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The influence of cognition on antidepressant and benzodiazepine-related fall risk in older adults.

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Abstract

Objectives: Falls in older adults (≥65 years) are an already existing and growing problem. The use of fall-risk-increasing drugs (FRIDs) and impaired cognition are two of the many risk factors for falling. Antidepressants and benzodiazepines are commonly used drugs by older adults even though they increase fall risk. This risk can vary between different patients. The aim of this study is to investigate the influence of cognition on the antidepressant and benzodiazepine-related fall risk in older adults. This could potentially improve the treatment of persons with various levels of cognitive performance.

Design: Prospective data from the harmonized cohort dataset that was created by researchers of the AD*F*ICE_IT study group were used in this observational study. The used data came from the cohort studies LASA, B-PROOF and ActiFE Ulm. In two separate logistic regression models, the effects of antidepressants and benzodiazepines on fall risk were determined. The models were corrected for confounders and an interaction term for cognition and antidepressant or benzodiazepine use was added to the model. If the interaction term was significant (P-value <0.1), the model was stratified for cognition.

Results: 5176 participants were included. The adjusted regression model for antidepressant use gave an odds ratio (OR) of 1.18 (0.72-1.94). For benzodiazepine use, the OR was 1.15 (0.80-1.67). A significant interaction was found between cognition and the fall risk increasing effect of benzodiazepines. This was not found for antidepressants. After stratification of the adjusted benzodiazepine model, an OR of 1.43 (0.96-2.11) was found for persons with a MMSE ≥ 25 (N=1929). For the group of cognitively impaired persons with a MMSE ≤ 24 (N=170), the OR was 0.22 (0.04-1.06).

Conclusions: In contrast with previous research, no associations were found between the use of antidepressants and benzodiazepines on fall risk in older adults. This could be related to a relatively healthier included population of older adults in this study. Furthermore, the results of this study show no differences in the fall risk increasing effect of antidepressants in persons with various levels of cognition. For benzodiazepines, a trend was found that implies that persons without cognitive loss are more vulnerable to the fall risk increasing effect of benzodiazepines. Due to a possible lack of statistical power in this study, the results don't have any direct clinical implications. Future research is needed to further investigate possible interactions between cognition and the use of FRIDs.

Introduction

The aging of the population and the risk of falling in older adults (≥65 years) make falls in older adults a serious problem now and in the future. Older adults have a higher fall risk compared to younger adults because of changes in several physiological and pathophysiological systems (1). Each year, one in three adults aged over 65 and one in two adults aged over 80 years old, experience one fall (2, 3). Furthermore, the number of older adults is growing. In 2019, there were 1 billion persons older than 60 years (4). In 2030 this number is estimated to be 1.4 billion and in 2050 this is estimated at an amount of 2.1 billion (4).

Approximately 20% of falls in older adults lead to serious injury like head injury (2, 5). Next to injuries, falls may also have other consequences. First of all, quality of life could be affected through loss of confidence and increased social isolation (6). After a fall older adults may also develop fear of falling, loss of independence and stress which all contributes to the morbidity of this group (3, 7). Furthermore, a fall can greatly affect caregiver burden (8). Moreover, healthcare that is needed after falls in older adults make up a great part of healthcare budget (8). Already 1% of healthcare costs is spent on fall-related health issues in high-income countries (9). Taking all these consequences of falls into account, it is important to understand the risk factors of falling and how to prevent falls in older adults.

There are multiple risk factors for falling that can be divided into two groups: intrinsic and extrinsic risk factors (1). Intrinsic risk factors include demographic characteristics like gender, race and age; system risk factors like strength, vision, gait, balance and cognition; and certain symptoms/diseases like dizziness, dementia, depression and cardiovascular diseases (1). Home situation, footwear and medication are extrinsic risk factors for falling (1).

Medicines can increase fall risk through various mechanisms. Psychotropics, like antidepressants, sedatives, anxiolytics and antipsychotics are an important class of these so called fall-risk-increasing drugs (FRIDs) (2, 10). Adverse effects of these drugs such as causing sedation, orthostatic hypertension, daytime sleepiness and motor disturbances could increase fall risk (11). Two frequently used classes of psychotropics in older adults are antidepressants and benzodiazepines.

Among community-dwelling older adults, almost 10% uses antidepressants and among nursing home residents this is approximately 33% (12). Antidepressants are frequently used because of the high incidence of depression in the geriatric population (12). A meta-analysis and systematic review published by Seppala et al. found an odds ratio (OR) of 1.57 for falls related to antidepressants as a group (2). A Delphi study that was done in 2020, found that experts think different pharmacological subclasses of antidepressants cause different effects on fall-risk (13).

Benzodiazepines are also frequently used sedatives in older adults (14). They are often prescribed to treat insomnia, anxiety, panic disorders and sometimes used as muscle relaxants (14). Benzodiazepines are also regularly used off-label for behavioural symptoms and agitation in patients suffering from dementia (15). The prevalence of benzodiazepine use in the group of older adults was 12.9% in 2019 (15). At the same time, it is known that benzodiazepines are medicines with many adverse effects, mostly in older adults (15). Depending on multiple factors like pharmacodynamics and pharmacokinetics, drug-drug interactions and multimorbidity, the adverse effects vary among all users. These adverse effects could lead to increased fall risk and cognitive impairment by inducing sedation and impaired psychomotor coordination and gait stability (15).

The world guidelines on falls prevention and management for older adults strongly recommend to assess cognitive function in older adults (9). It is known that the cognitive domains executive functioning and attention play an important role in preventing a fall (16). These two processes modulate different strategies for regaining postural stability if a perturbation occurs, process sensory input and adapt to environmental factors; all to prevent a fall (8). Next to this, impaired cognition may lead to the inability to prioritize postural balance over other cognitive tasks and the inability to appraise the (fall) risk of certain activities (8). If a person is cognitively impaired, all these processes will be negatively affected leading to a higher fall risk and those falls leading to severe injury.

The fall risk increasing effect of all FRIDs varies across groups of persons (17). Multiple characteristics, like age may explain these differences in effect size (17). Cognition could also be a possible explanation for differences between persons regarding the effect of medication use on fall risk. For example, cognitively impaired persons might be unable to comply to their treatment (18). These persons might not use their medication as prescribed which could possibly influence the interaction between the use of drugs and its medication-induced fall risk. On the other hand, a report done by Ebly et al. suggested that cognitively impaired persons without dementia and patients suffering from dementia, had a less abundant association between potential adverse outcomes caused by the use of psychotropics, than subjects without cognitive loss (19).

