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Risk of Falls Associated with Sedative-Hypnotics in Polymedicated Older Patients

Montero-Balosa MC[1*], Palma-Morgado D[2], Alvarado Fernández D[3], Vela-Márquez C[4], Gutiérrez-Gil JF[2], Sánchez-Blanco J[5], Pérez-Fuentes F[6], Sagristá-González M[1], Segura del Real FA[2] and Vilches-Arenas A[7]

[1]Aljarafe-Sevilla Norte Primary Care District, Andalusian Health Service, Seville, Spain.

[2]Seville Primary Care District, Andalusian Health Service, Seville, Spain.

[3]Virgen Macarena Hospital, Andalusian Health Service, Seville, Spain.

[4]Málaga-Guadalhorce Primary Care District, Andalusian Health Service, Málaga, Spain.

[5]Sevilla Sur Primary Care District, Andalusian Health Service, Seville, Spain.

[6]Jaén Norte Primary Care District, Andalusian Health Service, Jaén, Spain.

[7]Medical School, University of Seville, Seville, Spain.

[*]Correspondence:

MC Montero-Balosa, Servicio de Farmacia de Atención Primaria, Distrito de Atención Primaria Aljarafe-Sevilla Norte, C/ Avenida de Las Américas S/N, 41927-Mairena del Aljarafe, Sevilla, España, Tel: +34677778901; Fax: 34955515076.

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ABSTRACT

***Introduction and Objective**: To investigate whether reducing the use of ≥2 benzodiazepines and Z–drugs (BZD-Z) to ≤1 was associated with a decreased fall risk in polymedicated and elderly patients.*

***Material and Methods**: Prospective observational study to compare the fall risk in patients that remained taking 2 or more BZD-Z with those who tapered to 1 or none BZD-Z. Subjects were polymedicated patients, ≥65 years with concomitant use of ≥2 BZD-Z who received primary care in health centres. Main Measures: time to fall (Kaplan-Meier, Cox-regression model, multivariate analysis). Analyses was adjusted for confounder variables such as health problems and other treatments.*

***Results:** A total of 228 patients taking BZD-Z were followed during 1,085 days. Patients using ≥2 BZD-Z had 2.76 times (95%CI:1.34-5.68; p=0.006) greater risk of fall at any moment of the follow-up than those taking ≤1 BZD-Z. Antidepressants and oral corticosteroids were the other specific medication classes that showed a greater risk of fall:1.99 (95%CI:1.17-3.41; p=0.011) and 2.34 (95%CI:1.13-5.07; p=0.023), respectively. The Kaplan-Meier method revealed a significant increase of fall risk for patients continuously taking ≥2 BZD-Z compared with those intermittently taking ≥2 BZD-Z or taking ≤1 BZD-Z (p=0.008). Those patients concurrently using ≥2 BZD-Z and antidepressants showed a tendency to an increased fall risk (p<0,043).*

***Conclusions:** Reducing the number of BZD-Z to below 2 is associated with a reduced fall risk. The concomitant BZD-Z use with antidepressants is associated with an increased fall risk in polymedicated elderly patients.*

Keywords
Falls, Benzodiazepines, Polypharmacy, Elderly, Deprescribing.

Introduction
Sedative-hypnotic drugs, such as benzodiazepines and Z-drugs (BZD-Z), are one of the most commonly prescribed drugs to treat anxiety and sleep or mood disorders in elderly patients, who are more likely to experience adverse drug effects than younger populations [1]. Z-drugs were initially promoted as alternative treatment to benzodiazepines for insomnia because of their more selective hypnotic profile and shorter elimination half-life values [2]. Consequently, the trend of co-prescribing multiple benzodiazepines and Z-drugs to treat different clinical indications has been identified as a common prescribing pattern [2-5]. However, there is a lack of evidence of any clinically useful differences between both drug classes in terms of effectiveness, side effects, dependence or abuse [2].

BZD-Z are generally regarded by clinical practice guidelines as a short-term therapeutic option but long-term use, beyond 4 weeks, has actually become a common clinical practice [2,3,5,6]. Psychotropic drugs, specifically BZD-Z, are a therapeutic class that reveals a major difficulty for discontinuation [7-10].

