.00		1.00	
Private for commercial purposes	1.02 (.42–2.328)	.969	2.05 (.78–5.18)	.135
Public	.48 (.27–.81)	.008[b]	.53 (.29–.96)	.040[b]
No. of beds, per 10 beds	1.07 (1.02–1.12)	.004[b]	1.06 (1.01–1.12)	.025[b]
GP characteristics				
Age, per 10 y	.78 (.64–.95)	.015[b]	.84 (.68–1.05)	.133
No. of years of experience as a GP, per 10 y	.78 (.64–.95)	.015[b]		

Note: Dependency and number of years of experience as a GP per 10 years were not introduced as candidates for the final multivariable model because they presented a variance inflation factor >5.

Goodness-of-fit: Hosmer and Lemeshow test: *P* value = .337.

Abbreviations: BZRA, benzodiazepine receptor agonist (Anatomical Therapeutic Chemical classses N05BA, N05CD, and N05CF); BPSD, behavioral and psychological symptoms of dementia; CI, confidence interval; GP, general practitioner; NH, nursing home; NHR, nursing home resident; OR, odds ratio.

[a]Among NHRs with BZRA prescribed at baseline (N = 418) among the 418 people: 118 with BZRA deprescribing (28.2%).

[b]Significant: $P < .05$.

drug-disease interaction (BZRA and dementia, delirium, history of falls and fractures; 67.2% of users), or drug-drug interaction (BZRA and opioids or BZRA and two or more other CNS drugs; 21.1 and 67.2% of users, respectively) (Table 3).

In the intervention group, between baseline and end of study, we observed an absolute decrease in the prevalence of NHRs meeting each of these criteria, ranging from 1.3% to 5.3% of NHRs. In the control group, differences ranged from an absolute decrease of 2.4% to an absolute increase of 2.3% (Table 3).

BZRA Deprescribing and Associated Factors: Effect of the Intervention

Prevalence of BZRA use decreased from 52.3% (237/453) at baseline to 47.2% (214/453) at end of study in the intervention group (absolute decrease of 5.1%), and from 52.6% (181/344) to 50.3% (173/344) in the control group (absolute decrease of 2.3%).

Deprescribing at study end occurred in 32.9% of baseline users (78/237) in the intervention group and 22.1% (40/181) in the control group, with a combined deprescribing rate of 28.2% (118/418). A complete cessation of BZRA prescription was observed in 37 (47.4%) of the 78 NHRs with deprescribing in the intervention group and in 21 of 40 NHRs in the control group (52.5%) (combined study arms = 58/118 [49.2%]).

In the final multivariable model, the study arm, three NHR characteristics and two NH characteristics but no GP characteristic were associated with BZRA deprescribing (Table 4). The intervention group was associated with BZRA deprescribing. Dementia at baseline was highly associated with deprescribing. Parkinson's, extrapyramidal syndrome, and a history of hospitalization in the past 3 months were also associated with deprescribing. At the level of the NH, a higher number of beds was associated with deprescribing, whereas being institutionalized in a public NH was found to be associated with less deprescribing (Table 4 lists the ORs and 95%CIs). The complete analysis is available in Supplementary Table S5.

DISCUSSION

This post hoc analysis of the COME-ON study data reveals a high prevalence of BZRA use and of PIP related to BZRA use in NHRs in Belgium. Deprescribing occurred in 28% of NHRs, and the intervention had a significant impact on BZRA deprescribing. Several factors were found to be associated with BZRA use and with deprescribing, which is important to prepare improvement initiatives in the future. In contrast to the considerable attention that has been given to the use of antipsychotic drugs in NHs over the last decades, this is one of the first studies that evaluated the appropriateness of BZRA use, evolution over time, and factors associated with use and with deprescribing.

Use of BZRA was highly prevalent. At baseline, 52% of NHRs were receiving a BZRA. This is similar to a previous report from 2005 in which 53% of the 1,730 Belgian NHRs were BZRA users[14] and suggests no change over time in BZRA prescribing overall, despite rising awareness of their harms, strong international recommendations to avoid their use, and national campaigns.[35] The prevalence of BZRA use in NHRs in the present study was similar to the prevalence reported in NHRs in France (54.5%)[18] but much higher than the prevalence as reported in other countries such as Australia (31.8%) and Canada (14.6%).[17,22] Differences may be due to variations in terms of population, context, or culture. Indeed, in Belgium we also observed a very high overall prevalence of BZRA use in the ambulatory setting.[36] An in-depth evaluation of these differences and of the barriers and enablers of BZRA deprescribing in the NH setting in different countries would be highly valuable.

