The interaction effects of antihypertensives on the fall risk of antidepressant users among older adults, 1 + 1 = 3?

By: Carolien Dekker, Bsc
Referee: Prof. Dr. N. van der Velde
Examiner: Dr. M. Gemmeke
Daily supervisor: S. Lone, Msc

Abstract

Objective: Falling is a problem for older adults and a public health concern worldwide. Many factors could potentially increase fall risk. The use of medication and drug-drug interactions are two factors that potentially increase fall risk. This study aimed to investigate the possible (interaction) effects of the use of antihypertensives on the fall risk of antidepressant users.
Method: A prospective, observational study was conducted among older adults. Data from three databases (ActiFE Ulm, B-PROOF, and LASA c-wave) from the harmonised ADFICE_IT cohort was used. A cox-regression analysis was used to determine the hazard ratio of antidepressant users. Confounders were based on literature and were added to the model if there was no collinearity with the use of an antidepressant. In case of a significant interaction effect of (a subgroup) of antihypertensives on the fall risk of antidepressant users, the association between antidepressant use and fall risk was stratified. The stratified analysis was performed, using a cox-regression analysis. In the stratified analysis, there was an adjustment for the same confounders as in the multivariant analysis of antidepressant monotherapy.
Results: There was no significant association between antidepressant use and fall risk. There was also no interaction effect from antihypertensives on the fall risk of antidepressant users. Beta-blockers were the only subgroup with an interaction effect on the fall risk of antidepressant users. In the stratified analysis, users of beta-blockers and antidepressants had a decreased risk of falling in the unadjusted analysis, which did not remain significant after adjustment for confounders.
Discussion: In contrast with our hypothesis, there was no interaction effect of antihypertensives on the fall risk of antidepressant users. This could be due to the subgroups and their different effects on fall risk, the subgroups could nihilate each others effects on fall risk. The association between antidepressants and falls was not significant either. This could be because physicians hesitate to prescribe a FRID to patients with an elevated fall risk, but also because the patients in this study were slightly less fragile. Furthermore, beta-blocker usage might affect the fall risk of antidepressant users. However, after correction for confounders, significance was lost. This could be due to overcorrection or low power. Therefore, larger studies are needed on this topic to learn more about the interaction effects of the different subgroups of antihypertensives.
Conclusion: There was no significant interaction effect from the use of antihypertensives on the fall risk of antidepressant users. More investigation is needed on this topic among subgroups of antihypertensives and their possible interaction effect on the fall risk of antidepressant users.

Introduction

Falling is a problem for older adults and a public health concern worldwide. The number of falls among older adults is increasing. As a result, more and more older adults visit the emergency department because of a fall. Of the population older than 65 years, about one-third experience at least one fall annually. Falls are associated with premature institutionalization, decreased quality of life, impaired mobilization, and a substantial rise in health-care costs [1].

Factors that increase the fall risk

Many factors could potentially increase fall risk among older people. Individual-specific factors are, among others, age, several (chronic) diseases, muscle weakness, gait- and balance disorders, and cognitive impairment. Environmental factors include medication use, hazardous activities, and social demographic factors [2]. Fall risk may also increase further when a person has multiple fall risk-increasing factors, all these factors may also interact with each other, causing an extra increase in fall risk. Some medicines have an increased fall risk as a known adverse effect. These drugs are called fall risk-increasing drugs (FRIDs). Adverse effects that can lead to falling include dizziness, hypotension, and sleepiness. Polypharmacy is also associated with an increase in fall risk. Next to the additive risk of falls, polypharmacy potentially leads to falls because of the interaction between different drugs. However, not much is known about these specific drug-drug interactions and fall risk [3].

Antidepressants as a FRID

Antidepressants, who are mostly used to treat anxiety and/or depression are well-known FRIDs. In the standard of care, antidepressants of first choice for patients with depression or anxiety are selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs) [4, 5]. According to a meta-analysis from Seppala et al., SSRIs and TCAs significantly increase fall risk [6]. These antidepressants have various adverse effects, which could be related to the increased fall risk. These adverse effects include orthostatic hypotension, dizziness, extrapyramidal symptoms, sedation, confusion/delirium, visual impairment, and hyponatremia. Although these adverse effects are all similar for SSRIs and TCAs, the frequency at which they occur is different for TCA and SSRI users [7]. Common adverse effects, that can lead to a fall among SSRI users include sleep disturbances and extrapyramidal symptoms [7,8,9]. Examples of common fall-related adverse effects of TCAs include orthostatic hypotension, arrhythmia, conduction delay, confusion/delirium, and sedation [7, 8]. In 2021, about 10% of the people above 75 years in The Netherlands used antidepressants [10].