Several studies have shown that benzodiazepines independently increase the risk of fall, hip fractures and motor vehicle accidents [11-14]. People aged 65 and older have the highest risk of falling, with 30% of people older than 65 and 50% of people older than 80 falling at least once a year [12]. The human cost associated to falling includes distress, pain, injury, loss of confidence, loss of independence and mortality. Falling also affects the family members and carers of people who fall and have an impact on quality of life, health and healthcare costs [12].

Most of the previous studies that have evaluated the fall risk focused either on older people in hospital/nursing settings, the benzodiazepine half-life or the dosage of benzodiazepine [11,15-20]. However, it has not been consistently studied whether exposure duration to BZD-Z, the concomitant consumption of several BZD-Z or the uses of other simultaneous medication could lead to different fall risks. The goal of this study was to investigate whether reducing the use of two or more medications in the benzodiazepine and Z classes to one or fewer was associated with a decreased fall risk in community-dwelling, polymedicated, and elderly patients and whether the fall risk might be increased with other concomitant treatments.

Material and Methods
Design
We carried out a prospective observational study in an intervention population to compare the fall risk in the group of patients that remained taking 2 or more BZD-Z with those who tapered to 1 or none BZD-Z throughout the follow-up.

Setting
The scope of the study embraced 7 health areas of primary care, situated in 5 different provinces in Andalusia, Spain (Figure 1).

Cohort Identification
The selection of the primary care health centres in each province was carried out through random tables. The objective and methodology of the study were shown by primary care pharmacists or physicians to GPs belonging to the randomly selected centres to enlist their collaboration. A total of 144 GPs agreed to participate and signed a document of assignment to the study. Each GP would attend an average of 1,200 patients. The population sample of reference was obtained from all patients belonging to the medical

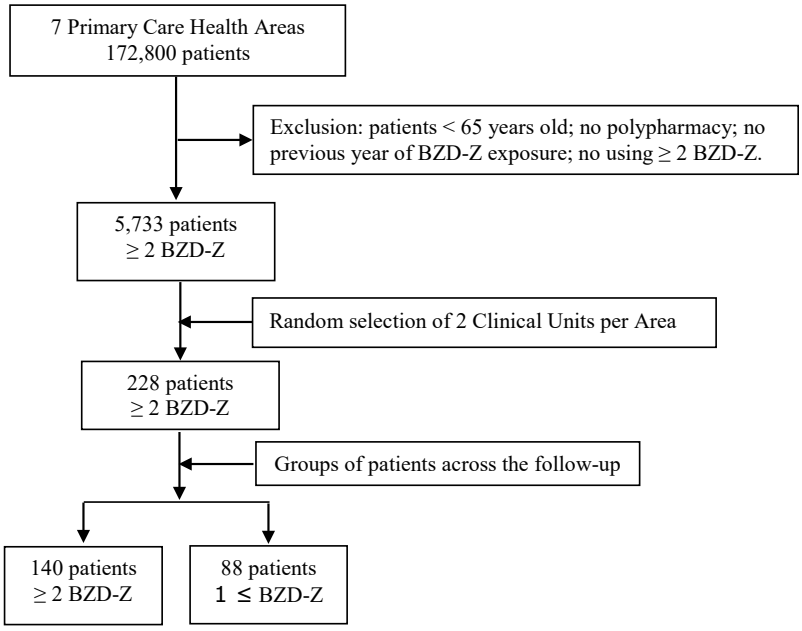

Figure 1: Study population. BZD-Z: benzodiazepines and Z-drugs. Clinical Units are constituted by several Primary Care Health Centres.

records of the GPs who agreed to participate in the study. The initially screened patients were 175,841. A total of 5,733 patients (3.3%) fulfilled the following inclusion criteria: polymedicated (≥ 5 drugs), 65 years or older, and a concomitant use of ≥2 short or long-acting benzodiazepines or Z-drugs (zolpidem, zopiclone). All benzodiazepines available in Spain during the follow-up were considered, i.e., alprazolam, bromazepam, clorazepate, diazepam, flurazepam, halazepam, lorazepam, lormetazepam, medazepam and triazolam.

Patients to be included in the cohort should have been taking ≥ 2 BZD-Z during 6-12 months over the year before the beginning of the study.

The exclusion criteria were: died before the completion of the pre-intervention phase, had unavailable computerized health records or belonged to private companies of health assistance. The cohort of patients was selected in March 2013. The follow-up was June 2013-June 2016. All patients were followed until the end of the study.

