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Effects of a geriatric intervention aiming to improve quality care in nursing homes on benzodiazepine use and discontinuation

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Despite the harmful consequences potentially related to the use of benzodiazepines and related-z drugs (zopiclone and zolpidem) are well-known in older people, they are often prescribed for about half of Nursing Home (NH) residents
- Some experiments were effective in reducing poly-pharmacy and benzodiazepine (BZD) in NH residents
- Nothing is known concerning the effects of a more general intervention aiming at improving quality of care on BZD use in NH residents, and no study examined the predictive value of organizational NH aspects on future use/discontinuation of BZD in NH residents

BACKGROUND

Benzodiazepines and "Z drugs" are often prescribed in residents of nursing homes (NH) despite their well-known deleterious effects. We aimed to investigate if a general intervention on quality of care led to discontinuation of benzodiazepine, and to examine which NH-related factors were associated in change of benzodiazepines use.

METHODS

IQUARE is a quasi-experimental study, investigating the impact of an intervention based on a geriatric education with NH staff on several quality indicators of care (including appropriate prescriptions). All participating NH received an initial and 18-month audit regarding drug prescriptions and other quality of care variables. The analysis included 3973 residents, 2151 subjects (mean age: 84.6 ± 8.5 years; 74.3% women) in the control group and 1822 (mean age: 85.5 ± 8.1 years; 77.4% women) in the intervention group. Outcomes at 18 months were benzodiazepines use, long-acting benzodiazepines use, new-use of benzodiazepines, and discontinuation. The effect of the intervention was investigated using mixed-effect logistic regression models, including NH variables and residents' health status as confounders.

RESULTS

Higher reductions in benzodiazepine use (−2.8% vs. −1.5%) and long-acting benzodiazepine (−3.7% vs. −3.5%) were observed in intervention group, but not statistically significant. None of the structural and organisational NH-related variables predicted either discontinuation or new-use of benzodiazepines; hospitalisations and initial use of meprobamate increased the likelihood of becoming a new-user of benzodiazepines. Multivariate analysis suggested that living in a particular NH could affect benzodiazepines discontinuation.

WHAT THIS STUDY ADDS

- A non-specific intervention aiming to improve NH quality of care through education and support of NH staff did not reduce the consumption of both BZD and long-acting BZD among NH residents
- The prevalence of BZD use was not modified by the intervention, whereas the use of long-acting BZD was reduced in a similar way from 9.3 to 5.6% in the intervention group, and from 10.1% to 6.6% in the control group
- Baseline use of meprobamate and hospitalization during the interval were the most important factors associated with new-use of BZD in both intervention and control groups

CONCLUSIONS

A general intervention designed to improve overall NH quality indicators did not succeed in reducing benzodiazepines use. External factors interfered with the intervention. Further studies are needed to examine which NH-related aspects could impact benzodiazepines discontinuation.

Background

Residents of nursing homes (NH) frequently have multimorbid conditions, with associated polypharmacy [1]. Despite the harmful consequences potentially related to the use of benzodiazepines and related-"z drugs" (zopiclone and zolpidem) in older people [2–6], these drugs are often prescribed for about half of NH residents [7–9], with long-acting BZD being prescribed to around 10% of this population [8, 10].

Some experiments were found to be effective in reducing poly-pharmacy in NH residents. Kojima *et al.* showed that elaborating individualized recommendations about the appropriateness of patients' prescriptions and discussing the recommendations with the patients' primary physician reduced the number of medications prescribed and led to a reduction in medication costs [11]. In a 6-month intervention (including medication audit and feedback, educational sessions for staff and interdisciplinary sedative review) aiming at reducing the use of antipsychotics and BZD, Westbury *et al.* showed a reduction in the use of BZD in the intervention group compared with controls; this difference favouring the intervention group remained significant in a 12-month follow-up [12]. However, these studies were specifically designed to reduce drugs consumption; as far as we know, there is no study that investigated the effects of a more general (not drug-specific) intervention aiming at improving quality indicators in the NH in reducing BZD in NH residents. Moreover, although a few longitudinal studies examined the predictors of both future BZD use and BZD discontinuation [13–15], no study examined the predictive value of organizational NH aspects on future use/discontinuation of BZD in NH residents.

The purposes of this study were: (a) to investigate the effects of an intervention aiming to improve NH quality indicators by promoting closer relationships between NH medical staff and hospital geriatricians on the reduction BZD prescriptions for NH residents; (b) to examine which NH-related aspects would predict the use of BZD in a 18-month follow-up among non-users at baseline as well as which NH-related aspects would predict discontinuation in the use of these medications among BZD users at baseline when subject-related characteristics are controlled for.