Antihypertensives as a FRID

Another commonly used class of FRIDs among older adults are antihypertensive drugs [10]. Depending on the class of antihypertensive, 22% up to 41% of the people aged ≥ 75 years in The Netherlands use an antihypertensive drug [10]. The four most prescribed drugs according to the Dutch guidelines are calcium channel blockers, beta-blockers, RAAS-inhibitors, and diuretics [11]. These drug classes can cause hypotension, which can lead to a fall, especially after the initiation of the treatment. The mechanism by which hypotension is caused is different among the four drug classes [1]. Diuretics induce volume depletion [12]. Calcium channel blockers cause vasodilation, by binding to the calcium receptors on the blood vessels [13]. RAAS-inhibitors cause vasodilation by inhibiting the effect of angiotensin II [14]. Beta-blockers lower the frequency of the heart and the heart volume, which lowers blood pressure [15]. These effects can lead to dizziness and falling. Despite these known side effects, the increased fall risk due to the use of antihypertensives has not yet been confirmed in the literature as a group risk, for example, Seppala et al. did not observe that the overall group of antihypertensives increased fall risk in their meta-analysis in most of the studies of the paper. This could also be because the different subclasses of antihypertensives all have a different effect on fall risk, these effects could nihilate each other [1].

Use of more than one FRID and falling

As mentioned in the previous sections, antidepressants and antihypertensives both have fall-related side effects. In the literature, an increased fall risk among patients with polypharmacy (using multiple drugs simultaneously) has been confirmed. Polypharmacy could be associated with falls due to comorbidity associated with polypharmacy or due to the increased likelihood of using FRIDs. Drug-drug interactions may also increase fall risk [3]. However, little is known about the specific drug-on-drug interaction between the two drugs [2]. Richardson et al. showed an interaction effect of polypharmacy on the fall risk in antidepressant users [16]. Polypharmacy was an effect modifier in the association between antidepressant use and fall risk. Richardson et al. stated that the increase in fall risk could be caused by drug-drug interactions. A drug-drug interaction is an enhancement or suppression of the action of one drug by another [17]. This could either be pharmacokinetic (changing what the body does with a drug, for example, by interfering with the metabolism of the drug) or pharmacodynamic by interfering with the action of the drug on the body). Antidepressants and antihypertensives theoretically have a pharmacodynamic interaction, they can cause hypotension by binding to different receptors. However, this is only one possible consequence of drug-drug interactions. The meta-analysis from Seppala et al. showed that fall risk differed among the classes of antihypertensives [1]. Therefore, the interaction effect may differ between the subgroups of antihypertensives. A higher number of medications is associated with an increase in fall risk, therefore it can be useful to examine the effect of using more than one antihypertensive on the fall risk of antidepressant users.

The aim of this paper

Therefore, this paper will aim to gain knowledge on the association between the use of more than one FRID and falling. First, the interaction effect of antihypertensives as a group on the fall risk of antidepressant users will be investigated. Antihypertensive monotherapy and the effect of using more than one antihypertensive will be investigated. After this analysis, the effect of different subgroups of antihypertensives on the fall risk of antidepressant users will be investigated. The interaction effect on fall risk will be investigated among older adults [2].

Method

Study design and background information on the study cohorts

A prospective, observational study was conducted among users of antidepressants from the harmonized ADFICE_IT cohort. Data from the following cohorts was used to examine the association between antidepressant use and falling: the LASA c-wave, B-PROOF, and ActiFE Ulm, these databases contained prospective data about falling. The LASA database is an ongoing interdisciplinary cohort study on predictors and consequences of changes in physical, cognitive, emotional, and social functioning in men and women aged 55-85 years at baseline in 1992 and 1993. The c-wave contained follow-up data on falling and medication use, collected two or three years after the baseline measurement. The c-wave included data from 2545 participants. The ActiFE Ulm database, is a cohort in which a random sample of 7460 persons aged 65 years and older were selected from the population registers in Ulm, Neu-Ulm, and Alb-Donau-Kreis. The primary focus of this database was physical activity (as measured by sensor technology) and the consequences of physical activity for cognitive, emotional, and social functioning. And lastly, the B-PROOF study (B vitamins for Prevention Of Osteoporotic Fractures) is a 2-year randomized double-blind placebo-controlled trial, including 2919 people aged 65 years and older, independently living or institutionalized. Participants of the B-PROOF study were recruited via registries of municipalities and elderly care homes around the research centres (Rotterdam, Amsterdam, and Wageningen) [18]. All studies were approved by medical ethics committees. The LASA study received approval by the METC of the VU University Medical Centre in Amsterdam. The B-PROOF study received approval by the METC of Wageningen University [19]. The ethics committee of Ulm University approved the ActiFE Ulm study [20]. The participants of the studies signed an informed consent before entering the study.