Sample size

In order to calculate the sample size from the total of 5,733 patients fulfilling inclusion criteria, it was assumed a 40% withdrawal resolution of the benzodiazepines during the follow-up time [21]. Considering an alpha risk of 0.05, through a bilateral hypothesis and study potential of 80% (beta=0.20), the final selected sample was 228 (Figure 1). A total of 2-3 patients fulfilling inclusion criteria per each GP were randomly selected to be included in the study to achieve that sample size.

Interventions

Interventions were addressed to all GPs who had agreed to participate in the study with the aim of enlisting their collaboration to reduce the number of patients taking BZD-Z. It would make possible to provide groups of patients with different BZD-Z regimens along the follow-up period.

Six semester interventions were carried out during the follow-up. The first intervention was carried out in June 2013 and the last one in December 2015. The interventions consisted of hour-long workshops on training in managing BZD-Z discontinuation, optimal gradual dose reduction, and patient information. Training was provided by primary care pharmacists or GPs with extensive experience in the management of BZD-Z withdrawal. The workshops were focused on discussing different clinical cases with barriers to deprescribing, and feedback information about success on BZD-Z withdrawals in their patients in the follow-up. Scientific information was sent to each GP by email about any recent research in relation to facilitating BZD-Z withdrawal.

Data source

Electronic clinical record and medication use were obtained from the health service prescription database and GPs' records. The first data were collected and evaluated in December 2013 (six months after the first intervention) and the last records in June 2016. The study was based on a time-varying BZD-Z exposure that changed in real time with each 6-month follow-up data collection. BZD-Z intermittent use was defined as a patient that stopped taking the drug for a period > 30 days.

Study Variables

The primary outcome was time to fall: time between the start of follow-up and registered fall. A fall incident was defined as an unintentional change in position resulting in coming to a rest at a lower level or on the ground [22]. Secondary variables were age, gender, morbidity, and type and duration of treatments. Variables such as socioeconomic status or history of falls or fracture were not considered due to an under reporting by clinicians and nurses in the medical records.

Monitoring of falls

All falls were collected from patient's medical history.

Statistical Analysis

Continuous variables were summarized with typical and average deviations and, in the case of very asymmetrical distributions, with medians and inter quartile procedures (P25 and P75). Kaplan-Meier survival curves were plotted to calculate the time to fall. The log-rank test was employed in order to compare the uniformity of the distributions of fall rates among the different groups. The Hazard Ratios for time-to-fall were calculated using a Cox-regression model. Subgroup analyses were performed to assess confounder variables such as health problems and other treatments. A prior univariate analysis was employed to identify other potential confounders to the time factor leading to fall. A multivariate analysis to construct the final model was created with such selected variables. A standard significance of < 0.05 in the univariate analysis prior to the multivariate analysis was taken into account. The hazard ratios and 95% CI were calculated for the selected variables. Results were assumed as statistically significant when the level of significance was below 0.05. All analyses were conducted using SPSS version 25.0.

Results

A total of 228 patients taking BZD-Z were followed for 1,085 days (3 years) (Figure1). The mean age of the participants was 74.1 years (range 65-90 years; standard deviation: 6.2), 73.2% were female. No age difference was observed in gender (women: 74.4±6.4; men: 73.4±5.5 years old; p=0.403). The duration of BDZ-Z therapy over the study period was: 75th percentile, 850 days; 50th percentile, 485 days and 25th percentile, 184 days. Of the 228 patients following the intervention, 88 reduced their number of BZD-Z prescriptions from 2 or more, to below 2. A total of 54 patients (23.6%) experienced a fall during the 1.085-day-follow-up and 28 patients of this group (51.9%) suffered a fracture. Fourteen patients fell down twice, one patient fell 4 times and, another 6 times.

Univariate analysis based on Cox-regression model showed that age, gender or health problems were not associated with fall risk (Table 1).

Table 1: Univariate analysis based on Cox regression for variables related to fall risk.