So, it is known that impaired cognition and the use of certain medicines (like psychotropics) both are risk factors for falling. It is, however, unclear what role cognition has on the fall-risk-increasing effect of these drugs in older adults. Therefore, the aim of this study is to investigate the influence of cognitive performance on the fall-risk-increasing effect of antidepressants and benzodiazepines in older adults. The findings of this study could facilitate physicians in making a better and more personalized choice of treatment for older adults with various levels of cognitive performance.

Methods

Study population

In this observational study a harmonized cohort dataset was used. The dataset was created by researchers of the AD*F*ICE_IT study group through harmonizing data from six existing cohort studies. Prospective data on falls were collected in three of the included cohort studies: The Longitudinal Aging Study Amsterdam (LASA), the B-vitamins for the Prevention Of Osteoporotic Fractures study (B-PROOF) and the Activity and Function in the Elderly in Ulm study (ActiFE Ulm) (20-22). The prospective data consisted of information about the participants at baseline and in most cases during a 1-year follow-up and all three cohort studies included information on falls, cognition and medication use.

LASA is an ongoing prospective cohort study that started collecting data in 1992 among Dutch, older adults (21). They collected information about determinants, consequences and trajectories of emotional, physical, social and cognitive functioning of these older adults (21). For this analysis, only the prospective data from wave C out of all LASA data were used. B-PROOF was a multicentre, randomized, placebo-controlled, double-blind trial, that investigated efficacy of folic acid and vitamin B12 supplementation on fracture-incidence in older adults with increased plasma homocysteine concentrations (22). This study found that the intervention had no effect and therefore the data were treated as a prospective cohort study (22). Participants were collected in three Dutch centres between 2008 and 2011 (22). ActiFE Ulm was a population-based cohort study among German community-dwelling older adults with an age between 65 and 90 years old (20). The data collections started in 2009 and ended in 2010 and was done in multiple areas of Germany (20).

All included participants gave informed consent to collect their data and the medical ethical committees of all local institutions approved the collection of the data.

Inclusion criteria for this study were an age of 65 years old or older, a follow-up period of 52 weeks or more, information on falls, an accurate status of medication and a known Mini-Mental State Examination (MMSE) score at baseline. All participants that missed information about cognition, medication use or falls or did not have a follow-up of at least 52 weeks were excluded.

Determinants

The first determinant was the use of antidepressants or benzodiazepines. There are multiple pharmacological subclasses of antidepressants, namely selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA) and other antidepressants like bupropion and venlafaxine (2). For the main analysis all antidepressants were included. As additional analyses, the pharmacological subclasses of antidepressants (TCAs and SSRIs) were assessed separately. The ATC-codes that were used to select the medication were N6AA, N06CA01 and N06CA02 for non-selective monoamine reuptake inhibitors (TCAs), N06AB and N06CA03 for SSRIs and N06AX, N06AF and N06AG for other antidepressants. For benzodiazepines, the ATC-codes N05BA and N05CD were used (23).

Medication use was documented through various ways. In the LASA cohort study, participants were asked to show the medication they used in the past two weeks that were prescribed by physicians (24). The B-PROOF study used questionnaires to retrieve information about medication use (22). In ActiFE Ulm

medication status was assessed at baseline by scanning the barcodes of every medicine in the participant's house (20).

The second determinant was MMSE score. This is a commonly used tool to asses cognitive functioning in research, clinical and community settings in older adults (25). The data of the three available cohort studies all comprised the MMSE scores of the participants. Therefore, this was the main determinant to appraise cognition in this study.

Outcomes

The primary outcome to assess fall risk in this study design was a fall within the 1-year follow-up period (yes/no). Recurrent falls (2 or more falls) during the 1-year follow-up period was the secondary outcome. According to the World Falls Guidelines, the definition of a fall is as follows: "An unexpected event in which an individual comes to rest on the ground, floor or lower level" (9). To keep track of the number of falls, the participants in all three cohort studies were asked to use a falls calendar. This calendar asked the participants to report falling every week. The calendars had to be returned every three months. If the calendar was not received or the answers were not clear, the participant was contacted. This was all in conformation with the recommendations of the ProFaNE statement (26).

Covariates

Based on literature, potential confounders were determined. The following characteristics were considered possible confounders: age, sex, body mass index (BMI), living status (community dwelling or institutionalized), education level, number of medications, number of chronic diseases, history of cancer, diabetes, heart disease (yes/no); depression, presence of pain (yes/no), hospital anxiety and depression scale (HADS)-anxiety score (range 0-21), frequency of alcohol use, smoking status and self-rated health (1: excellent, 5: poor). All of these covariates were determined at baseline through interviews or questionnaires. BMI was calculated using measured height and weight. Depression was determined by the 20-item Center for Epidemiologic Studies Depression Scale (CES-D), HADS-Depression or Geriatric Depression Scale, depending on the cohort. A Z-score for depression was used to harmonize the data from the three cohort studies. Other covariates that were dissimilar in the cohort studies were harmonized in various ways. Further details about the collection and harmonisation of these characteristics can be found in the data harmonization guide which is available online (23).

Statistical analysis

Descriptive statistics were applied to describe the baseline characteristics of the antidepressants users vs. non-users of antidepressants, and the benzodiazepine users vs. non-users of benzodiazepines. To present dichotomous or categorical variables, frequencies and percentages were used. Continuous variables were presented by the mean and the standard deviations if the variable was normally distributed and by the median and interquartile range if not. An independent T-test was used to compare characteristics with continuous variables that were normally distributed and a Mann-Whitney U test for non-normally distributed continuous variables. A X^2 test was used for characteristics with categorical results.