Definitions of medication use

The independent variable was the use of antidepressants. The use of an antidepressant was defined as using a SSRI or a TCA as monotherapy. Those classes are the first choice in the standard of care for depression and anxiety [4,5]. ATC codes were used to define the use of a SSRI or a TCA in the different cohorts. The ATC codes were N06AB (SSRIs) and N06AA (TCAs). The possible effect modifier was the use of antihypertensives. The use of an antihypertensive was defined as using a beta-blocker, calcium channel blocker, RAAS-inhibitor, or diuretic. These classes of drugs are the first choice for treating hypertension, according to the Dutch guidelines provided by NHG [11]. ATC codes were used to define the use of the antihypertensives in the different cohorts. The ATC codes were C07 (beta-blockers), C08 (calcium channel blockers), C03 (agents acting on the RAAS-system), and C09 (diuretics). The three cohorts used different methods for their medicine data collection. In the ActiFE Ulm cohort, medication was documented at the baseline interview and in a second sheet included in the fall calendar, which was used during the one-year follow-up [20]. LASA assessed the use of medication by using questionnaires and medication boxes, provided by participants. In the B-PROOF study, self-reported medication was assessed by questionnaires at the baseline [19].

Definition of falling

Time to first fall in the follow-up year served as a primary outcome measure. Falling in all three cohorts was measured by using a weekly fall-calendar over one year from the baseline measurement [18].

Covariates

Potential confounding variables, based on literature, were: sex, age, number of medications, living status (living together or alone), number of chronic diseases, Z-score depression, MMSE, BMI, sleeping problems (yes or no), urine incontinence (yes or no), Z-score gait speed, frequency of alcohol use, smoking status and self-rated health (on a scale from 1-5) [2], [6], [21], [22]. Covariates were measured at the baseline in all cohorts. By using questionnaires or interviews. The scores for depression and gait speed were harmonised after extracting them from different cohorts [18].

Statistical analysis

For the statistical analysis, IBM Statistics SPSS statistics 28 was used. The baseline characteristics were determined for antidepressant users and non-antidepressant users. Differences between groups were tested using a t-test for normally distributed variables, a Mann-Whitney U test for non-normally distributed continuous variables, and a Chi-square test for categorical variables. The hazard ratios for the association between falling and antidepressant use were calculated using a Cox-regression model. The significance level was 0.05. The time to first fall was calculated using the hazard ratio. Initially, the unadjusted hazard ratio was determined. For the potential confounders, a Spearman's rho correlation test was performed, to check for collinearity. Confounders with a correlation between -0.3 and 0.3, in correspondence with the rule of Thumb [23], were tested as potential confounders. Confounders that led to a change in the regression coefficient (B) of ≥10% and significantly improved the statistical model were included in the multivariate-adjusted regression model. Confounders with over 10% missing values were excluded to have enough participants for the multivariate analysis.

To test for effect modification by antihypertensives, an interaction term between antidepressant monotherapy and antihypertensive monotherapy was added to the unadjusted Cox-regression model. After the first analysis, interaction terms between two, three, and four antihypertensives and antidepressant monotherapy were analysed. The interaction terms of beta-blockers, calcium channel blockers, diuretics, and RAAS-inhibitors were analysed as well. In case of an interaction term with a p-value <0.1, a stratified analysis was performed. A stratified analysis was performed for the use of a beta-blocker. After the stratified analysis, a post hoc analysis was performed to compare the characteristics of antidepressant users who did use a beta-blocker versus antidepressant users who did not use a beta-blocker.

Results

Characteristics of the participants

A total of 7873 participants of the harmonized cohort were identified. Of these participants, 1991 participants were excluded due to missing data on antidepressant or antihypertensive use, and 96 participants due to missing data on time to first fall. One participant used more than one antidepressant. This left a total of 3923 participants that were included from the different cohorts, see figure 1. After the primary analysis of patients with one antidepressant and one antihypertensive, the different subgroups of antihypertensives were analyzed. The number of participants who used more than one antihypertensive was 1862, these participants were excluded from the primary analysis and analysed separately.