Variable	HR	95% CI	*p*
Age	1.00	0.96-1.05	0.924
Gender			
Woman	1.00		
Man	0,69	0.36-1.35	0.288
Medical history			
Hypertension	0.99	0.56-1.74	0.967
Stroke	1.76	0.55-5.64	0.342
Artrosis	0.91	0.51-1.63	0.752
Asthma	0.69	0.10-5.01	0.716
Mellitus Diabetes	0.38	0.14-1.05	0.061
Peripheral artery disease	0.73	0.22-2.23	0.569
Previous fracture	2.36	0.94-5.92	0.068
Atrial fibrillation	2.20	0.88-5.53	0.092
Benign prostatic hyperplasia	0.92	0.22-3.77	0.907
Hyperlipidemia	1.19	0.63-2.25	0.602
Hypothyroidism	0.56	0.14-2.28	0.416
Heart attack	1.80	0.44-7.34	0.416
Heart failure	1.35	0.42-4.33	0.614
Renal insufficiency	1.36	0.42-4.36	0.605
Osteoporosis	1.93	0.87-4.27	0.105
Peptic ulcer	1.80	0.44-7.38	0.416
Number of drug types (Polypharmacy)			
≤ 5	1		
6-10	1.91	0.81-4.49	0.139
> 10	1.95	0.63-6.05	0.247
Specific drug types			
Angiotensin conveting enzyme inhibitor	1.18	0.68-2.04	0.551
Angiotensin receptor blocker	0.94	0.52-1.71	0.843
Antiagregants	0.98	0.56-1.70	0.932
Antiarrhythmics	1.17	0.16-8.45	0.878
Antidepressants	1.99	1.17-3.41	0.011
Antipsychotics	1.15	0.42-3.20	0.785
≥ 2 Benzodiazepines-Z-drugs	2.76	1.34-5.68	0.006
β-adrenergics	1.53	0.66-3.59	0.323
β -blockers	1.03	0.53-2.00	0.940
Bronchodilators	1.41	0.71-2.81	0.325
Calcium antagonists	1.11	0.62-2.00	0.732
Digoxin	2.76	0.86-8.85	0.087
Diuretics	1.32	0.76-2.27	0.326
Fibrates	0.89	0.12-6.40	0.904
Fracture prevention drugs	1.15	0.58-2.30	0.685
Inhaled corticosteroids	1.30	0.59-2.89	0.515
Insulins	0.26	0.64-1.07	0.062
Nosteroidal anti-inflammatory drug	0.89	0.51-1.53	0.663
Oral corticosteroids	2.34	1.13-5.07	0.023
Protom Pump Inhibitors	1.41	0.66-2.98	0.374
Statins	1.05	0.61-1.81	0.849

Patients using ≥ 2 BZD-Z had 2.76 times (95%CI: 1.34-5.68; *p*=0.006) greater risk of fall at any moment of the follow-up than those taking ≤ 1 BZD-Z. Antidepressants and oral corticosteroids were the other specific medication classes that showed a greater risk of fall: 1.99 (95%CI: 1.17-3.41; *p*=0.011) and 2.34 (95%CI: 1.13-5.07; *p*=0.023), respectively (Table 1).

The final multivariate model showed that increased fall risk with ≥ 2 BZD-Z persisted after adjustment for antidepressants and oral corticosteroids (Table 2). The Kaplan-Meier method revealed a significant increase of fall risk for patients continuously taking ≥ 2 BZD-Z (n=25) compared with those intermittently taking ≥ 2 BZD-Z (n=115) or taking ≤ 1 BZD-Z (n=88) (*p*=0.008) (Figure 2). Those patients concurrently using ≥ 2 BZD-Z and antidepressants showed a tendency to a greater fall risk as it is illustrated in figure 3 (p<0,043).

Table 2: Multivariate analysis based on Cox Regression for drugs related to fall risk.

Drugs	HR	95% CI	*p*
≥ 2 Benzodiazepines-Z-drugs	2.72	1.30-5.71	0.008
Antidepressants	1.87	1.09-3.22	0.024
Oral Corticosteroids	2.82	1.31-6.07	0.008