A binary logistic regression was conducted to assess the effect of medication use (antidepressants or benzodiazepines) on the fall risk (yes/no fall in first year of follow-up) of older adults. ORs were found to compare the non-users with the users of antidepressants and benzodiazepines. The ORs had a 95% confidence interval (CI). Different predefined models were used. Model 1 used data adjusted for age and

sex. In model 2, data were adjusted to all possible confounders. All participants that missed information on the included confounders were excluded. The imputation of missing data was not feasible within this project. As a sensitivity analysis, a third model was performed to determine if the results were highly altered by adjusting the model. This model 3 contained a subset of confounders. This subset was determined by only including the confounders with mostly valid values, which were all confounders except for number of chronic diseases, HADS-Anxiety score, history of cancer and living situation. The level of significance was a P-value of <0.05.

An interaction term was added to regression model 2 to assess the influence of cognition on the association between the use of antidepressants and benzodiazepines on fall risk. This was separately done in the model of antidepressants and benzodiazepines by adding an interaction term between MMSE score and the use of antidepressants and benzodiazepines, respectively. An interaction term with a P-value of <0.1 was considered significant. In case of a significant interaction term, the logistic regression model was stratified for cognitive performance with a cut-off of MMSE ≥25.

After the analyses, the characteristics of the included group and the excluded group (participants that missed data on one or more confounders) of model 2 were compared to show possible differences. All of the statistical analyses were done by using IBM SPSS statistics 28.

Results

Baseline characteristics

The harmonized cohort dataset with data of the cohort studies LASA, B-PROOF and ActiFE Ulm consisted of 7532 patients. Figure 1 shows the inclusion of participants in the analyses. In total, 5176 patients met the inclusion criteria. Only 223 antidepressant users and 331 benzodiazepine users were identified among them. Table 1 summarizes the baseline characteristics of all the included patients in the analysis of antidepressants and table 2 of the analysis of benzodiazepines. The baseline characteristics for the users and non-users of antidepressants showed that relatively more females used antidepressants. Furthermore, antidepressant users were significantly more depressed and anxious, used more medication and less alcohol compared to the non-users. The group of benzodiazepines consisted of more females compared to the group of non-users. Next to this, benzodiazepines users were significantly older than the non-users. They also suffered more from heart disease, depression, pain and anxiety. Lastly, benzodiazepine users had a significantly higher number of chronic conditions and number of medication in comparison to the non-users group.

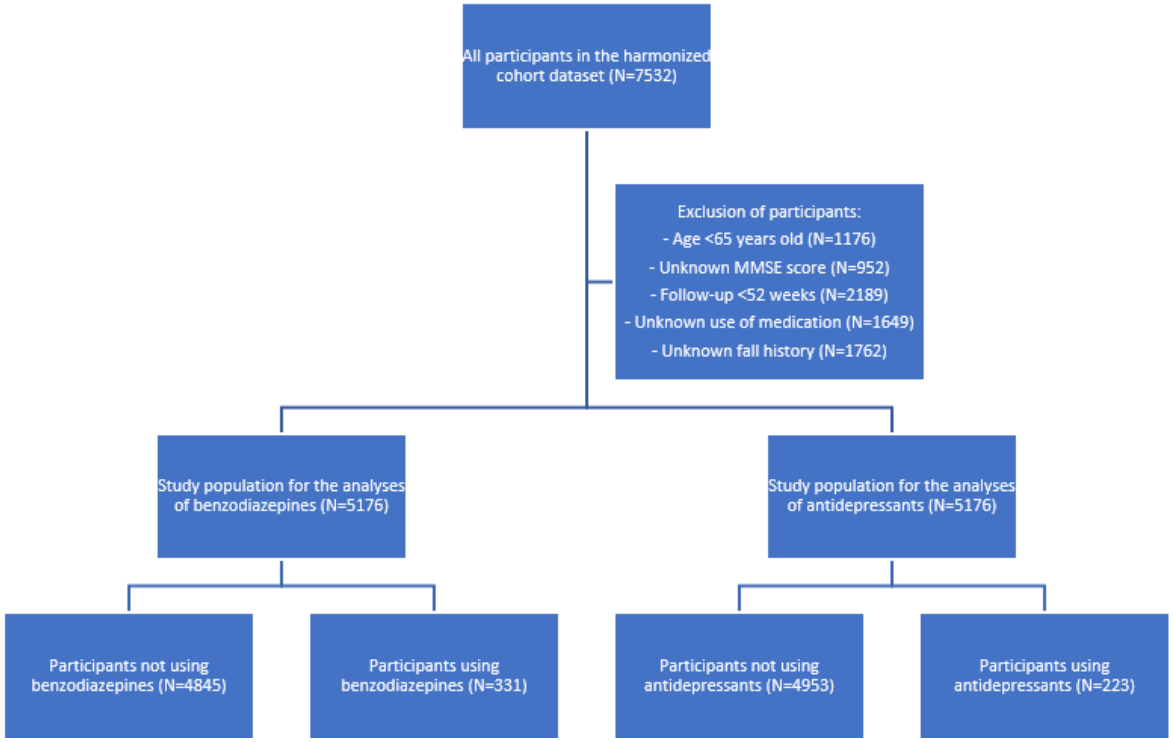

Figure 1: Flowchart of the inclusion of participants used for the analyses of the fall risk increasing effect of antidepressants and benzodiazepines.

Table 1: Baseline characteristics of participants not using and using antidepressants.