Methods

This analysis used data from the IQUARE (*Impact d'une démarche QUAlité sur l'évolution des pratiques et le déclin fonctionnel des Résidents en EHPAD*) study. IQUARE's protocol was fully described elsewhere [16]. Briefly, IQUARE is a pragmatic multicentric individually-tailored non-randomized controlled trial designed to improve quality indicators related with frequent medical problems faced by NH staff (e.g., behavioural disturbances, falls); it was developed in NHs from Midi-Pyrénées, France (trial registration number: NCT01703689). NHs were allocated to one of the following two groups: 1) audit and feedback intervention on quality indicators associated to cooperative work meetings between hospital geriatricians and NH staff (intervention group), or 2) audit and feedback only (control group). IQUARE followed the principles of the Declaration of Helsinki and complied with ethical standards in France; study protocol was approved by the ethic committee of the Toulouse University Hospital

and the Consultative Committee for the Treatment of Research Information on Health (CNIL: 07–438).

Procedures

Data were collected by using two questionnaires, completed on-line by the NH staff: the NH administrative staff completed a questionnaire about NH structure and internal organization and the NH medical staff (mainly the coordinating physician in each NH) completed the resident-related questionnaire after collecting information on residents' health status from resident's medical chart. NH staff responded to these two questionnaires in two time-points: at baseline (Wave 1; May–July 2011) and 18 months later (Wave 2; November 2012-March 2013). After baseline data collection, each participating NH received the descriptive statistics regarding its own structure (for both control and intervention groups), residents' health status and indicators of quality, and the same descriptive statistics on the sub-regional and regional levels; this was the audit and feedback phase of the study. Only NHs allocated to the intervention group received two half-day visits from a hospital geriatrician; during these visits, the NH staff and the hospital geriatrician worked together to identify poor NH quality indicators' areas according to the audit and to establish tailored strategies to improve these quality indicators.

All drug prescriptions for each participant prescribed in the week of data collection during the two waves were recorded. Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification. Although each registered NH is required to have in its staff a coordinating physician with academic training in the care of older people and who is responsible for the health care coordination in the NH (in average, coordinating physicians spend one day and a half working in the NH), drug prescription for NH residents remains under the responsibility of the resident's primary care physician.

Outcomes

The main outcome measures of this study was BZD use (dichotomy: yes vs. no) at the follow-up time-point (Wave2). The secondary outcome measures were: (a) the use of long-acting BZDs at Wave two (dichotomy: yes vs. no); (b) new users of BZD (people who were not on BZD at Wave1 but who were on these drugs at Wave2), and (c) discontinuation in the use of BZD (people who were on BZD at Wave1 but who were no longer taking these drugs at Wave2). The consumption of each of the 22 BZD available in France was screened using ATC codes, whatever their indication of use. Participants who had taken at least one of these drugs met criteria for BZD use. We defined as long-acting BZD, drugs that had a half-life >24 h (see the list of BZD screened for in this study in Appendix 1).

NH-related variables

Based on our clinical and research experience in the NH setting, and assuming that there is a high variation across NHs on the quality of the health care provided [17], we selected the following NH-related variables collected at baseline that could be associated with both new-use and discontinuation of BZD: full-time equivalents (FTE) for the NH coordinating physician per 100 beds (continuous variable), nurse FTE per 100 beds, the presence of an computerized and integrated system to handle information on resident health care (including drug prescriptions), systematic solicitation (yes vs. no) of drug prescriber to re-evaluate prescriptions after 30 days of BZD use, presence of a pharmacy for internal usage (PIU, e.g., a pharmacy and a pharmacist inside the NH), and the number of different general practitioners (GP) per 100 beds (continuous).

Confounders

Based on the literature about the factors associated with BZD use/discontinuation [12–14], we selected the following variables (collected at baseline unless otherwise stated) as confounders: gender, age, length of stay in the NH (days), Charlson Comorbidity Index (CCI), depression, psychiatric diseases (other than depression), falls in the last 12 months collected at Wave two (only for the "discontinuation of BZD" model), hospitalization in the last 12 months collected at Wave 2, complaints about pain, analgesics, antipsychotics, antidepressants, meprobamate use, number of medications (other than those indicated before and other than BZD), and behavioural disturbances, (e.g. patients presenting any of the following: wandering, trying to elope, screaming, or aggressive behaviour). Because all medications containing meprobamate have been withdrawn from the French market in January 2012 [18], we expected that some people who were on this drug at Wave1 were switched to BZD at Wave2.

Statistical analysis

To detect baseline differences between groups, χ^2 test was used for categorical variables and t-test for independent samples or the Wilcoxon Rank Sum Test (for non-normal distributed variables) for continuous/discrete variables, as appropriate. To test the effects of the IQUARE intervention, mixed-effect binary logistic regressions using a "group $\times$ time" approach were performed on BZD use and on long-acting BZD use; a random NH effect was added to both BZD and long-acting BZD models to take into account the cluster-correlated nature of the data. Both models were adjusted for the baseline value of BZD or long-acting BZD and for the variables that differed between groups at baseline at $P \leq 0.15$. Within-group changes in both BZD and long-acting BZD were examined using the McNemar test.