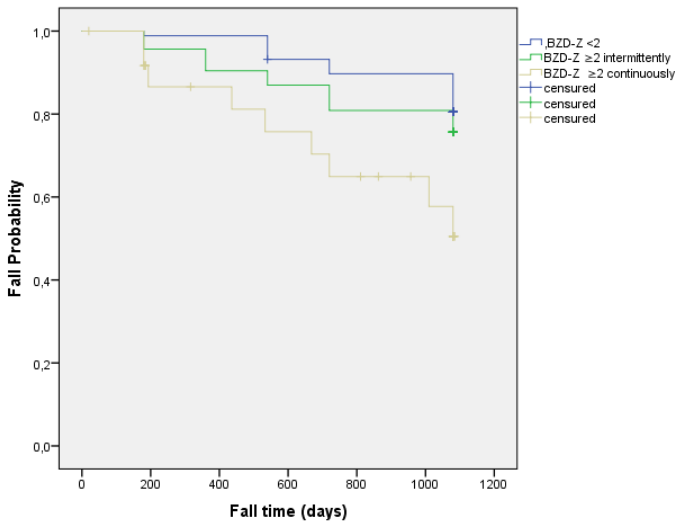

Figure 2: Kaplan-Meier fall risk and use of different doses of benzodiazepines and Z-drugs (BZD-Z). The data revealed a significant increase of fall risk for patients continuously taking ≥ 2 BZD-Z (n=25) compared with those intermittently taking ≥ 2 BZD-Z (n=115) or taking ≤ 1 BZD-Z (n=88) (*p*=0.008).

Discussion

The results of the study revealed that elderly patients who continuously took 2 or more medications in the BZD-Z class had a greater risk of falling than those who reduced the number of medications in this class to 1 or fewer. The tendency to fall also showed significant differences depending on the BZD-Z regimen (continuous or intermittent use). Those patients taking BZD-Z medications intermittently had a lower fall risk. However, the concurrent use of antidepressants and BZD-Z showed a greater fall risk.

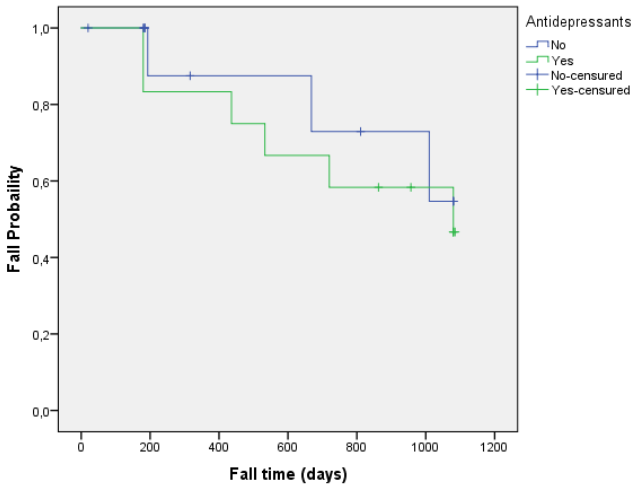

Figure 3: Kaplan-Meier fall risk: concomitantly use of antidepressants and ≥ 2 benzodiazepines and Z-drugs. Those patients concurrently using ≥ 2 BZD-Z and antidepressants showed a tendency to a greater fall risk (p<0,043).

An important issue to be highlighted in this study was the success of the interventions in reducing the number of patients taking 2 or more BZD-Z. These interventions were not the objective to be evaluated in this study. They were only designed to achieve the goal of creating two cohorts in the follow-up to be compared: patients taking ≥ 2 BZD-Z and 1 ≤ BZD-Z.

Kaplan-Meier analysis of fall risk showed a tendency toward falling with the use of BZD-Z through the follow-up. These findings were confirmed by multivariate Cox regression model, adjusting by other variables. The final results showed a greater fall risk (2.7 times) with 2 or more BZD-Z continued use.

These results are in line with those obtained in previous studies although researchers did not evaluate the fall risk associated with the concomitantly use of several benzodiazepines. The meta-analysis by Seppala et al. [20] indicated that benzodiazepines were associated with a higher risk of falls although the authors proposed more studies to investigate the effect of duration of medication use in relation to fall-risk.

Chang et al. [17] found that benzodiazepines were significantly associated with the falls of elderly people in hospital (Odd ratio= 2.3). Similar results were observed by Skinner et al. [19] who showed that patients who fell were nearly 2.5 times more likely to have initiated on a benzodiazepine or to have had their dose increased. In contrast, other researchers did not achieve relevant differences in falls after comparing benzodiazepine users over non-users [7,23-25].