Variable	Total (N= 5176)	Non-users (N= 4953)	AD users (N= 223)	P-value
Age in years[a]	5176	73 (69-79)	73 (70-78)	0.817
Sex[b]	5176			<0.001*
Female		2375 (47.9)	138 (61.9)	
Male		2578 (52.0)	85 (38.1)	
BMI[a]	5139	26.7 (24.5-29.4)	26.9 (24.7-29.5)	0.408
Living situation[b]	3531			0.918
Community-dwelling		3298 (97.3)	139 (97.2)	
Institutionalized		90 (2.7)	4 (2.8)	
Educational level[b]	5159			0.021*
Low (ISCED level 0, 1 and 2)		3512 (71.2)	172 (77.1)	
Average (ISCED level 3 and 4)		462 (9.4)	9 (4.0)	
High (ISCED level 5 through 8)		962 (19.5)	42 (18.8)	
Number of medications[a]	5175	2.00 (1.00-4.00)	5.00 (3.00-7.00)	0.000*
Number of chronic conditions[a]	2477	0.00 (0.00-1.00)	0.50 (0.00-1.00)	0.423
History of cancer[b]	2488			0.188
Yes		367 (15.3)	70 (79.5)	
History or presence of diabetes[b]	4595			0.290
Yes		445 (10.1)	15 (7.8)	
History of heart disease[b]	4595			0.470
Yes		1063 (24.1)	51 (26.4)	
Z-score depression[a]	5074	-0.23 (-0.74-0.29)	0.29 (-0.23-1.32)	0.000*
Presence of pain[b]	4948			<0.001*
Yes		2110 (44.6)	81 (37.9)	
HADS-Anxiety score (range 0-21) [a]	2417	3.00 (1.00-5.00)	4.00 (2.00-6.00)	<0.001*
Frequency of alcohol use[b]	5151			<0.001*
Non-drinker		643 (13.0)	52 (23.4)	
Less than once a month		550 (11.2)	21 (9.5)	
1-3 times a month		707 (14.3)	22 (9.9)	
1-4 days a week		1324 (26.9)	56 (25.2)	
(almost) daily		1705 (34.6)	71 (32.0)	
Smoking status[b]	5174			0.363
Never smoked		1878 (37.9)	77 (34.5)	
Ex-smoker		2537 (51.2)	116 (52.0)	
Current smoker		536 (10.8)	30 (13.5)	
Self-rated health[a] **(1: excellent, 5: poor)**	5172	3.00 (2.00-3.00)	3.00 (3.00-3.00)	<0.001*

*Significant if P-value <0.05

a: Characteristics presented as median (interquartile range). Significance was determined by using a Mann Whitney U-test.

b: Characteristics presented as N (%). Significance was determined by using a X^2-test.

Abbreviations: AD, antidepressant; BMI, body mass index; HADS, Hospital Anxiety and Depression Scale

Table 2: Baseline characteristics of participants not using and using benzodiazepines.

Variable	Total (N= 5176)	Non-users (N= 4845)	BZD users (N= 331)	P-value
Age in years[a]	5176	73 (69-79)	76 (71-82)	<0.001*
Sex[b]	5176			<0.001*
Female		2266 (46.8)	247 (74.6)	
Male		2579 (53.2)	84 (25.4)	
BMI[a]	5139	26.7 (24.6-29.4)	27.0 (24.0-29.5)	0.535
Living situation[b]	3531			<0.001*
Community-dwelling		3208 (97.8)	232 (92.8)	
Institutionalized		76 (2.3)	18 (7.2)	
Educational level[b]	5159			0.029*
Low (ISCED level 0, 1 and 2)		3430 (71.0)	254 (76.7)	
Average (ISCED level 3 and 4)		443 (9.2)	29 (8.8)	
High (ISCED level 5 through 8)		958 (19.8)	46 (14.0)	
Number of medications[a]	5175	2.00 (1.00-4.00)	4.00 (3.00-6.00)	0.000*
Number of chronic conditions[a]	2477	0.00 (0.00-1.00)	1.00 (0.00-1.00)	<0.001*
History of cancer[b]	2488			0.830
Yes		353 (15.4)	32 (16.0)	
History or presence of diabetes[b]	4595			0.253
Yes		424 (9.9)	36 (11.9)	
History of heart disease[b]	4595			<0.001*
Yes		1015 (23.6)	99 (32.8)	
Z-score depression[a]	5074	-0.23 (-0.74-0.29)	0.29 (-0.38-1.32)	0.000*
Presence of pain[b]	4948			<0.001*
Yes		2074 (44.5)	169 (59.1)	
HADS-Anxiety score (range 0-21)[a]	2417	2.00 (1.00-5.00)	4.00 (1.00-6.00)	<0.001*
Frequency of alcohol use[b]	5151			<0.001*
Non-drinker		598 (12.4)	97 (29.5)	
Less than once a month		533 (11.1)	38 (11.6)	
1-3 times a month		692 (14.4)	37 (11.2)	
1-4 days a week		1319 (27.4)	61 (18.5)	
(almost) daily		1680 (34.8)	96 (29.2)	
Smoking status[b]	5174			<0.001*
Never smoked		1811 (37.4)	144 (43.5)	
Ex-smoker		2525 (52.1)	128 (38.7)	
Current smoker		507 (10.5)	59 (17.8)	
Self-rated health[a] **(1: excellent, 5: poor)**	5172	3.00 (2.00-3.00)	3.00 (2.00-4.00)	<0.001*

*Significant if P-value <0.05

a: Characteristics presented as median (interquartile range). Significance was determined by using a Mann Whitney U-test.

b: Characteristics presented as N (%). Significance was determined by using a X^2-test.

Abbreviations: BZD, benzodiazepine; BMI, body mass index; HADS, Hospital Anxiety and Depression Scale

Logistic regression

For both antidepressants, as well as benzodiazepines the ORs of model 1 found a significant association between the use of these medicines and one fall within the first year of follow-up. The ORs for the use of an antidepressant and the use of a benzodiazepine can be found in table 3 and table 4, respectively. When the models were adjusted for all confounders (model 2), the model of antidepressants showed no association between antidepressant use and fall risk (OR= 1.18 (0.72-1.94)). There was also no association found between benzodiazepine use and fall risk (OR= 1.15 (0.80-1.67)) in the corrected model. This was the same for the analyses of the secondary outcome: recurrent falls within the first year of follow-up. These results can also be found in table 3 and 4. The sensitivity analyses (model 3, N=4216) gave non-significant and small changes for the ORs of the antidepressant and benzodiazepine models for a fall within the first year of follow-up. The sensitivity analysis (model 3) for recurrent falls within the first year of follow-up of antidepressants did however alter the OR to 1.60 (1.09-2.36). For benzodiazepines, the results of the sensitivity analysis for recurrent falls were similar to the adjusted model.

Table 3: Logistic regression models calculating OR for the association between one or recurrent falls within the first year of follow-up and antidepressant use

Regression models	N included participants (%)	OR (95% CI)	P-value
Analyses for a fall within the first year of follow-up			
Model 1*	5176 (100)	1.38 (1.05-1.82)	0.021#
Model 2**	2099 (40.6)	1.18 (0.72-1.94)	0.506
Analyses for recurrent falls within the first year of follow-up			
Model 1*	5176 (100)	1.83 (1.31-2.56)	<0.001#
Model 2**	2099 (40.6)	1.25 (0.66-2.38)	0.499

= significant if P-value <0.05

*Use of an antidepressant adjusted for age and sex

**Use of an antidepressant adjusted for all confounders: age, sex, body mass index, living situation, education level, number of medications, number of chronic conditions, history of cancer, history or presence of diabetes, history of heart disease, depression, presence of pain, HADS-Anxiety score (range 0-21), frequency of alcohol use, smoking status and self-rated health.