With regard to the value of NH-related variables in predicting both new-use and discontinuation of BZD, we performed mixed-effect binary logistic regression models stratified by group allocation (separate analysis for the intervention group and for the control group), with a random NH effect added to the models; in these models, all NH-related variables and confounders were entered into the model. We tested the NH random effect to examine whether living in a particular NH affects both new-use and discontinuation of BZD; for this, we used likelihood ratio test statistics, calculated by subtracting the negative log likelihood of the models without the NH effect from the negative log likelihood of the models with NH effects. The resulting values were compared with the critical levels of a χ^2 distribution (according with the degrees of freedom), thus providing conservative *p* value estimates.

Multicollinearity was checked by using the variance inflation factor (VIF). All analyses were performed using Stata version 11 (College Station, TX: StataCorp LP).

Results

Among the 6275 residents (from the 175 participating NHs) who had their data collected at baseline (Wave1), 3973 had their data also collected at follow-up (Wave2) (from 163 NHs that completed the entire study). Twelve NHs (and their corresponding residents) dropped out mainly due to administrative issues (e.g., change of coordinating physician). Thus, from the 163 NH completing data collection at Wave 2, 77 were in the intervention group (1822 residents) and 86 in the control group (2151 residents). Compared to dropouts (people who died ($n = 1895$) and those who lived in NHs lost to follow-up ($n = 407$), corresponding to a total of 2302 dropouts), participants took more often both BZD (54.5% vs. 51.4%; $P = 0.016$) and long-acting BZD (9.7% vs. 8.2%; $P = 0.049$), were younger (85 ± 8.3 vs. 87.6 ± 7.6 years; $P < 0.001$) and more often women (75.8% vs. 70%; $P < 0.001$). More dropouts occurred in the intervention group compared to controls ($n = 1195$ (39.6%) vs. $n = 1107$ (34%), respectively; $P < 0.001$). Data on the use of BZD was available for 3973 participants at both waves of data collection; the prevalence of the use of each BZD and related-z drug at both Wave1 and Wave2 is presented in Appendix 1. Mean time between Wave1 and Wave2 (about 18.8 months) did not differ between groups ($P = 0.24$). Two hundred and twenty eight subjects (12.5%) of the intervention group took ≥2 different BZD at Wave1 and 251 (13.8%) at Wave2, while in the control group, they were 311 (14.5%) at Wave1 and 299 (13.9%) at Wave2. Two hundred sixty-one people (14.3%) reduced and 232 (12.7%) increased the number of different BZDs taken between Wave1 and Wave2 in the intervention group, while in the control group they were 331 (15.4%) to reduce and 293 (13.6%) to increase the number of BZDs. Table 1 shows the characteristics of NHs and residents according to group allocation.

Among the 1822 participants in the intervention group, 1014 (55.6%) took BZD at Wave1, whereas they were 962 (52.8%) at Wave2, while among the 2151 subjects in the control group, 1153 (53.6%) were on these drugs at Wave1 and 1120 (52.1%) at Wave2. For long-acting BZD, 170 (9.3%) subjects in the intervention group took these drugs at Wave1 and 102 (5.6%) at Wave2, whereas 217 (10.1%) of control were on these drugs at Wave1 and 142 (6.6%) at Wave2. Mixed-effect binary logistic regressions did not show significant effects of the IQUARE intervention on both BZD ("group x time" interaction: Odds ratio (OR) = 0.94; 95% confidence interval (CI) = 0.78–1.13; $P = 0.52$) and long-acting BZD ("group x time" interaction: OR = 0.91; 95%CI = 0.64–1.28; $P = 0.59$). However, within-group analyses found significant reductions in both BZD and long-acting BZD for the intervention group ($P = 0.004$ and $P < 0.001$, respectively), whereas only long-acting BZD was significantly reduced in the control group ($P < 0.001$; *p*-value for BZD in the control group was 0.12).

Regarding the new-use of BZD, among the 1806 subjects ($n = 808$ in the intervention group; $n = 998$ in the control group) who were not on BZD at Wave1, 135 (16.7%) people in the intervention group and 194 (19.4%) in the control group took at least one BZD at Wave2. Table 2 shows the mixed-effect binary logistic regression on the new-use of BZD stratified by group allocation. Any of the NH-related variables were not associated with the new-use of BZD, whereas meprobamate use at baseline and hospitalization in the last 12 months were residents' characteristics associated with new-use. The subtraction of the negative log likelihood of the models without the NH effect from the negative log likelihood of the models with NH effects for the intervention group regression and the control group regression resulted in the values of 0 and 0.39 (degree of freedom = 20), respectively, indicating that living in a particular NH does not affect the new-use of BZD.