Cox et al. [26] observed a greater fall risk with antipsychotics and antidepressants but they found no statistical significance with benzodiazepines use in nursing home residents. The authors established as hypothesis for these results that the prolonged use of benzodiazepines might result in adaptation of benzodiazepine receptors and could lead to habituation. However, we disagree with this approach as the data showed that those patients with a continued BZD-Z use had an increased risk of falling. The results strengthen the evidence for the increased fall risk with BZD-Z use and add relevant information about the greater fall risk associated to the continued use of ≥2 BZD-Z.

Another important assessment was the effect of different medication classes on risk of falls. The results obtained with antidepressants, which led to a greater fall risk, have been found in other studies [18,22,27,28]. The particular mechanism by which antidepressants cause falls is not clear. Some researchers consider that these drugs have common side effects that could increase falls (e.g., orthostatic hypotension, sedation, slower gait speed, and sleep disturbance) [18,27]. Nevertheless, it is not easy to distinguish the effect from depression itself, as it could cause falls via similar mechanisms [22]. Cardiovascular depressant effects by inhibiting cardiovascular ion channels might be one of the possible mechanisms associated with the increased fall risk of antidepressants [27]. The concomitant use of ≥ 2 BZD-Z and antidepressants showed that patients started to fall earlier during the follow-up (compared with those only having ≥ 2 BZD-Z). This result could be attributed to sum side effects from both medication classes.

Further investigation should be carried out to evaluate the reasons related to the increased fall risk due to oral corticosteroid use. A hypothesis for this finding might be that the use of these drugs could be result in a severe bone health problem leading to a tendency to fall.

Strengths and limitations of the study

The study has several limitations. First, a possible limitation might have been an under-reporting of falls by clinicians and nurses in the computerized medical records. Secondly, it was assumed that the prescribed treatment corresponded to the medication dispensed and consumed by the patient.

Another possible confounder might be the fact that it was not taken into account the information about prescribed doses. However, assessment of the relationship between BZD-Z doses and risk of falling was beyond the scope of our study. The aim was to analyse the impact of the number of BZD-Z based on different regimens on fall risk without focusing on doses as this has been studied by other researchers [14,28]. The effect of taking BZD-Z continuously or intermittently on risk of falling had not been evaluated.

Furthermore, the effect could be affected by the different underlying risks of falls and not by the drug itself, such as the safety to reduce the risk of falling at home. It was not possible to mitigate this issue in the data analysis as this information was not available in the medical records. It was considered that one previous year of exposure to these drugs would allow to build a cohort of patients with similar BZD-Z consume patterns and reduce potential biases

associated with falls during the first period of the follow-up. As it would be difficult to generate equivalent doses of various BZD-Z medications, it was not considered average or cumulative dose or duration of exposure during the 6-12 months before the study period. Another issue to be considered is that those patients who were successfully deprescribed (88 patients) might have been inherently different from those that could not be deprescribed (144 patients). Further research should be carried out to analysis if those who were not deprescribed were older, frailer, drank more alcohol, etc.

Finally, we carried out an observational study and it means that a relationship could not be established for certain between analysed variables and the use of BZD-Z.

Although there are limitations, our study has major strengths. The patients were under close supervision by their GPs in an attempt to deprescribing BZD-Z and to report falls throughout the follow-up. GPs provided information to patients to achieve shared decision making aimed to discontinue the drug as soon as possible. Although it is widely accepted that the use of long-acting benzodiazepines is related to an increased risk of falls, the results obtained with short-acting benzodiazepines are more controversial [14,20]. Therefore, both types of benzodiazepines and Z-drugs were not evaluated separately, taking into account that one of the goals was to assess the effect on falls due to 2 or more BZD-Z use and the duration of medication.

It was a strong observational design to assess falls focusing on medication exposure measure across three years**.** Furthermore, the study analysed the fall risk associated to individual patient risks, including their health problems and other prescribed treatments, by using a study design based on long term BZD-Z users. The findings should generalize to a national target population.

Conclusions

The study revealed that the increased fall risk associated with the use of BZD-Z is strongly dependent on the BZD-Z regimens. The factors leading to an increase in the risk of falling were the continued use, the consumption of 2 or more BZD-Z, and the concomitant use with antidepressants. The results showed that it is really inappropriate therapeutic duplication.

The study highlights the importance of improving treatment review and encouraging deprescribing in elderly population. Clinicians should be aware of the risk-benefit balance of these treatments during prescription and avoid inappropriate medications for the elderly.

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