Abbreviations: OR, odds ratio; CI, confidence interval

Table 4: Logistic regression models calculating OR for the association between one or recurrent falls within the first year of follow-up and benzodiazepine use

Regression models	N included participants (%)	OR (95% CI)	P-value
Analyses for a fall within the first year of follow-up			
Model 1*	5176 (100)	1.27 (1.01-1.60)	0.043#
Model 2**	2099 (40.6)	1.15 (0.80-1.67)	0.456
Stratification for cognition after significant interaction term (P-value = 0.016)##			
Model 2, participants with MMSE≥25**	1929 (40.3)	1.43 (0.96-2.11)	0.075
Model 2, participants with MMSE≤24**	170 (43.1)	0.22 (0.04-1.06)	0.06
Analyses for recurrent falls within the first year of follow-up			
Model 1*	5176 (100)	1.42 (1.05-1.91)	0.022#
Model 2**	2099 (40.6)	1.05 (0.63-1.75)	0.857
Stratification for cognition after significant interaction term[a] (P-value = 0.070)##			
Model 2, participants with MMSE≥25**	1929 (40.3)	1.30 (0.77-2.20)	0.327

significant if P-value <0.05

significant if P-value <0.1

*Use of a benzodiazepine adjusted for age and sex

**Use of a benzodiazepine adjusted for all confounders: age, sex, body mass index, living situation, education level, number of medications, number of chronic conditions, history of cancer, history or presence of diabetes, history of heart disease, depression, presence of pain, HADS-Anxiety score (range 0-21), frequency of alcohol use, smoking status and self-rated health.

a: There were no users of benzodiazepines with impaired cognition that had the answer 'yes' for the recurrent falls outcome, making an analysis of this group impossible.

Abbreviations: OR, odds ratio; CI, confidence interval

Interaction term

The interaction terms between cognition and antidepressant or benzodiazepine use, were added to models 2 as described in table 3 and 4. In the model of antidepressant use, no significant effect was found for the interaction term for both the primary, as well as the secondary outcome. When the interaction term was added to the benzodiazepine model, a significant interaction term (P-value = 0.016) was found for the primary outcome. For the secondary outcome, recurrent falls within the first year of follow-up, there was also a significant interaction term found (P-value = 0.070).

Model 2 for one fall within the first year of follow-up of benzodiazepines was stratified for cognitive performance. The stratified analysis gave a non-significant OR of 1.43 (0.96-2.11) for the population with 1929 participants with normal cognitive performance (MMSE ≥25) in the adjusted model. For the population including 170 participants with impaired cognitive performance (MMSE ≤24), a non-significant OR of 0.22 (0.04-1.06) was found in the adjusted model. These results are presented in table 4.

The result of the stratification of the regression model for recurrent falls within the first year of follow-up can also be found in table 4. Stratification did not give a significant OR for the group with a normal cognition. The analysis was not possible for the group of participants with impaired cognition since there were no participants that used benzodiazepines and had recurrent falls in the one-year follow-up.

Post hoc analyses

Post hoc analyses comparing the characteristics of the included group (N=2099) and excluded group (N=3077) of the main regression models, showed no pertinent differences except for the origin of the cohort studies. Since the cohort study B-PROOF did not include information on number of chronic diseases, HADS-Anxiety score and history of cancer, these patients were excluded from the main analysis. The sensitivity analyses did include these participants.

Additional analyses

The results of the analyses of SSRIs and TCAs as separate groups can be found in the appendix. Both analyses found no significant association between the use of SSRIs or TCAs and fall risk and did also not find significant interaction terms for cognition.

Discussion

Main findings

This research project explored the influence of cognition on the antidepressant and benzodiazepine-related fall risk in older adults. The main findings were that no significant association was found between the use of antidepressants and benzodiazepines and fall risk in the adjusted regression models. Addition of an interaction term of cognition to the regression model did not give a significant association between cognition and the fall risk increasing effect of antidepressants. When added to the logistic regression model assessing the effect of benzodiazepines, the interaction term did give a significant effect. After stratification, the OR for falling was lower for the cognitively impaired participants compared to the people with normal cognition. Although this was not significant, it did show a trend that implied that persons without cognitive loss are more vulnerable to the fall risk increasing effect of benzodiazepines than persons that are cognitively impaired.

Interpretation of results

When comparing the results of the assessment of the fall risk increasing effect of antidepressants and benzodiazepines to the literature, the results are unexpected. In this study, the fall risk increasing effect of antidepressants was not found in the adjusted regression model. The fall risk increasing effect of both antidepressants, as well as benzodiazepines, have been proven in multiple previously done studies. The systematic review done by Seppala et al. found a clear association between the use of antidepressants and fall risk in older adults (2). 22 of the 107 investigated studies used adjusted data to determine the OR, of which the pooled OR also gave an increased fall risk for antidepressant users (2). The meta-analysis of Oderda et al. investigated the association between hip fractures and the use of antipsychotics and antidepressants in older adults (27). Hip fractures are often caused by falls and therefore this study is relevant for research on falls (27). The study found an increased risk of hip fracture when using a first or second generation antidepressant (27). The included studies were adjusted for different covariates and showed various effect sizes as results (27). Even though the effect size might be uncertain, as showed by a substantial heterogeneity, it is clear that antidepressant use leads to a higher fall risk.

There are multiple explanations for not finding the fall risk increasing effect of antidepressants in this study. First, it could be that the confounders for which our models were adjusted played an important role in the association of the fall risk increasing effect of antidepressants. For example the indications for which the drugs were prescribed also influence fall risk and could therefore lead to confounding by indication (28). Second, the in- and excluded group possibly differed. Participants that remained in the final regression model could differ from the whole study population. Although the post hoc analysis did not find abundant differences, it could be argued that the excluded group consisted of the more weak persons of the older population. Those vulnerable older adults might have been unable to complete the follow-up period because of illness or even mortality. It is known that more disease burden, thus more medication use and age-related physiological changes could lead to more adverse drug reactions in frail older adults (29). Moreover, previous research has shown that there is heterogeneity between the included cohort studies (30). In the adjusted model, only LASA and ActiFE Ulm patients were included and B-PROOF was excluded. The cohort studies differ, among others, in the level of frailty of the population, the use of medication and study procedures (30, 31). In general, ActiFE Ulm seemed to be a healthier population

than the two other cohort studies (31). This could potentially lead to a lack of association in the included healthy population.