Regarding the discontinuation of BZD, among the 2167 subjects ($n = 1014$ in the intervention group; $n = 1153$ in the control group) who were on BZD at Wave1, 187 (18.4%) people in the intervention group and 227 (19.7%) in the control group were no longer taking BZD at Wave2. Table 3 displays the mixed-effect binary logistic regression on discontinuation of BZD stratified by group allocation. Any of the NH-related variables were not associated with discontinuation of BZD, nor residents' factors such as falls in the last 12 months. The subtraction of the negative log likelihood of the models without the NH effect from the negative log likelihood of the models with NH effects for the intervention group regression and the control group regression resulted in the values of 34.7 and 33.1 (degree of freedom = 21), respectively, indicating that living in a particular NH affected discontinuation of BZD in both groups at $P < 0.05$.

Table 1

Baseline characteristics of intervention and control groups. Information on the NH-related variables is described at the NH level, whereas information on all the confounders is described for the 3973 participants (subject's level). Data are presented as mean and standard deviation (unless otherwise indicated) or percentage, as appropriate

Variables	Intervention group (N = 1822)	Control group (N = 2151)	*P*-value
Confounders			
Gender (women) (%)	77.4	74.3	0.023
Age (years)	85.5 (±8.1)	84.6 (±8.5)	<0.001
Length of stay in NH (days), median (25^{th}-75^{th} percentile)	1241 (528–2338)	1243 (528–2345)	0.83
Charlson Comorbidity Index	1.9 (±1.7)	1.9 (±1.7)	0.71
Depression (%)	35.8	32.7	0.036
Psychiatric diseases (other than depression) (%)	18.3	20.6	0.061
Falls in the last 12 months (%)	43.6	44.9	0.42
Hospitalisation in the last 12 months (%)	26.2	34.4	<0.001
Complaints about pain (%)	24	21.4	0.046
Analgesics (%)	47	45	0.19
Antipsychotics (%)	23.4	26.7	0.017
Antidepressants (%)	44.1	44.3	0.89
Meprobamate (%)	6	6.3	0.66
Behavioural disturbances (%)	31.8	31.7	0.94
Number of medications	6.5 (±3.1)	6.6 (±3.3)	0.19
NH-related variables			
FTE coordinating physician/100 beds, median (25^{th}-75^{th} percentile)	0.48 (0.31–0.53)	0.43 (0.26–0.53)	0.36
FTE nurse/100 beds, median (25^{th}-75^{th} percentile)	6.4 (5.3–7.1)	6.2 (5.1–6.9)	0.47
Computerized and integrated system (%)	80.5	82.6	0.74
Re-evaluate prescriptions after 30 days of BZD (%)	36.4	52.3	0.041
Pharmacy for internal usage (%)	14.3	18.6	0.46
GP/100 beds, median (25^{th}-75^{th} percentile)	17.3 (10–31.2)	13.5 (10–23.5)	0.024

BZD, benzodiazepine and related-z drugs; FTE, full-time equivalent; GP, general practitioner; NH, nursing home.

VIF values were <2 for all independent variables in all multivariate models (mean VIF value varied from 1.24 to 1.27), suggesting no multicollinearity.

Discussion

This study showed that an intervention aiming to improve NH quality indicators through education and support of NH staff did not reduce the consumption of both BZD and long-acting BZD among NH residents. Moreover, NH internal organization variables did not predict both the new-use and discontinuation of BZD. However, whereas living in a particular NH seems not to be important in determining future new-use of BZD, it probably plays a role in determining discontinuation of BZD.

Although, compared to controls, the intervention group have had higher reductions in both BZD (2.8% reduction vs. 1.5%) and long-acting BZD (3.7% reduction vs. 3.5%) consumption, these differences were not significant. Three main aspects could explain the lack of effect of our intervention on the consumption of BZD: IQUARE intervention, IQUARE design, and the functioning of the health system in France with regard to drug prescription. First, the IQUARE intervention constituted a general approach, with the purpose of improving the overall quality of care provided in NHs. The intervention was designed to NH staff rather than to residents. After data collection at baseline, all NH received descriptive statistics on their own structure, residents' health status and indicators of quality (for example prevalence of cognitive assessment performed in residents reported as dement; prevalence of residents evaluated for pain in the NH; prevalence of residents with more than two psychotropic drugs, prevalence of residents with long ½ life benzodiazepines…), compared to the same data presented as the mean value for all NH in the same area. In NH receiving intervention, these statistics were critically discussed during 2 half days meeting by a working group including the NH staff (coordinating physician, coordinating nurse and NH director) and a geriatrician. According to the specific weaknesses and strengths identified in the NH, strategies to improve quality indicators were decided on an individual case basis. Three levels of strategies were possible: 1- involving only NH internal organisation (implementation of regular use of scales for pain or behavioural disturbances); 2- involving complex collaborative strategies (establishing a framework for facilitating access to health care, for example dental care into the NH); 3- specific

Table 2

Mixed-effect binary logistic regression on future new-use of benzodiazepine/related-z drugs stratified by group allocation (intervention or control)*