Beyond the high prevalence, our data show that BZRA use was often inappropriate in several aspects. Potential overuse is a major concern because 42% of BZRA users had no insomnia or anxiety reported by the GP, and 98% had been receiving a BZRA for longer than 4 weeks. In terms of potential misuse, approximately two-thirds of NHRs had a drug-disease interaction (ie, use of BZRA in patients with delirium, cognitive impairment, history of falls or fractures), and a similar proportion had a drug-drug interaction (ie, simultaneous use of BZRA and at least two other CNS drugs). These are, to the best of our knowledge, the first published data on several BZRA-related PIPs in NHRs. Together with the high prevalence rate, they call for urgent action toward more rational use of BZRA in NHRs. Further education of healthcare professionals (HCPs) around these PIP criteria and use as quality indicators may help achieve this objective. A project of this kind is currently ongoing in Flanders.[37]

Eight patient-related and two GP-related factors were significantly associated with regular BZRA use. Comparison with other studies is difficult because very few studies have analyzed factors associated with BZRA use in the NH setting[14,31] compared with the outpatient setting.[25-30] First, dementia was significantly associated with less regular BZRA use but also with BZRA deprescribing. Current literature reports similar as well as conflicting findings.[14,29,31] There may be fewer barriers toward the nonuse or deprescribing of BZRA in patients with dementia.[14] Second, there were fewer regular BZRA use versus no use among trazodone users. Off-label use of trazodone for its sedative properties is frequent,[38] and a switch from BZRA to trazodone was described elsewhere,[39-42] despite no strong evidence that low-dose trazodone is safer than BZRAs among older adults.[38] Third, the use of antidepressants was associated with regular BZRA use as compared with no use. This association might be of concern because the combination of psychotropic drugs is potentially harmful. Guidelines recommend that the association should be limited to 8 weeks, which is far from what we observed.[43] Finally, less BZRA use occurred among NHRs treated by the coordinating physician of the NH. The coordinating physician is in charge of the medication policy of the NH. Given this positive association, the role of the coordinating physician in the implementation of local strategies toward BZRA deprescribing seems promising.

Over the 15-month study period, the prevalence of BZRA use decreased from 52.4% to 48.6%, and deprescribing, a distinct and complementary concept, occurred in 28.2% of BZRA users. These data are encouraging. Our data also suggest that the intervention group did better than the control group. The intervention group was one of the

few factors significantly associated with BZRA deprescribing in the multivariate analysis. These results confirm that reducing BZRA use in the NH setting is feasible, and it suggests that a global approach toward more appropriate prescribing to NHRs, such as the COME-ON intervention, can also specifically decrease BZRA overuse. However, BZRA use was high and could often be considered a PIP because of additional drug-drug or drug-disease interactions, placing NHRs at greater risk of harm. This calls for further wide-scale, dedicated, and long-term initiatives.