The sensitivity analyses included a substantial higher number of participants than the main analyses. In the sensitivity analysis determining the association between antidepressant use and recurrent falls a significantly higher fall risk for users of antidepressants compared to non-users was found. This suggests that there might be a lack of power in the adjusted model.

The systematic review of Seppala et al. also found an association between increased fall risk and the use of benzodiazepines (2). Fourteen studies used adjusted data which also showed an increased fall risk (2). Again a substantial heterogeneity has to be taken into consideration. In contrast to the literature, this study did also not find the fall risk increasing effect of benzodiazepines. Possible clarifications for not finding the fall risk increasing effect of benzodiazepines are similar to those of antidepressants: the corrected confounders influenced the fall risk or the included group was overall healthier than the excluded group.

Addition of the interaction term to the antidepressant model, gave no significant interaction. This suggests there is no influence of cognition on the fall risk increasing effect of antidepressants. A cohort study of Torvinen-Kisskinen et al. investigated the association between the use of antidepressants and the risk of hip fractures among older adults with and without Alzheimer's disease (32). It was found that the risk of hip fractures in older adults with and without Alzheimer's disease was increased by antidepressant use (32). In this study no interaction between cognition and the fall risk increasing effect of antidepressants was found. It could be argued that the interaction does not exist, but it could also be assumed that there were too few persons included with a low cognitive performance (N=170) to detect the interaction. Especially the cohort of ActiFE Ulm contained few participants with a MMSE score ≤24, since one of their inclusion criteria was a MMSE score ≥17.

When looking at the interaction term in the adjusted benzodiazepine model, the fall risk increasing effect of benzodiazepines was altered by cognitive performance. Stratification implied that persons with normal cognitive performance are more vulnerable to the fall risk increasing effect of benzodiazepines. The study done by Ebly et al. investigated potential adverse effects of psychotropics in older adults with different levels of cognitive performance (19). They suggested that especially persons without cognitive loss were at risk for potential adverse effects like falls (19). Whereas a retrospective cohort study done by Saarelainen et al. that investigated the risk of hip fractures in benzodiazepine users with and without Alzheimer's disease, found that all patients had a higher risk of hip fractures when using a benzodiazepine, regardless of Alzheimer's disease (33). Other previous research found a higher risk of falling and higher vulnerability to adverse effects in cognitively impaired adults than persons without cognitive loss (8, 34). These studies show very ambiguous results. This could mean that our findings could be caused by coincidence or other factors that affected the analysis.

First, a possible cause for finding a more abundant association between the use of benzodiazepines and fall risk in cognitively normal persons, is that there was less information on participants with impaired cognition in the dataset. Selection bias could also have played a role. Persons with a low cognition could have experienced more adverse drug effects and therefore stopped the therapy or the follow-up period earlier than the persons with a higher cognition. It has been proven in previous research that cognitively impaired older adults are at high risk for adverse drugs reactions (34). This could have led to a too low power to detect the effect in the group of persons without cognitive loss. A second clarification could be

that the persons with a low cognition had a low medication adherence. Previous research found that patients with dementia (and thus a low cognition) had low levels of medication adherence (35). Especially, the use of benzodiazepines that are often prescribed as pro re nata (when required) might be confusing for cognitively impaired persons (36). This could mean that these participants did actually not take their medication even though the data on medication use said so. Lastly, other fall risk increasing factors, like one of the confounders, could play a more important role in causing fall risk in cognitively impaired persons. This is in accordance with the findings of the study of Ebly et al. (19).

Strengths and limitations

One of the strengths of this study is that it used prospective information about falls that was collected on a weekly basis through a falls calendar, as recommended in the ProFaNE statement (26). Another strength of this study, is that it could give more insight in how to best treat cognitively impaired persons. Usually, cognitively impaired patients are excluded in studies (37). Due to this, little is known about the optimal treatment for these patients. More studies about treatment of this population could facilitate a better understanding of this condition and how to best treat these patients.

This study also has several limitations. Firstly, medication use was solely measured at baseline. There is no information about the duration of these therapies. According to the STOPP criteria, benzodiazepines should not be used for four weeks or more because of adverse effects and limited efficacy (38). Dutch guidelines on the treatment of depression advise continuation of antidepressants of at least 6 months after remission or at least a year after recurrence (39). This implies that particularly benzodiazepines, but also antidepressants, could have been used at baseline but way shorter than the follow-up period of a year and possibly not when a fall occurred. Another reason why the treatment period might be different than the follow-up period is the lack of information about adherence. As stated before, especially cognitively impaired patients might be unable to comply to their treatment (18). Furthermore, there was no information about the dosage and the use of concomitant over-the-counter medication, which could also affect medication-related fall risk.

Secondly, there was quite a lot of missing data. Instead of imputing the data, the participants with missing data were excluded, which led to a smaller study population. The original study population existed of 5176 participants. In the main analysis only 2099 participants were included. Among the excluded participants, were all participant from the B-PROOF cohort study. In the sensitivity model, these patients were included and the number of participants in that model was 4216. In these analyses, insignificant and small changes were found in the ORs. Only the found OR in the antidepressant model for recurrent falls was increased compared to the adjusted model and was significant.

Lastly, the occurrence of multicollinearity was not tested in this study. Especially the variables depression, anxiety and the use of antidepressants and benzodiazepines could potentially be correlated. If these variables would be correlated, it would be unable to predict the association with falls. The validity of the model would be highly decreased. Previous research that used the same cohort studies did investigate the collinearity, and no correlations were found. Therefore, it was assumed that multicollinearity was also not present in this study (40).