Variables	New-use of BZD					
	Intervention group			Control group		
	OR	95% CI	p	OR	95% CI	p
NH-related variables						
FTE coordinating physician/100 beds	1.69	0.47–6.10	0.43	1.71	0.67–4.38	0.26
FTE nurse/100 beds	0.91	0.76–1.09	0.29	1.00	0.89–1.11	0.95
Informatics system (ref.: no)	0.91	0.48–1.72	0.77	1.46	0.84–2.53	0.18
Re-evaluate prescriptions after 30 days of BZD (ref.: no)	0.82	0.53–1.26	0.36	0.86	0.59–1.26	0.44
Pharmacy for internal usage (ref.: no)	1.45	0.72–2.92	0.29	1.00	0.58–1.73	0.99
GP/100 beds	0.99	0.98–1.01	0.52	1.00	0.98–1.02	0.87
Confounders						
Gender (ref. men)	0.96	0.61–1.52	0.86	***1.86***	***1.22–2.81***	***0.003***
Age	0.96	0.94–0.99	0.003	0.98	0.96–1.00	0.053
Length of stay in the NH	0.99	0.99–1.00	0.07	1.00	1.00–1.00	0.35
Charlson Comorbidity Index	0.91	0.80–1.04	0.18	0.96	0.85–1.07	0.46
Depression (ref.: no)	***2.10***	***1.20–3.69***	***0.01***	1.11	0.70–1.76	0.65
Psychiatric diseases (other than depression) (ref.: no)	0.81	0.43–1.52	0.51	1.51	0.91–2.47	0.11
Hospitalisation in the last 12 months (ref.: no)	***1.76***	***1.14–2.73***	***0.011***	***1.56***	***1.08–2.24***	***0.017***
Complaints about pain (ref.: no)	0.67	0.38–1.17	0.16	***1.82***	***1.19–2.78***	***0.005***
Analgesics (ref.: no)	1.23	0.80–1.89	0.33	1.09	0.75–1.58	0.66
Antipsychotics (ref.: no)	1.01	0.60–1.69	0.98	1.55	0.99–2.42	0.053
Antidepressants (ref.: no)	0.72	0.42–1.25	0.25	1.22	0.80–1.84	0.36
Meprobamate (ref.: no)	***3.33***	***1.72–6.43***	***<0.001***	***5.41***	***3.13–9.35***	***<0.001***
Number of medications	1.04	0.97–1.12	0.25	1.00	0.94–1.06	0.97
Behavioural disturbances (ref.: no)	***2.26***	***1.48–3.45***	***<0.001***	1.36	0.93–1.99	0.11

Note BZD, benzodiazepine and related-z drugs; CI, confidence interval; FTE, full-time equivalent; GP, general practitioner; NH, nursing home. *This analysis was performed only among participants who were not using BZD at Wave1 (baseline).

interventions of geriatricians, including for example telemedicine to present patients with behavioural disturbances or specific training on pain, diabetes, or dementia care. Thus, we cannot exclude that a more specifically designed intervention to reduce the use of BZD is needed to obtain effective results in the NH setting. Indeed, the RedUse project [12, 19], a 6-month multi-domain intervention designed to reduce the consumption of BZD and antipsychotics, was effective in reducing the number of NH residents regularly taking BZD; this intervention also obtained positive results in dose reductions/cessation of residents on BZD at baseline. By contrast, we have also to keep in mind the need to examine drug prescription on a global perspective, to avoid switching from specific drugs to other ones not necessarily safer. Second, with regard to IQUARE design, the control group was also an active-control group since they participated in the audit and feedback phase of the study; because both intervention and control groups reduced the prevalence of BZD (statistically significant within-group changes only for the intervention group), particularly long-acting BZD (statistically significant within-group changes for both groups), we cannot exclude that the audit and feedback phase of IQUARE led to these reductions. Moreover, the fact that the French Health Technology Assessment Agency (*Haute Autorité de Santé*, HAS) released specific guidelines to reduce the use of long ½ life BZD in November 2011, i.e. after Wave 1 and before Wave 2, may partly explain our results, even though the impact of recommendations on rationale prescribing in France is generally questionable [20]. Further studies with a traditional control group (receiving no intervention at all) are needed to confirm or reject this hypothesis. Third, regarding the functioning of the French health system, drug prescription for NH residents is under the responsibility of the primary care physician. Therefore, the NH coordinating physician is not directly in charge of drug prescription for residents.