The percentage of participants who used an antidepressant was 3.6%, the percentage of participants who used an antihypertensive as monotherapy was 25.5%. The number of participants in the non-user group (n = 1226; 32%) and the user group (n = 55; 39%) experiencing a fall during the 1-year follow-up did not differ significantly (p = 0.116). Table 1 includes the baseline characteristics of the participants in the analysis of the association between fall risk and antidepressant monotherapy. The percentage of the participants who reported a fall in the year of follow-up was 21.3%, 47% were female, and the mean age of the participants was 72.3 years. Females used significantly more antidepressants than males, furthermore, users of antidepressants had more depressive symptoms, a worse self-rated health, used more alcohol, and used significantly more medication compared to non-users of an antidepressant. There were no significant differences among the other baseline characteristics between users and non-users of antidepressants.

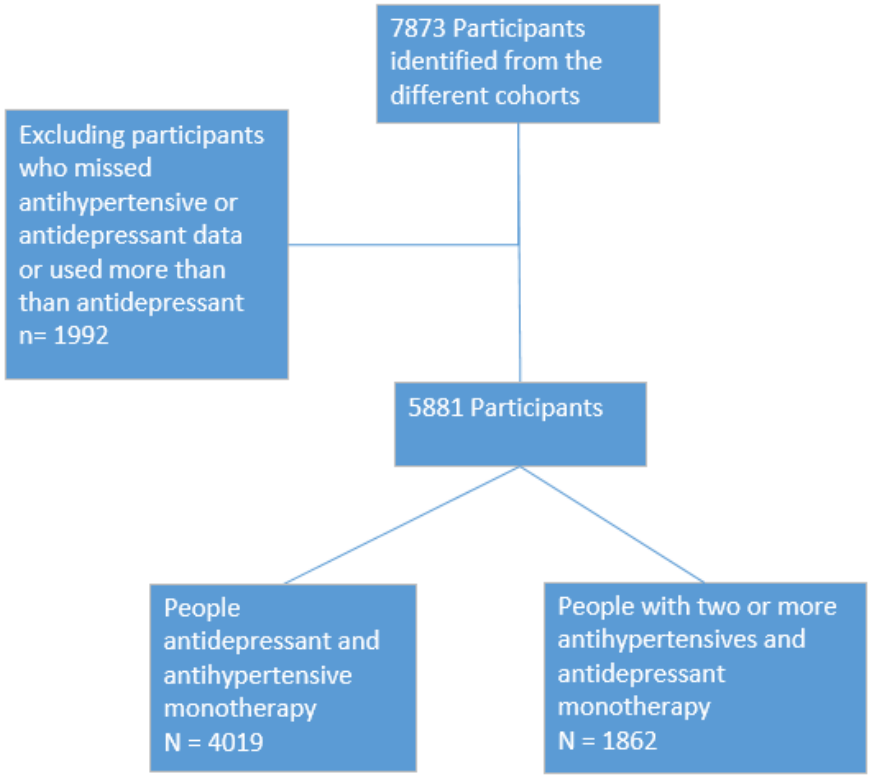

Figure 1: Flowchart inclusion participants in the multivariate analysis.

Table 1: baseline characteristics participants in the analysis of the association between antidepressant monotherapy and fall risk.

	Total n = 4019	User of an antidepressant n = 142	Non-user of an antidepressant n = 3877	P-value
Sex: n (%)				< 0,001#
Male	2121	55 (38.7)	2066 (53.3)	
Female	1998	87 (61.3)	1811 (46.7)	
Age: mean (sd)	4019	73.7(5.8)	74.2 (6.4)	0.66
Living status: n (%)				0.08
Living together	2563	81 (57.0)	2489 (64.2)	
Living alone	192	61 (43.0)	1388 (35.8)	
BMI: mean (sd)	3989	26.7 (3.4)	26.6 (3.8)	0.15
Frequency of alcohol use mean (sd), on a scale from 0-4+	2982	2,33 (1.6)	2,63 (1.4)	0.04#
Smoking status: mean (sd)				0.58
Never smoked	1542	51 (35.9)	1490 (38.4)	
Ex-smoker	1974	69 (48.6)	1905 (49.1)	
Current smoker	503	22 (15.5)	481 (12.4)	
Self-rated health: mean (sd)	4014	2.98 (0.79)	2.62 (0.84)	<0.001#
Z-score gait speed: mean (sd)	3896	-0.26 (0.92)	0.08 (0.99)	0.56
MMSE: mean (sd)	2930	27.4 (2.6)	27.7 (2.4)	0.07
Number of chronic conditions: mean (sd)	1607	0.6 (0.7)	0.5 (0.7)	0.19
Z-score depression: mean (sd)	2921	0.37 (1.1)	-0,09 (0.9)	<0.001#
Number of medications: mean (sd)	2994	4.0 (2.0)	2,0 (1.9)	0#
Antihypertensives monotherapy: n (%)				0.81
Yes	1025	35(24.6%)	990 (25.5%)	
No	2994	107(75.4%)	2887 (74.5%)	
Beta-blocker monotherapy: n (%)				0.66
Yes	463	18 (12.7%)	445 (11.5 %)	
No	3556	124 (87.3%)	3432 (88.8 %)	
Ca-blocker monotherapy: n (%)				0,66
Yes	169	7 (4.9%)	162 (4.2%)	
No	3850	135 (95.1%)	3715 (95.8%)	
Raas-inhibitor monotherapy: n(%)				0.26
Yes	393	10 (7.0)	383 (9.9)	
No	3926	132 (93.0)	3494 (90.1)	