A 2016 study in French NHs produced conflicting results, showing that a global geriatric intervention did not improve benzodiazepine discontinuation.[18] Possible explanations might be that the intervention did not target medications and could have been implemented with large variations between NHs. Moreover, this study used a control group that received an audit and feedback intervention. We may expect that higher rates of BZRA deprescribing could be achieved with an intervention targeting BZRA or psychotropic drugs. Indeed, in the COME-ON study, information on problems related to BZRA use was provided during training of HCPs but among other messages on many other medication classes. Specific barriers to BZRA deprescribing (eg, nonpharmacological approaches) were not addressed. Only one NH explicitly chose to focus an LIM on the use of BZRA. A retrospective propensity score-matched controlled study in 2019 among 1,653 NHRs with dementia in Spain found that team rounds, use of START/STOPP criteria, and use of patient decision aids were associated with a BZRA daily dose reduction of 23.1%, 39.5%, and 31.8%, respectively.[24] However, follow-up was limited to 4 weeks. In the RedUSe controlled trial led in 25 NHs in Australia, a multifaceted program that was very similar to the COME-ON intervention but focused on benzodiazepines and antipsychotics was implemented. At 6 months, a significant reduction was found in the prevalence of the use of benzodiazepines, from 31.8% to 26.9%.[22] This decrease is similar to that observed in our intervention group but not larger. Interestingly, benzodiazepine use continued to decline in intervention NHs in the year following the trial.[44] However, it is difficult to identify which part of the intervention had the greatest impact on BZRAs, and the study highlighted a lack of participation of physicians, which we think are important to involve. More recently, in Belgium, the effect of a practice improvement initiative including education, professional support, and transition to person-centered care at the NH level was reported. In five NHs over 12 months, the prevalence of BZRA use significantly decreased, from 32.2% to 23.4%.[45] The approach implemented, with an attention to psychotropic policy and nonpharmacological approaches at the NH level, is interesting, but the lack of a control group and the inclusion of only five NHs with baseline BZRA use lower than the national average limit the validity and generalizability of study findings. A detailed evaluation of barriers and enablers associated with BZRA deprescribing in our specific context could help the development of a theory-informed transferable intervention.

This study has several strengths. First, we analyzed the data of a large sample of NHRs, covering the two largest regions in Belgium (Wallonia and Flanders). Second, in contrast with other published data, we examined prescribing patterns in detail, including with regard to dosages and comorbidities, and we analyzed prescribing evolution case by case. Third, the study took place in real-life conditions with the involvement of HCPs working in the included NHs.

This study also has limitations. Several were related to its post hoc design. Indications for BZRA use were estimated by the research team, based on GP-recorded comorbidities, and there was no confirmation by HCPs. Some factors possibly associated with BZRA use or with deprescribing were not available from the research database, such as the availability and use of nonpharmacological alternatives or the attitude of residents or relatives toward BZRA deprescribing. Evolution of use over time and comparison of data from the intervention and control group remained descriptive only. We based the evaluation of PIPs on AGS Beers Criteria® and START/STOPP criteria. These are not specifically designed for NH use and therefore may not be relevant for some NHRs. Finally, a high number of patients were excluded due to missing data on comorbidities. Age, number of medicines, and BZRA use did not differ significantly between the group of NHRs included and excluded, but a selection bias cannot be ruled out.

In conclusion, this post hoc analysis highlighted the substantial and often inappropriate use of BZRAs among Belgian NHRs, the encouraging yet insufficient rate of deprescribing, and their associated factors including the complex intervention implemented in the COME-ON study. Future interventions should focus on the indication, duration of use, and drug-drug and drug-disease interactions, as well as paying attention to residents without dementia.

ACKNOWLEDGMENTS

Financial Disclosure: The COME-ON project was funded by the National Institute for Health and Disability Insurance (Belgium).

Conflict of Interest: The authors have declared no conflicts of interest for this article.

Author Contributions: *Conceptualized and designed the study*: Evrard and Spinewine. *Performed data cleaning and initial data analysis*: Evrard. *Performed statistical analyses*: Henrard. *Performed data analysis and interpretation*: All authors. *Wrote the initial draft of the manuscript*: Evrard. *Critically reviewed and edited the first and subsequent drafts of the manuscript*: Spinewine. *Critically revised the manuscript and read and approved the final manuscript*: All authors.

Sponsor's Role: The funding body had a limited role in the design of the COME-ON study, but it had no role in data collection, implementation, analysis, or the decision to publish the results.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Table S1: Factors analyzed for potential association with BZRA use in multinomial regression

Supplementary Table S2: Factors analyzed for potential association with BZRA deprescribing

Supplementary Table S3: Comparison of sociodemographic characteristics and baseline medication use between included and excluded nursing home residents

Supplementary Table S4: Factors associated with the type of use of BZRA at baseline in univariate and multivariable multinomial logistic regression

Supplementary Table S5: Factors associated with BZRA deprescribing at the end of the study in univariate and multivariate logistic regression among NHRs with BZRA prescribed at baseline (N = 418)

Supplementary Figure S1: Flowchart of nursing home residents selection for inclusion in the analysis