We were unable to identify any associations of NH organizational aspects with both new-use and discontinuation of BZD. However, the exploratory results of likelihood ratio test statistics suggest that living in a particular NH should influence BZD discontinuation. This finding suggests that other NH-related variables that were not observed in our study would contribute to explain discontinuation of BZD. Although further studies are needed to find out which NH organizational and structural aspects better determine discontinuation of

Table 3

Mixed-effect binary logistic regression on discontinuation of benzodiazepine/related-z drugs stratified by group allocation (intervention or control)*

Variables	Discontinuation of BZD					
	Intervention group			Control group		
	OR	95% CI	p	OR	95% CI	p
NH-related variables						
FTE coordinating physician/100 beds	1.80	0.23–13.98	0.57	0.32	0.07–1.51	0.15
FTE nurse/100 beds	1.24	0.93–1.64	0.13	0.97	0.82–1.15	0.75
Informatics system (ref.: no)	2.04	0.74–5.65	0.17	1.17	0.48–2.85	0.73
Re-evaluate prescriptions after 30 days of BZD (ref.: no)	1.14	0.57–2.28	0.72	0.90	0.49–1.68	0.75
Pharmacy for internal usage (ref.: no)	0.41	0.13–1.33	0.14	1.08	0.45–2.60	0.86
GP/100 beds	0.99	0.97–1.02	0.63	1.00	0.96–1.04	0.90
Confounders						
Gender (ref. men)	***0.56***	***0.35–0.91***	***0.02***	0.88	0.57–1.36	0.57
Age	1.02	0.99–1.05	0.14	1.01	0.99–1.04	0.27
Length of stay in the NH	1.00	1.00–1.00	0.88	1.00	1.00–1.00	0.72
Charlson Comorbidity Index	0.98	0.87–1.11	0.78	1.01	0.90–1.13	0.87
Depression (ref.: no)	0.67	0.42–1.07	0.10	0.98	0.63–1.54	0.94
Psychiatric diseases (other than depression) (ref.: no)	0.90	0.51–1.57	0.70	0.72	0.42–1.22	0.22
Hospitalisation in the last 12 months (ref.: no)	1.35	0.87–2.08	0.18	0.99	0.68–1.43	0.95
Falls in the last 12 months (ref.: no)	0.72	0.48–1.08	0.12	1.26	0.88–1.79	0.20
Complaints about pain (ref.: no)	1.10	0.69–1.75	0.69	0.66	0.42–1.05	0.08
Analgesics (ref.: no)	0.90	0.60–1.35	0.61	1.20	0.83–1.73	0.32
Antipsychotics (ref.: no)	0.94	0.58–1.53	0.82	0.90	0.57–1.42	0.65
Antidepressants (ref.: no)	***1.83***	***1.16–2.91***	***0.01***	0.87	0.57–1.34	0.53
Meprobamate (ref.: no)	0.53	0.19–1.43	0.21	***0.21***	***0.06–0.77***	***0.018***
Number of medications	0.96	0.90–1.04	0.33	***0.90***	***0.84–0.96***	***0.001***
Behavioural disturbances (ref.: no)	1.14	0.74–1.74	0.56	1.19	0.80–1.75	0.38

BZD, benzodiazepine and related-z drugs; CI, confidence interval; FTE, full-time equivalent; GP, general practitioner; NH, nursing home. *This analysis was performed only among participants who were using BZD at Wave1 (baseline).

BZD, our results indicate that a NH effect should be taken into account in the statistical approach when researchers wish to investigate the use of drugs in NH residents. Among confounders, it is noteworthy that baseline use of meprobamate and hospitalization during the previous 12 months were found to be associated with new-use of BZD in both intervention and control groups. Since meprobamate has been withdrawn from the market for safety reasons in January 2012, we can hypothesize that patients treated with this drug have been switched to BZD, which are indubitably safer than meprobamate (even though the French Medicine Agency guidelines recommended a progressive withdrawal rather than a switch to another drug [18]). Results concerning the negative impact of a recent hospitalization are consistent with previous reports of incident benzodiazepine use post-hospitalization. It is discouraging that these figures have not diminished over time [21, 22], but it outlines the need of additional strategies to prevent new onset benzodiazepines, which could target for example practicing hospital pharmacists as well as post-hospitalization medication review by community-based pharmacists.

The main strengths of this study are: 1) this is one of the first studies investigating BZD use in NHs using a prospective design; 2) the large sample size; 3) our statistical approach, which took into account the cluster-correlated structure of the data; 4) the quality of our data on drugs since we had direct access to drug prescriptions and compliance of drug treatment is high because NH residents are closely monitored. The main limitations of this study are related to the fact that IQUARE was a quasi-experimental study without allocation for intervention or control groups at random. This choice was determined by the feasibility of a closed geriatric intervention among NH staff in some NHs according to their environment (geriatric network in French "filière gériatrique"). We adjusted our main analyses to the confounding variables that differed between intervention and control groups at baseline, which partly limited the importance of this bias. Moreover, although reflecting the real world of the NH setting, the high rate of mortality (30.2% in this study) led to a very high overall dropout rate (36.7%), which may have somehow affected our results. Finally, misclassification related to occasional BZD use may represent a source of bias since we had information on drug prescriptions in the week of data collection (for both Wave1 and Wave2).

In summary, to reduce the use of BZD in the NH setting health authorities and administrators should consider to develop specifically designed interventions since, as showed in this study, a general intervention designed to improve overall NH quality indicators was insufficient for this purpose. Detecting which NH-related aspects impact changes in BZD consumption in NH residents, particularly discontinuation of these drugs, would inform about the development of future and potentially effective interventions.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work. This work has been performed in the context of the academic research activity of the University of Toulouse and the INSERM (Institut National de la Santé et de la Recherche Médicale).