 # = significant difference at p < 0.05 *+*

0, = non – drinker, 1 = less than once a month, 2 = 1-3 times a month, 3 = 1-4 days a week, 4 = almost daily

MMSE, Mini-Mental State Examination; BMI, Body Mass Index; ca-blocker, calcium channel blocker; RAAS-inhibitor, renin angiotensin aldosterone system inhibitor

Regression analysis

In table two, the unadjusted and adjusted hazard ratios of the regression analysis are shown. Antidepressant monotherapy did not significantly increase fall risk (HR = 1.28, CI = 0.98-1.68). When adjusted for sex, BMI, Z-score for depression, and number of medications, the analysis showed that antidepressant use did not influence fall risk (HR 0.98, CI = 0.74-1.31). Antihypertensive monotherapy was not associated with an increase in fall risk in both the adjusted and unadjusted analysis. The use of two antihypertensives did not significantly influence fall risk in the unadjusted analysis. After adjustment for sex, age, mean systolic blood pressure, mean diastolic blood pressure, presence of urinary incontinence, and number of medications, the use of two antihypertensives significantly decreased fall risk. The use of three and four antihypertensives was not associated with a significant change in fall risk. In the unadjusted analysis, the use of a beta-blocker was associated with a significant increase in fall risk (HR = 1.24, CI = 1.05-1.45), however, this did not remain significant after adjustment for confounders (HR = 1.27, CI = 0.87-1.86). Calcium channel blockers and RAAS-inhibitors did not significantly change fall risk in both the adjusted and unadjusted analysis.

Table 2: calculated Hazard Ratios for different medicine classes and different number of antihypertensives

	Unadjusted hazard ratio	**95% CI**	**Adjusted hazard ratio**	**95% CI**
Antidepressant users	1.28	0.98-1.68	0.91*	0.74-1.31
Antihypertensive monotherapy	1.08	0.96 – 1.23	0.95**	0.69 – 1.31
Two antihypertensives	1.05	0.91 – 1.22	0.63#/***	0.42 – 0.97
Three antihypertensives	1.03	0.89 – 1.20	0.80****	0.52 – 1.22
Four antihypertensives	1.01	0.84 – 1.23	0.62****	0.28 – 1.38
Beta-blocker users	1.24#	1.05-1.45	1.27**	0.87 – 1.86
Ca-blocker users	0.90	0.68 – 1.20	0.64**	0.26 – 1.55
RAAS-inhibitor users	0.96	0.80 – 1.16	0.65**	0.34 – 1.23

 # significant at p < 0.05

** adjustment for sex, BMI, z-score depression and number of medications*

*** adjustment for sex, age, z-score depression and presence of urinary incontinence*

**** adjustment for sex, age, mean systolic blood pressure, mean diastolic blood pressure, presence of urinary incontinence and number of medications*

***** adjustment for sex, age, presence of urinary incontinence and number of medications*

Analysis of the interaction effect

After calculating the hazard ratio among users of antidepressant monotherapy, interaction terms were made for the use of antihypertensive monotherapy, the use of two, three and four antihypertensives, and for the different subclasses of antihypertensives. The interaction term antidepressant monotherapy and antihypertensive monotherapy was not significant. The interaction terms of users of two, three, and four antihypertensives were not significant as well. The interaction terms of Calcium channel blockers and RAAS-inhibitors were not significant. The interaction term for beta-blockers and antidepressants was the only significant interaction term (p = 0.043) for subclasses of antihypertensives, which means there is only a significant interaction effect of beta-blockers on fall risk among antidepressant users.

Stratified analysis

Based on the significant interaction term of beta-blocker use and antidepressant use, the multivariate analysis was stratified for the use of beta-blockers (yes or no). The analysis stratified for use of a beta-blocker revealed that antidepressant use had a significantly increased fall risk in the unadjusted analysis of people who did not use a beta-blocker (HR = 1.42, CI = 1.09-1.91), but this did not remain significant after adjustment for confounders (HR = 1.21, CI = 0,90-1.63), see table 3. In the unadjusted analysis for antidepressants among users of a beta-blocker, fall risk was significantly decreased by antidepressant use (HR = 0.35, CI= 0.13-0.97), but this did not remain significant after adjustment for confounders (HR = 0.50, CI = 0.18-1.33), see table 3.