Future research and clinical implications

In this study we found a trend implying that cognitively normal persons are more vulnerable to the fall risk increasing effect of benzodiazepines. This would suggest that physicians should be extra careful in prescribing benzodiazepines in older adults with a normal cognitive performance. However, the stratified ORs were not significant and there were only a few participants included with a low cognition. Therefore, these results should be interpreted with caution. Hence, the results do not have any direct clinical implications.

It would be very interesting for future research to repeat this study, but with more participants and especially more patients with a low cognitive performance. This could affirm the found trend or lead to new insights. If a larger dataset would be used it would also be more feasible to analyse the fall risk increasing effect of different medicines within a subclass (like it has been tried in this study for SSRIs and TCAs separately). Next to this, it would be interesting to include more information about adherence to the therapy, use of concurrent over-the-counter medication and the dosage and duration of the therapy. The influence of cognition on the fall risk increasing effect of multiple other psychotropics like antipsychotics could be also investigated.

Conclusion

No significant association was found between cognition and the fall risk increasing effect of antidepressants and benzodiazepines in older adults. There was also no interaction found between the fall risk increasing effect of antidepressants and cognition. For benzodiazepines, a trend was found that showed that persons without cognitive loss are more vulnerable to the fall risk increasing effect of benzodiazepines. Because this study investigated these associations in a small study population, further research with a larger study population is recommended.

References

1. Ambrose AF, Paul G, Hausdorff JM. Risk factors for falls among older adults: a review of the literature. Maturitas. 2013;75(1):51-61.
2. Seppala LJ, Wermelink A, de Vries M, Ploegmakers KJ, van de Glind EMM, Daams JG, et al. Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: II. Psychotropics. J Am Med Dir Assoc. 2018;19(4):371 e11- e17.
3. Phelan EA, Ritchey K. Fall Prevention in Community-Dwelling Older Adults. Ann Intern Med. 2018;169(11):Itc81-itc96.
4. Ageing World Health Organization [cited 2023 September 4th]. Available from: https://www.who.int/health-topics/ageing#tab=tab_1.
5. Facts About Falls: Centers for Disease Control and Prevention; [updated 12-05-2023. Available from: https://www.cdc.gov/falls/facts.html.
6. Song J, Lee E. Health-Related Quality of Life of Elderly Women with Fall Experiences. Int J Environ Res Public Health. 2021;18(15).
7. Ang GC, Low SL, How CH. Approach to falls among the elderly in the community. Singapore Med J. 2020;61(3):116-21.
8. Montero-Odasso M, Speechley M. Falls in Cognitively Impaired Older Adults: Implications for Risk Assessment And Prevention. J Am Geriatr Soc. 2018;66(2):367-75.
9. Montero-Odasso M, van der Velde N, Martin FC, Petrovic M, Tan MP, Ryg J, et al. World guidelines for falls prevention and management for older adults: a global initiative. Age Ageing. 2022;51(9).
10. van der Velde N, Seppala LJ, Hartikainen S, Kamkar N, Mallet L, Masud T, et al. European position paper on polypharmacy and fall-risk-increasing drugs recommendations in the World Guidelines for Falls Prevention and Management: implications and implementation. Eur Geriatr Med. 2023;14(4):649-58.
11. Esumi S, Ushio S, Zamami Y. Polypharmacy in Older Adults with Alzheimer's Disease. Medicina (Kaunas). 2022;58(10).
12. van Poelgeest EP, Pronk AC, Rhebergen D, van der Velde N. Depression, antidepressants and fall risk: therapeutic dilemmas-a clinical review. Eur Geriatr Med. 2021;12(3):585-96.
13. Seppala LJ, Petrovic M, Ryg J, Bahat G, Topinkova E, Szczerbińska K, et al. STOPPFall (Screening Tool of Older Persons Prescriptions in older adults with high fall risk): a Delphi study by the EuGMS Task and Finish Group on Fall-Risk-Increasing Drugs. Age Ageing. 2021;50(4):1189-99.
14. Capiau A, Foubert K, Somers A, Petrovic M. Guidance for appropriate use of psychotropic drugs in older people. Eur Geriatr Med. 2021;12(3):577-83.
15. Gupta A, Bhattacharya G, Balaram K, Tampi D, Tampi RR. Benzodiazepine use among older adults. Neurodegenerative Disease Management. 2021;11(1):5-8.
16. Zhang W, Low LF, Schwenk M, Mills N, Gwynn JD, Clemson L. Review of Gait, Cognition, and Fall Risks with Implications for Fall Prevention in Older Adults with Dementia. Dement Geriatr Cogn Disord. 2019;48(1-2):17-29.
17. Hauff J, Rottenkolber M, Oehler P, Fischer S, Gensichen J, Drey M, et al. Single and combined use of fall-risk-increasing drugs and fracture risk: a population-based case-control study. Age Ageing. 2023;52(6).
18. Racey M, Markle-Reid M, Fitzpatrick-Lewis D, Ali MU, Gagne H, Hunter S, et al. Fall prevention in community-dwelling adults with mild to moderate cognitive impairment: a systematic review and meta-analysis. BMC Geriatr. 2021;21(1):689.
19. Ebly EM, Hogan DB, Fung TS. Potential adverse outcomes of psychotropic and narcotic drug use in Canadian seniors. J Clin Epidemiol. 1997;50(7):857-63.