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Contributors

Bruno Vellas and Yves Rolland designed the IQUARE study, Philipe de Souto Barreto and Maryse Lapeyre-Mestre undertook the statistical analysis, Philipe de Souto Barreto, Maryse Lapeyre-Mestre and Philippe Cestac searched literature, and Philipe de Souto Barreto wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Appendix 1

Benzodiazepines and related z-drugs available in France ($n = 22$) according to drug class, ATC code and half-life*, and prevalence among the 3 973 participants

BZD/Z molecules	ATC code	Half-life (hours)	Number of participants (%) Wave1	Number of participants (%) Wave2
Anxiolytics				
Diazepam	N05BA01	Long (32-47 h)	34 (0.9)	41 (1)
Alprazolam	N05BA12	Medium (10-20 h)	217 (5.5)	246 (6.2)
Bromazepam	N05BA08	Medium (20 h)	286 (7.2)	191 (4.8)
Clobazam	N05BA09	Medium (20 h)	18 (0.45)	22 (0.5)
Potassium clorazepate	N05BA05	Long (30-150 h)	49 (1.2)	0 (0)
Clotiazepam	N05BA21	Short (4 h)	23 (0.6)	16 (0.4)
Ethyl loflazepate	N05BA18	Long (77 h)	3 (0.08)	3 (0.08)
Lorazepam	N05BA06	Medium (10-20 h)	213 (5.4)	187 (4.7)
Nordazepam	N05BA16	Long (30-150 h)	3 (0.08)	2 (0.05)
Oxazepam	N05BA04	Short (8 h)	551 (13.9)	741 (18.6)
Prazepam	N05BA11	Long (30-150 h)	121 (3.05)	130 (3.3)
Hypnotics/Sedatives				
Estazolam	N05CD04	Medium (17 h)	7 (0.18)	6 (0.15)
Flunitrazepam	N05CD03	Long (16-35 h)	3 (0.08)	2 (0.05)
Loprazolam	N05CD11	Short (8 h)	22 (0.55)	21 (0.5)
Lormetazepam	N05CD06	Medium (10 h)	95 (2.4)	95 (2.4)
Midazolam	N05CD08	Short (1.5–2.5 h)	0 (0)	0 (0)
Nitrazepam	N05CD02	Long (16-48 h)	6 (0.15)	9 (0.2)
Temazepam	N05CD07	Short (5-8 h)	1 (0.03)	0 (0)
Zopiclone	N05CF01	Short (5 h)	512 (12.9)	503 (12.7)
Zolpidem	N05CF02	Short (0.7–3.5 h)	411 (10.3)	393 (9.9)
Muscle relaxants				
Tetrazepam	M03BX07	Long (18-26 h)	18 (0.45)	12 (0.3)
Antiepileptics				
Clonazepam†	N03AE01	Long (20-60 h)	163 (4.1)	53 (1.3)

*Half-life was defined as follows: short: < 10 h; medium: 10–24 h; long: >24 h. Half-life interval for flunitrazepam, nitrazepam, tetrazepam and clonazepam overlaps 24 h; all of them were considered as long-acting drugs. †The reduction in the consumption of clonazepam is probably related to changes in French rules with regard to the prescription and dispensation of this drug. These changes occurred in January 2012, i.e. after IQUARE's Wave1 and before Wave2 of data collection. From this date, prescription of clonazepam must be initially prescribed by a neurologist or a pediatrician, for a maximum duration of 28 days, and only for treating epilepsy.

REFERENCES

1 Cool C, Cestac P, Laborde C, Lebaudy C, Rouch L, Lepage B, Vellas B, De Souto BP, Rolland Y, Lapeyre-Mestre M. Potentially inappropriate drug prescribing and associated factors in nursing homes. J Am Med Dir Assoc 2014; 15: 850. e1–9. doi:10.1016/j.jamda.2014.08.003.

2 Wagner AK, Zhang F, Soumerai SB, Walker AM, Gurwitz JH, Glynn RJ, Ross-Degnan D. Benzodiazepine use and hip fractures in the elderly: who is at greatest risk? Arch Intern Med 2004; 164: 1567–72.

3 Souchet E, Lapeyre-Mestre M, Montastruc JL. Drug related falls: a study in the French pharmacovigilance database. Pharmacoepidemiol Drug Saf 2005; 14: 11–6.

4 Bierman EJ, Comijs HC, Gundy CM, Sonnenberg C, Jonker C, Beekman AT. The effect of chronic benzodiazepine use on cognitive functioning in older persons: good, bad or Indifferent? Int J Geriatr Psychiatry 2007; 22: 1194–200.

5 Peron EP, Gray SL, Hanlon JT. Medication use and functional status decline in older adults: a narrative review. Am J Geriatr Pharmacother 2011; 9: 378–91.