Table 3: Analysis antidepressants and fall risk, stratified by the use of beta-blockers

	Unadjusted hazard ratio	**95% CI**	**Adjusted hazard ratio**	**95% CI**
Antidepressant users, no use of a beta-blocker	1.44 #	1.09-1.91	1.21**	0.90-1.63
Antidepressant users, user of a beta-blocker	0.35#	0.13-0.97	0.50**	0.18-1.33

 # = significant at p<0.05

*** adjusted for sex, BMI, z-score for depression and number of medications*

Post hoc analysis

A post hoc analysis showed a higher prevalence of heart diseases among the users of antidepressants and beta-blockers (46.7%) versus non-beta-blocker users, who used an antidepressant (13.5%). The analysis also showed that users of beta-blockers and antidepressants used significantly more medication than people who only used antidepressants (5.0 medications versus 3.84 medications). There were no other significant differences between the two groups, see appendix 1.

Discussion

Main findings

This paper investigated the interaction effect of antihypertensives on the fall risk of antidepressant users. Unexpectedly, there was no significant association between the risk of falling and antidepressant use in this study. Neither was a significant interaction effect between antihypertensive monotherapy and antidepressant use on the fall risk found. For the subgroups of antihypertensives, only beta-blockers had a significant interaction effect on the fall risk of antidepressant users. The stratified analysis showed a decreased fall risk for users of antidepressants, who also used a beta-blocker in the unadjusted analysis only.

Possible explanation and comparison to the literature

The results on the fall risk of antidepressant users were unexpected, as usage of antidepressants is an established fall risk factor. In the literature, most papers reported a significant increase in fall risk among users of antidepressants. A significant increase in fall risk was reported in the meta-analysis of the systemic review of Seppala et al. [6], and in a systematic review from van Poelgeest et al. The pooled estimate of the odds ratio of fall risk of antidepressant use in this systematic review from van Poelgeest et al. was 1.57 (95% CI = 1.43–1.74) [7]. The B-PROOF study (HR = 1.30, 95% CI = 1.01–1.70), which was one of the cohorts that was included in the analysis of this study, also stated that antidepressants significantly increased fall risk [24]. However, the results of a paper published by the investigators of the ActiFE Ulm study were comparable to the results in this paper (HR = 1.35, 95% CI = 0.86–2.11) [25]. The ActiFE Ulm cohort was also used in the analysis of this paper. There were no results published by LASA about antidepressants and fall risk. The different results of the cohorts can be caused by differences between the cohorts. The participants from the ActiFE Ulm cohort appeared healthier in comparison to those from the LASA and B-PROOF cohorts [26]. These healthier patients, with a decreased fall risk, from the ActiFE Ulm study could have lowered the fall risk in the analysis on antidepressant users in this study. Besides that, in the analysis of antidepressant monotherapy, people with more than one antihypertensive were excluded, and the number of medications in use was relatively low compared to studies conducted among the ActiFE Ulm and B-PROOF cohorts. Therefore, some more fragile people with an increased fall risk could have been excluded from the analysis. This could have led to a decrease in fall risk in the analysis of this study. Another possible explanation for the lack of significant increase in fall risk by antidepressants could also be that potential FRIDS are well recognised by physicians, and physicians hesitate to prescribe antidepressants to patients with an elevated fall risk. Therefore, antidepressants are mostly used by people who have a relatively low fall risk. When prescribed to patients with an increased fall risk, the patients receive extra supervision to lower the risk of falling [25]. For most antidepressants, the lowest effective and maximal dose for geriatric patients has been established, so it is also possible to lower the dose to decrease the fall risk [7].