20. Denkinger MD, Franke S, Rapp K, Weinmayr G, Duran-Tauleria E, Nikolaus T, Peter R. Accelerometer-based physical activity in a large observational cohort--study protocol and design of the activity and function of the elderly in Ulm (ActiFE Ulm) study. BMC Geriatr. 2010;10:50.
21. Hoogendijk EO, Deeg DJH, de Breij S, Klokgieters SS, Kok AAL, Stringa N, et al. The Longitudinal Aging Study Amsterdam: cohort update 2019 and additional data collections. Eur J Epidemiol. 2020;35(1):61-74.
22. van Wijngaarden JP, Dhonukshe-Rutten RA, van Schoor NM, van der Velde N, Swart KM, Enneman AW, et al. Rationale and design of the B-PROOF study, a randomized controlled trial on the effect of supplemental intake of vitamin B12 and folic acid on fracture incidence. BMC Geriatr. 2011;11:80.
23. ADFICE_IT harmonized cohort data onderzoeknaarvallen.nl: Amsterdam UMC; 2020 [Available from: https://www.onderzoeknaarvallen.nl/wp-content/uploads/2021/06/ADFICE_IT-harmonized-cohort-data-November-2020.pdf.
24. Huisman M, Poppelaars J, van der Horst M, Beekman AT, Brug J, van Tilburg TG, Deeg DJ. Cohort profile: the Longitudinal Aging Study Amsterdam. Int J Epidemiol. 2011;40(4):868-76.
25. Chun CT, Seward K, Patterson A, Melton A, MacDonald-Wicks L. Evaluation of Available Cognitive Tools Used to Measure Mild Cognitive Decline: A Scoping Review. Nutrients. 2021;13(11).
26. Lamb SE, Jørstad-Stein EC, Hauer K, Becker C. Development of a common outcome data set for fall injury prevention trials: the Prevention of Falls Network Europe consensus. J Am Geriatr Soc. 2005;53(9):1618-22.
27. Oderda LH, Young JR, Asche CV, Pepper GA. Psychotropic-related hip fractures: meta-analysis of first-generation and second-generation antidepressant and antipsychotic drugs. Ann Pharmacother. 2012;46(7-8):917-28.
28. Capiau A, Huys L, van Poelgeest E, van der Velde N, Petrovic M, Somers A. Therapeutic dilemmas with benzodiazepines and Z-drugs: insomnia and anxiety disorders versus increased fall risk: a clinical review. Eur Geriatr Med. 2023;14(4):697-708.
29. Alhawassi TM, Krass I, Bajorek BV, Pont LG. A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. Clin Interv Aging. 2014;9:2079-86.
30. Seppala LJ, van de Loo B, Schut M, van Schoor NM, Stricker BH, Kenny RA, et al. A Propensity Score Matched Approach to Assess the Associations of Commonly Prescribed Medications with Fall Risk in a Large Harmonized Cohort of Older Ambulatory Persons. Drugs Aging. 2021;38(9):797-805.
31. van de Loo B, Seppala LJ, van der Velde N, Medlock S, Denkinger M, de Groot LC, et al. Development of the ADFICE_IT Models for Predicting Falls and Recurrent Falls in Community-Dwelling Older Adults: Pooled Analyses of European Cohorts With Special Attention to Medication. J Gerontol A Biol Sci Med Sci. 2022;77(7):1446-54.
32. Torvinen-Kiiskinen S, Tolppanen AM, Koponen M, Tanskanen A, Tiihonen J, Hartikainen S, Taipale H. Antidepressant use and risk of hip fractures among community-dwelling persons with and without Alzheimer's disease. Int J Geriatr Psychiatry. 2017;32(12):e107-e15.
33. Saarelainen L, Tolppanen AM, Koponen M, Tanskanen A, Sund R, Tiihonen J, et al. Risk of Hip Fracture in Benzodiazepine Users With and Without Alzheimer Disease. J Am Med Dir Assoc. 2017;18(1):87.e15-87.e21.
34. Kanagaratnam L, Dramé M, Trenque T, Oubaya N, Nazeyrollas P, Novella JL, et al. Adverse drug reactions in elderly patients with cognitive disorders: A systematic review. Maturitas. 2016;85:56-63.
35. El-Saifi N, Moyle W, Jones C, Tuffaha H. Medication Adherence in Older Patients With Dementia: A Systematic Literature Review. J Pharm Pract. 2018;31(3):322-34.
36. Gleason PP, Schulz R, Smith NL, Newsom JT, Kroboth PD, Kroboth FJ, Psaty BM. Correlates and prevalence of benzodiazepine use in community-dwelling elderly. J Gen Intern Med. 1998;13(4):243-50.
37. Taylor JS, DeMers SM, Vig EK, Borson S. The disappearing subject: exclusion of people with cognitive impairment and dementia from geriatrics research. J Am Geriatr Soc. 2012;60(3):413-9.

38. O'Mahony D, Cherubini A, Guiteras AR, Denkinger M, Beuscart JB, Onder G, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 3. Eur Geriatr Med. 2023;14(4):625-32.
39. Depressie NHG-Richtlijnen: Nederlandse Huisartsen Genootschap; 2019 [cited 2023 December 12th]. Available from: https://richtlijnen.nhg.org/standaarden/depressie#volledige-tekst-medicamenteuze-behandeling.
40. Pronk AC, Seppala LJ, Trajanoska K, Stringa N, van de Loo B, de Groot L, et al. Candidate genetic variants and antidepressant-related fall risk in middle-aged and older adults. PLoS One. 2022;17(4):e0266590.

Appendix

Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs)

There were 102 (2.0%) participants using SSRIs and 86 (1.7%) users of TCAs in the study population of 5176 participants.

Table 1: Logistic regression models calculating the OR for the association between a fall within the first year of follow-up and SSRI use.

Regression models	N included participants (%)	OR (95% CI)	P-value
Model 1*	5176 (100)	1.22 (0.82-1.83)	0.332
Model 2**	2099 (40.6)	1.26 (0.56-2.85)	0.574

= significant if P-value <0.05

*Use of a SSRI adjusted for age and sex

**Use of a SSRI adjusted for all confounders: age, sex, body mass index, living situation, education level, number of medications, number of chronic conditions, history of cancer, history or presence of diabetes, history of heart disease, depression, presence of pain, HADS-Anxiety score (range 0-21), frequency of alcohol use, smoking status and self-rated health.

Abbreviations: OR, odds ratio; SSRI, selective serotonin reuptake inhibitor; CI, confidence interval

Table 2: Logistic regression models calculating the OR for the association between a fall within the first year of follow-up and TCA use.

Regression models	N included participants (%)	OR (95% CI)	P-value
Model 1*	5176 (100)	1.44 (0.93-2.21)	0.101
Model 2**	2099 (40.6)	0.87 (0.44-1.73)	0.690

= significant if P-value <0.05

*Use of a TCA adjusted for age and sex

**Use of a TCA adjusted for all confounders: age, sex, body mass index, living situation, education level, number of medications, number of chronic conditions, history of cancer, history or presence of diabetes, history of heart disease, depression, presence of pain, HADS-Anxiety score (range 0-21), frequency of alcohol use, smoking status and self-rated health.

Abbreviations: OR, odds ratio; TCA, tricyclic antidepressant; CI, confidence interval

No significant interaction terms were found for the use of SSRIs or TCAs and cognition.