6 Olazarán J, Valle D, Serra JA, Cano P, Muñiz R. Psychotropic medications and falls in nursing homes: a cross-sectional study. J Am Med Dir Assoc 2013; 14: 213–7.

7 Bourgeois J, Elseviers MM, Azermai M, Van Bortel L, Petrovic M, Vander Stichele RR. Benzodiazepine use in Belgian nursing homes: a closer look into indications and dosages. Eur J Clin Pharmacol 2012; 68: 833–44.

8 Azermai M, Elseviers M, Petrovic M, Van Bortel L, Vander SR. Geriatric drug utilisation of psychotropics in Belgian nursing homes. Hum Psychopharmacol Clin Exp 2011; 26: 12–20.

9 De Souto BP, Lapeyre-Mestre M, Mathieu C, Piau C, Bouget C, Cayla F, Vellas B, Rolland Y. Indicators of benzodiazepine use in nursing home residents in France: a cross-sectional study. J Am Med Dir Assoc 2013; 14: 29–33.

10 Barnett K, McCowan C, Evans JM, Gillespie ND, Davey PG, Fahey T. Prevalence and outcomes of use of potentially inappropriate medicines in older people: cohort study stratified by residence in nursing home or in the community. BMJ Qual Saf 2011; 20: 275–81.

11 Kojima G, Bell C, Tamura B, Inaba M, Lubimir K, Blanchette PL, Iwasaki W, Masaki K. Reducing cost by reducing polypharmacy: the polypharmacy outcomes project. J Am Med Dir Assoc 2012; 13: 818.e11–5.

12 Westbury J, Tichelaar L, Peterson G, Gee P, Jackson S. A 12-month follow-up study of « RedUSe »: a trial aimed at reducing antipsychotic and benzodiazepine use in nursing homes. Int Psychogeriatr IPA 2011; 23: 1260–9.

13 Bartlett G, Abrahamowicz M, Grad R, Sylvestre M-P, Tamblyn R. Association between risk factors for injurious falls and new benzodiazepine prescribing in elderly persons. BMC Fam Pract 2009; 10: 1.

14 Fang S-Y, Chen C-Y, Chang I-S, Wu EC-H, Chang C-M, Lin K-M. Predictors of the incidence and discontinuation of long-term use of benzodiazepines: a population-based study. Drug Alcohol Depend 2009; 104: 140–6.

15 Alessi-Severini S, Dahl M, Schultz J, Metge C, Raymond C. Prescribing of psychotropic medications to the elderly population of a Canadian province: a retrospective study using administrative databases. Peer J 2013; 1: e168.

16 De Souto BP, Lapeyre-Mestre M, Mathieu C, Piau C, Bouget C, Cayla F, Vellas B, Rolland Y. A multicentric individually-tailored controlled trial of education and professional support to nursing home staff: research protocol and baseline data of the IQUARE study. J Nutr Health Aging 2013; 17: 173–8.

17 Tolson D, Rolland Y, Andrieu S, Aquino J-P, Beard J, Benetos A, Berrut G, Coll-Planas L, Dong B, Forette F, Franco A, Franzoni S, Salvà A, Swagerty D, Trabucchi M, Vellas B, Volicer L, Morley JE, The International Association of Gerontology and Geriatrics/World Health Organization/Society Française de Gérontologie et de Gériatrie Task Force. International Association of Gerontology and Geriatrics: a global agenda for clinical research and quality of care in nursing homes. J Am Med Dir Assoc 2011; 12: 184–9.

18 Agence Nationale du Médicament et des Produits de Santé (ANSM). Spécialités contenant du méprobamate seul: Suspension des autorisations de mise sur le marché (AMM) à compter du 10 janvier 2012 - Lettre aux professionnels de santé. Available at http://ansm.sante.fr/S-informer/Informations-de-securite-Lettres-aux-professionnels-de-sante/Specialites-contenant-du-meprobamate-seul-Suspension-des-autorisations-de-mise-sur-le-marche-AMM-a-compter-du-10-janvier-2012-Lettre-aux-professionnels-de-sante (last accessed 30 July 2015).

19 Westbury J, Jackson S, Gee P, Peterson G. An effective approach to decrease antipsychotic and benzodiazepine use in nursing homes: the RedUSe project. Int Psychogeriatr IPA 2010; 22: 26–36.

20 Gallini A, Andrieu S, Donohue JM, Oumouhou N, Lapeyre-Mestre M, Gardette V. Trends in use of antipsychotics in elderly patients with dementia: impact of national safety warnings. Eur Neuropsychopharmacol 2014; 24: 95–104.

21 Edwards C, Bushnell JL, Ashton CH, Rawlins MD. Hospital prescribing and usage of hypnotics and anxiolytics. Br J Clin Pharmacol 1991; 31: 190–2.

22 Halme AS, Beland SG, Preville M, Tannenbaum C. Uncovering the source of new benzodiazepine prescriptions in community-dwelling older adults. Int J Geriatr Psychiatry 2013; 28: 248–55.