The interaction terms of antihypertensives and antidepressant use were not significant. There was no literature published on this specific interaction effect. In the meta-analysis from Seppala et al., polypharmacy was associated with an increased fall risk [3]. Richardson et al. found an interaction effect between the use of an antidepressant and polypharmacy, regarding fall risk [16]. However, there were some differences between these papers and this paper. First, these papers had a larger sample size than this paper. The analysis from Seppala et al. and Richardson et al. also used a different definition for polypharmacy. They defined polypharmacy as the use of at least four or five drugs, which could be drugs from more than two different drug classes. In this paper, the interaction effect was investigated between two specific drug classes. Using more than two different drug classes could have a different effect on fall risk than using two drug classes. Furthermore, dosages of antihypertensives are mostly based on blood pressure. Therefore, the risk of orthostatic hypotension is probably decreased, and the fall risk is reduced. People with untreated hypertension, namely have an increased risk of orthostatic hypotension. Treating hypertension can therefore decrease the fall risk [28]. Also, when dosing based on blood pressure, good monitoring can be performed. Monitoring can decrease the risk of orthostatic hypotension, and thereby decrease the risk of a fall. Besides that antihypertensives are dosed on blood pressure, within the group of antihypertensives, different subgroups have different pharmacological properties, which can lead to a different effect on fall risk. Taking the subgroups together may nihilate the effects of the individual subgroups and lead to non-significant results [1].

Regarding the analysis of therapeutic subgroups of antihypertensives, beta-blockers were the only subgroup with a significant interaction effect on the fall risk of antidepressant users. Unexpectedly, antidepressant users who also used a beta-blocker had a decreased fall risk. However, there was no significance in the adjusted analysis, so the results could be caused by one of the confounders (sex, BMI, z-score for depression, or the number of medications). The observed interaction effect of beta-blockers on the fall risk of antidepressant users might be explained by drug–drug interactions. Though, this is not likely. Pharmacokinetically, some SSRIs (fluoxetine and paroxetine) inhibit CYP2D6, which metabolises metoprolol [29]. However, it is unlikely that this specific pharmacokinetic effect can cause an interaction effect for antidepressants and beta-blockers in general since most patients do not use this specific combination. Pharmacodynamically, both drug classes could cause hypotension, as mentioned in the introduction [7,15]. Theoretically, they can cause an extra decrease in blood pressure by decreasing blood pressure in different ways. Beta-blockers lower cardiac output by binding to the beta-1 receptor on the heart [15], and antidepressants cause vasodilation by binding to the alpha-1 receptor [7]. However, this pharmacodynamic interaction is more likely to increase fall risk and therefore cannot explain the results of the analysis. The post hoc analysis revealed that people who used a beta-blocker and an antidepressant had a significantly higher prevalence of heart diseases than people who only used an antidepressant. A history of heart diseases has previously been associated with an increased fall risk in a paper from Mikos et al. [27]. Because heart diseases cause an increase in fall risk, confounding by indication cannot play a role. A protective effect of beta-blockers has been described in the literature before. Seppala et al. reported a protective effect of beta-blockers on the fall risk of older people in general. They hypothesized that the protective effect of beta-blockers could be due to lowering elevated levels of catecholamine, which normally leads to fainting and therefore can lead to a fall [1]. The protective effect of beta-blockers has not been reported in all literature, some literature reported no significant change in fall risk for beta-blockers. On the possible interaction effect of beta-blockers, no literature has been published yet. Further research is needed to establish this.

Because the described theory is somehow conflicting, more research is needed to learn more about a (possible) interaction effect of beta-blockers on the fall risk of antidepressant users. Due to the small sample size, the fact that antidepressants did not significantly increase the fall risk, and the significant increase in fall risk from beta-blockers in the unadjusted regression analysis, coincidence cannot be ruled out as well.

Missing data

For diuretics, no analysis of fall risk or interaction terms could be performed due to the absence of data about diuretic monotherapy and fall risk. It is important to investigate this subgroup because (loop)diuretics are associated with a significant increase in fall risk, as opposed to the other subgroups of antihypertensives and therefore diuretics theoretically could have a stronger interaction effect on the fall risk of antidepressant users [1], [12].

Strengths and weaknesses

To our knowledge, this is the first paper to investigate the association between a specific drug-drug interaction and fall risk. In this paper, prospective data was used. This provides more knowledge about the medication in use at the time of a fall, compared to retrospective data. There are some limitations to this paper. First, the sample size was small. Although the cohort comprised 4019 participants, there were only 142 users of an antidepressant, which is low compared to most literature. This resulted in a relatively low power, which stresses the need for even bigger datasets to test this hypothesis and other drug-drug interactions. No data on the dosage or duration of use of the medication was known. These data could have been helpful because both dosage and duration of treatment affect the fall risk of both antidepressants and antihypertensives. An increase in fall risk is most prevalent in the first weeks after initiating antidepressant or antihypertensive use [1], [7]. However, in the study cohorts, most users had already used their medication for a longer period when entering the study, this could affect the fall risk in the analysis of this paper.

Clinical implications and future perspectives

In this paper, there was no significant interaction effect of antihypertensives on the fall risk of antidepressant users. Regarding specific drug subgroups, beta-blockers did show a significant interaction effect on the fall risk of antidepressant users. Although in the stratified analysis, after adjustment for confounding, no significant effect was observed. Power was, however, limited given the low prevalence of users. Thus, it is not ruled out that concurrent use of a beta-blocker might affect the fall risk of antidepressant users. This paper also revealed that an interaction effect of drugs does not necessarily mean a further increase in fall risk. This paper has no direct clinical implications regarding changing guidelines for patients with an increased fall risk, as no significant findings were reported. Also, this paper is the first to investigate a specific drug-drug interaction in relation to fall risk. Thus, more investigation on this topic is needed. However, when prescribing a FRID or a combination of FRIDs to a patient with an increased fall risk, close monitoring is needed as well as weighing advantages and disadvantages on an individual level. In future research, more information should be collected about dosage, duration of treatment, and underlying conditions of the patient groups. Future research should also have a larger sample size. Furthermore, the focus should be on subgroups of antihypertensives instead of antihypertensives in general because pharmacological effects differ between subgroups of antihypertensives and therefore interaction effects might differ. The four classes of antihypertensives are equally effective when it comes to treating hypertension and choice of antihypertensive should be at least partly based on side effects [11]. Future studies on this topic could contribute to better understanding which antihypertensive can be best prescribed to a patient with an elevated fall risk, who uses more than one drug. Of course, the other characteristics of the patient must be taken into account when prescribing an antihypertensive.

Conclusion

There was no significant interaction effect from the use of antihypertensives on the fall risk of antidepressant users. There is an indication that the beta-blocker subclass of antihypertensives could potentially have an interaction effect on the fall risk of antidepressant users. Thus, more investigation is needed on subgroups of antihypertensives and their effect on fall risk of antidepressant users.

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Appendix 1: results of the post hoc analysis among users of antidepressant monotherapy, stratified by the use of beta-blockers

	Total n = 142	Users of a beta-blocker n = 18	Non-users of a beta-blocker n = 124	P-value
Sex				0.62
Male	55	6 (33.3)	49 (39.5)	
Female	87	12 (66.7)	75 (60.5)	
Age: mean (sd)	142	75.89 (6.60)	73.41 (5.62)	0.14
Living status: n (%)				0.14
Living together	81	11 (61.1)	70 (56.5)	
Living alone	61	7 (38.9)	54 (43.5)	
BMI: mean (sd)	140	28.07 (3.49)	26.48 (3.33)	0.73
Frequency of alcohol use mean (sd)	141	1.71 (1.57)	2.41 (1.55)	0.08
Smoking status: n (%)				0.11
Never	51	9 (50)	42 (33.9)	
Ex-smoker	69	9 (50)	60 (48.4)	
Current smoker	22	0 (0)	22 (17.7)	
Self-rated health: mean (sd)	142	3.17 (0.86)	2.95 (0.77)	0.44
Z-score gait speed: mean (sd)		-0.6585 (1.14)	-0.1963 (0.87)	0.215
MMSE: mean (sd)	142	26.67 (3.07)	27.44 (2.55)	0.28
Number of chronic conditions: mean (sd)	58	0.8 (0.79)	0.58 (0.71)	0.39
History of heart disease n (%)				0.002#
Yes	22	7 (46.7)	15 (13.5)	
no	104	8 (53.3)	96 (86.5)	
Hypertension n (%)				0.29
Yes	58	5 (33.3)	53 (47.7)	
No	68	10 (66.7)	58 (52.3)	
Diabetes n (%)				0.16
Yes	7	2 (13.3)	5 (4.5)	
No	119	13 (86.7)	106 (95.5)	
Z-score depression: mean (sd)	135	1.07 (1.73)	0,65 (1.41)	0.30
Sleeping problems n (%)				0.60
Yes	16	2 (100)	14 (87.5)	
No	2	0 (0)	2 (12.5)	
Urinary incontinence n (%)				0.16
Yes	23	6 (60.0)	17 (36.2)	
No	34	4 (40.0)	30 (63.8)	
Lowest systolic blood pressure: mean (sd)	126	131.47 (16.41)	138.42 (17.60)	0.09
Lowest diastolic blood pressure: mean (sd)	126	72.87 (10.61)	76.87 (9.24)	0.77
Mean systolic blood pressure: mean (sd)	126	137.58 (14.55)	141.63 (16.97)	0.72
Mean diastolic blood pressure: mean (sd)	126	75.84 (10.58)	79 (10.19)	0.69
Number of medications: mean (sd)	142	5.0 (1.72)	3.84 (2.09)	0.01#

MMSE, Mini-Mental State Examination; BMI, Body Mass Index
 # = significant at p <0.05